Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis

Eleni Bekiari, Konstantinos Kitsios, Hood Thabit, Martin Tauschmann, Eleni Athanasiadou, Thomas Karagiannis, Anna-Bettina Haidich, Roman Hovorka, Apostolos Tsapas

ABSTRACT

OBJECTIVE
To evaluate the efficacy and safety of artificial pancreas treatment in non-pregnant outpatients with type 1 diabetes.

DESIGN
Systematic review and meta-analysis of randomised controlled trials.

DATA SOURCES
Medline, Embase, Cochrane Library, and grey literature up to 2 February 2018.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES
Randomised controlled trials in non-pregnant outpatients with type 1 diabetes that compared the use of any artificial pancreas system with any type of insulin based treatment. Primary outcome was proportion (%) of time that sensor glucose level was within the near normoglycaemic range (3.9-10 mmol/L). Secondary outcomes included proportion (%) of time that sensor glucose level was above 10 mmol/L or below 3.9 mmol/L, low blood glucose index overnight, mean sensor glucose level, total daily insulin needs, and glycated haemoglobin. The Cochrane Collaboration risk of bias tool was used to assess study quality.

RESULTS
40 studies (1027 participants with data for 44 comparisons) were included in the meta-analysis. 35 comparisons assessed a single hormone artificial pancreas system, whereas nine comparisons assessed a dual hormone system. Only nine studies were at low risk of bias. Proportion of time in the near normoglycaemic range (3.9-10.0 mmol/L) was significantly higher with artificial pancreas use, both overnight (weighted mean difference 15.15%, 95% confidence interval 12.21% to 18.09%) and over a 24 hour period (9.62%, 7.54% to 11.7%). Artificial pancreas systems had a favourable effect on the proportion of time with sensor glucose level above 10 mmol/L (~8.52%, -11.14% to -5.9%) or below 3.9 mmol/L (~-1.49%, -1.86% to -1.11%) over 24 hours, compared with control treatment. Robustness of findings for the primary outcome was verified in sensitivity analyses, by including only trials at low risk of bias (11.64%, 9.1% to 14.18%) or trials under unsupervised, normal living conditions (10.42%, 8.63% to 12.2%). Results were consistent in a subgroup analysis both for single hormone and dual hormone artificial pancreas systems.

CONCLUSIONS
Artificial pancreas systems are an efficacious and safe approach for treating outpatients with type 1 diabetes. The main limitations of current research evidence on artificial pancreas systems are related to inconsistency in outcome reporting, small sample size, and short follow-up duration of individual trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Individual studies have shown artificial pancreas use to be safe and efficacious in inpatients, patients under close monitoring, and outpatients with type 1 diabetes

The US Food and Drug Administration recently approved artificial pancreas use for patients aged 14 years and older with type 1 diabetes

Previous meta-analyses on artificial pancreas systems have provided limited findings, mainly owing to the low number of studies incorporated and heterogeneous definitions of outcomes

WHAT THIS STUDY ADDS

In view of all the available evidence from randomised controlled trials, artificial pancreas treatment significantly improves glycaemic control while reducing the burden of hypoglycaemia in outpatients with type 1 diabetes

Results are consistent for people using artificial pancreas systems unsupervised under normal living conditions, and for both single hormone and dual hormone systems

The current research evidence on artificial pancreas systems is limited by inconsistency in outcome reporting, small sample size, and short follow-up duration of individual trials

ARTICLE

BMJ 2018;361:k1310 doi: 10.1136/bmj.k1310

Accepted: 2 March 2018

Correspondence to: A Tsapas atsapas@auth.gr

Additional material is published online only. To view please visit the journal online.

Cite this as: BMJ 2018;361:k1310
patient to manually modify the insulin infusion rate according to continuous glucose monitoring values (known as sensor augmented pump treatment). The recent introduction of a low glucose suspend feature has allowed for automatic pump suspension when a preprogrammed threshold value of continuous glucose monitoring is reached. Based on a 2016 analysis, the use of sensor augmented pump treatment and the low glucose suspend feature was found to be cost effective compared with continuous subcutaneous insulin infusion and self-monitoring of blood glucose for patients with type 1 diabetes in the United Kingdom.

Artificial pancreas treatment, also referred to as closed loop glucose control, is an emerging treatment option combining an insulin pump and continuous glucose monitoring with a control algorithm to deliver insulin in a glucose responsive manner (that is, a single hormone artificial pancreas system). Glucagon can also be delivered in a similar glucose responsive fashion, as accommodated by dual hormone artificial pancreas systems. Therefore, compared with insulin pumps or sensor augmented pumps, artificial pancreas use can reduce the burden for patients by automatically adjusting the amount of insulin entering the body on the basis of sensor glucose levels. Several artificial pancreas systems have been developed, and their safety and efficacy have been evaluated in many studies, showing promising results. An early pooled analysis included only four studies in an inpatient setting, whereas an overview published in 2015 summarised existing data from randomised controlled trials up to September 2014. Finally, a recent meta-analysis summarised evidence from published trials of artificial pancreas systems in outpatients with type 1 diabetes. Notably, the US Food and Drug Administration has recently approved the first artificial pancreas system for use by people with type 1 diabetes over 14 years of age, based on a safety outpatient study. This systematic review and meta-analysis aimed to summarise and critically appraise all existing evidence on the clinical efficacy and safety of artificial pancreas systems for the management of type 1 diabetes in the outpatient setting.

Methods
This systematic review and meta-analysis is based on a prespecified protocol (appendix 1), and is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (appendix 2).

Search strategy and selection criteria
We searched Medline, Embase, Cochrane Database of Systematic Reviews, and the Central Register of Controlled Trials from inception to 2 February 2018. Our search strategy was based on search terms describing the intervention (artificial pancreas or closed loop system) in addition to a filter for randomised trials. We omitted terms related to type 1 diabetes to avoid missing potentially relevant studies. We used search terms that had been identified from initial scoping searches, target references, and browsing of database thesauruses (web appendix 3). We imposed no restrictions based on language or publication status, searched ClinicalTrials.gov, and sought for additional studies from snowballing of included records.

We included randomised controlled trials in non-pregnant adults, children, and adolescents with type 1 diabetes in the outpatient setting (including hotels, diabetes camps, or normal living conditions), irrespective of trial design (parallel or crossover) or duration of intervention, which compared artificial pancreas systems with any type of insulin based treatment. Such comparative treatments included multiple daily insulin injections, insulin pump treatment without continuous glucose monitoring or with blinded continuous glucose monitoring, and sensor augmented pumps with or without a low glucose suspend feature.

Data extraction
References identified were imported into a reference management software (Endnote, Clarivate Analytics) for deduplication. Potentially eligible records were exported to Covidence (Covidence, Veritas Health Innovation) for screening. Three reviewers (EB, EA, and KK) working independently, screened all records in duplicate, and disagreements were arbitrated by a senior team member (AT). Initially, records were screened at title and abstract level, and potentially eligible studies were assessed in full text.

If multiple records of one study were retrieved, we collated data from all records, and used data from the report with the longest duration of follow-up. We extracted data for study and participant baseline characteristics, interventions, comparators, and clinical outcomes in duplicate (EB, EA, and TK) by using an electronic, pilot tested, data extraction form (web appendix 4). Disagreements were resolved by consensus or following discussion with a senior reviewer (AT).

Outcomes
The primary outcome was proportion (%) of time when the sensor glucose level was within the near normoglycaemic range (3.9-10 mmol/L). Secondary outcomes included proportion (%) of time when the sensor glucose level was above 10 mmol/L or below 3.9 mmol/L, incidence of severe hypoglycaemia, mean sensor glucose level, total daily insulin needs, and glycated haemoglobin (HbA1c). We also used low blood glucose index overnight as an additional outcome to assess hypoglycaemia. Low blood glucose index is a weighted average of the number of hypoglycaemic readings with progressively increasing weights as glucose levels decrease and is associated with the risk of hypoglycaemia and prediction of severe hypoglycaemic episodes. When available, for proportion (%) of time in the near normoglycaemic range, hyperglycaemia (>10 mmol/L), or hypoglycaemia (<3.9 mmol/L), we extracted data both for 24 hour and overnight periods (as defined in each individual study).
Statistical analysis

We conducted meta-analyses when data were available for at least two studies. We calculated weighted mean differences with 95% confidence intervals, applying an inverse variance weighted random effects model using the DerSimonian and Laird estimation method.\(^1\) We also calculated 95% prediction intervals to estimate a predicted range for the true treatment effect in any one individual study.\(^1\) In addition, to account for uncertainty related to heterogeneity estimates, we calculated 95% confidence intervals applying the Hartung Knapp correction method.\(^1\) For trials reporting only medians and interquartile ranges, we retrieved mean and variance values from authors of original reports or used appropriate formulas to calculate mean and variance, making no assumption on the distribution of the underlying data.\(^1\) We combined data both from parallel group and crossover studies. Finally, for crossover studies that reported their results as parallel group trials, we used appropriate methods to impute within patient differences.\(^1\)

We conducted prespecified subgroup analyses based on the mode of use (overnight or over 24 hours) and type of artificial pancreas system (single or dual hormone). A series of a priori decided sensitivity analyses was conducted for the primary outcome, excluding trials at unclear or high risk of bias, trials recruiting people in diabetes camps, or trials with supervised use of artificial pancreas system. We assessed statistical heterogeneity by the \(\chi^2\) based Cochran Q test and the \(I^2\) statistics. For HbA\(_1c\), we synthesised only data from trials with at least eight weeks’ duration per intervention. All analyses were undertaken in RevMan 5.3 (Nordic Cochrane Centre) and Stata 13.0 (Stata Corporation).

Assessment of risk of bias in individual studies and across studies

Quality assessment was undertaken in duplicate by two independent reviewers (EB and EA), and disagreements were resolved by consensus or arbitrated by a third reviewer (AT). We used the Cochrane Collaboration risk of bias tool to assess risk of bias for the primary outcome for individual studies. For crossover studies, we also assessed a series of methodological challenges that are related to this specific design (appropriateness of crossover design, carry-over effects, unbiased data).\(^1\) We used results to provide an evaluation of the overall quality of the included studies (appendix 5) to inform a sensitivity analysis including only trials at low overall risk of bias.

We explored risk of bias across studies, both visually using a contour enhanced funnel plot, and formally using Egger’s statistical test.\(^2\) In case of evidence of small study effects, we used the trim and fill method as a sensitivity analysis, to provide an adjusted estimate of the meta-analysis.\(^3\)

Patient involvement

No patients were involved in definition of the research question or the outcome measures, and interpretation or writing up of results. Data relating to the impact of the intervention on participants’ quality of life were not extracted. Where possible, results of this systematic review and meta-analysis will be disseminated to the patient community or individual patients and families through the investigators of this meta-analysis.

Results

Characteristics of included studies

Figure 1 shows the study selection process. Of 10,054 records retrieved, 85 reports qualified for inclusion in our systematic review. After juxtaposing different reports that referred to the same study, 39 publications describing 41 trials (1042 participants with data for 45 comparisons) were used to inform our systematic review.\(^1\) One trial did not report data for outcomes assessed and was not included in the meta-analysis.\(^1\) Table 1 shows characteristics of the 41 studies included in the systematic review and their participants at baseline. The clear majority of included trials used a crossover design,\(^1\) whereas only seven trials were of parallel design.\(^1\)

The duration of 36 trials lasted up to four weeks,\(^1\) whereas the remaining five trials lasted from eight to 30 weeks.\(^1\) Seventeen trials recruited children or adolescents,\(^1\) whereas the remaining 25 trials\(^1\) and used over 24 hours in the remaining 25 trials.\(^1\) In 32 trials, a single hormone artificial pancreas system was assessed (mostly versus unblinded treatment using sensor augmented pump).\(^1\)
| Study author and year | Trial registration details | Setting | Population | Type of artificial pancreas | Type of comparator | Intervention duration | Length of follow-up* | No of patients |
|-----------------------|---------------------------|---------|------------|-----------------------------|-------------------|----------------------|---------------------|----------------|
| Bally 2017 | NCT02727231 | Home | Adults | Florence | SAP | 24 h | 4 weeks | 29 |
| Biester 2016 | NCT02636491 | Home | Adults and adolescents | MD-Logic | SAP | 24 h | 2 days | 10 |
| Blauw 2016 | NCT02160275 | Home | Adults | Infreda dual hormone CL | Insulin pump treatment | 24 h | 4 days | 10 |
| Breton 2017 | NCT02606524 | Winter camp | Adolescents | DiAs | SAP | 24 h | 5 days | 32 |
| Brown 2017 | NCT0131766, NCT01380888 | Hotel or research house | Adults | DiAs | SAP | 24 h | 1 day | 40 |
| Chernavecky 2016 | NCT01890954 | Research house | Adolescents | DiAs USS | Insulin pump treatment | 24 h | 1 day | 8 |
| De Bock 2015 | ACRN12614001005640 | Home | Adults and adolescents | Medtronic PID IFB | SAP+LGS | 24 h | 5 days | 8 |
| De Boer 2017 | NCT02750267 | Hotel or home | Children | DiAs | SAP+LGS | 24 h | 3 days | 12 |
| Eckhaispou 2016a | Not reported | Home | Adults | Single hormone | Insulin pump treatment | 24 h | 3 days | 20 |
| Eckhaispou 2016b | Not reported | Home | Adults | Dual hormone | Insulin pump treatment | 24 h | 3 days | 20 |
| El-Khatib 2016 | NCT02092220 | Home | Adults | Dual hormone | Insulin pump treatment or SAP | 24 h | 11 days | 39 |
| Favero 2016 | NCT0260878 | Diabetes camp | Children | DiAs | SAP | 24 h | 3 days | 30 |
| Forlenza 2017 | NCT02773875 | Home | Adolescents | DiAs | SAP | 24 h | 2 weeks | 19 |
| Forlenza 2017a | NCT01714972 | Home | Children and adolescents | Medtronic PHHM | Insulin pump treatment | 24 h | 11 days | 33 |
| Haidar 2015a | NCT0189694 | Diabetes camp | Adolescents | Single hormone | Insulin pump treatment | 24 h | 3 days | 33 |
| Haidar 2015b | NCT0189694 | Diabetes camp | Adolescents | Dual hormone | Insulin pump treatment | 24 h | 3 days | 33 |
| Haidar 2016a | NCT01905020 | Home | Adults and adolescents | Single hormone | Insulin pump treatment | 24 h | 2 days | 28 |
| Haidar 2016b | NCT01905020 | Home | Adults and adolescents | Dual hormone | Insulin pump treatment | 24 h | 2 days | 28 |
| Haidar 2017a | NCT01966393 | Home | Adults | Single hormone | SAP | 24 h | 60 hours | 23 |
| Haidar 2017b | NCT01966393 | Home | Adults | Dual hormone | SAP | 24 h | 60 hours | 23 |
| Hovorka 2014 | NCT01221467 | Home | Adolescents | Florence | SAP | 24 h | 3 weeks | 16 |
| Kingma 2017 | Not reported | Outpatient | Adults and adolescents | DiAs | SAP | 24 h | 5 weeks | 37 |
| Kovatchev 2016a | NCT01714505, NCT01727817, NCT01742741 | Hotel or guesthouse | Adults | DiAs | SAP+SM | 24 h | 40 hours | 20 |
| Krup 2015 | NCT02135390 | Home | Adults | Florence | SAP | 24 h | 8 days | 17 |
| Leelarantha 2014 | NCT01666028 | Home | Adults | Florence | SAP | 24 h | 8 days | 17 |
| Ly 2014 | NCT01973413 | Diabetes camp | Adults and adolescents | DiAs USS | SAP | 24 h | 5-6 days | 20 |
| Ly 2015a | NCT02636676 | Diabetes camp | Adults and adolescents | Medtronic PID IFB | SAP+LGS | 24 h | 6 days | 21 |
| Ly 2015b | Not reported | Diabetes camp | Adults and adolescents | SAP+LGS | SAP | 24 h | 5 days | 16 |
| Ly 2016a | NCT0189694 | Diabetes camp | Adolescents | Dual hormone | Insulin pump treatment | 24 h | 5 days | 33 |
| Ly 2016b | Not reported | Diabetes camp | Adults and adolescents | Medtronic PID IFB | SAP | Overnight | 1 day | 21 |
| Nimri 2014 | NCT01238406 | Home | Adults and adolescents | Med-Logic | SAP | Overnight | 6 weeks | 24 |
| Nimri 2016 | NCT01726829 | Home | Children, adolescents and adults | MD-Logic | SAP | Overnight | 4 days | 75 |
| Phillip 2013 | NCT01238406 | Diabetes camp | Adolescents | MD-Logic | SAP | Overnight | 1 day | 54 |
| Rentz 2016 | NCT01714972 | Home and hotel | Adults | DiAs | SAP+LGS | 24 h | 2 days | 24 |
| Russell 2014a | NCT01762059 | Home and hotel | Adults | Dual hormone | Insulin pump treatment or SAP | 24 h | 5 days | 20 |
| Russell 2014b | NCT01833888 | Diabetes camp | Adolescents | Dual hormone | Insulin pump treatment or SAP | 24 h | 5 days | 32 |
| Russell 2016 | NCT02105324 | Diabetes camp | Preadolescents | Dual hormone | Insulin pump treatment or SAP | 24 h | 5 days | 19 |
| Schierloh 2015 | Not reported | Home | Children | Florence | SAP | Overnight | 4 days | 15 |
| Sharifi 2016 | Not reported | Home | Adults and adolescents | Medtronic PID IFB | SAP+LGS | Overnight | 4 days | 28 |
| Spak 2017 | NCT02438189 | Home | Adults and adolescents | Medtronic PHHM | SAP+LGS | Overnight | 21 nights | 30 |
| Tauschmann 2016a | NCT01873066 | Home | Adolescents | Florence | SAP | 24 h | 7 days | 12 |
| Tauschmann 2016b | NCT01873066 | Home | Adolescents | Florence | SAP | 24 h | 3 weeks | 12 |
| Thabit 2014 | NCT01400140 | Home | Adolescents | Florence | SAP | Overnight | 4 weeks | 24 |
| Thabit 2015a | NCT01961622 | Home | Adults | Florence | SAP | Overnight | 12 weeks | 50 |
| Thabit 2015b | NCT01778368 | Home | Adolescents | Florence | SAP | Overnight | 12 weeks | 50 |

DiAs=Diabetes Assistant; USS=Unified Safety System; SAP=sensor augmented pump treatment; MPC=model predictive control; PID=proportional integral derivative; IFB=insulin feedback; LGS=low glucose suspend; PHHM=predictive hyperglycaemia and hypoglycaemia minimisation; SM=safety supervision module.

*For crossover trials, length of follow-up refers to the duration of each period, excluding washout period.

†Not included in the meta-analysis.
Five trials assessed a dual hormone artificial pancreas system, mainly by comparison with insulin pump treatment (consisting of continuous subcutaneous insulin infusion combined with a blinded system of continuous glucose monitoring). Additionally, four studies evaluated both a single hormone and a dual hormone system against control treatment (as three way crossover trials). In six studies assessing sensor augmented pump treatment, control treatment comprised a sensor augmented pump combined with an low glucose suspend feature. Among trials evaluating single hormone artificial pancreas systems, 13 used the DiAs platform, 28-30 32 35 37 42 44 46 47 54 eight used the Florence implementation, 25 41 45 57 60-63 four used the MD-Logic platform, 26 51-53 and six used a Medtronic device. Most trials used a model predictive control algorithm, 25 29 34 35 37-41 43-45 54-57 60-63 five used a proportional integral derivative algorithm, 27 31 48 50 58 four used a fuzzy logic algorithm, 26 51 52 55 four used a control to range algorithm, 30 32 46-49 and the remainder used other algorithms or did not provide relevant details. 28 33 36 42 47 59 Twenty one comparisons used a Dexcom sensor for continuous glucose monitoring, 28 30 32 34 35 37 38 40 42-44 46 47 49 54-56 58 59 and nine 25 41 45 57 60-63 comparisons used an Enlite Sensor or a FreeStyle Navigator in the artificial pancreas systems, respectively. Type of sensor for continuous glucose monitoring was not reported in two trials. In 41 comparisons, the type of sensor for continuous glucose monitoring was identical between artificial pancreas and control arms, whereas four trials did not report information for type of sensor used in the control arm. In terms of setting, 13 trials were held in a diabetes camp or a guesthouse, 28 29 35 38 43 46-50 53 55 56 and in 26 trials, participants were at home. Only in a small subset of trials were participants using artificial pancreas unsupervised under normal living conditions; the remaining studies either used remote monitoring or did not provide relevant details. Participants’ mean age and HbA1c, at baseline ranged from 7.0 to 47.0 years and from 6.9% to 8.6%, respectively.

Risk of bias assessment results
Risk of bias assessment for the primary outcome is presented in appendices 6 and 7. Only nine studies were at low risk of bias. Most studies were deemed at high risk for bias, because either they reported median values instead of mean values, or reported results that required extensive use of imputation methods to be used in meta-analyses.

Primary outcome
All meta-analysis results are presented as summary effect estimates for artificial pancreas systems versus control treatment. Compared with control treatment, use of artificial pancreas was associated with an increased percentage of time (140 additional minutes) in near normoglycaemia (3.9-10.0 mmol/L) over 24 hours (overall weighted mean difference 9.62% (95% confidence interval 7.54% to 11.7%); I^2=78%, τ^2=24.09, 32 studies). This effect was consistent both for trials using artificial pancreas overnight (7.16% (5.73% to 8.58%); 0%, 0.0, seven studies) or over 24 hours (10.79% (7.88% to 13.7%); 81%, 39.21, 25 studies; fig 2). The confidence interval for the overall effect estimate after applying the Hartung Knapp correction was 7.83% to 12.41%, whereas the 95% prediction interval was −0.63% to 19.87%. Of note, the 95% prediction interval was above zero when the artificial pancreas was used overnight (5.29% to 9.02%), suggesting that artificial pancreas use will be beneficial in at least 95% of the individual study settings when applied overnight. However, the prediction interval contained negative values when applied over 24 hours (~2.52% to 24.1%), and therefore might not be beneficial in some settings.

The favourable effect of artificial pancreas use over control treatment was more evident on the proportion of time in near normoglycaemia overnight (overall weighted mean difference 15.15% (95% confidence interval 12.21% to 18.09%); I^2=73%, τ^2=43.48, 31 studies). This effect was consistent when artificial pancreas was used either only overnight (14.25% (11.13% to 17.37%); 63%, 19.39, 14 studies) or over 24 hours (16.44% (10.88% to 22.01%); 78%, 99.63, 17 studies; fig 3), even when the Hartung Knapp correction was applied (appendix 13). Respective 95% prediction intervals suggested that effect on time in near normoglycaemia overnight would be beneficial in at least 95% of the individual study settings when artificial pancreas was applied overnight (4.04% to 24.45%), but not when applied over 24 hours (~5.68% to 38.56%).

Secondary outcomes
Use of artificial pancreas had a favourable effect on time in hyperglycaemia (glucose concentrations >10 mmol/L) during the entire day. Compared with control treatment, this period was shortened by about two hours (overall weighted mean difference ~8.52% (95% confidence interval -11.14% to -5.9%); I^2=80%, τ^2=28.98, 22 studies), both in trials using artificial pancreas overnight (~6.0% (~8.4% to -3.6%); 0%, 0.0, three studies) and those using artificial pancreas over 24 hours (~9.08% (~12.23% to -5.93%); 83%, 37.53, 19 studies; fig 4). Similarly, the time when glucose concentrations were higher than 10.0 mmol/L was shortened compared with control treatment (~11.12% (~13.8% to ~8.44%); 71%, 26.13, 23 studies), both in trials that used artificial pancreas either only overnight (~9.23% (~11.67% to ~6.79%); 51%, 8.26, 12 studies) or over 24 hours (~13.86% (~19.83% to ~7.9%); 80%, 77.07, 11 studies; appendix 8).

Time when glucose concentrations were lower than 5.7 mmol/L was shortened both in trials using artificial pancreas either only overnight (~6.79% (~9.08% to ~4.42%); 83%, 37.53, 19 studies) or over 24 hours (~10.08% (~12.34% to ~7.8%); 88%, 75.07, 11 studies; appendix 8).
overnight blood glucose index (−0.37 (−0.56 to −0.18)); 85%, 0.06, 11 studies).

The incidence of severe hypoglycaemia was very low both in groups using artificial pancreas (six episodes) and control treatment (three episodes). Use of artificial pancreas was also associated with a reduction in overnight low blood glucose index (−0.37 (−0.56 to −0.18); 85%, 0.06, 11 studies).

Compared with control treatment, use of artificial pancreas had a favourable effect on mean levels of sensor blood glucose over 24 hours, which fell by 0.48 mmol/L (95% confidence interval 0.3 to 0.66; $\chi^2=84\%$, $\chi^2=0.18$, 32 studies; fig 6). Results were more favourable for mean levels of sensor blood glucose overnight (overall weighted mean difference −0.81 mmol/L (−1.03 to −0.6); 78%, 0.3, 35 studies; appendix 10). These findings were consistent with the effect of artificial pancreas use on HbA$_1c$ (−0.26% (−0.38% to −0.13%); 0%, 0.0, three studies; fig 7).

Finally, no difference between artificial pancreas use and control treatment was seen in the mean daily
needs for insulin (−0.21 IU (−1.64 to 1.22)); 77%, 4.45, 14 studies; appendix 11). Appendix 12 presents 95% Hartung Knapp confidence intervals and prediction intervals for all outcomes.

**Sensitivity and subgroup analyses**

Results for the proportion of time in near normoglycaemia were similar in a sensitivity analysis including only trials at low risk of bias, both over 24 hours (overall weighted mean difference 11.64% (95% confidence interval 9.1% to 14.18%); 10 studies) and overnight (20.18% (13.18% to 27.19%); five studies; fig 8 and fig 9). Similarly, results for near normoglycaemia did not differ in a series of sensitivity analyses excluding trials that used artificial pancreas in diabetes camps or including only trials using artificial pancreas in unsupervised patients in normal living conditions. This similarity was seen both for the 24 hour period (10.42% (95% confidence interval 8.63% to 12.2%) and 10.67% (8.33% to 13.01%), respectively; appendices 13 and 14) and overnight period (13.47% (10.41% to 16.54%) and 15.53% (10.12% to 20.94%), respectively; appendixes 15 and 16).

We also did a post hoc sensitivity analysis excluding trials comparing artificial pancreas systems with low glucose suspend systems, to explore their effect on hypoglycaemia. Time when concentrations were lower than 3.9 mmol/L was shortened compared with control

---

**Fig 3 | Weighted mean difference in proportion (%) of overnight period in near normoglycaemic range (glucose concentration 3.9-10.0 mmol/L), artificial pancreas use versus control treatment**

| Study or subgroup | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------|--------------------------|--------------------------|
| **24h use of artificial pancreas** | | |
| Bally 2017 | 17.20 (1.58 to 32.82) | |
| Blauw 2016 | 25.00 (11.72 to 38.28) | |
| Breton 2017 | 10.50 (-3.65 to 24.65) | |
| De Bock 2015 | 1.10 (-5.68 to 7.88) | |
| DeBoer 2017 | 44.60 (24.90 to 64.30) | |
| El-Khatib 2017 | 24.50 (13.45 to 35.55) | |
| Favero 2016 | -3.70 (-12.76 to 5.36) | |
| Forlenza 2017a | 7.60 (1.76 to 13.44) | |
| Haidar 2017a | 6.77 (-1.01 to 14.55) | |
| Haidar 2017b | 5.97 (-0.78 to 12.72) | |
| Ly 2015a | 11.70 (-2.02 to 25.42) | |
| Ly 2015b | 20.10 (5.75 to 34.45) | |
| Ly 2016a | 23.10 (10.60 to 35.60) | |
| Renard 2017 | 26.00 (12.47 to 39.53) | |
| Russell 2014a | 30.90 (15.31 to 46.49) | |
| Russell 2014b | 20.20 (9.30 to 31.10) | |
| Russell 2016 | 33.10 (20.03 to 46.17) | |
| **Subtotal** | 16.44 (10.88 to 22.01) | |
| **Total (95% CI)** | | |
| Test for heterogeneity: χ²=99.63, df=16, P<0.001, I²=78% | |
| Test for overall effect: z=5.79, P<0.001 | |
| **Study or subgroup** | Mean difference (95% CI) | Mean difference (95% CI) |
| **Overnight use of artificial pancreas** | | |
| Brown 2017 | 18.10 (8.13 to 28.07) | |
| Forlenza 2017b | 10.00 (4.69 to 15.31) | |
| Haidar 2015a | 24.00 (12.51 to 35.49) | |
| Haidar 2015b | 33.34 (18.63 to 48.05) | |
| Haidar 2016a | 16.00 (6.45 to 25.55) | |
| Haidar 2016b | 18.00 (8.16 to 27.84) | |
| Hovorka 2014 | 19.58 (12.61 to 26.55) | |
| Kropff 2015 | 8.60 (4.82 to 12.38) | |
| Ly 2014 | 12.70 (4.16 to 29.56) | |
| Ly 2016b | 19.90 (11.31 to 28.49) | |
| Nimri 2014 | 14.35 (8.95 to 19.75) | |
| Sharifi 2016 | 9.50 (2.26 to 16.74) | |
| Spaic 2017 | 7.00 (3.25 to 10.75) | |
| Thabit 2014 | 12.00 (6.32 to 17.68) | |
| **Subtotal** | 14.25 (11.13 to 17.37) | |
| Test for heterogeneity: χ²=19.39, df=13, P=0.001, I²=63% | |
| Test for overall effect: z=8.95, P=0.001 | |

| Study or subgroup | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------|--------------------------|--------------------------|
| **Overnight use of artificial pancreas** | | |
| Brown 2017 | 18.10 (8.13 to 28.07) | |
| Forlenza 2017b | 10.00 (4.69 to 15.31) | |
| Haidar 2015a | 24.00 (12.51 to 35.49) | |
| Haidar 2015b | 33.34 (18.63 to 48.05) | |
| Haidar 2016a | 16.00 (6.45 to 25.55) | |
| Haidar 2016b | 18.00 (8.16 to 27.84) | |
| Hovorka 2014 | 19.58 (12.61 to 26.55) | |
| Kropff 2015 | 8.60 (4.82 to 12.38) | |
| Ly 2014 | 12.70 (4.16 to 29.56) | |
| Ly 2016b | 19.90 (11.31 to 28.49) | |
| Nimri 2014 | 14.35 (8.95 to 19.75) | |
| Sharifi 2016 | 9.50 (2.26 to 16.74) | |
| Spaic 2017 | 7.00 (3.25 to 10.75) | |
| Thabit 2014 | 12.00 (6.32 to 17.68) | |
| **Subtotal** | 14.25 (11.13 to 17.37) | |
| Test for heterogeneity: χ²=19.39, df=13, P=0.001, I²=63% | |
| Test for overall effect: z=8.95, P=0.001 | |

---
### Fig 4 | Weighted mean difference in proportion (%) of 24 hour period in hyperglycaemia (glucose concentration >10.0 mmol/L), artificial pancreas use versus control treatment

| Study or subgroup | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------|--------------------------|--------------------------|
| **Overnight use of artificial pancreas** |                        |                          |
| Brown 2017        | -4.90 (-9.16 to -0.64)   | -6.00 (-8.40 to -3.60)   |
| Hovorka 2014      | -6.54 (-11.83 to -1.25)  | -6.50 (-9.98 to -3.02)   |
| Thabit 2014       | -6.00 (-10.99 to -1.01)  | -6.00 (-10.99 to -1.01)  |
| **Total**         | -6.90 (-10.23 to -3.57)  | -12.99 (-22.21 to -3.77) |
| Test for heterogeneity: $\tau^2=0.00, \chi^2=0.37, df=2, P=0.83, I^2=0\%$ | | |
| Test for overall effect: $z=4.90, P<0.001$ | | |

| 24h use of artificial pancreas | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------------------|--------------------------|--------------------------|
| Bally 2017                    | -6.90 (-10.23 to -3.57)  | -12.99 (-22.21 to -3.77) |
| Blauw 2016                    | -15.11 (-29.63 to -0.59) | -23.56 (-43.02 to -4.11) |
| DeBoer 2017                   | -10.90 (-18.81 to -2.99) | -17.30 (-26.03 to -8.57) |
| El-Khatib 2017                | -9.60 (-15.17 to -4.03)  | -19.08 (-27.61 to -11.99) |
| Forlenza 2017a                | -1.30 (-3.18 to -1.42)   | -2.53 (-4.35 to -0.71)   |
| Forlenza 2017b                | -1.30 (-3.18 to -1.42)   | -2.53 (-4.35 to -0.71)   |
| Haidar 2017a                  | -8.61 (-14.05 to -3.17)  | -3.60 (-7.76 to 14.96)   |
| Haidar 2017b                  | -10.90 (-18.81 to -2.99) | -17.30 (-26.03 to -8.57) |
| Kingman 2017                  | -9.00 (-17.70 to -0.30)  | -5.10 (-6.65 to 10.85)   |
| Kovatchev 2014                | -9.00 (-17.70 to -0.30)  | -5.10 (-6.65 to 10.85)   |
| Leelarantha 2014              | -9.00 (-17.70 to -0.30)  | -5.10 (-6.65 to 10.85)   |
| Ly 2015a                     | -3.60 (-7.76 to 14.96)   | -3.60 (-7.76 to 14.96)   |
| Ly 2016a                     | -10.90 (-18.81 to -2.99) | -17.30 (-26.03 to -8.57) |
| Russell 2014a                 | -19.08 (-27.61 to -11.99) | -23.56 (-43.02 to -4.11) |
| Russell 2014b                 | -10.90 (-18.81 to -2.99) | -17.30 (-26.03 to -8.57) |
| Russell 2016                  | -19.08 (-27.61 to -11.99) | -23.56 (-43.02 to -4.11) |
| Tauschmann 2016a              | -19.30 (-25.69 to -12.91) | -23.56 (-43.02 to -4.11) |
| Tauschmann 2016b              | -9.60 (-12.82 to -6.38)  | -19.30 (-25.69 to -12.91) |
| Thabit 2015a                  | -7.70 (-10.83 to -4.57)  | -9.60 (-12.82 to -6.38)  |
| Thabit 2015b                  | -9.08 (-12.23 to -5.93)  | -7.70 (-10.83 to -4.57)  |
| **Subtotal**                  | -8.52 (-11.14 to -5.90)  | -8.52 (-11.14 to -5.90)  |
| Test for heterogeneity: $\tau^2=37.53, \chi^2=104.83, df=18, P<0.001, I^2=83\%$ | | |
| Test for overall effect: $z=5.65, P<0.001$ | | |

**treatment** (overall weighted mean difference −1.59% (95% confidence interval −2.23% to −0.95%) for 24 hour period, −2.53% (−3.18% to −1.87%) for overnight period; appendices 17 and 18). Finally, for all outcomes, results were consistent with those of the main analysis in a prespecified subgroup analysis based on type of artificial pancreas used (that is, single hormone versus dual hormone artificial pancreas; table 2).

### Small study effects

Both visually and formally, no evidence of small study effects was seen for the proportion of time in near normoglycaemia over 24 hours (P=0.129). However, evidence of small study effects was seen (P<0.001) for the proportion of time in near normoglycaemia overnight, and visual inspection of the contour enhanced funnel plot suggested that small negative studies were missing (appendix 19). Nevertheless, the adjusted meta-analytical estimate after use of the trim and fill method remained in favour of artificial pancreas use (weighted mean difference 10.39% (95% confidence interval 7.30% to 13.49%), P<0.001).

### Discussion

#### Key findings

Our data suggest that use of artificial pancreas is associated with almost two and a half additional hours in near normoglycaemia over a 24 hour period compared with control treatment, mainly due to its favourable effect during the overnight period. This finding was also verified by its effect on time in hyperglycaemia (two hours less than control treatment) and in hypoglycaemia (two hours less than control treatment) with control treatment, mainly due to its favourable effect during the overnight period. This finding was also verified by its effect on time in hyperglycaemia (two hours less than control treatment) and in hypoglycaemia (two hours less than control treatment). Results were robust both for single and dual hormone systems, and were consistent in all sensitivity analyses performed—including an analysis restricted to trials under normal living conditions without remote monitoring, supporting the convenience and ease of use of artificial pancreas systems.

Finally, this favourable effect was also evident in the relative reduction of mean blood glucose levels by 0.48 mmol/L, which is consistent with the HbA1c reduction of about 0.3% recorded in trials with a duration of more than eight weeks per intervention.

Overall, our results reflect the progress made over recent decades of extensive research and development in artificial pancreas use.
Artificial pancreas systems in the outpatient setting were examined in only four studies in an inpatient setting. The effect of artificial pancreas systems, published in 2011, included a pooled analysis of randomised controlled trials with median values, and exclusion of evidence from grey literature sources, potentially missing a substantial amount of evidence. Our systematic review and meta-analysis incorporated a much larger pool of eligible studies (n=41) and participants (n=1042) and assessed a broader variety of outcomes, focusing on outcome definitions considered most important in trials evaluating artificial pancreas systems.

Furthermore, Weisman and colleagues analysed only 24 hour outcomes for studies investigating artificial pancreas use for 24 hour periods and analysed only overnight outcomes for studies investigating artificial pancreas use overnight, even when individual trials provided data for both periods. Instead, our systematic review dealt with the research question of the effect of artificial pancreas use overnight, even when individual trials provided data for both periods.
### Fig 6 | Weighted mean difference in mean levels of sensor blood glucose (mmol/L) over 24 hours, artificial pancreas use versus control treatment

| Study or subgroup       | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------------|--------------------------|--------------------------|
| Overnight use of artificial pancreas |                         |                          |
| Brown 2017              | -0.28 (-0.55 to -0.01)   |                          |
| Hovorka 2014            | -0.50 (-1.62 to 0.62)    |                          |
| Kropff 2015             | -0.17 (-0.33 to 0.00)    |                          |
| Sharifi 2016            | -0.13 (-0.52 to 0.26)    |                          |
| Thabit 2014             | -0.50 (-0.78 to -0.22)   |                          |
| Thabit 2015b            | -0.50 (-0.87 to -0.13)   |                          |
| Subtotal                | -0.29 (-0.43 to -0.16)   |                          |
| Test for heterogeneity: $\chi^2=0.01$, $I^2=62.62$, df=5, $P=0.28$, $I^2=20\%$ | | |
| Test for overall effect: $z=4.19$, $P<0.001$ | | |

**24h use of artificial pancreas**

| Study or subgroup       | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------------|--------------------------|--------------------------|
| Baily 2017              | -0.40 (-0.70 to -0.10)   |                          |
| Biester 2016            | -0.94 (-2.16 to 0.28)    |                          |
| Blauw 2016              | -0.70 (-1.33 to -0.07)   |                          |
| Breton 2017             | -0.18 (-0.41 to 0.05)    |                          |
| Chernavsky 2016         | -2.16 (-3.52 to -0.80)   |                          |
| De Bock 2015            | -0.40 (-1.43 to 0.63)    |                          |
| DeBoer 2017             | -2.11 (-3.04 to -1.18)   |                          |
| Ekhlaspour 2016a        | 0.17 (0.02 to 0.36)      |                          |
| Ekhlaspour 2016b        | -0.11 (0.24 to 0.02)     |                          |
| El-Khatib 2017          | -1.20 (-1.74 to -0.66)   |                          |
| Favero 2016             | 1.22 (0.57 to 1.87)      |                          |
| Forlenza 2017a          | -0.59 (-1.17 to -0.01)   |                          |
| Haidar 2017a            | 0.40 (0.15 to 0.95)      |                          |
| Haidar 2017b            | 0.47 (0.18 to 1.12)      |                          |
| Kovatchev 2014          | 0.51 (0.06 to 0.96)      |                          |
| Leelarantha 2014        | -0.70 (-1.27 to -0.13)   |                          |
| Ly 2015a                | 0.55 (-0.12 to 1.22)     |                          |
| Ly 2015b                | -0.46 (-1.21 to 0.29)    |                          |
| Ly 2016a                | -0.72 (-1.38 to -0.06)   |                          |
| Renard 2017             | -1.11 (-1.69 to -0.53)   |                          |
| Russell 2014a           | -1.44 (-2.17 to -0.71)   |                          |
| Russell 2014b           | -0.89 (-1.45 to -0.33)   |                          |
| Russell 2016            | -1.70 (-2.46 to -0.94)   |                          |
| Tauschmann 2016a        | -1.37 (-1.99 to -0.75)   |                          |
| Tauschmann 2016b        | -1.80 (-2.54 to -1.06)   |                          |
| Thabit 2015a            | -0.61 (-0.90 to -0.32)   |                          |
| Subtotal                | -0.54 (-0.78 to -0.31)   |                          |
| Test for heterogeneity: $\chi^2=0.28$, $I^2=87\%$, df=5, $P=0.001$ | | |
| Test for overall effect: $z=4.47$, $P<0.001$ | | |

**Total (95% CI)**

| Study or subgroup       | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------------|--------------------------|--------------------------|
| **Total** (95% CI)      | -0.48 (-0.66 to -0.30)   |                          |
| Test for heterogeneity: $\chi^2=0.18$, $I^2=84\%$, df=5, $P=0.001$ | | |
| Test for overall effect: $z=5.22$, $P<0.001$ | | |

**Test for subgroup differences: $\chi^2=3.25$, df=1, $P=0.07$, $I^2=69.3\%$**

### Fig 7 | Weighted mean difference in change in HbA$_1c$ (%), artificial pancreas use versus control treatment

#### Study or subgroup

| Study or subgroup | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------|--------------------------|--------------------------|
| Kropff 2015       | -0.20 (0.39 to -0.01)    |                          |
| Thabit 2014       | -0.30 (0.49 to -0.11)    |                          |
| Thabit 2015b      | -0.30 (0.63 to 0.03)     |                          |
| **Total (95% CI)** |                         |                          |
| Test for heterogeneity: $\chi^2=0.00$, $I^2=0\%$, df=2, $P=0.74$, $I^2=0\%$ | | |
| Test for overall effect: $z=4.04$, $P<0.001$ | | |
To ensure internal validity of our conclusions, we included methodological and field expertise, but also access to appropriate tools to account for inappropriate reporting. Furthermore, we synthesised existing data using valid methodological tools. Moreover, we implemented current guidelines for the conduct and reporting of systematic reviews, and adhered to a prespecified protocol with minimal deviations. We undertook a comprehensive search of multiple databases without imposing any restrictions based on language or publication type, and assessed quality of trials using valid methodological tools. Moreover, we synthesised existing data using appropriate methodology to account for inappropriate reporting and analysis methods used in some of the trials.

### Strengths and limitations of study

Composition of the review team ensured appropriate methodology to account for inappropriate reporting and analysis methods used in some of the trials. To ensure internal validity of our conclusions, we implemented current guidelines for the conduct and reporting of systematic reviews, and adhered to a prespecified protocol with minimal deviations. We undertook a comprehensive search of multiple databases without imposing any restrictions based on language or publication type, and assessed quality of trials using valid methodological tools. Moreover, we synthesised existing data using appropriate methodology to account for inappropriate reporting and analysis methods used in some of the trials.

### Fig 8 | Weighted mean difference in proportion (%) of 24 hour period in near normoglycaemic range (glucose concentration 3.9-10.0 mmol/L), artificial pancreas use versus control treatment. Sensitivity analysis includes only trials at low risk of bias

by conducting separate analyses based on all four combinations of outcome assessment period (24 hours or overnight) and duration of intervention use (for 24 hours or solely overnight).

| Study or subgroup | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------|-------------------------|-------------------------|
| **Overnight use of artificial pancreas** |                        |                         |
| Hovorka 2014      |                         |                         |
| Thabit 2014       |                         |                         |
| Thabit 2015b      |                         |                         |
| Subtotal          |                         |                         |
| Test for heterogeneity: $\chi^2 = 18.21$, df=1, $P=0.10$, $I^2 = 63\%$ |   |   |
| Test for overall effect: $z=4.10$, $P=0.001$ |   |   |
| **24h use of artificial pancreas** |                        |                         |
| Bally 2017        |                         |                         |
| El-Khatib 2017    |                         |                         |
| Leelarantha 2014  |                         |                         |
| Russell 2016      |                         |                         |
| Tauschmann 2016a  |                         |                         |
| Tauschmann 2016b  |                         |                         |
| Thabit 2015a      |                         |                         |
| Subtotal          |                         |                         |
| Test for heterogeneity: $\chi^2 = 9.27$, df=2, $P=0.30$, $I^2 = 17\%$ |   |   |
| Test for overall effect: $z=6.09$, $P=0.001$ |   |   |
| **Total (95% CI)** |                         |                         |
| Test for heterogeneity: $\chi^2 = 37.49$, df=4, $P=0.03$, $I^2 = 63\%$ |   |   |
| Test for overall effect: $z=5.65$, $P=0.001$ |   |   |
| Test for subgroup differences: $\chi^2 = 3.16$, df=1, $P=0.08$, $I^2 = 68.4\%$ |   |   |

**Fig 9 | Weighted mean difference in proportion (%) of overnight period in near normoglycaemic range (glucose concentration 3.9-10.0 mmol/L), artificial pancreas use versus control treatment. Sensitivity analysis includes only trials at low risk of bias**

| Study or subgroup | Mean difference (95% CI) | Mean difference (95% CI) |
|-------------------|-------------------------|-------------------------|
| **Overnight use of artificial pancreas** |                        |                         |
| Hovorka 2014      |                         |                         |
| Thabit 2014       |                         |                         |
| Subtotal          |                         |                         |
| Test for heterogeneity: $\chi^2 = 18.21$, df=1, $P=0.01$, $I^2 = 66\%$ |   |   |
| Test for overall effect: $z=4.10$, $P=0.001$ |   |   |
| **24h use of artificial pancreas** |                        |                         |
| Bally 2017        |                         |                         |
| El-Khatib 2017    |                         |                         |
| Russell 2016      |                         |                         |
| Tauschmann 2016a  |                         |                         |
| Tauschmann 2016b  |                         |                         |
| Thabit 2015a      |                         |                         |
| Subtotal          |                         |                         |
| Test for heterogeneity: $\chi^2 = 9.27$, df=2, $P=0.30$, $I^2 = 17\%$ |   |   |
| Test for overall effect: $z=6.09$, $P=0.001$ |   |   |
| **Total (95% CI)** |                         |                         |
| Test for heterogeneity: $\chi^2 = 37.49$, df=4, $P=0.03$, $I^2 = 63\%$ |   |   |
| Test for overall effect: $z=5.65$, $P=0.001$ |   |   |
| Test for subgroup differences: $\chi^2 = 3.16$, df=1, $P=0.08$, $I^2 = 68.4\%$ |   |   |
*Studies with single hormone systems mainly used sensor augmented pump treatment as a comparator; those with dual hormone systems mainly used insulin pump treatment as a comparator.

These differences could explain wide prediction intervals that included zero values for most outcomes in trials using artificial pancreas over 24 hours; thus, related findings should be interpreted with caution. By contrast, strong evidence indicated that overnight use of artificial pancreas would be beneficial for outcomes regarding time in normoglycaemia, hyperglycaemia, or hypoglycaemia (95% prediction intervals excluding zero values), suggesting that this treatment effect can be expected in future patients.

**Implications**

Our study highlights some pitfalls in the conduct and reporting of artificial pancreas trials. Many trials had a short duration or were designed to assess the feasibility or safety, rather than long-term effectiveness. Despite existing guidance, we noted significant variation in outcomes assessed and metrics used.72 73 Research groups should report a minimum set of agreed outcome measures and respective metrics.71 To ensure the clinical relevance and feasibility of this core outcome set, it is crucial that its development involves all key stakeholders, including patients, their families, clinicians, researchers, statisticians, methodologists, industry representatives, regulatory authorities, and funders. To maximise the yield of information and to facilitate analysis and synthesis of evidence overall, the use of a common repository for data on individual patients could be agreed on.72 73 Such repositories would facilitate free dissemination of raw trial data, allowing for replication of previous research findings using various analysis approaches (for example, a repeated measures analysis) of clinically relevant outcomes. Moreover, to enhance the external validity of evidence, future trials should broaden inclusion criteria and recruit more heterogeneous populations, including ethnic minorities.

The performance of current artificial pancreas systems could be enhanced by the optimisation of system components. Use of novel insulin analogues with faster pharmacokinetics,74 the development of...
glucagon preparation stable at room temperature, and integration of artificial pancreas components into one device could further enhance user experience and artificial pancreas usefulness, and thus increase uptake. Future research should explore the potential differences between individual components (algorithms, continuous glucose monitoring) and determine their clinical relevance.

Upcoming trials should clarify the differences between single hormone and dual hormone systems, and explore artificial pancreas use in relevant groups of people with type 2 diabetes such as those with inpatient hyperglycaemia.75 Moreover, the effect of artificial pancreas use on quality of life and on reducing patient burden should be further explored,76 considering that patients with type 1 diabetes and their carers have shown a positive attitude towards artificial pancreas systems.77,79 Finally, to support adoption, cost effectiveness should be assessed to allow for reimbursement by various healthcare systems, and ensure that adequate infrastructure exists.

Conclusions

Our systematic review and meta-analysis has shown that artificial pancreas systems are an efficacious and safe treatment approach for people with type 1 diabetes, leading to increased time in near normoglycaemic range, and reduced time in hypoglycaemia and hyperglycaemia. The results were verified for all types of artificial pancreas and in all sensitivity analyses. Further research with rigorous studies, cooperation of research groups in terms of outcome reporting, and cost effectiveness data are required to verify these findings and support adoption of artificial pancreas systems in clinical practice.

Contributors: EB, HT, and AT conceived and designed the study. EB and EA did the scientific literature search. EB, KK, EA, and AT did literature screening. EB, EA, TK, and AT extracted data. EB, EA, AT did quality assessment of the included studies. EB, TK, A-BH, RH, and AT did the analyses. EB, KK, HT, MT, TK, RH, and AT wrote the first draft of the report. All authors contributed to interpretation and edited the draft report. AT is the study guarantor, had full access to all the trial level data in the study, takes responsibility for the integrity of the data, and accuracy of the data analysis, and had the final responsibility to submit for publication.

Funding: The study was partly funded by the Aristotle University Research Committee (ELKE AUTH), and supported by the National Institute for Health Research Cambridge Biomedical Research Centre and Wellcome Strategic Award (100574/2/12/2). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the Aristotle University Research Committee, National Institute for Health Research Cambridge Biomedical Research Centre, and Wellcome Strategic Award for the submitted work; KK reports honorarium fees from Medtronic, Novo Nordisk, and Sanofi outside the submitted work. MT reports personal fees from Medtronic and Novo Nordisk outside the submitted work; RH reports personal fees from Eli Lilly, Novo Nordisk, B Braun, and Medtronic, grants from the National Institute for Health Research Cambridge Biomedical Research Centre, and Wellcome Strategic Award outside the submitted work, and reports patents and patent applications; AT reports honorarium fees from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval not required.

Data sharing: No additional data available.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/.
Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol 2002;31:140-9. doi:10.1093/ije/31.1.140

Ding H, Hu GL, Zheng YX, Chen Q, Threakle DE, Zhou ZH. The method quality of cross-over studies involved in Cochrane Systematic Reviews. PLoS One 2015;10:e0120519. doi:10.1371/journal.pone.0120519

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34. doi:10.1136/bmj.315.7109.629

Peter JS, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008;61:991-6. doi:10.1016/j.jclinepi.2007.11.010

Peter JS, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat Med 2007;26:4544-62. doi:10.1002/sim.2889

Bally L, Thabit H, Kojarz H, et al. Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol 2017;5:261-70. doi:10.1016/S2213-8587(17)30001-3

Bjister T, Muller I, Remus K, et al. 60 hours hybrid-closed-loop (HCL) artificial pancreas for fully automated glucose control at home. Diabetes Technol Ther 2015;17:1644-50. doi:10.2337/dct.15-0883

Brown SA, Breton MD, Anderson SM, et al. Overnight closed-loop control improves glycemic control in a multicenter study of adults with type 1 diabetes. J Clin Endocrinol Metab 2017;102:3674-82. doi:10.1210/jc.2017-00556

Cherlavsky DR, DeBoer MD, Keith-Hynes P, et al. Use of an artificial pancreas across adolescents for a missed snack bolus and an underestimated meal bolus. Pediatr Diabetes 2016, 17.346. doi:10.1111/pedi.12230

de Bock MI, Roy A, Cooper MN, et al. Feasibility of outpatient 24-hour day-and-night glucose control with dual-hormone artificial pancreas. Diabetes Obes Metab 2015;3:939-47. doi:10.1111/pedi.12230

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Bias in meta-analysis: an open-label, randomised, crossover, controlled trial. Diabetes Care 2017;40:359-66. doi:10.2337/dc16-1794

Haidar A, Messier V, Legault L, Ladouceur M, Rabasa-Lloret R. Outpatient 60-hour day-and-night glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or sensor-augmented pump therapy in adults with type 1 diabetes: An open-label, randomised, crossover, controlled trial. Diabetes Obes Metab 2017;19:713-20. doi:10.1111/dob.12880

Hovorka R, Eller 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. doi:10.2337/dc13-2644

Kong JS, Rota C, Buckingham BA, Clinton P, Kovatchev BP, Anderson SM. Restoration of hypoglycemia awareness with closed-loop therapy. Diabetes 2017;66(suppl 1):A94-5.

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. doi:10.2337/dc13-2076

Kropp DJ, DelFavero S, Defalco B, Johnson GW, Blomgren H. Day and night closed-loop control with a Diabetes Care Med. 2015;17:1931-7. doi:10.2337/dc13-3911

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;37:2310-6. doi:10.2337/dc14-1014

Niymi 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. doi:10.2337/dc14-0835

Pham NV, Kaptoge S, Balkau B, et al. Current use of home glucose monitoring in type 1 diabetes: a multinational, multinational, single blind, randomized trial. Diabetes Technol Ther 2015;17(A97).

Pham NV, Kaptoge S, Balkau 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 Technol Ther 2015;17:1201-7. doi:10.1089/dia.2015.0431

Russell SJ, Hillard MA, Balliro C, et al. Day and night closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Technol Ther 2014;371:313-25. doi:10.1056/NEJMoa1314474

Kropp DJ, DelFavero S, Defalco B, Johnson GW, Blomgren H. Day and night closed-loop control with a Diabetes Care Med. 2015;17:1931-7. doi:10.2337/dc13-3911

Niymi R, Bhatia N, Kondounori O, et al. MD-Logic overnight type 1 diabetes control in home settings: multicenter, multinational, single blind, randomized trial. Diabetes Obes Metab 2017;19:53-61. doi:10.1111/pedi.12603

Philip M, Batteine T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas. N Engl J Med 2013;368:824-33. doi:10.1056/NEJMoa1206881

Renard E, Tubiana-Rufi N, Bonnemaison-Gilbert E, et al. Closed-loop outperforms threshold-low-glucose suspend insulin delivery on glucose control in prepubertal outpatients with type 1 diabetes. Diabetes 2017;66(suppl 1):A79.

Russell SJ, El-Kabbath PH, Sinha M, et al. Patient-outcome glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2017;377:186-7. doi:10.1056/NEJMoa1711646.

Russell SJ, Hillard MA, Balliro C, et al. Day and night glycemic control with a bionic pancreas versus conventional insulin pump therapy in prepubertal children with type 1 diabetes: a randomized crossover study. Lancet Diabetes Endocrinol 2016;4:233-43. doi:10.1016/S2213-8587(15)00489-1

Schierloh U, Wilinska M, Thabit H, et al. Validation of a closed-loop artificial pancreas among adolescents for a missed snack bolus and an underestimated meal bolus. Pediatr Diabetes 2016;17:1931-7. doi:10.1111/pedi.12603
62 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;2:701-9. doi:10.1016/S2213-8587(14)70114-7

63 Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. *N Engl J Med* 2015;373:2129-40. doi:10.1056/NEJMoa1509351

64 Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2017;19:155-63. doi:10.1089/dia.2016.0421

65 Bekian E, Karagannis T, Haidich AB, Tsapas A. Meta-analysis of artificial pancreas trials: methodological considerations. *Lancet Diabetes Endocrinol* 2017;5:685. doi:10.1016/S2213-8587(17)30261-9

66 Agiostatidou G, Anhalt M, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M and Harry B Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care* 2017;40:1622-30. doi:10.2337/dc17-1624

67 Barnard KD, Hood KK, Weissberg-Benchell J, Aldred C, Oliver N, LaFell L. Psychosocial assessment of artificial pancreas (AP): commentary and review of existing measures and their applicability in AP research. *Diabetes Technol Ther* 2015;17:295-300. doi:10.1089/dia.2014.0305

68 Elleri D, Acerini CL, Allen JM, et al. Parental attitudes towards overnight closed-loop glucose control in children with type 1 diabetes. *Diabetes Technol Ther* 2010;12:35-9. doi:10.1089/dia.2009.0084

69 van Bon AC, Brouwer TB, von Basum G, Hoekstra JB, DeVries JH. Future acceptance of an artificial pancreas in adults with type 1 diabetes. *Diabetes Technol Ther* 2011;13:731-6. doi:10.1089/dia.2011.0013

**Web appendix:** Appendices