REVIEW

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Glucose control and psychosocial outcomes with use of automated insulin delivery for 12 to 96 weeks in type 1 diabetes: a meta-analysis of randomised controlled trials

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Abstract

Background Glycaemic control of Type 1 Diabetes Mellitus (T1DM) remains a challenge due to hypoglycaemic episodes and the burden of insulin self-management. Advancements have been made with the development of automated insulin delivery (AID) devices, yet, previous reviews have only assessed the use of AID over days or weeks, and potential benefits with longer time of AID use in this population remain unclear.

Methods We performed a systematic review and meta-analysis of randomised controlled trials comparing AID (hybrid and fully closed-loop systems) to usual care (sensor augmented pumps, multiple daily insulin injections, continuous glucose monitoring and predictive low-glucose suspend) for adults and children with T1DM with a minimum duration of 3 months. We searched PubMed, Embase, Cochrane Central, and Clinicaltrials.gov for studies published up until April 4, 2023. Main outcomes included time in range 70–180 mg/dL as the primary outcome, and change in HbA1c (%, mmol/mol), glucose variability, and psychosocial impact (diabetes distress, treatment satisfaction and fear of hypogly-caemia) as secondary outcomes. Adverse events included diabetic ketoacidosis (DKA) and severe hypoglycaemia. Statistical analyses were conducted using mean differences and odds ratios. Sensitivity analyses were performed according to age, study duration and type of AID device. The protocol was registered in PROSPERO, CRD42022366710.

Results We identified 25 comparisons from 22 studies (six crossover and 16 parallel designs) including a total of 2376 participants (721 in adult studies, 621 in paediatric studies, and 1034 in combined studies) which were eligible for analysis. Use of AID devices ranged from 12 to 96 weeks. Patients using AID had 10.87% higher time in range [95% CI 9.38 to 12.37; p < 0.0001, $l^2 = 87\%$) and 0.37% (4.77 mmol/mol) lower HbA1c (95% CI – 0.49% (– 6.39 mmol/mol) to – 0.26 (– 3.14 mmol/mol); p < 0.0001, $l^2 = 77\%$]. AID systems decreased night hypoglycaemia, time in hypoglycaemia. No difference was found regarding treatment satisfaction or fear of hypoglycaemia. Among children, there was no difference in glucose variability or time spent in hypoglycaemia between the use of AID systems or usual care. In sensitivity analyses, results remained consistent with the overall analysis favouring AID.

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Conclusion The use of AID systems over 12 weeks, regardless of technical or clinical differences, improved glycaemic outcomes and diabetes distress without increasing the risk of adverse events in adults and children with T1DM.

Keywords Closed-loop, Automated insulin delivery, HbA1c, TIR, Time in range, Hypoglycaemia, Glucose control, Diabetes technology, Type 1 diabetes, T1DM

Background

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease, characterised by the progressive destruction of pancreatic beta cells [1, 2]. Intensive insulin treatment is the current standard of care for T1DM. Unfortunately, the proportion of patients achieving a controlled HbA1c and their time in range (TIR) glycaemic level is low. A large proportion of individuals with type 1 diabetes are unable to meet recommended glycaemic targets [3, 4] and severe hypoglycaemia is a recurrent problem [5].

Since the 1960s, several automated insulin delivery (AID) systems have been developed. The goal of such devices is to achieve better glycaemic control, reduce glucose variability, and decrease the risk of micro and macrovascular complications as well as treatment distress [6]. An AID system consists of three components: a continuous glucose monitor (CGM), a pump able to continuously deliver insulin, and a computer algorithm controlling insulin delivery through glucose-responsive feedback [7]. In the last 15 years, multiple closed-loop (CL) systems were developed, such as predictive low-glucose suspend (PLGS) systems, hybrid closed-loop (HCL) systems, and fully closed-loop (FCL) systems, however, their longterm impact on clinical and functional outcomes is still unclear. Previous randomised controlled trials (RCTs) have obtained variable conclusions. While some showed no significant difference in mean overnight blood glucose when comparing CL and Sensor-augmented Insulin Pump (SAP) in adults [8], adolescents [9], and children [10], others showed no difference in time spent in hypoglycaemia [11]. Recent trials using more advanced AID systems have demonstrated better therapeutic efficacy regarding HbA1c levels and TIR [12].

During the last decade, several meta-analyses of RCTs have been reported and show encouraging results on the effectiveness of AID devices in optimising glycaemic control, but assessments have only focused on studies with limited time of AID use, mostly hours or days [13]. To our knowledge, only one published meta-analysis with 11 RCTs has discussed the potential of these devices up to 8 weeks of use [14]. However, no previous meta-analysis has exclusively assessed studies with over 12 weeks of AID use, which is a more appropriate period of time to properly detect changes in HbA1c levels [15]. Furthermore, we did not find any meta-analyses assessing

the longer use of AID systems according to different age groups compared to usual care (UC), which currently represents the use of multiple daily insulin injections (MDII), SAP, CGM or PLGS. Lastly, severe adverse events (AEs) and psychosocial outcomes, which can influence clinical decisions, have not yet been assessed in the setting of longer and continuous use of AID systems.

In this updated systematic review and meta-analysis, our objective was to investigate the impact of AID systems compared to UC on glucose control, as well as treatment satisfaction and distress based on the evidence from RCTs with a duration above 12 weeks. We aimed to determine whether the use of AID systems improved TIR, HbA1c, and glycaemic variability, reduced AEs, and impacted psychosocial outcomes from a functional perspective.

Methods

This review was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement and recommendations of the Cochrane Collaboration Handbook for Systematic Reviews of Interventions [16]. The protocol of this metaanalysis was registered on PROSPERO on October 22, 2022 (ID CRD42022366710).

Search strategy

We systematically searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials. gov databases up to April 4, 2023, using terms such as: 'Type 1 Diabetes', 'T1DM', 'closed-loop', 'automated insulin delivery', 'AID', 'randomized' and 'RCT'. The complete search strategy is available in Supplementary Appendix A. No filters or language restrictions were applied in our search. Grey literature was not searched. We also utilised a technique of backward snowballing, searching for additional eligible studies through a review of the references from prior publications [17]. Three authors performed the literature search independently (AG, AM, and LH) following predefined search criteria. Eventual conflicts were resolved by consensus among the authors.

Study selection

The research question was defined according to the PICOTT framework and studies were included in the

systematic review if they met the following eligibility criteria: (1) enrolling adult or paediatric patient population with T1DM; (2) comparing CL systems with UC; (3) assessing any of the outcomes of interest; (4) RCTs with parallel or crossover designs; and (5) with a minimum duration of at least 12 weeks. We included both hybridloop and fully CL systems in our analysis. UC was considered to include SAP, MDII, CGM, or PLGS. A full description of the current insulin devices can be found in Additional file 1: Table S1.

We excluded studies with overlapping patient populations, understood as derived from overlapping institutions, patients and recruitment periods, and clinical trials with no results after contacting the primary investigator. Additionally, crossover studies with less than 12 weeks of washout periods were excluded from the analysis of change in HbA1c (%), unless outcomes from each phase of the study were reported. In this case, only phase 1 results were included in our HbA1c analysis. If two or more studies with overlapping populations reported different outcomes of interest, they were included if these could be analysed in a non-overlapping manner.

Data collection and extraction

Two authors (AG and EMHP) extracted outcome data independently using a standardised document and disagreements were resolved by consensus. Four corresponding authors were contacted for additional data (one provided the information). Furthermore, three independent authors (IRM, VCSM and ACS) extracted additional baseline data for individual studies, including study and patient characteristics (Tables 1, 2). Participant-level data was not requested.

For studies reporting data for paediatric and adult patients separately, we planned to analyse these as separate comparisons. For crossover studies, we planned a priori to analyse group means and standard deviations, assuming no correlation between groups (as parallel study designs). The bias introduced with this assumption is generally conservative [18]. For missing means data, we used the formula proposed by Wan et al. [19] using medians and interquartile ranges as recommended by the Cochrane Collaboration [18]. We collected adjusted mean differences (MD) as originally reported in each study when available.

Outcome measurements

Our main outcomes were TIR 70-180 mg/dL as the primary outcome and HbA1c (%) change. Secondary outcomes of interest included coefficient of glucose variability (CV), % time < 70 mg/dL, % time < 54 mg/dL, nocturnal hypoglycaemia (< 70 mg/ dL), and %time > 250 mg/dL. We assessed the following psychosocial outcomes: Hypoglycaemia Fear Survey (HFS) [20]; Diabetes Treatment Satisfaction Questionnaire (DTSQ) [21]; treatment distress measured by the scales Diabetes Distress Scale (DDS) [22] and Problem Areas in Diabetes (PAID) [23]. Safety endpoints included diabetic ketoacidosis (DKA) and severe hypoglycaemia.

Quality assessment

Each included study was appraised using the Cochrane Risk of Bias Assessment Tool (RoB-2) for RCTs [24] by at least two independent investigators (AG, CH, IS, and CG). Further, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was employed by two independent authors (IAM and IRM) using the GRADEpro Guideline Development Tool [25] to evaluate the level of certainty of the evidence in this meta-analysis, with categorizations ranging from high to very low [26]. Any disagreements were discussed and resolved through a consensus.

Statistical analysis

Binary adverse outcomes were summarised using the Mantel–Haenszel test, with an odds ratio (OR) and 95% confidence interval (CI) as a measure of effect size. Continuous outcomes were compared with weighted and standardised MDs. Statistical heterogeneity was assessed by I^2 and sources of heterogeneity were sought if I^2 was greater than 50%. When low heterogeneity was identified ($I^2 < 25\%$), a fixed-effects model was used. We performed sensitivity analyses using the leave-one-out strategy as well as Baujat plots. We further investigated causes of heterogeneity by performing subgroup analyses according to type of AID device.

In addition, a random effect meta-regression analysis was performed to assess the impact of baseline HbA1c and study duration on overall MD. Publication bias was assessed for HbA1c and TIR 70–180 mg/dL through the generation of a funnel plot and Egger's test, where a p-value less than 0.05 indicates the presence of publication bias. Review Manager 5.4.1 software (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and RStudio version 4.1.2 (R Foundation for Statistical Computing) were used for the statistical analysis.

Role of the funding source

There was no funding source for this study. AG and EMHP had full access to all the data in the study and all authors had responsibility for the final publication.

Table 1 Baseline qualitative characteristics of included studies

Study	NCT ID	Country	Intervention	Control	Population	Primary outcome	Outcomes measured ^a
Abraham [26]	ACTRN12616000753459	Australia	MiniMed 670G	MDI/SAP therapy	Adults and Children	TIR 70–180 mg/dL	Clinical and functional
ADAPT (Choudhary [27])	NCT04235504	France, Ger- many And UK	MiniMed 670G	MDI therapy	Adults	Change in HbA1c	Clinical and functional
APCam11 (Tauschmann [28])	NCT02523131	USA and UK	Modified FlorenceM	SAP therapy	Adults and children	TIR 70–180 mg/dL	Clinical and functional
AP@home (Thabit [29])	NCT01778348 + NCT01961622	UK, Germany and Austria	FlorenceD2A and Flor- enceD2W	SAP therapy	Adults and children	TIR 70–180 mg/dL for adults and TIR 70–145 mg/ dL for children and adolescents	Clinical
Boughton [30]	NCT04025762	UK and Aus- tria	CamAPS FX	SAP therapy	Adults	TIR 70–180 mg/dL	Clinical
Brown [31]	NCT03591354	USA	t:slim X2 with control- IQ	PLGS therapy	Adults	TIR 70–180 mg/dL	Clinical
Burnside [32]	ACTRN12620000034932	New Zealand	AndroidAPS 2.8	SAP	Adults and children	TIR 70–180 mg/dL	Clinical
DAN05 (Ware [33],Hood [46])	NCT02925299	UK and USA	FlorenceM or CamAPS FX	SAP therapy	Children	Change in HbA1c	Clinical and functional
DAN06 (Boughton [34])	NCT02871089	UK	FlorenceM/ CamAPS FX	MDI therapy	Children and adoles- cents	AUC for the plasma C-peptide	Clinical
DCPL3 (Brown [<mark>35</mark>], Kudva [47])	NCT03563313	USA	t:slim X2 with Control- IQ	SAP therapy	Adults and children	TIR 70–180 mg/dL	Clinical and functional
DCLP4 (Pin- sker [36])	NCT04436796	USA	Interoperable artificial pan- creas system (iAPS)	SAP/PLGS therapy	Adults	TIR 70–180 mg/dL	Clinical and functional
DCLP5 (Breton [37], Cobry [48])	NCT03844789	USA	t:slim X2 with control- IQ	SAP/PLGS therapy	Children	TIR 70–180 mg/dL	Clinical and functional
DIABELOOP WP7 (Ben- hamou [38])	NCT02987556	France	Diabeloop Generation 1 (DBLG1)	SAP therapy	Adults	TIR 70–180 mg/dL	Clinical and functional
iDCL (Kovatchev [39])	NCT02985866	USA	Control-IQ	SAP therapy	Adults	Time below 70 mg/dL and above 180 mg/ dL	Clinical
Garg [40]	NCT02748018	USA and Canada	MiniMed 670G hybrid closed loop	CSII	Children, adolescents and adults	Group 1: change in HbA1c Group 2: reducing %TBR < 70 mg/dL	Clinical and functional
Matejko [7]	NCT04616391	Poland	MiniMed 780G	MDI therapy	Adults	TIR 70–180 mg/dL	Clinical and functional
McAuley [41]	ACTRN12617000520336	Australia	MiniMed 670G	MDI/SAP therapy	Adults	TIR 70–180 mg/dL	Clinical and functional
ORACL (McAuley [42])	ACTRN126190000516190	Australia	MiniMed 670G	SAP therapy	Adults	TIR 70–180 mg/dL	Clinical and functional
PEDAP trial (Wadwa) [43])	NCT04796779	USA	T:slim X2 with Control- IQ	MDI/SAP therapy	Children	TIR 70–180 mg/dL	Clinical
Reiss [44]	NCT03428932	USA	MiniMed 670G	MDI/SAP therapy	Children	Metrics of gray matter	Clinical and functional

Table 1 (continued)

Study	NCT ID	Country	Intervention	Control	Population	Primary outcome	Outcomes measured ^a
Russell [11]	NCT04200313	USA	iLet device	PLGS/SAP/ MDI therapy	Adults and children	Change in HbA1c	Clinical
Ware [45]	NCT03784027	Austria, Germany, Luxembourg and UK	CamAPS FX	SAP therapy	Children	TIR 70–180 mg/dL	Clinical

CGM Continuous glucose monitor, TIR Time in Range, MDI Multiple Daily Injections, SAP sensor augmented pump, AUC Area under the curve, PLGS, Predictive lowglucose suspend system, HbA1c Glycated Hemoglobin, UK United Kingdom, USA United States of America

^a Functional outcomes include participant-reported questionnaires/patients reported outcomes

Results

Our search identified a total of 3839 unique studies, of which 25 reports from 22 RCTs, including 2376 randomised participants, fulfilled the study eligibility criteria (Fig. 1) [27]. Of the 25 reports identified, 22 assessed primarily clinical outcomes [8, 12, 28–47], while 3 studies [48–50] assessed solely patient-reported outcomes.

Characteristics of included studies

Characteristics of studies contributing data to this metaanalysis are presented in Tables 1 and 2. The trials were conducted across eight countries spanning three continents. Seventeen studies had a parallel-group design, while five were crossover studies. Most RCTs included only adults (n=9), while a similar number included only children (n=6) or mixed both adults and children (n=7). Females comprised 46.6% (n=1068) of the included population. The mean age of adult participants ranged from 32 to 68 years, and of paediatric participants ranged from 3.8 to 15.4 years. The mean duration of T1DM ranged from 1 to 38 years, with a mean Body Mass Index ranging from 18.9 to 29.1 kg/m², and a baseline HbA1c ranging from 6.9 to 10.7%. Among the 19 included trials, four (n=380) assessed the use of CamAPS FX (CamDiab) [31, 36, 38, 46]; five (n=636) assessed MiniMed 670G (Medtronic) [28, 34, 43, 44, 46]; five (n=605) assessed t:slim X2 with Control IQ (Tandem) [33, 35, 36, 38, 45]; two (n=144) assessed Modified Florence [30, 31]; two (n=119) assessed MiniMed 780G (Medtronic) [8, 29]; two assessed openAPS (n=129) [34, 41]; one (n=63)assessed DBLG1 (Dbl-diabetes) [40]; and one (n=219)assessed iLet Bionic Pancreas (Beta Bionics) [12]. Duration of CL or UC use ranged from 12 to 96 weeks.

Effects on glucose control

In a pooled analysis of 19 studies (n=2210) for the primary outcome displayed in Fig. 2A and Table 3, treatment with CL systems led to a significant decrease in HbA1c % (MD - 0.37; 95% CI - 0.49 to - 0.26; p<0.0001) and mmol/mol (MD - 4.77; 95% CI - 6.39 to - 3.14;p<0.001), for adults (MD - 0.38; 95% CI - 0.63 to -0.12; p = 0.004), children (MD -0.31; 95% CI -0.44to -0.19; p < 0.001) and mixed populations (MD -0.46; 95% CI - 0.56 to - 0.30; p < 0.0001). There was a high statistical heterogeneity for the overall ($I^2 = 77\%$), adult $(I^2=88\%)$, and mixed analyses $(I^2=62\%)$, but not for children ($I^2 = 0\%$). In the overall analysis of 22 studies (n=2499), there was also a significant 10.87% increase in TIR 70-180 mg/dL for the CL group when compared to UC (95% CI 9.38 to 12.37; p<0.0001; Fig. 2B), which was similarly seen in adults (MD 11.69; 95% CI 8.65 to 14.62; p<0.0001), children (MD.9.97; 95% CI 8.36 to 11.58; p < 0.0001) and mixed populations (MD 11.21; 95% CI.9.39 to 13.03; p < 0.0001). Statistical heterogeneity was high $(I^2 = 81\%)$, but decreased in the children subgroup $(I^2 = 38\%).$

Further analyses for glycaemic control significantly favoured the use of CL systems for endpoints of CV (MD -1.09; 95% CI -1.80 to -0.39; p=0.0007; Fig. 3A), % time < 70 mg/dL (MD - 0.65; 95% CI - 1.05 to - 0.26; p=0.009), % time<54 mg/dL (MD - 0.14; 95% CI -0.22 to -0.07; p<0.0001), % time>250 mg/dL (MD − 4.46; 95% CI − 5.79 to − 3.14; p < 0.0001), and nocturnal hypoglycaemia (MD - 1.28; 95% CI - 1.76 to - 0.79; p < 0.0001; Fig. 3B). No significant differences were found for the use of CL in children for % time < 54 mg/dL (p=0.32); <70 mg/dL (p=0.62); and CV (p=0.88) when compared to UC. Further detailed findings for age subgroups can be seen in Table 3. As shown in Fig. 4, the rate of episodes of DKA (Additional file 1: Figure S1A) and severe hypoglycaemia (Additional file 1: Figure S1B) was not significantly different between groups (p=0.31 andp = 0.32, respectively).

Effects on psychosocial outcomes

The pooled analysis for patient-reported outcomes found decreased diabetes distress for the CL group (SMD

Study	Patient No, I/C	Female %, I/C	Age, years, I/C ^d	Duration of assessment, wks	Study design	Baseline HbA1c, % (mmol/mol) ^d	Duration of diabetes, years ^d	BMI, kg/m ^{2d}	Baseline daily insulin dose, units/kg ^d
Abraham [26]	67/68	55/57	15.2±3.3/15.4±3.0	24	Parallel	8.0±1.0 (64±10)/7.9±1.0 (63±11)	7.9±4.2/7.6±3.4	0.7±0.8/0.7±0.7 ^c	0.8±0.2/0.9±1.2
ADAPT (Choud- hary [27])	41/41	54/39	41.5±11.63/39.7±13.12	24	Parallel	9.0±1.0 (75.7±7.83)/9.1±0.7 (74.9±10.64)	18.8±11.4/18.1±10.0	27.0±4.4/25.8±4.9	54.3±25.9/53.3±22.3 ^e
APCam11 (Tauschmann [28])	46/40	48/55	22 (13–36)/21 (11–36) ^a	12	Parallel	8.3±0.6(68±7)/8.2±0.5 (66±5)	13 (7–20)/10 (7–19) ^a	28±4)/27±3	0.76±0.25/0.69±0.8
AP@home (Thabit [29]) ^b	33/ 25	45/44	40.0±9.4/12.0±3.4	12	Crosso- ver	$8.5 \pm 0.7 (69 \pm 7)/8.1 \pm 0.9$ (65 ± 10)	20.9±9.3/4.7±2.6	25.5±4.4/18.9±3.5	0.62±0.15/0.89±0.24
Boughton [30]	20/17	40/47	68(63–70)/67 (62–70) ^a	16	Crosso- ver	7.5 ± 1.0 (57 ± 10)/7.4 ± 0.9 (58 ± 10)	38 (32–48)/38 (32–48) ^a	28.2 (25.4–31.7)/27.4 (24.9–38.5) ^a	45.8 (38.3–51.1)/40.0 (35.4–62.4) ^e
Brown [31]	54/55	52/45	32±14/34±17	13	Parallel	7.0 ± 0.8 (54 ± 8.5)/7.1 ± 0.8 (54 ± 8.4)	18±8.3/16±7.3	26 (23, 30)/25 (23, 29) ^a	0.59 (0.49, 0.86)/0.68 (0.46, 0.93) ^a
Burnside [32]	44/53	52/48	26.59±14.33/23.29±17.51	24	Parallel	7.55 (60.0±13.7)/7.65 (62.1±9.1) ^f	15.20±13.42/12.33±11.82	24.40 ± 5.86/23.67 ± 6.42	44.6±16.17/43.01±17.36
DAN05 (Ware [33], Hood [46]	65/68	57/57	13.1±2.6/12.8±2.9	24	Parallel	8.2 ± 0.7 (66 ± 8)/8.3 ± 0.8 (67 ± 8) ^c	6.3 ± 3.3/6.6 ± 3.1	$0.35 \pm 0.86/0.58 \pm 0.89^{\circ}$	0.93±0.23/0.95±0.24
DAN06 (Boughton [34])	51/46	49/39	12±2/12±2	96	Parallel	10.7±1.8 (93±18)/10.5±1.6 (94±20)	Ϋ́Α	53±29/51±34 ⁹	0.87±0.33/0.82±0.38
DCPL3 (Brown [35], Kudva [47])	112/56	48/54	33±16/33±17	24	Parallel	7.4 ± 1.0/7.4 ± 0.8	17 (8, 28)/15 (7, 23) ^a	25 (23, 29)/25 (22, 28) ^a	46 (31, 62)/45 (35, 61) ^{a,e}
DCLP4 (Pinsker 2022) [36])	18/16	36.8/56.3	41 ± 16/37 ± 15	13	Crosso- ver	6.9±1.0	18 (12, 29) ^a	28±5	NA
DCLP5 (Breton [37], Cobry [48])	78/23	49/52	11.3±2.0/10.8±2.4	16	Parallel	7.7 ± 1.1/8.0 ± 1.1	5.0±2.8/6.0±2.8	$0.4 \pm 1.0/0.5 \pm 1.0^{c}$	0.89±0.24/0.94±0.24
DIABELOOP WP7 (Ben- hamou [38])	32/31	62	48.2±13.4	12	Crosso- ver	7.6±0.9 (59.4±9.8)	28.0±13.6	24.8±3.5	36.3±8.9 ^e
iDCL (Kovatchev [39])	65/62	49/45	33±16/32±14	12	Parallel	7.4 ± 0.9 (57 ± 9.8)/7.4 ± 0.8 (57 ± 8.7)	19 (7, 27)/16 (11, 27) ^a	27 (24, 31)/25 (23, 29) ^a	0.73±0.22/0.68±0.25
Garg [40]	151/151	47/62	39.9±19.8/35.7±18.4	24	Parallel	8.2 ± 1.3/8.1 ± 1.2	21.5±13.6/19.6±13.1	26.8±5.8/27.0±6.9	NA
Matejko [7]	20/17	40/47·1	39.8±8.3/40.9±7.8	12	Parallel	7.05±0.8 (54±9)/7.4±1.2 (57±13)	17.1 ± 12.2/17.6 ± 12.2	24.5±3.3/25.6±2.64	NA

 Table 2
 Baseline quantitative characteristics of included studies

Study	Patient No, I/C	Female %, I/C	Age, years, I/C ^d	Duration of assessment, wks	Study design	Baseline HbA1c, % (mmol/mol) ^d	Duration of diabetes, years ^d	BMI, kg/m ^{2d}	Baseline daily insulin dose, units/kg ^d
McAuley 2020 [41]	61/59	54/53	43.7±11.7/44.7±11.8	26	Parallel	7.4±0.9 (62±12)/7.5±0.8 (61±10)	24.0±12.0/24.1±12.5	26.8±5.3/26.0±4.0	0.51 (0.41, 0.63)/0.54 (0.45, 0.66) ^a
ORACL (McAu- ley [42])	15/15	63	67±5	16	Crosso- ver	7.6 ± 0.9 (58 ± 7)	38 (20–47) ^a	27.6 (26.4–31.0) ^a	0.55 (0.41–0.66) ^a
PEDAP trial (Wadwa [43])	68/34	49/56	3.84±1.23/4.06±1.25	13	Parallel	7.5 ± 1.2/7.7 ± 0.9	1.04 (0.71·1.85)/1.40 (0.91,2·11)	81 (57,94)/77 (56,9) ^g	0.66±0.17/0.66±0.23
Reiss [44]	21/21	40/47	14-17	24	Parallel	8.7/ 8.45 ^f	NA	NA	NA
Russell [11]	147/72	49/38	28±19/28±20	13	Parallel	7.9±1.2/7.7±1.1	16±14/18±15	28.9±5.5/29.1±6.9	0.75 (0.57, 1.00)/0.75 (0.56, 0.94) ^a
Ware [45]	39/35	54/29	5.6±1.4/5.6±1.7	16	Crosso- ver	7.3±0.7 (56.3±7.4)/7.4±0.6 (57±7.1)	2.5±1.7/2.7±1.9	67.3±23.2/71.1±24.6 ⁹	0.76 (0.67–0.83)/0.77 (0.69–0.86) ^a

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	2
	-
	Z
	2

^a Median (IQR)

^b Data are reported as *Adults/Children and Adolescents*

^c Reported as Body-mass index Z score

 $^{\rm d}$ Reported values as mean \pm SD unless specified

 $^{\rm e}$ Values are reported in units per day, not units/kg

^f No SD available

⁹ Age and sex-adjusted BMI percentile

Table 2 (continued)



Fig. 1 PRISMA flow of study selection

- 0.18; 95% CI - 0.34 to - 0.03; p=0.02; Fig. 4A), but no significant differences for fear of hypoglycaemia (p=0.11, Fig. 4B) and treatment satisfaction (p=0.83, Fig. 4C).

Risk of bias in included studies

The risk of bias assessment of each RCT is provided in the Additional file 1: Appendix A for clinical (Additional file 1: Figure S3) and functional (Additional file 1: Figure S4) outcomes. For clinical outcomes, three were rated as "some concerns" due to missing outcome data [7] and deviations from the protocol (machine errors) [35, 40], and seven were rated as "high risk" due to lack of laboratory-measured HbA1c assessment [44, 46] or due to insufficient washout time [36, 38, 43, 47] in crossover studies. All trials were open-label but used adequate

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(A) HbA1c %

	Closed-loop	Usual Care		Mean Difference	Mean Difference
Mean Difference	SE Tota	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
-0.15 0.0	0918 63	63	6.1%	-0.15 [-0.33, 0.03]	
-0.23 0.0	0714 36	37	6.5%	-0.23 [-0.37, -0.09]	
-0.7 0.2	2041 22	26	3.9%	-0.70 [-1.10, -0.30]	
-1.42 0.1	1633 36	38	4.7%	-1.42 [-1.74, -1.10]	
0 0.1	1531 64	61	4.9%	0.00 [-0.30, 0.30]	
-0.57 0.1	1786 20	17	4.4%	-0.57 [-0.92, -0.22]	
-0.4 0	.102 61	59	5.9%	-0.40 [-0.60, -0.20]	
-0.1363 0.1	1804 15	15	4.4%	-0.14 [-0.49, 0.22]	
0.3 0	.279 18	16	2.8%	0.30 [-0.25, 0.85]	
	335	332	43.6%	-0.38 [-0.63, -0.12]	◆
8, df = 8 (P < 0.00001); l ²	² = 88%				
U4)					
-0.36 0.1	1888 46	39	4.2%	-0.36 [-0.73, 0.01]	
-0.4 0.2	2551 78	23	3.1%	-0.40 [-0.90, 0.10]	
-0.52 0.5	5357 20	27	1.1%	-0.52 [-1.57, 0.53]	
-0.25 0.3	3163 21	21	2.4%	-0.25 [-0.87, 0.37]	
-0.42 0	.102 68	34	5.9%	-0.42 [-0.62, -0.22]	
0 0.4	1531 73	74	4.9%	0.00 [-0.30, 0.30]	_ _
-0.317 0.1	1413 65	68	5.1%	-0.32 [-0.59, -0.04]	
	371	286	26.8%	-0.31 [-0.44, -0.19]	◆
df = 6 (P = 0.46); I ² = 0%	%				
0001)					
-0.27 0.1	1173 58	53	5.6%	-0.27 [-0.50, -0.04]	
-0.33 0).102 112	56	5.9%	-0.33 [-0.53, -0.13]	
-0.58 0.1	1327 151	151	5.3%	-0.58 [-0.84, -0.32]	
-0.57 0.0	0663 147	72	6.6%	-0.57 [-0.70, -0.44]	-
-0.36 0.0	0867 46 514	40 372	6.2% 29.6%	-0.36 [-0.53, -0.19] -0.43 [-0.56, -0.30]	→
df = 4 (P = 0.06); l ² = 56	5%				•
0001)					
	1220	990	100.0%	-0.37 [-0.49, -0.25]	•
3, df = 20 (P < 0.00001);	l ² = 77%			-	
0001)					-2 -1 0 1 2
59 df = 2 (P = 0.45) l^2 =	0%				Favours closed-loop Favours usual care
	Mean Difference -0.15 0. -0.23 0. -0.7 0. -0.72 0. -0.72 0. -0.72 0. -0.57 0. -0.1363 0. 0.3 0 0.3 0 0.3 0 -0.4 0. -0.4 0. -0.4 0. -0.4 0. -0.4 0. -0.4 0. -0.4 0. -0.42 0. -0.27 0. -0.317 0. 0.031 0. -0.325 0. -0.57 0. -0.36 0. 0.057 0. -0.36 0. 0.057 0. 0.051 0. 0.011 0. 0.021 0. <td< td=""><td>Closed-loop Mean Difference SE Total -0.15 0.0918 63 -0.23 0.0714 36 -0.7 0.203 0.0714 36 -0.7 0.203 0.0714 36 -0.7 0.203 0.0714 36 -0.7 0.1531 64 -0.57 -0.57 0.1633 0.164 15 -0.3 0.1786 20 -0.4 -0.4 0.102 61 -0.363 0.79 18 3, df = 8 (P < 0.00001); P = 88%</td> 335 34 -0.4 0.2551 720 -0.25 0.3537 200 -0.25 0.3537 20 -0.25 0.3163 21 -0.42 0.102 68 -0.4 0.2551 73 -0.33 0.102 68 -0.33 0.102 112 -0.58 0.1327 151 -0.57 0.0663 147 -0.36 0.0867 46</td<> <td>Closed-loop Usual Care Mean Difference SE Total -0.15 0.0918 63 63 -0.23 0.0714 36 37 -0.7 0.2041 22 26 -1.42 0.1633 36 38 0 0.1531 64 61 -0.57 0.1786 20 17 -0.4 0.102 61 59 -0.1363 0.1804 15 15 0.3 0.279 18 16 0.3 0.279 18 16 0.3 0.279 18 16 0.3 0.279 18 16 0.053 720 27 -0.25 0.3557 20 27 -0.25 0.3557 20 27 -0.25 0.363 21 21 -0.4 0.2551 73 74 -0.317 0.1413 65 68 -0.58 0.1327</td> <td>Closed-loop Usual Care Mean Difference SE Total Weight -0.15 0.0918 63 63 6.1% -0.23 0.0714 36 37 6.5% -0.7 0.2041 22 26 3.9% -1.42 0.1633 36 38 4.7% 0 0.1531 64 61 4.9% -0.57 0.1786 20 17 4.4% -0.4 0.102 61 59 5.9% -0.1363 0.1804 15 15 4.4% -0.3 0.279 18 16 2.8% 335 332 43.6% 12 12.4% -0.4 0.2551 72 27 1.1% -0.52 0.3537 20 27 1.1% -0.25 0.3163 21 21 2.4% -0.4 0.2551 73 74 4.9% -0.33 0.102 <td< td=""><td>Closed-loop Usual Care Mean Difference SE Total Volage V, Random, 95% CI -0.15 0.0918 63 6.1% -0.15 [-0.33, 0.03] -0.23 0.0714 36 37 6.5% -0.23 [-0.37, -0.09] -0.7 0.2041 22 26 3.9% -0.70 [-1.10, -0.30] -1.42 0.1633 36 38 4.7% -1.42 [-1.74, -1.10] 0 0.1531 64 61 4.9% -0.00 [-0.30, 0.30] -0.4 0.102 61 59 5.9% -0.40 [-0.60, -0.20] -0.363 0.1804 15 15 4.4% -0.14 [-0.49, 0.22] -0.3 0.279 18 16 2.8% -0.36 [-0.73, 0.01] -0.4 0.102 61 39 4.2% -0.36 [-0.73, 0.01] -0.52 0.5357 20 27 1.1% -0.52 [-1.57, 0.52 [-1.57, 0.52 [-1.57, 0.57] -0.52 0.5357 20 27 1.1% -0.52 [-1.57, 0.50, -0.04]</td></td<></td>	Closed-loop Mean Difference SE Total -0.15 0.0918 63 -0.23 0.0714 36 -0.7 0.203 0.0714 36 -0.7 0.203 0.0714 36 -0.7 0.203 0.0714 36 -0.7 0.1531 64 -0.57 -0.57 0.1633 0.164 15 -0.3 0.1786 20 -0.4 -0.4 0.102 61 -0.363 0.79 18 3, df = 8 (P < 0.00001); P = 88%	Closed-loop Usual Care Mean Difference SE Total -0.15 0.0918 63 63 -0.23 0.0714 36 37 -0.7 0.2041 22 26 -1.42 0.1633 36 38 0 0.1531 64 61 -0.57 0.1786 20 17 -0.4 0.102 61 59 -0.1363 0.1804 15 15 0.3 0.279 18 16 0.3 0.279 18 16 0.3 0.279 18 16 0.3 0.279 18 16 0.053 720 27 -0.25 0.3557 20 27 -0.25 0.3557 20 27 -0.25 0.363 21 21 -0.4 0.2551 73 74 -0.317 0.1413 65 68 -0.58 0.1327	Closed-loop Usual Care Mean Difference SE Total Weight -0.15 0.0918 63 63 6.1% -0.23 0.0714 36 37 6.5% -0.7 0.2041 22 26 3.9% -1.42 0.1633 36 38 4.7% 0 0.1531 64 61 4.9% -0.57 0.1786 20 17 4.4% -0.4 0.102 61 59 5.9% -0.1363 0.1804 15 15 4.4% -0.3 0.279 18 16 2.8% 335 332 43.6% 12 12.4% -0.4 0.2551 72 27 1.1% -0.52 0.3537 20 27 1.1% -0.25 0.3163 21 21 2.4% -0.4 0.2551 73 74 4.9% -0.33 0.102 <td< td=""><td>Closed-loop Usual Care Mean Difference SE Total Volage V, Random, 95% CI -0.15 0.0918 63 6.1% -0.15 [-0.33, 0.03] -0.23 0.0714 36 37 6.5% -0.23 [-0.37, -0.09] -0.7 0.2041 22 26 3.9% -0.70 [-1.10, -0.30] -1.42 0.1633 36 38 4.7% -1.42 [-1.74, -1.10] 0 0.1531 64 61 4.9% -0.00 [-0.30, 0.30] -0.4 0.102 61 59 5.9% -0.40 [-0.60, -0.20] -0.363 0.1804 15 15 4.4% -0.14 [-0.49, 0.22] -0.3 0.279 18 16 2.8% -0.36 [-0.73, 0.01] -0.4 0.102 61 39 4.2% -0.36 [-0.73, 0.01] -0.52 0.5357 20 27 1.1% -0.52 [-1.57, 0.52 [-1.57, 0.52 [-1.57, 0.57] -0.52 0.5357 20 27 1.1% -0.52 [-1.57, 0.50, -0.04]</td></td<>	Closed-loop Usual Care Mean Difference SE Total Volage V, Random, 95% CI -0.15 0.0918 63 6.1% -0.15 [-0.33, 0.03] -0.23 0.0714 36 37 6.5% -0.23 [-0.37, -0.09] -0.7 0.2041 22 26 3.9% -0.70 [-1.10, -0.30] -1.42 0.1633 36 38 4.7% -1.42 [-1.74, -1.10] 0 0.1531 64 61 4.9% -0.00 [-0.30, 0.30] -0.4 0.102 61 59 5.9% -0.40 [-0.60, -0.20] -0.363 0.1804 15 15 4.4% -0.14 [-0.49, 0.22] -0.3 0.279 18 16 2.8% -0.36 [-0.73, 0.01] -0.4 0.102 61 39 4.2% -0.36 [-0.73, 0.01] -0.52 0.5357 20 27 1.1% -0.52 [-1.57, 0.52 [-1.57, 0.52 [-1.57, 0.57] -0.52 0.5357 20 27 1.1% -0.52 [-1.57, 0.50, -0.04]

(B) TIR 70-180 mg/dL

			Closed-loop	Usual Care		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Tota	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3.5.1 Adults							
Benhamou 2019 (DIABELOOP WP7)	9.2	1.4286	63	63	4.9%	9.20 [6.40, 12.00]	
Boughton 2022	8.6	1.1735	36	37	5.2%	8.60 [6.30, 10.90]	-
Brown 2020	5.93	1.2041	54	55	5.2%	5.93 [3.57, 8.29]	-
Burnside 2022 (CREATE) - Adults	15.38	3.4388	22	26	2.7%	15.38 [8.64, 22.12]	
Choudhary 2022 (ADAPT)	27.6	3.046	36	38	3.1%	27.60 [21.63, 33.57]	
Kovatchev 2020 (iDCL)	4.82	1.7602	64	61	4.5%	4.82 [1.37, 8.27]	
Matejko 2022	21.5	2.9592	20	17	3.2%	21.50 [15.70, 27.30]	
McAuley 2020	14.77	1.9235	61	59	4.3%	14.77 [11.00, 18.54]	
McAuley 2022 (ORACL)	6.2	0.9184	30	30	5.5%	6.20 [4.40, 8.00]	-
Pinsker 2022 (DCLP4)	11	8.1634	35	35	0.8%	11.00 [-5.00, 27.00]	
Thabit 2015 - Adults (AP@home)	10.7	1.3112	32	33	5.1%	10.70 [8.13, 13.27]	
Subtotal (95% CI)			453	454	44.6%	11.69 [8.65, 14.72]	•
Heterogeneity: Tau ² = 20.78; Chi ² = 90.8	4, df = 10 (P < 0.000	01); I ² =	89%				
Test for overall effect: Z = 7.54 (P < 0.00	001)						
3.5.2 Children and Adolescents							
Boughton 2022 (DAN06)	9.7	3.7756	46	39	2.4%	9.70 [2.30, 17.10]	
Breton 2020 (DCLP5)	10.8	1.7857	78	23	4.5%	10.80 [7.30, 14.30]	
Burnside 2022 (CREATE) - Paediatrics	12.6	3.5205	20	27	2.6%	12.60 [5.70, 19.50]	
Reiss 2022	16.43	4.0052	21	21	2.3%	16.43 [8.58, 24.28]	
Thabit 2015 - Paediatrics (AP@home)	8.87	1.4949	25	24	4.9%	8.87 [5.94, 11.80]	
Wadwa 2023 (PEDAP)	12.4	1.4796	68	34	4.9%	12.40 [9.50, 15.30]	
Ware 2022	8.67	0.648	73	74	5.7%	8.67 [7.40, 9.94]	-
Ware 2022 (DAN05)	6.72	2.3266	65	68	3.8%	6.72 [2.16, 11.28]	
Subtotal (95% CI)			396	310	31.2%	9.97 [8.36, 11.58]	•
Heterogeneity: Tau ² = 1.79; Chi ² = 11.36	, df = 7 (P = 0.12); l ²	= 38%					
Test for overall effect: Z = 12.13 (P < 0.0	0001)						
3.5.3 Mixed							
Abraham 2021	6.74	2.0613	58	53	4.2%	6.74 [2.70, 10.78]	
Brown 2019 (DCLP3)	11.3	1.2755	112	56	5.1%	11.30 [8.80, 13.80]	
Garg 2023	11.99	1.6072	151	151	4.7%	11.99 [8.84, 15.14]	
Russel 2022	13.4	1.2245	147	72	5.2%	13.40 [11.00, 15.80]	-
Tauschmann 2018 (APCam11)	10.83	1.3521	46	40	5.0%	10.83 [8.18, 13.48]	
Subtotal (95% CI)			514	372	24.3%	11.21 [9.39, 13.03]	•
Heterogeneity: Tau ² = 2.14; Chi ² = 8.09,	df = 4 (P = 0.09); l ² =	= 51%					
Test for overall effect: Z = 12.07 (P < 0.0	0001)						
Total (95% CI)			1262	1126	100 0%	10 97 [0 29 12 27]	
	0 -16 - 00 (D - 0 000	041-12-	1303	1130	100.0%	10.07 [9.30, 12.37]	▼
Heterogeneity: $1au^2 = 9.73$; Chi ² = 120.8	9, at = 23 (P < 0.000	(01); I ² =	81%				-20 -10 0 10 20
Test for overall effect: $Z = 14.25$ (P < 0.0	0001)	2 - 00/					Favours usual care Favours closed-loop
Test for subgroup differences: Chi ² = 1.5	u, at = 2 (P = 0.47),	* = 0%					

Fig. 2 Forest plots for (A) HbA1c % and (B) TIR 70–180 mg/dL

Adults

Mixed

Pediatric

717 (9)

474 (6)

470 (2)

Outcome No of patients (no of Pooled Result (CI 95%) P value Heterogeneity comparisons) HbA1c (%)^a Overall 2210 (20) - 0.37 (- 0.49 to - 0.26) < 0.001 77% Adults 667 (9) - 0.38 (- 0.63 to - 0.12) 0.004 88% Pediatric 657 (7) -0.31(-0.44 to - 0.19)< 0.001 0% Mixed 886 (4) - 0.46 (- 0.56 to - 0.30) < 0.001 62% HbA1c (mmol/mol)^a Overall 1229 (13) - 4.77 (- 6.39 to - 3.14) 85% < 0.001 91% Adults 596 (7) - 4.87 (- 7.66 to - 2.97) 0.001 - 6.77 (- 11.90 to - 1.64) Pediatric 327 (3) 0.010 83% Mixed 306 (6) - 3.70 (- 5.00 to - 2.39) < 0.001 0% TIR^a Overall 2499 (24) 10.87 (9.38 to 12.37) < 0.001 81% Adults 89% 907 (11) 11.69 (8.65 to 14.72) < 0.001 Pediatric 706 (8) 9.97 (8.36 to 11.58) < 0.001 38% Mixed 886 (5) 11.21 (9.39 to 13.03) < 0.001 51% DKAb Overall 2413 (22) 1.62 (0.64 to 4.12) 0.31 0% Adults 0% 1020 (11) 0.85 (0.22 to 3.25) 0.81 Pediatric 669 (7) 3.06 (0.63 to 14.85) 0.17 0% Mixed 724 (4) 2.67 (0.11 to 67.40) 0.55 NA Severe hypoglycaemia^b Overall 2244 (22) 1.29 (0.78 to 2.15) 0.32 0% Adults 915 (11) 1.24 (0.64 to 2.38) 0.53 0% Pediatric 773 (8) 2.35 (0.89 to 6.20) 0.08 0% Mixed 556 (3) 0.11 (0.01 to 2.03) Not estimable NA Pro Distress 763 (7) -0.18 (-0.34 to -0.03) 0.02 8% FOH^b - 2·35(- 5·21 to 0·51) 403 (5) 0.11 45% Satisfaction^a 569 (6) 0.00 (- 3.10 to 3.10) 0.83 79% % Time (< 54 mg/dl)^a 1917 (19) < 0.001 Overall - 0.14 (- 0.22 to - 0.07) 77% Adults 842 (10) - 0.23 (- 0.37 to - 0.10) < 0.001 85% Pediatric -0.03 (-0.09 to - 0.03)577 (6) 0.32 0% Mixed 498(3) - 0.15 (- 0.31 to 0.02) 0.08 83% % Time (< 70 mg/dl)^a Overall 2499 (24) - 0.65 (- 1.05 to - 0.26) 0.001 95% Adults 907 (11) -0.82(-1.43 to - 0.21)0.008 96% Pediatric 706 (8) - 0.14 (- 0.41 to 0.68) 0.62 83% Mixed 886 (5) - 1.39 (- 2.17 to - 0.60) < 0.001 92% % Time (> 250 mg/dl)^a Overall 1731 (16) - 4.46 (- 5.79 to - 3.14) 93% < 0.001 Adults - 3.51 (- 4.97 to - 2.05) 90% 769 (9) < 0.001 Pediatric 464 (4) - 6.63 (- 8.14 to - 4.92) 0.009 32% Mixed 498 (3) - 4.24 (- 9.16 to 0.67) 0.09 97% Nocturnal hypoglycaemia^a Overall 1661 (17) - 1.28 (- 1.76 to - 0.79) < 0.001 84%

- 1.03 (- 1.70 to - 0.36)

- 1.18 (- 1.91 to - 0.45)

- 3.17 (- 7.37 to 1.03)

0.003

0.002

0.14

87%

55%

96%

Table 3 Summary results of overall meta-analysis for each outcome and according to age subgroups

Outcome	No of patients (no of comparisons)	Pooled Result (Cl 95%)	P value	Heterogeneity
CV ^a				
Overall	2197 (23)	- 1.09 (- 1.80 to - 0.39)	< 0.001	81%
Adults	907 (11)	- 1.74 (- 2.79 to - 0.70)	0.002	83%
Pediatric	706 (8)	0.33 (- 0.88 to 1.55)	0.88	77%
Mixed	584 (4)	− 1.81 (− 3.38 to − 0.25)	0.02	82%

Table 3 (continued)

TIR time in range, PRO Patients-Reported Outcomes, FOH Fear of hypoglycaemia, HP hyperglycemia, CV coefficient of variation

^a Mean difference, ^bOdds ratio, ^cStandardized mean difference

methods for allocating participants and objective measurements of clinical outcomes. For patient-reported outcomes, trials were assessed as "some concerns" due to the subjective nature of the assessment (Additional file 1: Figure S4).

GRADE assessment and publication bias

Following the GRADE criteria (Additional file 1: Table S3), there was moderate certainty of evidence for HbA1c reduction in the mixed and paediatric populations, and for TIR 70–180 mg/dL in the paediatric population. In contrast, there was low certainty of evidence for HbA1c reduction in the adult population, for TIR 70–180 mg/dL in the mixed and adult populations, and for CV and night hypoglycaemia. Funnel plots for HbA1c showed no indication of publication bias visually (Additional file 1: Figure S5) or based on Egger's regression test (p=0.93; Additional file 1: Figure S6A), yet a significant value was found for TIR (p=0.02; Additional file 1: Figure S6B).

Sensitivity analyses

We explored the consistency of treatment effects using the leave-one-out strategy (Additional file 1: Figure S7), which revealed that Choudhary 2022 [29] was the study responsible for driving the heterogeneity from 58 to 77%, also confirmed by the Baujat plot (Additional file 1: Figure S8). Yet, results remained statistically significant to favour CL systems even when each individual study was removed from the analysis (Additional file 1: Figure S7). To further investigate reasons for the observed heterogeneity of effect for glycaemic control endpoints, we stratified our analyses by type of AID machines (Additional file 1: Table S2). As seen in Fig. 5, heterogeneity decreased substantially for most machine subgroups and findings remained mostly consistent with the overall analysis, favouring CL systems over UC. Nonetheless, the openAPS subgroup revealed no significant differences between CL and UC for change in HbA1c. MiniMed 780G and iLet Pancreas were found to be most effective to improve HbA1c and TIR outcomes (Fig. 5), MiniMed 670G was most effective to improve CV (Additional file 1: Figure S1), and openAPS was most effective at preventing nocturnal hypoglycaemia when compared to other machines (Additional file 1: Table S2). In addition, we performed a meta-regression based on follow-up duration and baseline HbA1c (Additional file 1: Figure S5). Although the results showed no significant association between the study duration and the mean differences for change in HbA1c (p=0.57; Additional file 1: Figure S9), higher baseline HbA1c was significantly associated with greater change scores (p=0.02; Additional file 1: Figure S10).

Discussion

In this systematic review and meta-analysis of 22 RCTs and 2376 patients, we compared the use of AID devices versus UC during a period of 12 to 96 weeks. Our main findings were: (1) A significantly improved HbA1c level, % TIR 70–180 mg/dL, CV, % time < 54 mg/dL, < 70 mg/dL, < 250 mg/dL and risk of nocturnal hypoglycaemia, with the use of AID devices; (2) a significant improvement in diabetes distress in the CL group; (3) no significant difference in the risk of DKA or severe hypoglycaemia between groups; (4) no significant reduction in % time < 54 mg/dL, < 70 mg/dL, and CV observed between paediatric groups, and (5) no significant improvement in fear of hypoglycaemia and treatment satisfaction.

Achieving glycaemic control of T1DM while also avoiding hypoglycaemia is a challenge for patients [51, 52]. A high cognitive load for T1DM patients and care team is required and previous studies show distress or depressive symptoms in up to 40% of patients [53]. Although HbA1c is currently the metric of choice by most endocrinology and diabetes societies [54, 55], TIR and HbA1c should

(A) CoV

			Closed-loop	Usual Care		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.17.1 Adults							
Benhamou 2019 (DIABELOOP WP7)	-2.3	0.4082	63	63	5.8%	-2.30 [-3.10, -1.50]	-
Boughton 2022	-0.3	0.4592	36	37	5.7%	-0.30 [-1.20, 0.60]	
Brown 2020	-0.9	0.8112	54	55	4.7%	-0.90 [-2.49, 0.69]	+
Burnside 2022 (CREATE) - Adults	-1.22	1.25	22	26	3.6%	-1.22 [-3.67, 1.23]	
Choudhary 2022 (ADAPT)	0.57	0.9949	36	38	4.2%	0.57 [-1.38, 2.52]	_ _
Kovatchev 2020 (iDCL)	-1	0.7653	64	61	4.9%	-1.00 [-2.50, 0.50]	+
Matejko 2022	-9.36	1.898	20	17	2.3%	-9.36 [-13.08, -5.64]	
McAuley 2020	-4.7	0.9184	61	59	4.4%	-4.70 [-6.50, -2.90]	
McAuley 2022 (ORACL)	-3.0018	0.728	30	30	5.0%	-3.00 [-4.43, -1.57]	
Pinsker 2022 (DCLP4)	-0.5	0.8163	35	35	4.7%	-0.50 [-2.10, 1.10]	-+-
Thabit 2015 - Adults (AP@home)	-0.2	0.7653	32	33	4.9%	-0.20 [-1.70, 1.30]	-+-
Subtotal (95% CI)			453	454	50.2%	-1.74 [-2.79, -0.70]	\bullet
Heterogeneity: Tau ² = 2.34; Chi ² = 53.95	5, df = 10 (P < 0.0000	1); l ² = 8	1%				
Test for overall effect: Z = 3.27 (P = 0.00	01)						
5.17.2 Children and Adolescents							
Boughton 2022 (DAN06)	4.2	1.7857	46	39	2.5%	4.20 [0.70, 7.70]	
Breton 2020 (DCLP5)	-1.6	0.6123	78	23	5.3%	-1.60 [-2.80, -0.40]	
Burnside 2022 (CREATE) - Paediatrics	2.1	1.2755	20	27	3.5%	2.10 [-0.40, 4.60]	+
Reiss 2022	-3.607	1.7924	21	21	2.5%	-3.61 [-7.12, -0.09]	
Thabit 2015 - Paediatrics (AP@home)	1.7	0.8674	25	24	4.6%	1.70 [-0.00, 3.40]	⊢
Wadwa 2023 (PEDAP)	0.3	0.6123	68	34	5.3%	0.30 [-0.90, 1.50]	
Ware 2022	-0.705	0.3852	73	74	5.8%	-0.70 [-1.46, 0.05]	-
Ware 2022 (DAN05)	2.5	1.9898	65	68	2.1%	2.50 [-1.40, 6.40]	
Subtotal (95% CI)			396	310	31.6%	0.33 [-0.88, 1.55]	•
Heterogeneity: Tau ² = 1.88; Chi ² = 27.14	l, df = 7 (P = 0.0003)	l ² = 749	6				
Test for overall effect: Z = 0.54 (P = 0.59	9)						
5.17.3 Mixed							
Abraham 2021	-5.7	2.449	58	53	1.6%	-5.70 [-10.50, -0.90]	
Brown 2019 (DCLP3)	-3	0.5102	112	56	5.6%	-3.00 [-4.00, -2.00]	
Russel 2022	-1	0.5102	147	72	5.6%	-1.00 [-2.00, -0.00]	
Tauschmann 2018 (APCam11)	-0.38	0.5408	46	40	5.5%	-0.38 [-1.44, 0.68]	
Subtotal (95% CI)			363	221	18.2%	-1.81 [-3.38, -0.25]	\bullet
Heterogeneity: Tau ² = 1.81; Chi ² = 16.79 Test for overall effect: Z = 2.27 (P = 0.02	9, df = 3 (P = 0.0008) 2)	; I² = 82%	6				
Total (95% CI)			1212	985	100.0%	-1.09 [-1.80, -0.39]	•
Heterogeneity: Tau ² = 2.07; Chi ² = 114.4	8, df = 22 (P < 0.000	01); l ² =	81%			-	
Test for overall effect; Z = 3.03 (P = 0.00)2)						-10 -5 0 5 10
Test for subgroup differences: Chi ² = 7.6	df = 2 (P = 0.02)	² = 73.7	%				Favours closed-loop Favours usual care

(B) Nocturnal hypoglycemia

			Closed-loop	Usual Care		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.12.1 Adults							
Benhamou 2019 (DIABELOOP WP7)	-2.88	0.3878	63	63	7.4%	-2.88 [-3.64, -2.12]	-
Boughton 2022	-0.0131	0.2371	36	37	8.3%	-0.01 [-0.48, 0.45]	+
Brown 2020	-0.023	0.2719	54	55	8.1%	-0.02 [-0.56, 0.51]	+
Burnside 2022 (CREATE) - Adults	0.1	0.7143	22	26	5.2%	0.10 [-1.30, 1.50]	+-
Choudhary 2022 (ADAPT)	-0.5	0.7143	36	38	5.2%	-0.50 [-1.90, 0.90]	-+
Kovatchev 2020 (iDCL)	-2.32	0.5816	64	61	6.0%	-2.32 [-3.46, -1.18]	
Matejko 2022	-6.95	3.3776	20	17	0.5%	-6.95 [-13.57, -0.33]	
McAuley 2022 (ORACL)	-0.83	0.1122	30	30	8.8%	-0.83 [-1.05, -0.61]	•
Thabit 2015 - Adults (AP@home)	-1.4576	0.6468	32	33	5.6%	-1.46 [-2.73, -0.19]	
Subtotal (95% CI)			357	360	55.3%	-1.03 [-1.70, -0.36]	◆
Heterogeneity: Tau ² = 0.73; Chi ² = 60.84,	df = 8 (P < 0.00001); l ² = 87	%				
Test for overall effect: Z = 3.01 (P = 0.003	3)						
5.12.2 Children and Adolescents							
Breton 2020 (DCLP5)	-0.4838	0.3723	78	23	7.5%	-0.48 [-1.21, 0.25]	
Burnside 2022 (CREATE) - Paediatrics	-2	0.7143	20	27	5.2%	-2.00 [-3.40, -0.60]	
Reiss 2022	-1.37	1.949	21	21	1.4%	-1.37 [-5.19, 2.45]	
Thabit 2015 - Paediatrics (AP@home)	-0.7275	0.8521	25	24	4.4%	-0.73 [-2.40, 0.94]	-+
Wadwa 2023 (PEDAP)	-0.6	0.5135	68	34	6.5%	-0.60 [-1.61, 0.41]	-+
Ware 2022 (DAN05)	-2.1526	0.4465	65	68	7.0%	-2.15 [-3.03, -1.28]	
Subtotal (95% CI)			277	197	32.0%	-1.18 [-1.91, -0.45]	◆
Heterogeneity: Tau ² = 0.41; Chi ² = 11.04,	df = 5 (P = 0.05); I ²	= 55%					
Test for overall effect: Z = 3.15 (P = 0.002	2)						
5.12.3 Mixed							
Brown 2019 (DCLP3)	-1.11	0.2143	112	56	8.4%	-1.11 [-1.53, -0.69]	-
Garg 2023	-5.4	0.8674	151	151	4.3%	-5.40 [-7.10, -3.70]	
Subtotal (95% CI)			263	207	12.8%	-3.17 [-7.37, 1.03]	
Heterogeneity: Tau ² = 8.80; Chi ² = 23.05,	df = 1 (P < 0.00001); I ² = 96	%				
Test for overall effect: Z = 1.48 (P = 0.14))						
							.
Total (95% CI)			897	764	100.0%	-1.28 [-1.76, -0.79]	•
Heterogeneity: Tau ² = 0.69; Chi ² = 102.82	2, df = 16 (P < 0.000	001); l² =	84%			-	
Test for overall effect: Z = 5.11 (P < 0.000	001)						Favours closed-loop Eavours usual care
Test for subgroup differences: Chi ² = 1.01	1, df = 2 (P = 0.60),	l² = 0%					

Fig. 3 Forest plots for (A) CV and (B) nocturnal hypoglycaemia

(A) Distress

			Closed-loop	Usual care		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Abraham 2021	-0.2729	0.1909	58	53	17.2%	-0.27 [-0.65, 0.10]	
Cobry 2021 (DCLP5)	-0.4339	0.2434	78	23	10.6%	-0.43 [-0.91, 0.04]	
Hood 2022 (DAN05)	0.2619	0.2386	65	68	11.0%	0.26 [-0.21, 0.73]	
Kudva 2021 (DCLP3)	-0.1769	0.1652	112	56	22.9%	-0.18 [-0.50, 0.15]	
McAuley 2020	-0.3744	0.1842	61	59	18.4%	-0.37 [-0.74, -0.01]	
McAuley 2022 (ORACL)	-0.097	0.2584	30	30	9.4%	-0.10 [-0.60, 0.41]	
Pinsker 2022 (DCLP4)	0	0.2425	35	35	10.6%	0.00 [-0.48, 0.48]	
Total (95% CI)			439	324	100.0%	-0.18 [-0.34, -0.03]	•
Heterogeneity: Chi ² = 6.52	, df = 6 (P = 0.37); l ² = 8	%					
Test for overall effect: Z =	2.31 (P = 0.02)						Favours closed-loop Favours usual care

(B) Satisfaction

			Closed-loop	Usual care		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Tota	l Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Abraham 2021	-3.3 1	1.3776	55	55	20.4%	-3.30 [-6.00, -0.60]	
Abraham 2021	-5.2 2	2.0409	12	13	17.4%	-5.20 [-9.20, -1.20]	
Benhamou 2019 (DIABELOOP WP7)	-0.8 1	1.3384	63	63	20.6%	-0.80 [-3.42, 1.82]	
Choudhary 2022 (ADAPT)	6.18 1	1.6582	36	38	19.2%	6.18 [2.93, 9.43]	
McAuley 2020	0.98 0	0.8929	61	59	22.3%	0.98 [-0.77, 2.73]	+ - -
Total (95% CI)			227	228	100.0%	-0.34 [-3.53, 2.85]	-
Heterogeneity: $Tau^2 = 11.05$; $Chi^2 = 27.6$ Test for overall effect: Z = 0.21 (P = 0.83	68, df = 4 (P < 0.0001 3)	1); I² = 8	6%				-10 -5 0 5 10 Favours usual care Favours closed-loop

(C) Hypoglycemia fear



Fig. 4 Meta-analysis of patient-reported outcomes of (A) diabetes distress measured by Diabetes Distress Survey (DDS) and Problem Areas in Diabetes (PAID), B Diabetes Treatment Satisfaction Questionnaire (DTSQ), and (C) Hypoglycaemia Fear Scale (HFS)

be used as complementary parameters to guide care [56] and allow evaluation in clinical research [57].

To our knowledge, our study is the most comprehensive meta-analysis of use of AID for 12-96 weeks. Our analysis integrated data from 25 reports and 2376 participants, a population that almost tripled compared to a previous meta-analysis [14]. Furthermore, this is the first analysis with studies over 12 weeks of duration, stratified by age groups and type of AID device used. Our findings augment the certainty about the beneficial effects of the continuous use of CL systems on HbA1c, TIR, hypoglycaemia, and distress of patients, without increasing the risk of AEs. Given that glycaemic variability has been linked to chronic diabetic complications [58], respective reductions of 0.37% (4.77 mmol/mol) in HbA1c levels and 1.09% in CV have important implications for patient care. As the mean baseline HbA1c in our population was 7.73% (61 mmol/mol), our findings present a conservative and safe strategy to avoid the risk of hypoglycaemia commonly associated with large changes in HbA1c [59]. Furthermore, an increase of 10% TIR has been correlated with an HbA1c reduction of 0.5–0.8% [60], which is slightly higher compared to our TIR and HbA1c assessment. Our analyses also show that higher HbA1c levels at baseline are correlated with greater changes in HbA1c after the use of such devices, which may lead to further benefits to certain patient groups. Our findings are similar to the analyses by Weinsman and colleagues [13], although our results for reduction of time in hypoglycaemia are much smaller. The longer periodicity of the studies included provides a pragmatic setting for assessment, where greater variables and confounding factors reflect a better real-life picture of treatment impact.

In addition, our meta-analysis provides a unique framework for comparing 7 permutations of different technologies. The breadth of these findings provides estimates of treatment effects with particular relevance to clinical decision-making and cost-effectiveness analyses. The application of our results may be illustrated through an approach to device selection. For example, some devices appeared to offer the greatest potential for improved

A) HbA1c %

Study or Subgroup	Mean Difference S	Closed-loop	Usual Care	Weight	Mean Difference	Mean Difference
2.4.1 CamAPS FX Bourbloo 2022	.0.23 0.071	4 26	37	6.5%	-0.23 L0.37 -0.091	
Boughton 2022 (DAN06)	-0.36 0.188	- 36 8 46	3/	4.3%	-0.36 [-0.73, 0.01]	
Ware 2022 (DAN05) Subtotal (95% CI)	-0.317 0.141	3 65	68	5.2%	-0.32 [-0.59, -0.04]	
Heterogeneity: Tau ² = 0.00; Chi ² = 3.10,	, df = 3 (P = 0.38); l ² = 3%	220	210	20.075	-0.22 [-0.34, -0.11]	•
2.4.2 trailine X2 with Control IO	001)					
Breton 2020 (DCLP5)	-0.4 0.255	1 78	23	3.2%	-0.40 [-0.90, 0.10]	
Brown 2019 (DCLP3) Kovatchev 2020 (iDCL)	-0.33 0.10 0 0.153	2 112 1 64	56 61	6.0% 5.0%	-0.33 [-0.53, -0.13] 0.00 [-0.30, 0.30]	
Wadwa 2023 (PEDAP) Subtotal (95% CI)	-0.42 0.10	2 68 322	34 174	6.0% 20.1%	-0.42 [-0.62, -0.22] -0.29 [-0.47, -0.12]	•
Heterogeneity: Tau ² = 0.01; Chi ² = 5.42, Test for overall effect: Z = 3.22 (P = 0.0	, df = 3 (P = 0.14); l ² = 45% 01)					
2.4.3 DBLG1						
Benhamou 2019 (DIABELOOP WP7) Subtotal (95% CI)	-0.15 0.091	8 63 63	63 63	6.1% 6.1%	-0.15 [-0.33, 0.03] -0.15 [-0.33, 0.03]	•
Heterogeneity: Not applicable Test for overall effect: Z = 1.63 (P = 0.1)	0)					
2.4.4 MiniMed 670G						
Abraham 2021 Gara 2023	-0.1 0.181	5 58	53	4.4%	-0.10 [-0.46, 0.26]	
McAuley 2020	-0.4 0.10	2 61	59	6.0%	-0.40 [-0.60, -0.20]	
Reiss 2022 Subtotal (95% CD)	-0.25 0.316	3 21	21	2.5%	-0.25 [-0.87, 0.37]	
Heterogeneity: Tau ² = 0.02; Chi ² = 6.61,	, df = 4 (P = 0.16); l ² = 40%	300	299	22.175	-0.34 [-0.32, -0.15]	•
Test for overall effect: Z = 3.6Z (P = 0.0	003)					
2.4.5 MiniMed 780G Choudhary 2022 (ADAPT)	-1.42 0.163	3 36	38	4.8%	-1.42 [-1.74, -1.10]	<u> </u>
Matejko 2022 Subtotal (95% CI)	-0.57 0.178	6 20 56	17 55	4.5% 9.2%	-0.57 [-0.92, -0.22] -1.00 [-1.83, -0.17]	
Heterogeneity: Tau ² = 0.33; Chi ² = 12.3- Test for overall effect: Z = 2.35 (P = 0.0)	4, df = 1 (P = 0.0004); l ² = 9; 2)	2%				
2.4.6 iLet Bionic Pancreas						
Russel 2022 Subtotal (95% CI)	-0.57 0.066	3 147 147	72 72	6.6% 6.6%	-0.57 [-0.70, -0.44]	∓
Heterogeneity: Not applicable	0001)					
2.4.7 Elorence						
Tauschmann 2018 (APCam11)	-0.36 0.086	7 46	40	6.2%	-0.36 [-0.53, -0.19]	T
Subtotal (95% CI) Heterogeneity: Not applicable		46	40	6.2%	-0.36 [-0.53, -0.19]	-
Test for overall effect: Z = 4.15 (P < 0.0	001)					
2.4.8 OpenAPS Burnside 2022 (CREATE) - Adults	-0.7 0.204	1 22	26	4.0%	-0.70 [-1.10, -0.30]	
Burnside 2022 (CREATE) - Paediatrics Pinsker 2022 (DCLP4)	-0.52 0.535	7 20 9 18	27	1.1%	-0.52 [-1.57, 0.53] 0.30 [-0.25, 0.85]	
Subtotal (95% CI) Heterogeneity: Tau ² = 0.30° Chi ² = 8.46	df = 2 (P = 0.01); l ² = 76%	60	69	8.1%	-0.29 [-1.02, 0.43]	
Test for overall effect: Z = 0.80 (P = 0.4)	3)					
Total (95% CI)	a	1220	990	100.0%	-0.36 [-0.49, -0.24]	◆
Test for overall effect: Z = 5.85 (P < 0.0	2, df = 20 (P < 0.00001); P = 0001)	17%				-1 -0.5 0 0.5 1 Favours closed-loop Favours usual care
rest for subgroup differences. Chir = 22	1.96, di = 7 (P = 0.002), P = 0	39.3%				
D) TID 70 190 mg/d	r					
D) IIK /0-100 mg/u	L					
B) 11K /0-180 mg/u	L	Closed-loop	Usual Care		Mean Difference	Mean Difference
Study or Subgroup 3.4.1 CamAPS FX	Mean Difference	Closed-loop SE Tota	Usual Care I Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
Study or Subgroup 3.4.1 CamAPS FX Boughton 2022 Breton 2020 (DCLP5)	Mean Difference 8.6 1.17 10.8 1.78	Closed-loop SE Tota 35 3 57 4	Usual Care I Total	Weight 5.4% 4.6%	Mean Difference IV, Random, 95% Cl 8.60 [6.30, 10.90] 10.80 [7.30, 14.30]	Mean Difference IV, Random, 85% CI
Study or Subgroup 3.4.1 CamAPS FX Boughton 2022 Breton 2020 (DCLP5) Brown 2019 (DCLP3) Ware 2022	L Mean Difference 8.6 1.17 10.8 1.76 11.3 1.27 8.67 0.6	Closed-loop SE Tota 35 3 57 44 55 7, 48 6	Usual Care I Total 3 37 3 39 3 74 5 68	Weight 5.4% 4.6% 5.3% 5.9%	Mean Difference IV, Random, 95% Cl 8.60 (6.30, 10.90) 10.80 (7.30, 14.30) 11.30 (8.80, 13.80) 8.67 (7.40, 9.94)	Mean Difference IV, Random, 95% Cl
Study or Subgroup 3.4.1 CamAPS FX Boughton 2022 Breton 2020 (DCLP5) Brown 2019 (DCLP3) Ware 2022 Subtotal (95% CI) Heterogenety Tayl = 0.61: ChP = 4.4	L <u>Mean Difference</u> 8.6 1.17 10.8 1.76 11.3 1.22 11.3 1.22 4. df = 3 (P = 0.22): P = 32%	Closed-loop SE Tota 35 3 57 4 55 7 48 6 221	Usual Care <u>I</u> Total 3 37 3 39 3 74 5 68 0 218	Weight 5.4% 4.6% 5.3% 5.9% 21.1%	Mean Difference IV, Random, 95% CI 8.60 (6.30, 10.90) 10.80 (7.30, 14.30) 11.30 (8.80, 13.80) 8.67 (7.40, 9.94) 9.45 [8.12, 10.77]	Mean Difference IV, Random, 95% CI
Study or Subgroup Study or Subgroup 3.4.1 CemMPS PX Boughton 3020 Breten 2020 (DCLP5) Brown 2020 (DCLP5) Work 2020 (DCLP5) Work 2020 (DCLP5) Heterogeneity: Tau' = 0.61; Chi ² = 4.4 Test for overall effect Z = 13.99 (P < C)	Mean Difference 8.6 1.17 10.8 1.76 11.3 1.27 8.67 0.6 4. df = 3 (P = 0.22); I ² = 329 0.00001)	Closed-loop SE Tota 35 3 57 4 55 7; 48 6 221	Usual Care <u>I Total</u> 3 37 3 39 3 74 5 68 9 218	Weight 5.4% 4.6% 5.3% 5.9% 21.1%	Mean Difference IV, Random, 95% Cl 8.60 (6.30, 10.90) 10.80 (7.30, 14.30) 11.30 (8.80, 13.80) 8.67 (7.40, 9.94) 9.45 (8.12, 10.77)	Maan Difference IV, Random, 855 Cl
B) TTR //0-TOO IIIg/ul Study or subgroup 3.4.1 CamAPS FX Boughton 2022 Breton 2020 (DCLPS) Breton 2019 (DCLPS) Brown 2019 (DCLPS) Subtotal (BS% C) Heterogeneity: Tau ² = 0.61; Ch ² = 4.4 Test for overall effect. Z = 13.90 (P < C 3.4.2 t: tilm X2 with Control-IQ	Mean Difference 8.6 1.11 10.8 1.76 11.3 1.27 11.3 1.27 4. df = 3 (P = 0.22); P = 329 0.00001)	Closed-loop SE Tota 35 3 57 4 55 7 48 6 221	Usual Care <u>1</u> Total 3 37 3 39 3 74 5 68 0 218	Weight 5.4% 4.6% 5.3% 5.9% 21.1%	Mean Difference IV, Random, 95% C1 0.807 (6.30, 10.90) 10.80 (7.30, 14.30) 11.30 (8.80, 13.80) 8.67 (7.40, 9.94) 9.45 [8.12, 10.77]	Maan Difference IV, Random, 95% Cl
D) T LTK //O-100 Illig/ull Study or Subgroup 3.4.1 CanAPS FX Booglion 2022 Beten 2020 (DCLPS) Beten 2020 (DCLPS) Beten 2020 (DCLPS) Marcogrammity, T and * 0.5 (CLP = 1.4.1 Test for ownall effect X = 13.90 (P < 0.1.1	Mean Difference 8.6 1.17 10.8 1.76 11.3 1.27 8.67 0.6 4. df = 3 (P = 0.22); I ² = 32% 0.00001) 9.7 3.77 5.53 1.20	Closed-loop SE Tota 35 33 57 44 55 77 48 68 224 56 77 41 11	Usual Care I Total 3 37 3 39 3 74 5 68 9 218 3 23 2 56	Weight 5.4% 5.3% 5.9% 21.1% 2.5% 5.3%	Mean Difference IV, Random, 95% C1 0.80 (6.30, 10.90) 10.80 (7.30, 14.30) 11.30 (8.80, 13.80) 8.67 (7.40, 9.94) 9.45 [8.12, 10.77] 9.45 [8.12, 10.77] 9.70 [2.30, 17.10] 5.83 (3.57, 8.29]	Mean Difference IV, Randon, 955 Cl
B) 111K //0-120 Illigrat Study or Subgroup 3.4.1 Can.489 FX Bitds or 2001 (DCLPS) Bitds 2001 (DCLPS) Bitds 2002 (DCLPS) Bitds 2001 (DCLPS) Valideal (BSV Can ² = 0.61; CLPS = 1.4.1 Bitds 2001 (DCLPS) Bitds 2001 (DCLPS) Bitds 2001 (DCLPS) Bitds 2001 (DCLPS) Bitds 2001 (DCLPS) Bitds 2001 (DCLPS) Bitds 2001 (DCLPS) Water 2002 (DCL) Water 2001 (DCL) Water 2003 (PCL) Water 2001 (PCL)	Mean Difference 8.6 1.17 10.8 1.76 11.3 1.22 8.67 0.6 4. df = 3 (P = 0.22); P = 32% 0.00001) 9.7 3.77 5.93 1.20 4.82 1.76 12.4 1.47	Closed-loop SE Tota 35 3 57 4 55 7 48 6 221 56 7 41 11: 02 6 96 6	Usual Care <u>1</u> Total 3 37 3 39 3 74 5 68 9 218 3 23 2 56 4 61 3 34	Weight 5.4% 4.6% 5.3% 21.1% 2.5% 5.3% 4.6% 5.0%	Mean Difference IV, Random, 95% CI 8.60 (6.30, 10.00) 11.30 (8.80, 13.80) 8.67 (7.40, 9.94) 9.45 (8.12, 10.77) 9.70 (2.30, 17.10) 5.93 (3.57, 8.29) 4.82 (1.37, 8.27) 12.40 (9.80, 15.30)	Maan Difference IV, Random, 955 Cl
Study or Subgroup 5.4.1 CarnAPS FX Boughton 2022 Boughton 2022 Boughton 2022 Study or SUDOLP(3) Ware 2020 Studtoral (95% CI) Heat for consell affact.2 = 13.08 (P < C)	Mean Difference 8.6 1.17 10.8 1.76 11.3 1.22 4. df = 3 (P = 0.22); P = 329 0.00001) 9.7 3.7 4.22 1.22 4.22 1.72 4.22 1.72 4.22 1.72 4.22 1.22 4.22 1.72 4.22 1.22 4.22 1.22	Closed-loop SE Tota 35 3 57 4 55 7, 48 6 22 56 7 41 11; 02 6 56 5 56 5 56 37/	Usual Care 1 Total 3 37 5 39 6 88 9 218 8 23 2 56 8 61 8 34 8 55 6 229	Weight 5.4% 4.6% 5.3% 21.1% 2.5% 5.3% 4.6% 5.0% 3.9% 21.4%	Mean Difference IV, Random, 95% C1 8.60 [6.30, 10.90] 10.80 [7.30, 14.30] 9.67 [7.40, 9.94] 9.45 [8.12, 10.77] 9.70 [2.30, 17.10] 5.81 [5.57, 8.29] 4.82 [1.37, 8.27] 12.40 [5.80, 15.30] 6.72 [2.16, 11.28] 7.78 [4.58, 10.88]	Maan Difference IV, Bandon, 855 Cl
Study or Subgroup Study or Subgroup Sta1 CaraNPS FX Boughton 2022 Boughton 2022 Boughton 2022 Stathead (BSX CDCLP3) Ware 3020 (CDCLP3) Ware 3020 (CDCLP3) Stathead (BSX CDCLP3) Stathead (BSX CDCLP3) Stathead (BSX CDCLP3) Ware 3020 (CDCLP3) Ware 3020 (CDCL)	L Mean Difference 8.6 113 10.6 176 113.3 22 8.67 06 4. df = 3 (P = 0.22); P = 329 0.00001) 9.7 3.77 5.93 120 4.82 127 12.4 14) 12.4 14 12.4 23 30. df = 4(P = 0.004); P = 7	Closed-loop SE Tota 57 4 55 7, 4 48 6 224 56 7 41 11; 02 6 96 6 56 5 374 4%	Usual Care 1 Total 3 37 3 39 3 74 5 68 0 218 3 23 2 56 6 61 8 34 8 55 6 229	Weight 5.4% 4.6% 5.3% 5.9% 21.1% 2.5% 5.3% 4.6% 5.0% 3.9% 21.4%	Mean Difference IV, Random, 95% CI 8,60 (6.30, 10.90) 10.80 (7.30, 14.30) 9,45 (8,12, 10,77] 9,45 (8,12, 10,77) 9,45 (8,12,12,12) 9,45 (8,12,12) 9,45 (8,12,12)9,45 (8,12,12) 9,45 (8,12,12)9,45 (8,12) 9,45 (8,12)9,45	Maan Difference IV, Random, 95% Cl
Study or Subgroup Study or Subgroup Staf Cam/APS FX Back 1000 Back 1000 <td>Mean Difference 8.6 1.1 10.6 1.7 11.3 1.2 8.6 1.1.3 4. df = 3 (P = 0.22); P = 323 9.7 3.7 9.3 1.2 4.2 1.4 6.72 2.33 39. df = 4 (P = 0.044); P = 7000001) 0.004; P = 7000001)</td> <td>Closed-loop SE Tota 35 7 41 55 7 7 44 6 56 77 41 11: 102 6 56 77 41 11: 102 6 56 5 371 45</td> <td>Usual Care 1 Total 3 37 3 39 3 74 5 68 0 218 3 23 2 56 4 61 3 44 5 55 5 229</td> <td>Weight 5.4% 4.6% 5.3% 5.9% 21.1% 2.5% 5.3% 4.6% 5.0% 3.9% 21.4%</td> <td>Mean Difference IV, Random, 95% CI 8.60 (6.30, 10.90) 10.80 (7.30, 14.30) 8.67 (7.40, 3.94) 9.46 (8.12, 10.77) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.77 (2.30, 17.1</td> <td>Mean Difference IV, Random, 955 CI</td>	Mean Difference 8.6 1.1 10.6 1.7 11.3 1.2 8.6 1.1.3 4. df = 3 (P = 0.22); P = 323 9.7 3.7 9.3 1.2 4.2 1.4 6.72 2.33 39. df = 4 (P = 0.044); P = 7000001) 0.004; P = 7000001)	Closed-loop SE Tota 35 7 41 55 7 7 44 6 56 77 41 11: 102 6 56 77 41 11: 102 6 56 5 371 45	Usual Care 1 Total 3 37 3 39 3 74 5 68 0 218 3 23 2 56 4 61 3 44 5 55 5 229	Weight 5.4% 4.6% 5.3% 5.9% 21.1% 2.5% 5.3% 4.6% 5.0% 3.9% 21.4%	Mean Difference IV, Random, 95% CI 8.60 (6.30, 10.90) 10.80 (7.30, 14.30) 8.67 (7.40, 3.94) 9.46 (8.12, 10.77) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.70 (2.30, 17.10) 9.77 (2.30, 17.1	Mean Difference IV, Random, 955 CI
B) T1RK //O-1300 Illigrad Study or Subgroup 3.4.1 Cam.487 PK Barder 2002 (DC, PS) Barder 2002 (DC, PS) Brown 2016 (DC, PS) Water 2002 (DC, PS) Water 2022 (SW and PG) Tanle 10 (SW and PG) Bodgroupsky, Tanle 0 (ST, CHP = 4.4 Bodgroupsky, Tanle 0 (SW and PG) Bodgroupsky, Tanle 0 (SW and PG) SW and PG) Statistical (SSG (CA), ONARD) SW and PG) Statistical (SGG (CA), ONARD) SW and PG) SW and PG (SGG (CA)	L Mean Difference 108 r.7 108 r.7 1	Closed-loop SE Tota 35 3 357 4 455 7 448 6 55 7 221 56 7 56 7 56 7 56 7 56 5 371 45 56 5 371 45 56 5 371 56 5 371 56 5 371 56 5 371 56 5 371 56 5 371 57 5 57 7 58 5 58 7 58 5 58 7 58 7	Usual Care i Total 3 37 3 39 5 68 0 218 8 236 6 68 6 68 6 218 8 236 6 68 6 68 6 68 6 229 8 229 8 34 8 35 8 229 8 36 8 37 8 37 8 39 8	Weight 5.4% 5.3% 5.9% 21.1% 2.5% 5.3% 4.6% 5.0% 3.9% 21.4%	Mean Difference IV, Random, 95% CI 860 (63 30 1090) 1130 (63 30 1090) 1130 (63 30 1090) 8.67 (740, 9.94) 9.45 (8.12, 103, 112) 9.70 (2.30, 17.10) 5.93 (35.75, 8.29) 4.82 (137, 8.27) 4.82 (137, 8.27) 7.78 (4.85, 10.89) 7.78 (4.85, 10.89) 9.20 (64.0, 12.20) 9.20 (64.0, 12.20)	Maan Difference IV, Random, 955 CI
By TIRK // 0-100 Illigr(ii) Study or Subgroup 3.4.1 Cam/H8 PX Boughton 2022 Boughton 2020 Boughton 2020 Boughton 2020 Studtoral (95% Ct) 1.4.0 Cam/H8 Ct Test for owned lateX 2 = 13.0 (PC - 10.0 Ct) 1.4.4 Cam/H8 Ct Boughton 2020 Boughton 2020 Studtoral (95% Ct) 1.4.4 Ct Boughton 2020 (ECL) Weit Boughton 2020 (ECL) Wordsthy 2020 (ECL) Weit Boughton 2020 (ECL) Weit Boughton 2020 (ECL) Hearogeneity, Tau' = 9.15; Ct) ² = 1.5. Test for orward lateX 2 = 4.7 (PC - 10.0 Ct) Hearogeneity, Tau' = 9.15; Ct) ² = 1.5. Benhamoug 2019 (DUBELZ OP WP7) Studtoral (95% Ct) Hearogeneity, Not applicable 1.4.3 DBLo1	L Mean Difference 8.6 1,17 19.6 1,17 19.6 7, 02 4. df = 3 (P = 0.22); P = 329 0.00001) 9.7 3,77 5.93 1,20 4.8 1,20 4	Closed-loop SE Tota 35 3 357 4 455 7 448 6 55 7 744 56 7 56 7 56 7 56 7 56 3 57 47 56 5 57 66 5 57 56 3 77 44 11 11 10 22 45 56 5 57 58 58 58 58 58 58 58 58 58 58	Usual Care i Total 3 37 3 39 5 68 0 218 8 232 5 68 6 68 9 218 8 232 5 68 6 18 5 58 6 229 8 34 8 35 8 36 8 36 8 36 8 36 8 36 8 36 8 37 8 37	Weight 5.4% 4.6% 5.9% 21.1% 2.5% 5.3% 4.6% 5.3% 5.0% 3.9% 21.4% 5.1% 5.1%	Moan Difference IV, Random, 95% C1 0.80 (7.30, 14.30) 11.30 (8.80, 13.80) 9.45 (8.12, 18.77) 9.70 (2.30, 17.10) 9.45 (8.12, 18.77) 4.82 (13.78, 8.27) 12.40 (9.50, 15.30) 9.778 (4.58, 18.89) 9.778 (4.58, 18.89) 9.20 (6.40, 12.00) 9.20 (6.40, 12.00)	Maan Difference IV, Bandon, 955 Cl
B) THK //P-100 Img/ul Study or Subgroup Sub	Mean Difference 10.6 1.17 10.6 1.17 11.3 1.22 8.6 1.13 4.6 4.9 0.00001) 9.7 9.7 3.77 1.6 1.12 9.7 3.12 1.6 1.12 1.0 1.12 1.0 1.12 1.0 1.12 1.0 1.12 1.0 1.12 1.0 1.12 1.0 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.12	Closed-loop SE Tota 35 3: 55 7: 46 6: 55 7: 47 41 11: 102 6: 96 5: 86 6: 56 56 6: 57 45 56 6: 57 41 11: 102 6: 88 6: 65 6: 56	Usual Care 1 Total 3 37 5 39 8 74 5 68 9 238 9 238 9 238 9 248 9 238 9 248 9 248	Weight 5.4% 4.6% 5.3% 21.1% 2.5% 5.3% 5.0% 5.0% 5.0% 5.1% 5.1%	Moan Difference IV, Random, 95% CI 8.60 (6.30, 10.60) 11.30 (7.30, 14.30) 11.30 (8.00, 13.80) 9.45 (8.14, 14.80) 9.45 (8.14, 16.84) 9.45 (8.14, 16.87) 9.45 (8.14, 16.87) 9.70 (2.30, 17, 16) 9.45 (8.13, 8.27) 12.40 (9.50, 15.30) 7.72 (4.45, 10.88) 7.72 (4.45, 10.88) 9.20 (6.40, 12.00) 9.20 (6.40, 12.00)	Maan Difference IV, Bandon, 555 Cl ++++++++++++++++++++++++++++++++++++
B) Titk //> //> Study or Subgroup 3.41 Cam.APS PX Back 1000 2000 2000 Back 1000 2000 2000 Brown 2019 2000 2000 Brown 2019 2000 2000 Brown 2019 2000 2000 Haterogenety, Tau ⁺ to 51; Chort = 4.4 Test for overall effect 2 = 1.30 (P < 0.4)	L Mean Difference 106 1/1 106 1/2 107 1/2 8.67 02 4.47 - 3 (P = 0.22); (P = 325 0.00001) 9.7 3/7 10.5 1/2 4.62 1/7 12.2 4/3 6.7 2 2.3 39.07 4 (P = 0.004); (P = 7 0.0001) 9.2 1.42 0.0001) 6.7.4 2.00 0.7.4 2.00	Closed-loop SE Tota 35 3 55 7 46 6 221 56 7 41 111 02 6 56 5 56 5 371 45 86 6 6 88 6 6 13 5	Usual Care 1 Total 3 37 3 39 3 74 5 68 9 218 3 238 5 68 6 1 3 34 5 56 6 61 6 1 3 34 5 56 6 61 6 1 3 34 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3	Weight 5.4% 4.6% 5.9% 21.1% 2.5% 3.9% 21.4% 5.1% 5.1%	Mean Difference IV, Random, 95% CI 10.80 (7.30, 14.30) 11.00 (7.30, 14.30) 11.00 (7.30, 14.30) 11.00 (7.40, 9.44) 9.45 (8.12, 10.77) 9.9.45 (8.12, 10.77) 9.9.45 (8.12, 10.77) 9.07 (2.30, 17.10) 9.07 (2.30, 17.10) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00)	Maan Difference IV, Random, 955 Cl
B) TIRK / VP-130 Illigr Li Study or Subgroup 3.4.1 Cam.495 PK Borghousson	L <u>Mean Difference</u> 108 4.11 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 108 4.7 109 4.7 1	Closed-loop SE Tota 35 3 55 7 56 7 56 7 56 7 56 7 56 7 56 7 56 7	Usual Care 4 Total 3 37 3 39 745 689 2 28 3 23 2 56 6 61 3 34 5 229 3 63 4 63 3 63 4 63 5 55 5 229	Weight 5.4% 4.6% 5.9% 21.1% 2.5% 4.6% 5.3% 21.4% 5.1% 5.1% 4.3% 4.3%	Mostn Difference IV, Random, 95% C1 10.00 [7:30, 14:30] 11.30 [97:00, 13.80] 9.45 [8:12, 18.77] 9.70 [2.30, 17:10] 9.70 [2.30, 17:10] 9.70 [2.30, 17:10] 14.27 [137, 8.27] 14.27 [137, 8.27] 14.27 [137, 8.27] 15.20 [8.40, 12.00] 9.20 [8.40, 12.00] 8.74 [2.70, 10.70] 11.90 [8.44, 11.20] 8.74 [2.70, 10.70] 11.90 [8.44, 11.20] 11.90 [8.44, 11.20] 11.9	Maan Difference IV, Random, 855 CI
D THK // V - 1 cor ling/ut Bindy or Support 3.4 4.4 Standy or Support 3.4 5.4 Bindy or Support 3.4 5.4 5.4 Bindy or Support 3.4 5.6 7.6 7.7 7.0 7.0 7.4 5.6 7.6	L Mean Difference 8.6 1.17 10.6 1.77 10.3 7.72 10.3 7.72 10.3 7.72 10.3 7.72 10.3 7.72 10.3 7.72 10.3 7.72 10.3 7.72 10.3 7.72 10.3 7.72 10.4 7.75 10.4 7.75 10.	Closed-loop SE Tota 35 3 55 7 48 6 56 7 41 11 56 7 56 7 41 11 57 3 56 7 41 15 56 7 41 15 56 3 57 3 58 6 58 6 59 5 50 50 5 50 50 5 50 5	Usual Care i Total 3 37 3 39 745 689 2 28 3 232 5 68 6 1 3 232 5 68 6 1 5 55 5 229 3 63 6 3 4 63 5 55 5 229 3 63 6 83 6 85 5 229 3 63 6 83 6 83 6 85 6 9 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	Weight 5.4% 5.3% 5.9% 21.1% 2.5% 5.3% 5.0% 21.4% 5.1% 5.1% 5.1% 5.1% 5.1% 5.5%	Moan Difference IV, Random, 95% CI 10.80 [7:30, 14:30] 11.30 [8:80, 13.80] 9.45 [8:12, 18.77] 9.70 [2.30, 17.10] 9.45 [8:12, 18.77] 4.82 [3:37, 8.27] 2.40 [9:30, 15.30] 7.78 [4:58, 18.98] 7.78 [4:58, 18.98] 9.20 [6:40, 12.00] 9.20 [6:40, 12.	Maan Difference IV, Bandon, 855 Cl
Study or Subgroup Study or Subgroup Study or Subgroup	L Mean Difference 108 / 11 108 / 12 108 /	Closed-loop SE Tots 35 3 55 4 55 7 56 7 56 7 56 7 56 7 56 5 56 5 56 5	Usual Care 4 Total 3 37 3 39 7 48 9 218 3 23 2 55 4 61 3 34 5 55 2 29 3 63 3 53 1 55 5 53 1 55 5 53 1 55 5 74 5 74 5 74 5 75 5 74 5 75 5	Weight 5.4% 4.6% 5.3% 5.9% 21.1% 2.5% 5.0% 21.4% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1%	Mean Difference IV, Random, 95% CI (0.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.40, 9.44] 9.45 [8.12, 10.77] 12.00 [8.12, 10.77] 13.00 [8.12, 10.77] 13.00 [8.12, 10.77] 13.00 [8.12, 10.77] 13.00 [8.40, 12.00] 9.20 [8.40, 12.00] 14.27 [11.00, 15.51] 14.27 [11.00, 15.51]14.27 [11.00, 15.51] 1	Mean Difference IV, Random, 955 CI
B) Titk //> //> Study or Subgroup 3.4.1 Cam.APS PK Bardson 2000 (DCL.PS) Bardson 2000 (DCL.PS) Brown 2019 (DCL.PS) Bardson 2000 (DCL.PS) Study of The Y Total Y	L Mean Difference Mean Difference 108 .72 108 .72 108 .72 8.67 02 4.47 -3 (P = 0.022); P = 329 1.00001) 6.7 4.72 1.53 1.22 4.42 17 1.52 4.14 6.7 2 2.33 3.6 (f = 4 (P = 0.000); P = 7 1.59 1.62 1.59 1.62	Closed-loop SE Tota 35 3 55 7 44 56 7 7 48 22 56 7 56 7 56 7 56 7 56 7 56 7 56 7 57 44 56 7 56 5 57 50 5 50 50 5 50 50 50 50 50 50 50 50 50 50 50 50	Usual Care 4 Total 3 37 3 39 74 5 68 9 218 3 23 2 56 4 61 3 34 4 55 5 229 3 63 6 63 6 63 6 63 6 63 6 63 6 63 6 63 6 7 6 7 6 8 6 9 7 4 8 9 7 4 8 9 8 9 8 9 8 9 8 9 8 9 8 9 8 9	Weight 5.4% 4.6% 5.3% 5.3% 21.1% 4.6% 5.3% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1%	Most Difference IV, Random, 95% CI 10.80 (7.30, 14.30) 11.80 (7.30, 14.30) 11.80 (7.40, 30.41, 30) 11.80 (7.40, 30.41, 30) 11.80 (7.40, 30.41, 30) 9.45 (8.12, 10.77) 9.70 (2.30, 17.10) 5.80 (3.57, 8.20) 6.72 (2.30, 17.10) 5.80 (3.57, 8.20) 6.72 (2.30, 17.10) 5.20 (6.40, 12.00) 9.20 (6.40, 12.00) 9.20 (6.40, 12.00) 6.74 (2.70, 10.78) 11.99 (8.41, 51.40) 6.74 (2.70, 10.78) 11.99 (8.41, 51.40) 9.82 (5.46, 13.89) 9.82 (5.46, 13.89)	Maan Difference IV, Random, 955 Cl
B) TIRK //P-ISO IIIIgraf Study or Subgroup 3.4.1 Cam.APS PK Boxplion 2022 Boxplion 2022 Study or SUBS CD(PA) Boxplion 2022 Studiotal (BSS CD) Heinrogeneity, Tau ² 0.51:CU ² = 1.4. Test for ownait effect 2 × 13.90 (P < CD	L Mean Difference 10.6.117 10.6.7 10.6.7 10.6.7 10.6.7 10.6.7 10.6.7 10.6.7 10.6.7 10.6.7 10.6.7 10.6.7 10.6 10.7 10.7 10.6 10.7 10.7 10.7 10.7 10.7 10.7 10.7 10.7	Closed-loop 5E Tota 55 44 55 7 44 56 7 7 44 6 56 7 56 7 56 7 56 7 56 8 56 6 56 6 56 6 56 6 56 6 56 6 51 7 51	Usual Care i Total 3 37 5 66 9 218 8 232 2 66 5 44 6 55 6 249 1 63 6 34 6 3 6 34 6 3 8 53 1 151 1 51 1	Weight 5.4% 5.3% 5.3% 21.1% 2.5% 3.9% 3.9% 3.9% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1%	Most Difference IV, Bandom, 95% C1 0.80 (7.30, 14.30) 11.30 (8.80, 13.80) 9.45 (8.12, 18.77) 9.45 (8.12, 18.77) 9.70 (2.30, 17.10) 9.45 (8.12, 18.77) 12.77 (2.30, 17.10) 9.42 (13.78, 273) 12.77 (2.30, 17.10) 9.20 (8.40, 12.00) 9.20 (8.40, 13.00) 11.97 (8.40, 13.00) 11.97 (8.40, 13.00) 9.20 (8.40,	Maan Difference IV, Bandom, 855 Cl
B) Title // 0-100 million 34.1 (1.4.904) (1.4.904) 34.1 (1.4.904) (1.4.904) 34.1 (1.4.904) (1.4.904) 34.1 (1.4.904) (1.4.904) 34.1 (1.4.904) (1.4.904) 34.1 (1.4.904) (1.4.904) Bedra 2020 (1.0.2.49) (1.4.904) Bedra 2020 (1.0.2.49) (1.4.904) Bedra 2020 (1.2.904) (1.4.904) Bedra 2020 (1.4.904) (1.4.904) Bound 2020 (1.4.904) (1.4.904) Bound 2020 (1.4.904) (1.4.904) Bound 2020 (1.4.904) (1.4.904) Montage 2020 <td< td=""><td>L Mean Difference 4. df = 0 (2) (2) (2) (2) (2) (2) (2) (2) (2) (2)</td><td>Closed-loop SE Tota 35 33 35 33 36 7 41 15 41 22 41 23 41 23 41</td><td>Usual Care i Total 3 37 5 68 9 23 5 68 9 23 5 68 9 23 5 68 9 23 5 68 9 23 9 53 1 55 1 151 1 151 1 151 1 151 1 151 1 293 3 293 3 293 3 293 5 38 9 293 1 293 5 38 9 293 1 293 5 38 9 293 1 29</td><td>Weight 5.4% 4.6% 5.3% 5.3% 2.5% 5.3% 2.5% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.1% 5.1% 5.1% 19.2% 3.1%</td><td>Mean Difference IV, Random, 95% CI (bal) (7.30, 14.30) (1.40, 17.30, 14.30) (1.40, 17.30, 14.30) (1.40, 17.40, 19.41) (1.40, 19.41) (1.41, 19.</td><td>Mean Difference IV, Random, 955 CI</td></td<>	L Mean Difference 4. df = 0 (2) (2) (2) (2) (2) (2) (2) (2) (2) (2)	Closed-loop SE Tota 35 33 35 33 36 7 41 15 41 22 41 23 41	Usual Care i Total 3 37 5 68 9 23 5 68 9 23 5 68 9 23 5 68 9 23 5 68 9 23 9 53 1 55 1 151 1 151 1 151 1 151 1 151 1 293 3 293 3 293 3 293 5 38 9 293 1 293 5 38 9 293 1 293 5 38 9 293 1 29	Weight 5.4% 4.6% 5.3% 5.3% 2.5% 5.3% 2.5% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.1% 5.1% 5.1% 19.2% 3.1%	Mean Difference IV, Random, 95% CI (bal) (7.30, 14.30) (1.40, 17.30, 14.30) (1.40, 17.30, 14.30) (1.40, 17.40, 19.41) (1.40, 19.41) (1.41, 19.	Mean Difference IV, Random, 955 CI
	L Mean Difference Kan	Closed-loop SE Tots SG 7 3 SG 3 SG 4 SG 4 SG 7 SG 7 S	Usual Care 1 Tetalité 3 373 3 373 3 373 3 474 4 5 5 255 3 434 4 5 5 255 3 434 4 5 5 259 3 63 3 53 3 53 5 229 3 63 5 229 5 239 5	Weight 5.4% 4.6% 5.3% 5.3% 2.5% 5.3% 2.5% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.1% 5.1% 4.3% 5.1% 19.2% 3.1% 3.2% 6.3%	Mean Difference IV, Random, 95% CI 10.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.40, 9.44] 9.45 [81, 2, 10, 77] 9.45 [81, 2, 10, 77] 9.45 [81, 2, 10, 77] 12.40 [80, 153, 0, 153, 0] 9.20 [84, 0, 153, 0] 9.20 [84, 0, 12, 00] 9.20 [84, 0, 12, 00] 11.99 [84, 51, 14] 9.20 [84, 0, 12, 00] 6.74 [2.70, 10, 18, 34] 9.20 [84, 0, 13, 00] 8.20 [84, 0, 12, 00] 8.20 [84, 0, 12, 00] 8.20 [84, 0, 12, 00] 8.20 [84, 0, 12, 00] 8.20 [84, 0, 13, 0] 8.20 [Maan Difference IV, Random, 955 cl
Budy or Subgroup Study or Subgroup Sta1 CamaRP R Bards 2003 (DC, PS) Brown 2019 (DC, PS) Wather all (PS) (DA = 0.51; CDF = 4.5 Brown 2019 (DC, PS) Wather 2020 (DAN06) Brown 2019 (DC, PD, P) Wather 2020 (DAN06) Brown 2019 (DC, PD, P) Wather 2020 (DAN06) Brown 2019 (DAR2, DC, PD + 15; Test for overall effect: Z = 4.47 (P < 0)	L Mean Difference 6.6 117 108 172 108 172 108 172 108 172 108 172 108 172 108 172 109 172 109 172 109 172 109 172 109 172 109 174 109	Closed-loop SE Tots 36 3 36 3 36 7 36 4 26 7 44 2 56 7 56 7 56 7 56 7 56 7 56 7 56 7 56 6 5 56 5 5 56 5 5 5 6 6 6 6 6 6 6 6 6 7 7 11 15 15 15 15 15 15 15 15 15	Usual Cere 1 Tetal 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	Weight 4 6% 5 4% 5 9% 5 9% 21.1% 25,5% 5 3% 3 9% 21.4% 5 5,3% 5 1% 5 1% 5 1% 5 6% 6 3% 6 3%	Mostri Difference IV, Random, 95% CI 10.80 [7.30, 14.30] 11.30 [7.30, 14.30] 11.30 [7.30, 14.30] 11.30 [7.40, 369] 9.45 [8.12, 10.77] 9.70 [2.30, 17.10] 5.80 [5.76, 829] 12.40 [10.3, 15.76, 829] 13.20 [8.40, 12.00] 9.20 [8.40, 12.00] 9.20 [8.40, 12.00] 9.20 [8.40, 12.00] 9.20 [8.40, 12.00] 14.97 [11.00, 18.54] 8.22 [5.46, 13.30] 14.77 [11.00, 18.54] 8.22 [5.46, 13.30] 14.77 [11.00, 18.54] 8.22 [5.46, 13.30] 12.100 [15.70, 27.30] 24.51 [18.53, 30.44]	Maan Difference IV, Random, 855 Cl
B) THX //P-100 Imgrui Subprov	L Mean Difference Mean Difference 4. gf = 3 (P = 0.22); P = 323 0.00001) 9.7 377 4. gf = 3 (P = 0.045); P = 323 0.0001) 9.2 1.42 0.0001) 6.74 2.02 0.0001) 6.74 2.02 0.0001; P = 23 0.0001; P = 23 0.0000; P = 23 0.0000; P =	Closed-loop SE Tota 55 7 4 357 4 221 56 7 56 7 56 7 56 7 56 7 56 7 56 7 56 7	Usual Care 1 Total 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	Weight 4 6% 5 54% 4 6% 5 59% 21.1% 21.1% 25.5% 5 33% 4 6% 5 51% 5 51% 5 51% 5 6% 6 3% 6 3%	Mean Difference IV, Random, 95% C1 10.00 [7:0.01430] 11.20 [8:0.11300] 12.00 [8:0.11300] 13.20 [8:0.11300] 9.45 [8:12, 18:77] 9.70 [2:0.17:10] 9.70 [2:0.17:10] 4.82 [137, 8:27] 12.42 [14, 137, 9] 9.20 [8:40, 12.00] 9.20 [8:40, 12.00] 13.90 [11:01, 27.23] 24.51 [18:53, 30.46] 13.40 [11:00, 15.87]	Maan Difference IV, Bandon, 855 Cl
Budy or Subgroup Study or Subgroup	L Mean Difference 10.6 / 11 10.6 / 12 10.6 / 12 10	Closed-loop 5E Tots 5G 7 4 5G 7 4 5G 7 4G 6 5G 7 4G 6 5G 7 4G 7 5G 7	Usual Center 1 Total 3 Total 3 Total 3 Total 3 Total 4 Total 3 Total 3 Total 4 Total 5 Total	Weight 6.4% 4.6% 5.9% 2.5% 2.5% 2.5% 2.1.% 2.5% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.3	Mean Difference IV, Random, 95% CI 8,00 (63,01 030) 110,00 (73,01 43,30) 111,00 (73,01 43,30) 111,00 (73,01 43,30) 111,00 (74,0, 394) 9,45 (81,21,01,77) 9,47 (43,94) 9,47 (43,94) 9,47 (43,94) 9,47 (44,10,10,00) 9,20 (8,40,120,00) 9,20 (8,40,	Maan Difference IV, Random, 955 CI
	L Mean Difference 108 . 11 108 . 12 108 . 12 108 . 12 108 . 12 8.6 . 11 108 . 12 8.6 . 12 8.7 . 02 10.00001) 9.7 . 27 12.2 . 12 1.5 . 12 4. 47 - 3.0 P = 0.004; P = 7 10.0001) 9.2 . 142 0.0001) 9.2 . 142 0.0001) 9.2 . 142 0.0001) 9.2 . 142 0.0001) 0.7.4 . 20 1.5 . 16 1.5 . 16 1.5 . 16 1.5 . 25 1.6 . 25 1.5 . 25 1.6 . 25 1.5 . 25 1.6 . 25 1.5 . 25 1.	Closed-loop SE Tots 335 3 355 4 244 1 244 1 256 7 244 256 6 256 6 257 2 15 366 6 257 2 15 366 6 13 5 13 5 2 2 2 2 30 13 5 14 5 14 5 14 1 14 1 15 1	Usual Care i Totala 3 77 3 8 3 78 3 78 4 76 4 77 4 77 7 7	Weight 5.4% 4.6% 5.9% 2.1.1% 2.5% 5.5% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.3% 5.3% 5.3%	Most Difference IV, Random, 95% CI 10.80 (7.30, 14.30) 11.80 (7.30, 14.30) 11.80 (7.30, 14.30) 11.80 (7.40, 39.44) 9.45 (8.12, 10.77) 9.70 (2.30, 17.10) 5.80 (3.57, 6.29) 12.40 (19.50, 15.76, 12.97) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.20 (8.40, 12.00) 9.22 (8.40, 12.00) 9.22 (8.40, 12.00) 9.22 (8.40, 12.00) 9.22 (8.40, 12.00) 9.22 (8.40, 13.00) 9.22 (8.40, 13.00) 9.22 (8.40, 13.00) 9.22 (8.40, 13.00) 9.23 (8.40, 13.00) 13.40 (11.00, 15.80) 13.40 (11.00, 15.80)	Maan Difference IV, Random, 955 cl • • • • • •
B) TIRK //P-100 Img/II Binds or Business Binds or Business Binds or Business Bogston 2020 (DCLP6) Binds or 2010 (DCL) Wine 2020 (DCLC) Binds or 2010 (DCL) Wine 2020 (DCHC) Binds or 2010 (DCL) Binds Or 2010 (DCL) <td>Mean Difference Mean Difference 106 11 105 12 107 13 108 12 109 12 100 12 101 12 102 12 103 12 104 12 105 12 107 12 107 12 107 12 100001 97 107 12 100001 97 100001 97 100001 14.4 100001 14.4 100001 12.4 112 12.5 113.4 12 12.00001 13.4</td> <td>Closed-loop SE Tots 35 3 35 3 35 7 44 2 56 7 44 2 56 7 44 111 111 111 111 111 111 111</td> <td>Usual Cene i Totala 3 77 3 30 3 40 3 40 3</td> <td>Weight 5.4% 4.6% 5.9% 21.1% 2.5% 5.3% 5.3% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.3% 5.3% 5.3% 5.3%</td> <td>Most Difference IV, Random, 95% CI 8.00 (6.30, 10.90) 11.30 (7.90, 11.30) 11.30 (7.90, 11.30) 9.45 (8.12, 18.77) 9.70 (2.30, 17.10) 5.90 (3.57, 8.27) 14.27 (13.7, 8.27) 14.27 (13.7, 8.27) 15.20 (5.40, 12.00) 9.20 (6.40, 12.00) 9.20 (6</td> <td>Maan Difference IV, Random, 855 CI</td>	Mean Difference Mean Difference 106 11 105 12 107 13 108 12 109 12 100 12 101 12 102 12 103 12 104 12 105 12 107 12 107 12 107 12 100001 97 107 12 100001 97 100001 97 100001 14.4 100001 14.4 100001 12.4 112 12.5 113.4 12 12.00001 13.4	Closed-loop SE Tots 35 3 35 3 35 7 44 2 56 7 44 2 56 7 44 111 111 111 111 111 111 111	Usual Cene i Totala 3 77 3 30 3 40 3	Weight 5.4% 4.6% 5.9% 21.1% 2.5% 5.3% 5.3% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.3% 5.3% 5.3% 5.3%	Most Difference IV, Random, 95% CI 8.00 (6.30, 10.90) 11.30 (7.90, 11.30) 11.30 (7.90, 11.30) 9.45 (8.12, 18.77) 9.70 (2.30, 17.10) 5.90 (3.57, 8.27) 14.27 (13.7, 8.27) 14.27 (13.7, 8.27) 15.20 (5.40, 12.00) 9.20 (6.40, 12.00) 9.20 (6	Maan Difference IV, Random, 855 CI
By Tark / VP-100 migrat Study or Subgroup AL (1 a MM (2 A MM (L Mean Difference 8.6 1:17 10.8 17 10.8 17 10.8 17 10.8 17 10.8 17 10.8 17 10.8 17 10.8 17 10.8 17 10.8 17 10.7 12 10.00001) 10.7 137 10.8 1 10.8 17 10.8 17	Closed-loop EE Tota Tota Second Second Closed-loop Second Second Closed-loop Second Second Closed-loop Second Secon	Usual Core t Total 3 37 3 39 3 49 3 59 3 59 5 55 5 5	Weight 5.4% 4.6% 5.3% 4.6% 5.3% 4.5% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.3% 4.8% 5.3% 5.2%	Mean Difference IV, Random, 95% CI 10.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.30, 14.30] 11.00 [7.40, 9.44] 9.45 [8:12, 10.77] 12.00 [8:12, 10.77] 12.00 [8:30, 15.30] 6.77 [2.46, 11.20] 9.20 [6.40, 12.00] 9.20 [5.66, 13.98] 9.21 [5.66, 13.98] 13.40 [11.00, 15.80] 13.40 [11.00, 15.80] 10.83 [8.16, 13.42]	Maan Difference IV, Random, 955 CI
B) Title /// - Ioo/ Inigrat Study or Subgroup Study or Subgroup Study or Subgroup Sta1 Cam/MP FX Bedro 2000 (DCLPS) Bedro 2000 (DCLPS) Brown 2019 (DCLPS) Weine 2020 (DCLPS) Weine 2020 (DCLPS) Weine 2020 (DCLPS) Weine 2020 (DCLPS) Weine 2020 (DCLPS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Weine 2020 (DCLS) Fail for constal flatts 2 = 6.4 (P = 0.0 Annuhan 2011 (DCLBELCORD WF7) Statestal (BFS CD) List Ido constal flatts 2 = 6.4 (P = 0.0 Annuhan 2011 (DCLBELCORD WF7) Statestal (BFS CD) List Ido constal flatts 2 = 6.4 (P = 0.0 Annuhan 2011 (DCLBELCORD WF7) Statestal (BFS CD) List Ido constal flatts 2 = 6.4 (DCLBELCORD WF7) Statestal (BFS CD) List Ido constal flatts 2 = 6.4 (DCLBELCORD WF7) List Ido constal flatts 2 = 6.4 (DCLBELCORD WF7	L Mean Difference 108 a 11 108 a 12 108 a 12 108 a 12 108 a 12 8.6 a 13 108 a 12 8.7 0 4. 4f = 3 (P = 0.22); (P = 25) 1.00001) 9.7 a 12 4. 42 a 27 1.2 4 a 14 6.7 2 2.33 39. df = 4 (P = 0.004); (P = 7) 00001) 6.74 2.06 1.59 1.62 1.59 1.59 1.59 1.59 1.	Closed-loop 55 Tots 56 Tots 56 Tots 57 Tots 56 Tots 57 Tots 57 Tots 56 Tots 56 Tots 56 Tots 56 Tots 56 Tots 56 Tots 57 Tots	Usual Core 1 Total 3 37 3 5 3 5 3 5 4 6 4 5 5 7 5 7 7 7 7 7 7 7 7 7 7 7 7	Weight 5.4% 4.6% 5.9% 2.1% 5.3% 5.3% 5.0% 5.3% 5.0% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3%	Mean Difference IV, Random, 95% CI 10.00 [7:30, 14:30] 11.00 [7:30, 14:30] 11.00 [7:30, 14:30] 11.00 [7:30, 14:30] 11.00 [7:40, 39:4] 9.45 [8:12, 10.77] 9.70 [2:30, 17, 10] 5.90 [37, 8:29] 9.45 [8:12, 10.77] 12.40 [8:30, 15:30] 6.72 [2:16, 11:28] 9.20 [8:40, 12.00] 9.20 [8:40, 12.00] 9.20 [8:40, 12.00] 9.20 [8:40, 12.00] 6.74 [2:70, 10.78] 11.99 [8:44, 15:40] 13.40 [11.00, 15:80] 13.40 [11.00, 15:80] 13.40 [11.00, 15:80] 13.40 [11.00, 15:80] 10.28 [8:16, 13.48] 10.28 [8:1, 13.4	Maan Difference IV, Random, 955 cl • • • • • •
B) THX //ν-iou ling/u Binds on Biograph Binds on Biograph Binds on Biograph Binds on Biograph Biodylina 2020 Binds 2020 B	L Mean Difference 108 .72 108 .72 108 .72 109 .72 109 .72 109 .72 109 .72 109 .72 109 .72 109 .72 109 .72 107 .73 107	Closed-loop 56 Tots 36 3 36 3 36 7 36 7 37 4 48 221 56 7 56 7 56 7 56 7 56 7 56 7 56 7 56 7 56 5 57 50 6 6 6 6 6 6 5 5 5 5 5 5 5 5 5 5 5 5 5	Usual Cene i Totlavia 3 77 3 30 3 30 3 30 3 30 3 30 3 30 4 40 4 55 5 77 7 72 5 40 6 40 6 40 7 72 7 72 5 40 6 40 7 72 7 72 5 40 6 40 7 70 7 72 7 7 7 72 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	Weight 5.4% 5.5% 5.5% 21.1% 5.5% 5.5% 5.1% 5.1% 5.1% 5.1% 5.1% 5.5% 5.3	Most Difference IV, Random, 95% CI 8.00 (6.30, 10.90) 11.30 (7.30, 14.30) 11.30 (7.30, 14.30) 11.30 (7.30, 14.30) 11.30 (7.90, 13.80) 9.45 (8.12, 16.77) 9.70 (2.30, 17.10) 5.80 (5.7, 82.30) 14.40 (15.0, 82.7) 14.40 (15.0, 82.7) 14.40 (15.0, 82.7) 14.40 (15.0, 82.7) 14.20 (15.40, 12.00) 9.20 (6.40, 12.00) 11.40 (11.00, 15.60) 13.40 (11.00, 15.60) 14.40 (11.00, 15.60) 14.40 (11.00, 15.60) 14.40 (11.00, 15.60) 14.40 (11.00, 15.60) 14.40 (11.00, 15.60) 14.40 (11.00, 15.60)	Maan Difference IV, Random, 855 CI
Study or Subgroup	L Mean Difference 8.6 1.17 10.8 17 10.8 17 10.7 12 10.0001) 10.8 17 10.8 17 10.7 13 10.7 13	Closed-loop 5E Tota 55 7 4 56 7 4 56 7 4 56 7 57 7 58 7 59 7 50	Usual Care 1 Total 3 37 3 39 3 49 3 49 3 49 3 49 3 49 3 59 3 59 5 5	Weight 5.4% 4.5% 5.5% 5.1% 2.5% 4.4% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.3% 5.3% 5.3% 5.3% 5.3% 5.2% 5.2% 5.2% 5.2% 5.2% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.1% 5.3%	Mean Difference IV, Random, 95% CI (0.00 [7:30, 14:30] 11.00 [7:30, 14:30] 11.00 [7:30, 14:30] 11.00 [7:30, 14:30] 11.00 [7:40, 0.94] 9.45 [8:12, 10.77] 12.00 [8:12, 10.77] 12.00 [8:30, 15:30] 6.77 [2:46, 11:30] 7.77 [2:46, 11:30] 9.20 [6:40, 12:00] 9.20 [6:40	Maan Difference IV, Random, 955 CI
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Fig. 5 Subgroup analysis based on CL systems for (A) HbA1c % and (B) TIR 70–180 mg/dL

glycaemia compared to other systems in our sensitivity analyses, although no definite conclusions can be as no head-to-head comparisons were performed. Furthermore, there is a growing body of literature assessing the use of openAPS, or "do-it-yourself" (DIY) devices which are remotely controlled by open-source algorithms [61]. Given the limited knowledge about DIY systems [62], our analysis provides insight into the potential benefit of openAPS.

Most studies in our analysis did not assess fully automated systems [8, 29, 31-38, 40-46], which still require manual input from the user [63]. Therefore, the use of such devices in children and adolescents remains a challenge. Previous meta-analyses on paediatric populations, such as a recent one by Michou and colleagues [64], have shown a reduced risk of hypoglycaemia when assessing RCTs of mostly less than 12 weeks duration. Nonetheless, our analysis with RCTs of 12 to 96 weeks duration did not show a significantly reduced risk of hypoglycaemia nor coefficient of variation for the paediatric population, which could have been due to several reasons. For instance, children are more likely to experience hypoglycaemia due to increased physical activity, hormonal changes, varied eating habits and lifestyle, and inability to communicate symptoms appropriately [65]. Furthermore, considerable proportion of RCTs included have reported system errors and malfunctioning during the longer duration of the trials, potentially having important impacts for children and adolescents who are at a higher risk of hypoglycaemia or those not achieving target control [4]. These findings have important implications to the design of future paediatric trials, which should consider placing significant focus on patient education, device functioning and type of system used.

Finally, this was the first meta-analysis to assess how long-term use of AID impacts patient-reported outcomes with a considerable number of studies. Although our findings show significantly improved diabetes distress and a tendency for reduced fear of hypoglycaemia, no benefits were seen for treatment satisfaction. The high cost of AID devices, connectivity problems, automationrelated errors, pump glitches, and other issues associated with insulin pumps have been perceived as drawbacks by T1DM patients [5]. Moreover, most studies included in our analyses use CL algorithms that still require manual bolus input. Further improvements towards fully AID may result in improved quality of life and treatment satisfaction. Lastly, psychosocial measures varied between trials, limiting the populations of our analyses. Given that such outcomes have been recently receiving increased attention [5], future studies may consider using more consistent and widely used measures to aid interpretation of psychosocial impact.

Our study has important limitations. The lack of blinding in the studies, as it is potentially unfeasible to blind patients in such RCTs, reduced the certainty of evidence for our findings. It is important to note that heterogeneity was high for most glycaemic outcomes, especially in the adult and mixed populations. However, this finding was expected given the highly variable clinical and technical factors involved in studies performed in real-life conditions without supervision. Subgroup analyses of different machines and metaregression were performed to minimise and interpret such heterogeneities. Furthermore, we did not search the grey literature, which can increase the risk of publication bias. However, we believe that restricting our research to peer-reviewed sources minimised other sources of bias ensuring a more rigorous evaluation. Unfortunately, no study used outcomes such as mortality or macrovascular and microvascular complications as outcomes. Therefore, our study relies on surrogate measures for patient-oriented outcomes. Finally, recent bihormonal CL systems were not included as the RCTs on these devices only had a short follow-up period.

Conclusion

This systematic review and meta-analysis confirms previous findings in the literature of short-duration studies, showing that the prolonged use of AID devices under pragmatic settings results in a small, but important 0.37% (4.77 mmol/mol) reduction in HbA1c levels and may lead to a large 10.87% increase in TIR. Findings also suggest reductions in nocturnal and daily hypoglycaemia as well as patient distress without increasing the risk of DKA and severe hypoglycaemia. This estimate is beneficial in planning future long-term clinical trials assessing the use of fully automated and bihormonal AID devices. The synthesis of all system subgroups emphasises the potential benefits of certain CL systems, although this finding requires head-to-head comparisons before definitive conclusions can be made. Our results show that use of CL technology between 12 and 96 weeks has considerable benefits in a variety of clinical settings. Ultimately, it will be at the discretion of clinicians and patients to understand the potential benefits associated with different CL systems and decide on the most optimal insulin delivery method to improve patient outcomes.

Abbreviations

- AE Adverse event
- AID Automated insulin delivery
- CGM Continuous glucose monitoring
- CI Confidence interval
- CL Closed-loop
- CV Coefficient of glucose variability
- DDS Diabetes distress scale

DIY	Do It Yourself
DKA	Diabetic ketoacidosis
DTSQ	Diabetes Treatment Satisfaction Questionnaire
HCL	Hybrid Closed-loop
HFS	Hypoglycaemia Fear Survey
MDII	Multiple daily insulin injections
OR	Odds ratio
PLGS	Predictive low-glucose suspend
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PAID	Problem areas in diabetes
RCT	Randomised controlled trial
SAP	Sensor-augmented Insulin Pump
TIR	Time in range
T1DM	Type 1 diabetes mellitus
UC	Usual care

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s13098-023-01144-4.

Additional file 1: Appendix A. Search Strategy. Table S1. Descriptions of current insulin delivery devices. Table S2. Additional glycemic outcomes based on CL machines. Table S3. GRADE assessment. Figure S1. Forest plots for (A) DKA and (B) severe hypoglycaemia. Figure S2. Subgroup analysis based on closed-loop system devices for the outcomes of (A) CV and (B) nocturnal hypoglycemia. Figure S3. Critical appraisal according to the Cochrane Collaboration's tool for assessing risk of bias in randomised trials for clinical outcomes. Figure S4. Critical appraisal according to the Cochrane Collaboration's tool for assessing risk of bias in randomised trials for functional outcomes. Figure S5. Funnel plots for (A) HbA1c % and (B) TIR 70-180 mg/dL show no evidence of publication bias. Figure S6. Egger's regression test does not suggest significant publication bias for (A) HbA1c (%) endpoint; but suggests significant publication bias for (B) % TIR 70-180 mg/dL endpoint. Figure S7. Leave-one-out sensitivity analysis for the outcome of HbA1c (%). Figure S8. Baujat plot for the outcome of HbA1c (%). Figure S9. Meta-regression exploring the association between mean differences of HbA1c level (%) and duration of follow-up (weeks). Figure S10. Meta-regression exploring the association between mean differences of HbA1c level (%) and baseline HbA1c (%).

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Author contributions

EMHP, AM, IRM and AG wrote the study protocol and designed the statistical analyses. AG, AM, and LCH. assessed the eligibility of studies for inclusion in this analysis. IA.FS, CG, CH, and AG assessed the risk of bias, and IAM. and IRM. performed the GRADE assessment. AG and EMHP had access to, and verified, the underlying data from all original research articles, and conducted statistical analyses. AG, IRM, JERLJ and JRS wrote the first draft of the report. All authors were involved in data interpretation, manuscript writing, and manuscript editing. JRS provided senior supervision. All authors critically revised the report for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

All data are publicly available in the relevant primary and secondary papers from relevant trials as listed in the References.

Declarations

Ethics approval and consent to participate Not applicable.

Not applicable.

Consent for publication Not applicable.

Competing interests

We declare no competing interests.

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