Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials

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Summary

Background Closed-loop artificial pancreas systems have been in development for several years, including assessment in numerous varied outpatient clinical trials. We aimed to summarise the efficacy and safety of artificial pancreas systems in outpatient settings and explore the clinical and technical factors that can affect their performance.

Methods We did a systematic review and meta-analysis of randomised controlled trials comparing artificial pancreas systems (insulin only or insulin plus glucagon) with conventional pump therapy (continuous subcutaneous insulin infusion [CSII] with blinded continuous glucose monitoring [CGM] or unblinded sensor-augmented pump [SAP] therapy) in adults and children with type 1 diabetes. We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for studies published from 1946, to Jan 1, 2017. We excluded studies not published in English, those involving pregnant women or participants who were in hospital, and those testing adjunct medications other than glucagon. The primary outcome was the mean difference in percentage of time blood glucose concentration remained in target range (3·9–10 mmol/L or 3·9–8 mmol/L, depending on the study), assessed by random-effects meta-analysis. This study is registered with PROSPERO, number 2015:CRD42015026854.

Findings We identified 984 reports; after exclusions, 27 comparisons from 24 studies (23 crossover and one parallel design) including a total of 585 participants (219 in adult studies, 265 in paediatric studies, and 101 in combined studies) were eligible for analysis. Five comparisons assessed dual-hormone (insulin and glucagon), two comparisons assessed both dual-hormone and single-hormone (insulin only), and 20 comparisons assessed single-hormone artificial pancreas systems. Time in target was 12·59% higher with artificial pancreas systems (95% CI 9·02–16·16; p<0·0001), from a weighted mean of 58·21% for conventional pump therapy (I^2=84%). Dual-hormone artificial pancreas systems were associated with a greater improvement in time in target range compared with single-hormone systems (19·52% [95% CI 15·12–23·91] *vs* 11·06% [6·94 to 15·18]; p=0·006), although six of seven comparisons compared dual-hormone systems to CSII with blinded CGM, whereas 21 of 22 single-hormone comparisons had SAP as the comparator. Single-hormone studies had higher heterogeneity than dual-hormone studies (I^2 79% *vs* 66%). Bias assessment characteristics were incompletely reported in 12 of 24 studies, no studies masked participants to the intervention assignment, and masking of outcome assessment was not done in 12 studies and was unclear in 12 studies.

Interpretation Artificial pancreas systems uniformly improved glucose control in outpatient settings, despite heterogeneous clinical and technical factors.

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Introduction

Intensive insulin therapy for type 1 diabetes prevents microvascular complications and cardiovascular morbidity.[1–3] However, intensive insulin theray is also associated with higher risk of hypgolycaemia and weight gain, and greater burden of self-management.[4,5] According to both observational data and evidence from clinical trials, a large proportion of individuals with type 1 diabetes are unable to meet recommended HbA_{1c} targets.[6,7] Technologies that could provide intensive insulin therapy and thereby improve glycaemic control while minimising hypoglycaemia and the burden of disease self-management are therefore highly desirable.

A closed-loop system or artificial pancreas consists of three components—a continuous glucose monitor (CGM), infusion pumps to deliver hormones, and a sophisticated dosing algorithm to control hormone delivery.[8,9] Two types of artificial pancreas have been developed: single-hormone systems that infuse insulin and dual-hormone systems that infuse both insulin and glucagon. The dual-hormone artificial pancreas, although more complex, has the putative benefit of allowing more aggressive insulin administration.[10]

Although there have been several reviews of clinical research into artificial pancreas systems, to our knowledge, no systematic review or meta-analysis of trials has been reported. Using a meta-analytical approach to obtain a unified estimate of the effect of artificial pancreas systems compared with conventional insulin pump therapy in outpatient trials is important to determine whether

Research in context

Evidence before this study

Numerous clinical trials have been done to assess closed-loop (artificial pancreas) systems in outpatient settings, but these trials have included small numbers of participants and have varied substantially in clinical and technical characteristics. To our knowledge, no previous systematic review or meta-analysis of outpatient trials of artificial pancreas systems has been reported. On Jan 4, 2017, we searched for reports of randomised clinical trials of artificial pancreas systems in an outpatient setting in Medline, Embase, and the Cochrane Central Register of Controlled Trials published before Jan 1, 2017. The search strategy included keyword and subject heading terms for type 1 diabetes, artificial pancreas, and their synonyms. Studies not reported in English those involving pregnant women or participants in hospital, and those testing adjunct medications (other than glucagon) were excluded.

Added value of this study

To our knowledge, this systematic review and meta-analysis is the first to provide a unified estimate of the efficacy of artificial pancreas systems in outpatient clinical trials. Our results show that artificial pancreas systems uniformly and similarly improve glucose control in outpatient settings compared with conventional pump therapy, despite variable clinical and technical characteristics. Although overall there was a reduction in hypoglycaemia, the presence or absence of remote monitoring seemed to affect hypoglycaemia outcomes. Insulin dose was unchanged by artificial pancreas systems compared with conventional pump therapy.

Implications of all the available evidence

The efficacy of artificial pancreas systems is robust across settings with varied clinical and technical factors. Based on its ability to improve time in blood glucose target range (which might translate to lowered HbA_{1c}), artificial pancreas systems will be implemented in long-term clinical trials and clinical practice in the near future. In future studies done without remote monitoring, the effect of artificial pancreas on hypoglycaemia can be more definitively assessed.

improved time in target blood glucose range (which is generally reported as about 20% higher with artificial pancreas systems in inpatient studies (Weisman A, unpublished) is translated to outpatient settings, to assess efficacy and safety in a larger number of participants, and to investigate the effect of differences in artificial pancreas technology and variable clinical settings.[10–20]

In this study, our primary objective was to determine whether use of artificial pancreas systems in adults and children with type 1 diabetes results in improved time in target glucose range compared with conventional pump therapy (continuous subcutaneous insulin infusion [CSII] with blinded CGM or unblinded sensor-augmented pump [SAP] therapy) in outpatient settings. Our secondary objectives were to determine whether use of artificial pancreas systems results in reduced time in hypoglycaemia or lowered total daily insulin dose. We also explored the effects of varied technical and clinical factors, as well as approaches to statistical analysis, on the potential benefit of artificial pancreas systems.

Methods

Search strategy and selection criteria

An electronic search was run by a professional librarian (EU) on the OvidSP search platform on Jan 4, 2017, in Medline (1946, to December week 1, 2016), Embase (1980, to week 1, 2017), and the Cochrane Central Register of Controlled Trials (November, 2016). Subject headings and keyword terms for diabetes and artificial pancreas were used and results were limited to clinical trial study terms (appendix pp 9–13). The first 200 hits of a Google Scholar search of "closed loop system" or "artificial pancreas" and "clinical trial" were also reviewed. Our search was restricted to reports published in English.

See Online for appendix

Trials comparing an artificial pancreas system (insulin only or insulin and glucagon) with conventional insulin pump therapy in an outpatient setting were potentially eligible for inclusion. Outpatient setting was defined as the participant's home, hotel, or a diabetes summer camp. Random allocation of the sequence of interventions was required and both crossover and parallel-group designs were included. Observational studies, narrative reviews, letters, editorials, and commentaries were excluded. Studies involving pregnant or acutely ill (admitted to hospital) patients, studies involving the use of intraperitoneal insulin delivery, and studies assessing an adjunct were excluded. Conventional pump therapy could consist of CSII alone, CSII with blinded CGM, or unblinded SAP therapy. Many studies in which the comparator arm was CSII with blinded CGM permitted unblinded SAP if participants had chosen it as part of usual care. We defined the comparator arm as SAP only if by study protocol unblinded SAP was assigned to all participants.

The primary outcome was the difference in percentage of time of the total duration of the intervention that blood glucose was within target range (time in target) compared to conventional pump therapy. The secondary outcomes were the difference in the percentage of time glucose concentration was less than 3·9 mmol/L per individual per 24 h (time in hypoglycaemia) and the difference in total insulin requirements in units per kg/h. Studies that reported any of these outcomes were included. Subgroup analyses (overnight versus 24 h, adult versus paediatric, single versus dual hormone, and algorithm type) were planned a priori. Subgroup analyses by target range (3·9–10 mmol/L *vs* 3·9–8 mmol/L) and by presence or absence of remote monitoring were done post-hoc. We

reported 24 h outcomes for studies done over 24 h and overnight outcomes for studies done overnight.

All search results were screened from titles and abstracts by two independent reviewers (AW and J-WB) and selected studies were reviewed in full text. Disagreements were resolved by consensus after discussion.

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and is registered with the International Prospective Register of Systematic Reviews (PROSPERO, number 2015:CRD42015026854).[21]

Data extraction and quality assessment

Two independent reviewers (AW and MC) extracted data using a standardised form. Disagreements were resolved by discussion and joint review of original studies to achieve consensus. Supplementary material was reviewed if necessary.

Following The Cochrane Handbook for Systematic Reviews of Interventions, studies were rated as having high, low, or unclear risk of bias.[22] Records of trial registration were reviewed to assess for incomplete outcome reporting. Authors were contacted to clarify study design characteristics when necessary.

Data synthesis and analysis

The primary outcome was analysed as mean differences in time in blood glucose target range during artificial pancreas compared with conventional pump therapy. A target range of 3·9–10 mmol/L was reported for most studies; however, for studies not reporting this range, 3·9–8 mmol/L was used. For outpatient studies, CGM values are an appropriate outcome measure and therefore our analysis did not consider whether stochastic adjustments were made. Time in hypoglycaemia and change in total daily insulin dose were also analysed as mean differences. 95% CIs were calculated for all outcomes. For studies reporting data for paediatric and adult patients separately, we planned to analyse these as separate comparisons. For studies comparing both dual-hormone and single-hormone artificial pancreas with conventional pump therapy (three-way crossover), we planned to do a fixed-effects model meta-analysis of single-hormone artificial pancreas versus conventional pump therapy and dual-hormone artificial pancreas versus conventional pump therapy for each study and subsequently enter a single weighted mean difference and weighted error estimate for each study into the final meta-analysis.

Crossover trials should report paired outcomes. Because this is often not reported, we planned a priori to analyse all studies using group means and SDs, assuming no correlation between groups (ie, as if studies were parallel-group designs). Bias introduced by this assumption is generally conservative.[22] As a sensitivity analysis, we planned to analyse those studies reporting paired differences using the mean and SE of the paired differences as well as using the group means and SDs. Medians were assumed to equal means and SD was calculated as IQR/1·35, as recommended by the Cochrane Collaboration.[22] Participant-level data was not requested; however, two studies that did not report paired differences reported participant-level data (in the published report or supplementary appendices) and these were used to calculate the mean and SE of the paired differences for time in target range for a sensitivity analysis.[23,24]

Data were combined in a random-effects model meta-analysis using Review Manager version 5.3, because clinical and statistical heterogeneity between studies was expected. Studies were weighted by a generic inverse-variance method. No adjustments for multiple comparisons were made.

Three sensitivity analyses were prespecified: first, to analyse studies reporting paired differences using two methods, as described above; second, to adjust for within-person differences using the method of Elbourne and colleagues (in which the correlation between artificial pancreas and conventional pump therapy outcomes in the same patient was determined from studies reporting paired differences, and the resultant mean correlation was imputed for studies not reporting paired differences);[25] and third, to repeat the meta-analysis with only studies at low risk of bias.

Statistical heterogeneity was assessed by I^2 and sources of heterogeneity were sought if I^2 was greater than 50%. Publication bias was assessed through generation of a funnel plot for the primary outcome and Egger's test, where a p value less than 0·05 indicates the presence of publication bias.

Role of the funding source

There was no funding source for this study. AW and BAP had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The search results and the number of studies reviewed, excluded, and included are reported in figure 1. 95 articles were reviewed in detail and 24 studies were included in the analysis.[23,24,2646] Cohen's kappa statistic for agreement for selection of articles to be included or excluded after full text review was 0·89. One study had a parallel-group design;[39] all other studies had crossover designs. In three studies, paediatric (≤18 years) and adult (>18 years) patients' data were entered as separate comparisons in the meta-analysis.[23,26,27] Five comparisons assessed dual-hormone artificial pancreas systems only, two comparisons assessed both dual-hormone and single-hormone systems in a three-way crossover design, and 20 comparisons assessed single-hormone systems. Of 22 single-hormone artificial pancreas comparisons, 21 were compared with SAP, and one was compared with CSII with blinded CGM. Of seven dual-hormone artificial pancreas comparisons, six were compared with CSII

with blinded CGM and one was compared with SAP. Characteristics of included studies are shown in table 1. It should be noted that many of the studies comparing artificial pancreas with CSII with blinded CGM allowed participants' usual care of unblinded SAP to be continued, but investigators did not systematically assign SAP in the comparator group.

71 articles were excluded after detailed review (figure 1, appendix pp 14–16). All 24 included studies were pooled in the meta-analysis. Details regarding study design were often not included in study reports. None of the trials masked participants to the intervention. Crossover studies with washout periods less than 24 h between artificial pancreas and conventional pump therapy were rated as having a high risk of bias in the category of 'other bias'. Attrition and reporting biases were generally low risk. Other than masking, most studies were at low risk or unclear (if the information was not available) risk of bias (appendix pp 1–2). We considered studies with low risk for each component other than masking to be low risk for bias. Requests from authors for clarifications of study design were received for 14 studies. A funnel plot for the primary outcome did not show evidence of publication bias visually or based on Egger's test (p=0·55, appendix p 3).

There was clinical heterogeneity across studies, but a meta-analysis is justified because pragmatically an artificial pancreas needs to function under variable clinical conditions. All studies reported the primary outcome as a single outcome rather than both adjusted and unadjusted outcomes. 17 comparisons adjusted outcomes for period effect. Some studies adjusted for baseline glucose and randomisation sequence, and no studies adjusted for clinical variables.

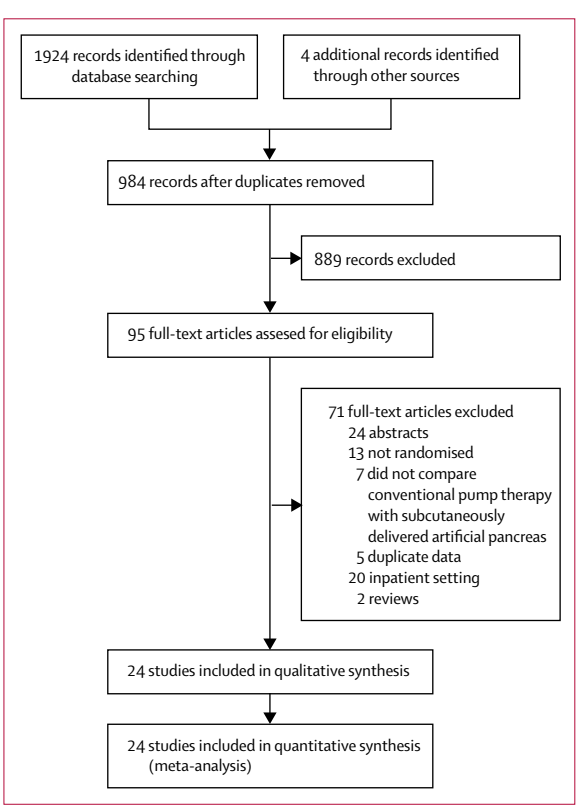

Figure 1: **Flowchart for selection of studies for inclusion**

27 comparisons from 24 studies with 585 participants (219 in adult studies, 265 in paediatric studies, and 101 in combined studies) were pooled for the primary outcome of time in target blood glucose range (figure 2). Time in target range was 12·59% (95% CI 9·02–16·16; p<0·0001) higher with artificial pancreas systems, from a weighted mean of 58·21% for conventional pump therapy (equivalent to a difference of 172 min per 24 h). There was high statistical heterogeneity (I^2=84%). Effect sizes of individual studies ranged from a mean difference of –6·30% to 26·68%. Dual-hormone artificial pancreas systems had a greater difference in time in target compared with single-hormone artificial pancreas, even when restricted to studies with model predictive control (MPC) algorithms (table 2; appendix p 6).

Subgroup analyses were done to explore sources of heterogeneity (table 2; appendix pp 4–6). Artificial pancreas systems showed a greater difference for time in target in overnight studies than in studies done over 24 h. Proportional integrative derivative (PID) algorithms were associated with lower difference for time in target compared with MPC and fuzzy logic algorithms, although tests for subgroup differences were not significant. The subgroup analyses for target range specified, age category, and overnight versus 24 h reduced statistical heterogeneity. Time in target did not differ based on presence or absence of remote monitoring (appendix p 4).

21 comparisons with 463 participants were pooled for time in hypoglycaemia (<3·9 mmol/L; table 2; appendix p 7). Hypoglycaemia thresholds of less than 3·9 mmol/L and less than 3·3 mmol/L are common; however, more studies reported less than 3·9 mmol/L and therefore this threshold was selected to maximise the number of included studies. One study did not report the threshold of less than 3·9 mmol/L and was not included.[32] Time in hypoglycaemia was 2·45% (95% CI 1·11–3·79; p<0·0001; 35 min per 24 h; I^2=94%) lower with artificial pancreas systems, from a weighted mean of 4·88% for conventional pump therapy, equivalent to a relative risk reduction of 50%. Differences in reduction in hypoglycaemia were higher in studies with remote monitoring compared with those with no remote monitoring (–3·92 *vs* –0·63%; p value for subgroup differences=0·01). Only the subgroup analysis for age category explained substantial heterogeneity (table 2). A post-hoc analysis was done in which studies with remote monitoring were further classified as having non-differential or differential monitoring between artificial pancreas and conventional pump therapy arms of the studies, and reduction in hypoglycaemia was noted both for studies with non-differential and differential monitoring.

	Participants (n)	Participant characteristics*	Age category†	Artificial pancreas device components	Artificial pancreas algorithm	Meals announced	Single or dual hormone	Remote monitoring (artificial pancreas/ CSII)	24 h or overnight	Comparator	Study duration	Setting
Blauw et al, 2016[30]	10 (5 male, 5 female)	Age 41 years (26·5–52·3), diabetes duration 18 years (14·8–29·5), BMI 24·5 kg/m² (22·6–26·6), HbA_{1c} 7·7% (7·4–8; 60·7 mmol/mol)	Adult	Inreda Diabetic	PID	Yes	Dual	Yes/Unclear	24 h	Usual insulin pump with blinded CGM	4 days	Home
Brown et al, 2015[31]	10 (2 male, 8 female)	Age 46·8 years (8·5), diabetes duration 20·9 years (11·1), TDD 0·4 units/kg (0·1), BMI 22·9 kg/m² (2·9), HbA_{1c} 7·01% (1·05; 53·1 mmol/mol)	Adult	Accu-Check Spirit Combo pump or personal pump, with DiAs system	PID	Yes	Single	Yes/Unclear	Overnight	SAP	8 h × 5 consecutive nights	Research house or hotel
De Bock et al, 2015[32]	8 (male:female not reported)	HbA_{1c} 7·5% (0·6; 58·5 mmol/mol)	Both	Medtronic MiniMed Hybrid Closed Loop System	PID with IFB and upper limit of insulin as safety feature	Yes	Single	Yes/Unclear	24 h	SAP with low glucose suspend at 3·3 mmol/L	5 days	Outpatient
Del Favero et al, 2016[33]	30 (19 male, 11 female)	Age 7·6 years (1·2), diabetes duration 4·7 years (1·6), TDD 0·78 units/kg (0·16), BMI 16·9 kg/m² (2·1), HbA_{1c} 7·3% (0·9; 56·3 mmol/mol)	Paediatric	Accu-Chek Spirit Combo pump with DiAs system	MPC	Yes	Single	Yes/Unclear	24 h	SAP	72 h	Camp
El-Khatib et al, 2017[34]	39 (18 male, 21 female)	Age 33·3 years (11·1), diabetes duration 16·9 years (9·6), TDD 0·6 units/kg (0·14), BMI 25·9 kg/m² (4·8), HbA_{1c} 7·7% (1·2; 60·7 mmol/mol)	Adult	Two (one for insulin, one for glucagon) t:Slim infusion pumps	MPC	Optional (estimation)	Dual	Yes/Yes	24 h	Usual pump with blinded CGM (own CGM use permitted if usual care)	11 days	Home
Haidar et al, 2015[28]	33 (male:female not reported)	Age 13·3 years (3), TDD 0·89 units/kg (0·2), BMI 22·2 kg/m² (3·9), HbA_{1c} 8·3% (0·8; 67·2mmol/mol)	Paediatric	Accu-Chek Combo system and second pump with glucagon	MPC (manually entered)	Yes (snack only)	Both	Yes/Yes	Overnight	Usual pump with quasi-blinded CGM (action taken if glucose <3·1 mmol/L or >20 mmol/L, values reviewed following morning)	8 h × 3 nights	Camp
Haidar et al, 2016[29]	28 (15 male, 13 female)	Age 33·3 years (17), diabetes duration 18 years (12), TDD 0·66 units/kg (0·24), BMI 24·9 kg/m² (3·8), HbA_{1c} 7·5% (1; 58·5 mmol/mol)	Both	Medtronic Paradigm Veo pump	MPC (manually entered)	Yes	Both	Yes/Yes	Overnight	SAP	8 h × 2 consecutive nights	Home
Hovorka et al, 2014[35]	16 (10 male, 6 female)	Age 15·6 years (2·1), duration 7·2 years (4·3), TDD 0·8 (0·2), HbA_{1c} 8·0% (0·9); BMI 22·4 kg/m² (0·7)	Paediatric	Animas pump	MPC	NA	Single	No/No	Overnight	SAP with glucose threshold 3·5 mmol/L	21 days	Home
Kovatchev et al, 2014[24]	18 completers (15 male, 5 female enrolled)	Age 46 years (10), HbA_{1c} 7·4% (0·7; 57·4 mmol/mol)	Adult	Tandem t:slim pump, with DiAs system (safety mode overnight in US centres)	PID	Yes	Single	Yes/Yes	24 h	SAP	40 h	Hotel or guesthouse

(Table 1 continues on next page)

	Participants (n)	Participant characteristics*	Age category†	Artificial pancreas device components	Artificial pancreas algorithm	Meals announced	Single or dual hormone	Remote monitoring (artificial pancreas/ CSII)	24 h or overnight	Comparator	Study duration	Setting
(Continued from previous page)												
Kropff et al, 2015[36]	32 (18 male, 14 female)	Age 47 years (11·2), diabetes duration 28·6 years (10·8), TDD 0·6 units/kg (0·1), BMI 25·1 kg/m² (3·5), HbA_{1c} 8·2% (0·6; 66·1 mmol/mol)	Adult	Accu-Chek Spirit Combo with DiAs system	MPC	Yes	Single	Yes/Unclear	Overnight	SAP with alarms initially set at 5 mmol/L and 11·1 mmol/L, but could be modified	12 h × 12 weeks	Home
Leelarathna et al, 2014[37]	17 (10 male, 7 female)	Age 34 years (9), diabetes duration 19 years (9), TDD 0·53 units/kg (0·12), BMI 26·2 kg/m² (3·2), HbA_{1c} 7·6% (0·8; 59·6 mmol/mol)	Adult	DANA Diabecare R pump	MPC	Yes if >30 g carbohydrates	Single	No/No	24 h	SAP	8 days	Home (first day in clinical research facility)
Ly et al, 2014[38]	20 (10 male, 10 female)	Age 15·3 years (2·9), diabetes duration 5·6 years (3·5), HbA_{1c} 8·1% (1·1; 65 mmol/mol)	Paediatric	Tandem t:slim pump with DiAs system	PID	NA	Single	Yes/No	Overnight	SAP with alarms for glucose <3·9 mmol/L and >13·8mmol/L	8 h × 5–6 days (alternating intervention each night)	Camp
Ly et al, 2015[39]	20 (10 AP: 5 male, 5 female; 10 CSII: 4 male, 6 female)‡	Age 18·6 years (3·7), diabetes duration 9·1 years (4·7), TDD 0·8 units/kg (0·2), HbA_{1c} 8·6% (1·5; 70·5 mmol/mol)	Both	Medtronic MiniMed Hybrid Closed Loop System	PID with IFB	Yes	Single	No/No	24 h	SAP with alert at 3·9 mmol/L and suspend at 3·3 mmol/L; high alert at 13·8 mmol/L	6 days	Camp
Ly et al, 2016[40]	21 (10 male, 11 female)	Age 14·7 years (3·9), diabetes duration 7·9 years (5·3), TDD 0·8 units/kg (0·2), HbA_{1c} 7·9% (1·4; 62·8 mmol/mol)	Both	Medtronic MiniMed Paradigm Revel 2·0 pump	PID with IFB	Yes	Single	Yes/No	Overnight	SAP with alerts at 3·9 mmol/L and 13·8 mmol/L	8 h × 5–6 days (alternating nights)	Camp
Nimri et al, 2014[41]	19 (male:female not specified)	Age 21·2 years (8·9), diabetes duration 11·5 years (8·8), TDD 0·8 units/kg (0·3), BMI 22·7 kg/m² (4), HbA_{1c} 8·5% (0·8; 69·4 mmol/mol)	Both	MD-Logic system with Medtronic Paradigm Veo pump	Fuzzy logic	Yes	Single	Yes/Unclear	Overnight	SAP with high and low glucose alarms at 20·4 mmol/L and 4·1 mmol/L	Overnight × 1·5 months	Home
Nimri et al, 2014[42]	15 (6 male, 9 female)	Age 19 years (10·4), diabetes duration 9·9 years (8·2), TDD 0·9 units/kg (0·3), BMI 22·8 kg/m² (4·1), HbA_{1c} 7·5% (0·5; 58·5 mmol/mol)	Both	MD-Logic system with Medtronic Paradigm Veo pump	Fuzzy Logic	Yes	Single	Yes/Yes	Overnight	SAP with high and low glucose alarms at 20·4 mmol/L and 4·1 mmol/L	Overnight × 4 days	Home
Phillip et al, 2013[43]	54 completers (31 male, 25 female enrolled)	Age 13·8 years (1·8), diabetes duration 7 years (3·5), TDD 0·8 units/kg (0·3), BMI 20·8 kg/m² (2·9), HbA_{1c} 8% (0·7; 63·9 mmol/mol)	Paediatric	MD-Logic system with Medtronic Paradigm Veo pump	Fuzzy Logic	NA	Single	Yes/No	Overnight	SAP with high and low glucose alarms at 20·4 mmol/L and 4·1 mmol/L	12 h × 1 night	Camp
Russell et al, 2014[23]	Adults: 20 (8 male, 12 female); children: 32 (16 male, 16 female)	Adults: age 40 years (16), diabetes duration 21 years (11), TDD 0·5 units/kg (0·11), HbA_{1c} 7·1% (0·8; 4·1 mmol/mol); adolescents: age 16 years (3), diabetes duration 9 years (5), TDD 0·8 units/kg (0·18), HbA_{1c} 8·2% (1; 66·1 mmol/mol)	Both	Two tandem t:slim infusion pumps (one for insulin, one for glucagon)	MPC	Yes (estimation)	Dual	Adult: Yes/No; Paediatric: Yes/Yes	24 h	Pump plus blinded CGM	5 days	Home for adults; camp for children

(Table 1 continues on next page)

	Participants (n)	Participant characteristics*	Age category†	Artificial pancreas device components	Artificial pancreas algorithm	Meals announced	Single or dual hormone	Remote monitoring (artificial pancreas/ CSII)	24 h or overnight	Comparator	Study duration	Setting
(Continued from previous page)												
Russell et al, 2016[44]	19 (6 male, 13 female)	Age 9·8 years (1·6), diabetes duration 5 years (2·2), TDD 0·74 units/kg (0·15), BMI 17·8 kg/m² (2·1), HbA_{1c} 7·8% (0·8; 61·7 mmol/mol)	Paediatric	Two tandem t:slim pumps, one for insulin and one for glucagon	MPC	Yes (estimation)	Dual	No/No	24 h	Pump plus blinded CGM (own CGM use allowed if usual care); low glucose alarm at 2·8 mmol/L	5 days	Camp
Sharifi et al, 2016[26]	Adults, 16 (7 male, 9 female); children, 12 (4 male, 8 female)	Adults: age 42·1 years (9·6), diabetes duration 26·9 years (6·5), TDD 42·9 units (12·2), BMI 26·8 kg/m² (4·4), HbA_{1c} 7·3% (0·6; 56·3 mmol/mol); children: age 15·2 years (1·6), diabetes duration 6·6 years (4), TDD 54 units (13·4), HbA_{1c} 7·8% (0·5; 61·7 mmol/mol)	Both	Hybrid artificial pancreas with Medtronic Paradigm Veo pump	PID	Yes	Single	Yes/Yes	Overnight	SAP with low glucose suspend at 3·3 mmol/L	8 hours × 4 nights	Home
Tauschmann et al, 2016 (pp 2019–25)[45]	12 (7 male, 5 female)	Age 14·6 years (3·1), diabetes duration 7·8 years (3·5), TDD 0·82 units/kg (0·18), BMI 21·3 kg/m² (4·4), HbA_{1c} 8·5% (0·7; 69·4 mmol/mol)	Paediatric	DANA Diabecare R pump	MPC	Yes	Single	No/No	24 h	SAP	3 weeks	Home
Tauschman et al, 2016 (pp 1168–1174)[46]	12 (8 male, 4 female)	Age 15·4 years (2·6), diabetes duration 8·2 years (3·4), TDD 0·84 units/kg (0·22), BMI 21·4 kg/m² (2·7), HbA_{1c} 8·3% (0·9; 67·2 mmol/mol)	Paediatric	DANA Diabecare R pump	MPC	Yes	Single	No/No	24 h	SAP	7 days	Home
Thabit et al, 2014[47]	24 (13 male, 11 female)	Age 43 years (12), diabetes duration 20 years (11), TDD 0·5 units/kg (0·1), BMI 26·0 kg/m² (3·5), HbA_{1c} 8·1% (0·8; 65 mmol/mol)	Adult	DANA Diabecare R pump	MPC	Yes	Single	No/No	Overnight	SAP with alarm at 3·5mmol/L	Overnight × 4 weeks	Home (first night in clinical research facility)
Thabit et al, 2015[27]	Adults: 33 (18 male, 15 female); children: 25 (14 male, 11 female)	Adults: age 40 years (9·4), diabetes duration 20·9 years (9·3), TDD 0·62 units/kg (0·15), BMI 25·5 kg/m² (4·4), HbA_{1c} 8·5% (0·7; 69·4 mmol/mol); children: age 12 years (3·4), diabetes duration 4·7 years (2·6), TDD 0·89 units/kg (0·24), BMI 18·9 kg/m² (3·5), HbA_{1c} 8·1% (0·9; 65 mmol/mol)	Both	DANA Diabecare R pump	MPC	Yes	Single	No/No	Adults, 24 h; children: overnight	SAP	Adult, 12 weeks; children, overnight × 12 weeks	Home

HbA_{1c} units reported as mean or median in % (SD or IQR) and mean in SI units. CSII=continuous subcutaneous insulin infusion. PID=proportional integrative derivative. CGM=continuous glucose monitor. DiAs= diabetes assistant. SAP=sensor augmented pump therapy. IFB=insulin feedback. MPC=model predictive control. TDD=total daily dose. *Characteristics reported as mean (SD) or median (IQR). †Age category can be adult, paediatric, or both. ‡Parallel-group study.

Table 1: **Description of included studies**

18 comparisons with 389 participants were pooled for change in insulin dose. Insulin dose was unchanged by use of artificial pancreas systems compared with conventional pump therapy (non-significantly higher by 0·07 units per h (95% CI –0·01 to 0·15; p=0·08; I^2=34%) from a weighted mean of 1 unit per h (appendix p 8). Differences in insulin dose with artificial pancreas were significantly higher in children compared with in adults (table 2).

The unweighted mean percentage of time the artificial pancreas remained active during the intervention was 81% (reported by 14 comparisons). Episodes of severe hypoglycaemia (loss of consciousness or requiring third-party assistance) were reported in 22 studies: six events occurred during artificial pancreas use and five occurred during conventional pump therapy.

Using ten, nine, and nine comparisons at low risk of bias, respectively, time in target was higher by 14·15% (95% CI 10·21 to 18·10; p<0·0001; I^2=55%), time in hypoglycaemia was unchanged (non-significant decrease of 1·05% [95% CI –0·37 to 2·47]; p=0·11; I^2=86%), and insulin dose was unchanged (non-significant increase of 0·03 units per h, [95% CI –0·09 to 0·14]; p=0·64; I^2=23%).[26,27,37,42,44,45–47]

We repeated the meta-analysis for the primary outcome using only one comparison from each study that used a three-way crossover design and the results were unchanged (data not shown).[28,29] We also repeated the analysis for the primary outcome using only the 21 comparisons for which time in target glucose range for a target 3·9–10 mmol/L were available and the result was unchanged (mean difference 12·90%, 95% CI 8·51–17·29; p<0·0001; table 2). 14 comparisons reported paired outcomes; when analysed as paired studies and parallel-group studies, mean differences in time in target

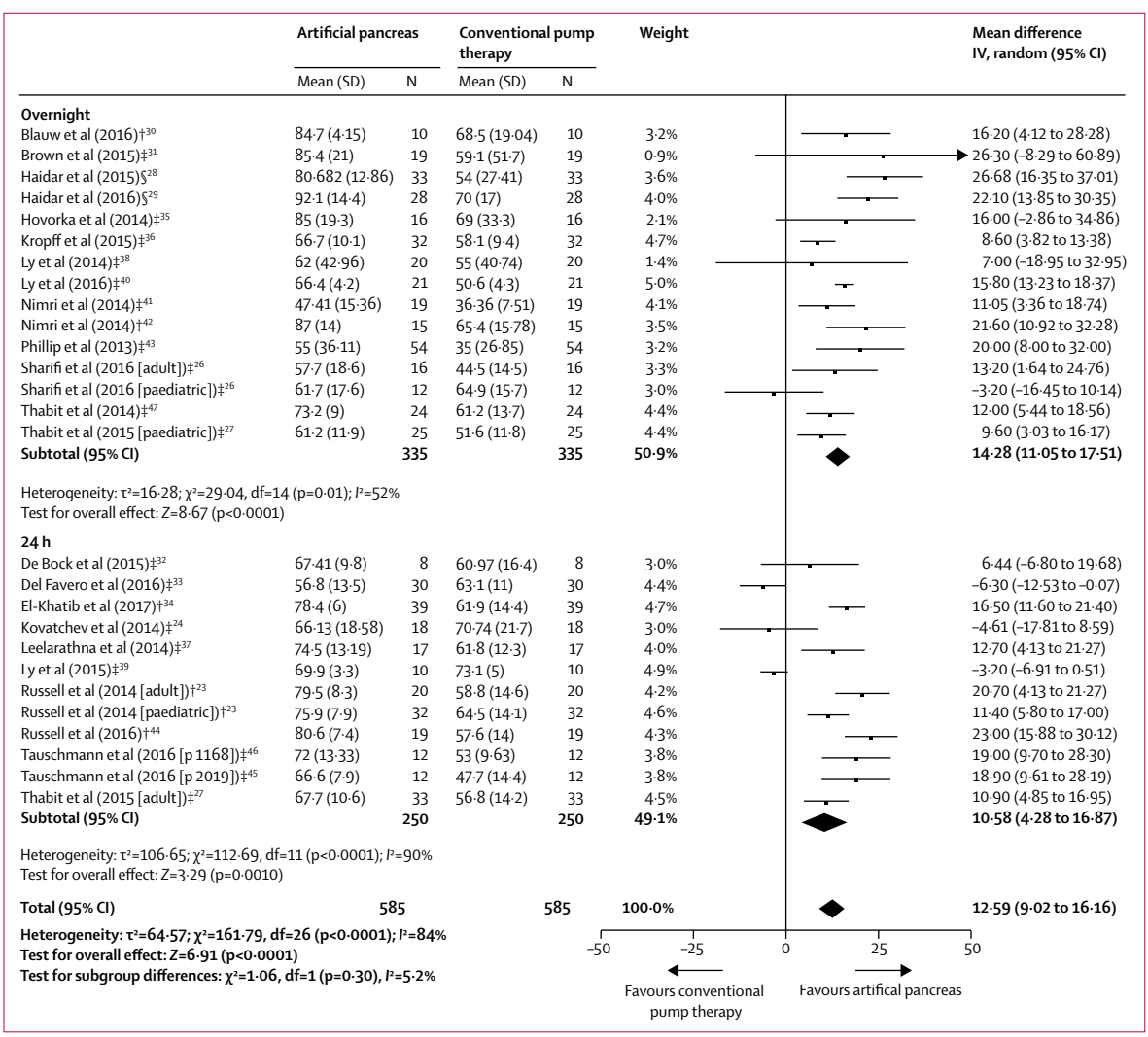

Figure 2: **Forest plot for time in target by study duration as overnight or 24 h***

IV=inverse variance. *Time in target reported as 24 h for 24 h studies and overnight for overnight studies. †Dual-hormone artificial pancreas. ‡Single-hormone artificial pancreas. §Both dual-hormone and single-hormone artificial pancreas.

were 12·54% (95% CI 10·13–14·94; p<0·0001; I^2=83%) and 13·81% (10·61–17·01; p<0·0001; I^2=61%), respectively. We also adjusted for within-person differences in studies not reporting paired outcomes and the estimate for time in target was 12·67% (95% CI 10·24–15·10; p<0·0001).[25]

Discussion

In this systematic review and meta-analysis of randomised trials comparing artificial pancreas systems with conventional pump therapy in outpatient settings in adults and children with type 1 diabetes, use of artificial pancreas systems resulted in a 12·59% (95% CI 9·02–16·16) increased time in target blood glucose range, equivalent to nearly 3 h per day. Although HbA_{1c} was assessed in two studies,[27,36] only one of these studies[27] had continuous artificial pancreas use over 3 months; in that study, HbA_{1c} was reduced by 0·3% with a concomitant 11% increased time in blood glucose target range. If improvement in time in target is associated with change in HbA_{1c}, we expect that use of artificial pancreas systems would reduce HbA_{1c} by a minimum of 0·3%. Our results also suggest additional benefits beyond HbA_{1c} reduction, such as reduction of hypoglycaemia and lessened burden of disease self-management.

Our results suggested greater improvement in time in target for dual-hormone compared with single-hormone artificial pancreas systems. Advantages and disadvantages of insulin-only and combined insulin and glucagon artificial pancreas systems have been reviewed in detail.[48] In direct comparison, dual-hormone systems have been shown to be superior to single-hormone systems in preventing hypoglycaemia and achieving target glucose concentrations in response to meals and exercise.[10,49] There are several potential explanations for the differences between dual-hormone and single-hormone systems in our meta-analysis. First, there were fewer dual-hormone artificial pancreas studies included in the analysis, which means there is less certainty in this estimate compared to single-hormone systems. Second, subgroup analyses primarily explain heterogeneity rather than differences between subgroups, and our findings should not be considered conclusive, particularly because distribution of other study features can differ within each subgroup. Importantly, dual-hormone systems were almost exclusively compared with CSII with blinded CGM, whereas single-hormone systems were compared almost exclusively with SAP, precluding additional analysis examining the effect of the comparator therapy on outcomes. Future studies are required in which dual-hormone and single-hormone artificial pancreas systems are compared directly to each other, and also compared with SAP as the conventional therapy, because it is the integration of CGM and the sophisticated dosing algorithm that needs be assessed, rather than the efficacy of CGM.

Greater time in target was robust across a range of clinical variables, timing of the intervention, and technical factors. PID algorithms had substantially less improved time in target compared with MPC and fuzzy logic algorithms, although the analysis of subgroup differences was not significant. This finding is consistent with a recent trial directly comparing MPC and PID, in which time in target was higher and mean glucose was lower with MPC. [50]

	Number of comparisons	Mean difference between artificial pancreas and conventional pump therapy (%, 95% CI)	p value for overall effect	Weighted mean for conventional pump therapy (% for time in target and time in hypoglycemia)‡	I^2
Time in target range (%)					
All comparisons	27	12·59% (9·02 to 16·16)	<0·0001	58·21%	84%
Target range (mmol/L)					
3·9-8	6	12·50% (7·23 to 17·77)	<0·0001	46·63%	38%
3·9-10	21	12·90% (8·51 to 17·29)	<0·0001	61·11%	86%
Timing of intervention					
Overnight	15	14·28% (10·05 to 17·51)	<0·0001	55·56%	52%
24 h	12	10·58% (4·28 to 16·87)	0·001	60·95%	90%
Age					
Paediatric	11	12·30% (5·99 to 18·60)	0·0001	58·48%	84%
Adult	10	12·67% (9·13 to 16·21)	<0·0001	59·98%	49%
Hormone*					
Single	22	11·06% (6·94 to 15·18)	<0·0001	57·22%	79%
Dual	7	19·52% (15·12 to 23·91)	<0·0001	62·10%	66%
Algorithm					
MPC	15	14·31% (10·19 to 18·44)	<0·0001	59·09%	80%
PID	9	6·97% (–1·67 to 15·62)	0·11	61·27%	90%
Fuzzy logic	3	16·49% (9·40 to 23·57)	<0·0001	45·37%	35%
Remote monitoring					
Yes	18	12·59% (8·52 to 16·66)	<0·0001	57·64%	79%
No	9	12·75% (5·87 to 19·63)	0·0003	59·24%	88%
Time in hypoglycaemia (<3·9 mmol/L; %)					
All comparisons	21	–2·45% (–3·79 to –1·11)	0·0003	4·88%	94%
Timing of intervention					
Overnight	10	–3·38% (–5·81 to –0·96)	0·006	5·37%	95%
24 h	11	–1·70% (–3·18 to –0·21)	0·03	4·58%	91%
Age					
Paediatric	8	–1·58% (–3·66 to 0·50)	0·14	4·40%	87%
Adult	8	–1·23% (–1·99 to –0·47)	0·002	3·37%	44%
Hormone*					
Single	16	–1·88% (–3·40 to –0·36)	0·02	4·42%	94%
Dual	7	–3·78% (–5·58 to –1·97)	<0·0001	6·10%	75%
Algorithm					
MPC	15	–1·95% (–3·14 to –0·76)	0·001	4·67%	84%
PID	4	–3·98% (–10·16 to 2·21)	0·21	6·38%	98%
Fuzzy logic	2	–2·45% (–3·79 to –1·11)	<0·001	3·81%	0%
Remote monitoring‡					
Yes‡	12	–3·92% (–6·05 to –1·79)	0·0003	6·09%	94%
Non-differential	6	–2·82% (–4·45 to –1·19)	0·0007	4·69%	79%
Differential	6	–4·58% (–9·02 to –0·15)	0·04	7·54%	97%
No	9	–0·63% (–2·01 to 0·74)	0·37	2·94%	88%

(Table 2 continues on next page)

	Number of comparisons	Mean difference between artificial pancreas and conventional pump therapy (%, 95% CI)	p value for overall effect	Weighted mean for conventional pump therapy (% for time in target and time in hypoglycemia)†	I^2
(Continued from previous page)					
Daily insulin dose (units per kg/hour)					
All comparisons	18	0·10% (–0·04 to 0·16)	0·08	1·00	31%
Timing of intervention					
Overnight	13	0·09% (0·01 to 0·18)	0·03	0·93	34%
24 h	5	–0·04% (–0·22 to 0·14)	0·64	2·00	4%
Age					
Paediatric	7	0·19% (0·11 to 0·27)	<0·0001	0·98	0%
Adult	7	–0·01% (-0·17 to 0·14)	0·86	1·34	45%
Hormone*					
Single	17	0·06% (–0·02 to 0·14)	0·12	1·09	33%
Dual	3	0·14% (–0·01 to 0·29)	0·06	0·79	48%
Algorithm					
MPC	10	0·06% (–0·04 to 0·16)	0·23	1·16	34%
PID	5	0·06% (–0·07 to 0·19)	0·36	1·10	0%
Fuzzy logic	3	0·06% (–0·31 to 0·42)	0·76	0·86	71%
Remote monitoring					
Yes	11	0·08% (–0·03 to 0·18)	0·14	0·98	43%
No	7	0·05% (–0·08 to 0·18)	0·44	1·33	17%

MPC=model predictive control. PID=proportional integrative derivative. *For subgroup analysis by dual or single-hormone, Haidar and colleagues, 2015,[28] and Haidar and colleagues, 2016,[29] were separated into single-hormone system *vs* conventional pump therapy and dual-hormone system *vs* conventional pump therapy comparisons. †Weighted mean value in % for time in target and time in hypoglycaemia, and units per kg/hour for insulin dose. ‡Table shows post-hoc analysis as described in the main text.

Table 2: **Prespecified subgroup analyses for primary and secondary outcomes**

Artificial pancreas systems reduced time in hypoglycaemia by 2·45% compared with conventional pump therapy, which is equivalent to 35 min less per day spent in hypoglycaemia and a 50% relative risk reduction. Generally, artificial pancreas systems have been reported to reduce hypoglycaemia to a greater extent in the overnight period than throughout the day.[13,51,52] The results of our meta-analysis suggest that reduction in hypoglycaemia occurred in both overnight studies and in 24 h studies. Other studies have shown reduction in hypoglycaemia of a similar magnitude with the use of CGM in addition to CSII; however, results of the effect of CGM on the reduction of hypoglycaemia have been inconsistent.[53–57] A lower threshold for hypoglycaemia might be of greater clinical relevance in artificial pancreas studies; however, thresholds below 3·9 mmol/L were not uniform between studies. Future trials require standardisation of glucose thresholds reported to allow full comparison of results.[58] Importantly, hypoglycaemia of less than 3·9 mmol/L was not reduced in studies in which remote monitoring was not done. However, time in hypoglycaemia was significantly reduced in studies with both differential and non-differential monitoring, suggesting that remote monitoring could not fully account for the reduction in hypoglycaemia associated with artificial pancreas systems. Future trials that can be implemented without remote monitoring should provide more conclusive evidence for the independent effect of artificial pancreas systems on time in hypoglycaemia.

Studies have also had conflicting results with respect to the effect of artificial pancreas systems on daily insulin dose.[31,59] Higher insulin doses are associated with weight gain and hypoglycaemia and therefore significant increases in insulin dose—although not of greatest clinical relevance—remain a potential concern.[60] In our meta-analysis, there was a non-significant increase in insulin dose with artificial pancreas systems compared with conventional pump therapy. In subgroup analyses, insulin dose was non-significantly higher in studies done overnight, in paediatric age groups, and with dual-hormone artificial pancreas systems. Rather than an inappropriately high insulin dose, this finding might simply indicate underdosing of insulin at study baseline, especially in the overnight period and in children, where fear of hypoglycaemia might be most pronounced.

The strengths of this analysis are the comprehensive search strategy and inclusion of studies with varied technical and clinical factors. Limitations include statistical assumptions, such as deriving means and SDs from medians and IQRs, respectively, although these assumptions were robust in several sensitivity analyses. There was a small inflation of the estimate of the mean difference of time in target by the group means method. Because the correct statistical outcome for crossover trial is paired difference, this finding reinforces the need for reporting of paired outcomes in future trials. Additionally, selection of outcomes should be standardised to allow comparison between trials.[58] Adequate assessment of risk of bias of included studies was limited because many study reports did not include sufficient information regarding generation of randomisation sequence, allocation concealment, and whether outcome assessors or data analysts were masked to treatment allocation. Heterogeneity was high for time in target and time in hypoglycaemia. However, this finding was not unexpected in view of the highly variable clinical and technical factors included, and this results was partly explained in subgroup analyses.[61] Finally, the results of this meta-analysis might not be generalisable to the entire type 1 diabetes population, because participants in artificial pancreas trials have better glycaemic control (lower HbA_{1c}) than most patients and have experience using insulin pump therapy.[5]

In conclusion, this systematic review and meta-analysis confirms a robust 12% greater time in blood glucose target range for artificial pancreas systems compared with conventional pump therapy. This estimate is beneficial in planning longer-term clinical trials in larger numbers of participants and in more pragmatic settings. The synthesis

of all outpatient clinical trials emphasises the potential benefits of dual-hormone compared with single-hormone artificial pancreas for time in target, although this finding requires further research before definitive conclusions can be made. Our finding of a differential reduction in hypoglycaemia based on the presence or absence of remote monitoring highlights the importance of pragmatic designs of future clinical trials to accurately assess the effectiveness of artificial pancreas systems. Our results show that closed-loop technology is feasible and beneficial in a variety of clinical settings and as such it is likely artificial pancreas systems will transform the management of type 1 diabetes in the near future.

Contributors

AW did the literature search, data analysis, and generated the figures. AW and BAP designed the study, interpreted the data, and wrote the first draft of the report. J-WB and MC collected the data and reviewed and edited the report. CKK designed the study, interpreted the data, and reviewed and edited the report.

Declaration of interests

BAP has received fees for continuing medical education events from Abbott, Animas, Boehringer Ingelheim, Dexcom, Janssen, and Medtronic, and has participated in advisory boards for Abbott, Boehringer Ingelheim, and Insulet. His institution has received operating research funds on his behalf from Boehringer Ingelheim and Novo Nordisk. All other authors declare no competing interests.

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References

1 Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329:** 977–86.

2 Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; **353:** 2643–53.

3 Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2014; **2:** CD009122.

4 Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 1997; **46:** 271–86.

5 Wood JR, Miller KM, Maahs DM, et al. Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. *Diabetes Care* 2013; **36:** 2035–37.

6 Bergenstal RM, Tamborlane WV, Ahmann A, et al, for the STAR 3 Study Group. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010; **363:** 311–20.

7 Miller KM, Foster NC, Beck RW, et al, for the T1D Exchange Clinic Network. Current state of type 1 diabetes treatment in the US: updated data from the T1D Exchange clinic registry. *Diabetes Care* 2015; **38:** 971–78.

8 Kudva YC, Carter RE, Cobelli C, Basu R, Basu A. Closed-loop artificial pancreas systems: physiological input to enhance next-generation devices. *Diabetes Care* 2014; **37:** 1184–90.

9 Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabet Med* 2006; **23:** 1–12.

10 Haidar A, Legault L, Dallaire M, et al. Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. *CMAJ* 2013; **185:** 297–305.

11 Hovorka R, Kumareswaran K, Harris J, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ* 2011; **342:** d1855.

12 Breton M, Farret A, Bruttomesso D, et al. Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. *Diabetes* 2012; **61:** 2230–37.

13 Dauber A, Corcia L, Safer J, Agus MS, Einis S, Steil GM. Closed-loop insulin therapy improves glycemic control in children aged <7 years: a randomized controlled trial. *Diabetes Care* 2013; **36:** 222–27.

14 Elleri D, Allen JM, Kumareswaran K, et al. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. *Diabetes Care* 2013; **36:** 838–44.

15 Luijf YM, Hans DeVries J, Zwinderman K, et al. Day and night closed-loop control in adults with type 1 diabetes: a comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient self-management. *Diabetes Care* 2013; **36:** 3882–87.

16 Sherr JL, Cengiz E, Palerm CC, et al. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. *Diabetes Care* 2013; **36:** 2909–14.

17 Capel I, Rigla M, Garcia-Saez G, et al. Artificial pancreas using a personalized rule-based controller achieves overnight normoglycemia in patients with type 1 diabetes. *Diabetes Technol Ther* 2014; **16:** 172–79.

18 Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* 2010; **375:** 743–51.

19 Schmidt S, Boiroux D, Duun-Henriksen AK, et al. Model-based closed-loop glucose control in type 1 diabetes: the DiaCon experience. *J Diabetes Sci Technol* 2013; **7:** 1255–64.

20 Elleri D, Maltoni G, Allen JM, et al. Safety of closed-loop therapy during reduction or omission of meal boluses in adolescents with type 1 diabetes: a randomized clinical trial. *Diabetes Obes Metab* 2014; **16:** 1174–78.

21 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62:** 1006–12.

22 Higgins J, Green S (eds). Cochrane handbook for systematic reviews of interventions, version 5.1.0. The Cochrane Collaboration, updated March, 2011.

23 Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N Engl J Med* 2014; **371:** 313–25.

24 Kovatchev BP, Renard E, Cobelli C, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. *Diabetes Care* 2014; **37:** 1789–96.

25 Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002; **31:** 140–49.

26 Sharifi A, De Bock MI, Jayawardene D, et al. Glycemia, treatment satisfaction, cognition, and sleep quality in adults and adolescents with type 1 diabetes when using a closed-loop system overnight versus sensor-augmented pump with low-glucose suspend function: a randomized crossover study. *Diabetes Technol Ther* 2016; **18:** 772–83.

27 Thabit H, Tauschmann M, Allen JM, et al, for the APCam Consortium and AP@home Consortium. Home use of an artificial beta cell in type 1 diabetes. *N Engl J Med* 2015; **373:** 2129–40.

28 Haidar A, Legault L, Matteau-Pelletier L, et al. Outpatient overnight glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or conventional insulin pump therapy in children and adolescents with type 1 diabetes: an open-label, randomised controlled trial. *Lancet Diabetes Endocrinol* 2015; **3:** 595–604.

29 Haidar A, Rabasa-Lhoret R, Legault L, et al. Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes. *J Clin Endocrinol Metab* 2016; **101:** 214–23.

30 Blauw H, van Bon AC, Koops R, DeVries JH, on behalf of the PCDIAB consortium. Performance and safety of an integrated bihormonal artificial pancreas for fully automated glucose control at home. *Diabetes Obes Metab* 2016; **18:** 671–77.

31 Brown SA, Kovatchev BP, Breton MD, et al. Multinight "bedside" closed-loop control for patients with type 1 diabetes. *Diabetes Techn Ther* 2015; **17:** 203–09.

32 De Bock MI, Roy A, Cooper MN, et al. Feasibility of outpatient 24-hour closed-loop insulin delivery. *Diabetes Care* 2015; **38:** e186–87.

33 Del Favero S, Boscari F, Messori M, et al. Randomized summer camp crossover trial in 5-to 9-year-old children: outpatient wearable artificial pancreas is feasible and safe. *Diabetes Care* 2016; **39:** 1180–85.

34 El-Khatib FH, Balliro C, Hillard MA, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. *Lancet* 2017; **389:** 369–80.

35 Hovorka R, Elleri D, Thabit H, et al. Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care* 2014; **37:** 1204–11.

36 Kropff J, Del Favero S, Place J, et al, for the AP@home consortium. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. *Lancet Diabetes Endocrinol* 2015; **3:** 939–47.

37 Leelarathna L, Dellweg S, Mader JK, et al, on behalf of the AP@home Consortium. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. *Diabetes Care* 2014; **37:** 1931–37.

38 Ly TT, Breton MD, Keith-Hynes P, et al. Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. *Diabetes Care* 2014; **37:** 2310–16.

39 Ly TT, Roy A, Grosman B, et al. Day and night closed-loop control using the integrated Medtronic hybrid closed-loop system in type 1 diabetes at diabetes camp. *Diabetes Care* 2015; **38:** 1205–11.

40 Ly TT, Keenan DB, Roy A, et al. Automated overnight closed-loop control using a proportional-integral-derivative algorithm with insulin feedback in children and adolescents with type 1 diabetes at diabetes camp. *Diabetes Technol Ther* 2016; **18:** 377–84.

41 Nimri R, Muller I, Atlas E, et al. MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. *Diabetes Care* 2014; **37:** 3025–32.

42 Nimri R, Muller I, Atlas E, et al. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. *Pediatr Diabetes* 2014; **15:** 91–99.

43 Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N Engl J Med* 2013; **368:** 824–33.

44 Russell SJ, Hillard MA, Balliro C, et al. Day and night glycaemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomised crossover trial. *Lancet Diabetes Endocrinol* 2016; **4:** 233–43.

45 Tauschmann M, Allen JM, Wilinska ME, et al. Home use of day-and-night hybrid closed-loop insulin delivery in suboptimally controlled adolescents with type 1 diabetes: a 3-week, free-living, randomized crossover trial. *Diabetes Care* 2016; **39:** 2019–25.

46 Tauschmann M, Allen JM, Wilinska ME, et al. Day-and-night hybrid closed-loop insulin delivery in adolescents with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care* 2016; **39:** 1168–74.

47 Thabit H, Lubina-Solomon A, Stadler M, et al. Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. *Lancet Diabetes Endocrinol* 2014; **2:** 701–09.

48 Bakhtiani PA, Zhao LM, El Youssef J, Castle JR, Ward WK. A review of artificial pancreas technologies with an emphasis on bi-hormonal therapy. *Diabetes Obes Metab* 2013; **15:** 1065–70.

49 Haidar A, Legault L, Messier V, Mitre TM, Leroux C, Rabasa-Lhoret R. Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. *Lancet Diabetes Endocrinol* 2015; **3:** 17–26.

50 Pinsker JE, Lee JB, Dassau E, et al. Randomized crossover comparison of personalized MPC and PID control algorithms for the artificial pancreas. *Diabetes Care* 2016; **39:** 1135–42.

51 Elleri D, Allen JM, Kumareswaran K, et al. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. *Diabetes Care* 2013; **36:** 838–44.

52 Del Favero S, Bruttomesso D, Di Palma F, et al, on behalf of the AP@home Consortium. First use of model predictive control in outpatient wearable artificial pancreas. *Diabetes Care* 2014; **37:** 1212–15.

53 Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008; **359:** 1464–76.

54 Beck RW, Riddlesworth T, Ruedy K, et al, for the DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* 2017; **317:** 371–78.

55 Anderson J, Attvall S, Sternemalm L, et al. Effect on glycemic control by short- and long-term use of continuous glucose monitoring in clinical practice. *J Diabetes Sci Technol* 2011; **5:** 1472–79.

56 Battelino T, Conget I, Olsen B, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012; **55:** 3155–62.

57 Langendam M, Luijf YM, Hooft L, Devries JH, Mudde AH, Scholten RJ. Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2012; **1:** CD008101.

58 Maahs DM, Buckingham BA, Castle JR, et al. Outcome measures for artificial pancreas clinical trials: a consensus report. *Diabetes Care* 2016; **39:** 1175–79.

59 El-Khatib FH, Russell SJ, Magyar KL, et al. Autonomous and continuous adaptation of a bihormonal bionic pancreas in adults and adolescents with type 1 diabetes. *J Clin Endocrinol Metab* 2014; **99:** 1701–11.

60 Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983–2005). *Arch Intern Med* 2009; **169:** 1307–16.

61 Higgins JPT. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol* 2008; **37:** 1158–60.