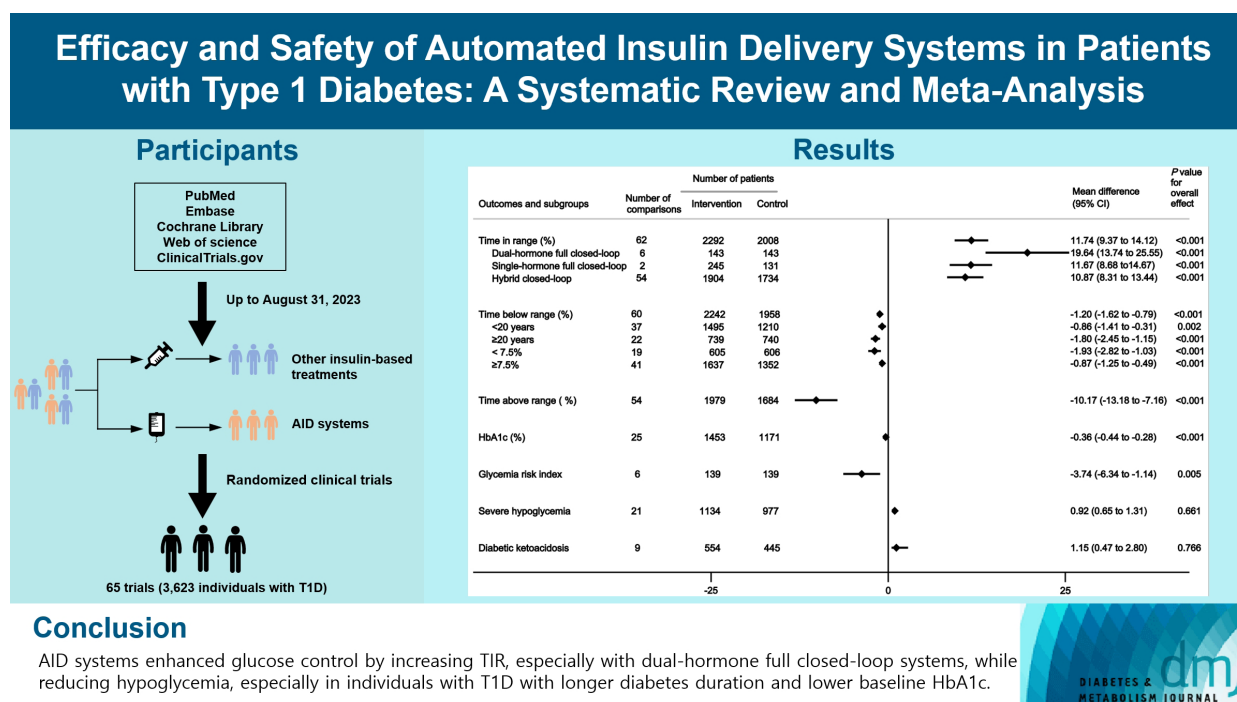


Efficacy and Safety of Automated Insulin Delivery Systems in Patients with Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Highlights

- This analysis of AID systems in T1D includes data from 65 RCTs with 3,623 patients.
- AID systems improved TIR by 11.74% and GRI by 3.74 compared to other therapies.
- Dual-hormone FCL systems showed greater TIR improvement than HCL systems.
- The benefits for TBR were more pronounced in patients with longer diabetes duration.

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Efficacy and Safety of Automated Insulin Delivery Systems in Patients with Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Background: Automated insulin delivery (AID) systems studies are upsurging, half of which were published in the last 5 years. We aimed to evaluate the efficacy and safety of AID systems in patients with type 1 diabetes mellitus (T1DM).

Methods: We searched PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov until August 31, 2023. Randomized clinical trials that compared AID systems with other insulin-based treatments in patients with T1DM were considered eligible. Studies characteristics and glycemic metrics was extracted by three researchers independently.

Results: Sixty-five trials (3,623 patients) were included. The percentage of time in range (TIR) was 11.74% (95% confidence interval [CI], 9.37 to 14.12; $P < 0.001$) higher with AID systems compared with control treatments. Patients on AID systems had more pronounced improvement of time below range when diabetes duration was more than 20 years (-1.80% vs. -0.86% , $P = 0.031$) and baseline glycosylated hemoglobin lower than 7.5% (-1.93% vs. -0.87% , $P = 0.033$). Dual-hormone full closed-loop systems revealed a greater improvement in TIR compared with hybrid closed-loop systems (-19.64% vs. -10.87%). Notably, glycemia risk index (GRI) (-3.74 ; 95% CI, -6.34 to -1.14 ; $P < 0.01$) was also improved with AID therapy.

Conclusion: AID systems showed significant advantages compared to other insulin-based treatments in improving glucose control represented by TIR and GRI in patients with T1DM, with more favorable effect in euglycemia by dual-hormone full closed-loop systems as well as less hypoglycemia for patients who are within target for glycemic control and have longer diabetes duration.

Keywords: Diabetes mellitus, type 1; Insulin infusion systems; Meta-analysis; Systematic review

INTRODUCTION

Type 1 diabetes mellitus (T1DM), resulting from insulin deficiency caused by autoimmunity mediated destruction of β -cells, requires lifelong treatment with exogenous insulin. Adjustments in daily insulin dosing based on carbohydrate counting

and frequent self-monitoring of blood glucose are arduous and challenging for both patients with T1DM and their caregivers [1]. Therefore, many patients with T1DM fail to meet the glycemic target goals in all age groups, e.g., target goals were achieved in only 17% for youth and by only 21% for adults [2] and life expectancy remains significantly 24 years shorter than

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in the non-diabetic population [1]. To improve this situation, insulin therapy has been improved by multiple daily injection (MDI), continuous subcutaneous insulin infusion (CSII), sensor-augmented pump (SAP), SAP with low-glucose suspend feature (SAP+LGS) and SAP with predictive low-glucose suspend feature (SAP+PLGS) in recent years, with consequent glucose improvement in patients with T1DM [3-5].

Automated insulin delivery (AID) system, is a closed-loop system that can deliver insulin automatically according to the glucose level by combining an insulin pump, continuous glucose monitoring (CGM), and a control algorithm, including full closed-loop (FCL) systems and hybrid closed-loop (HCL) systems; AID systems are emerging as a promising therapy for T1DM by providing appropriate insulin dosing in real-time, to limit both hyperglycemia and hypoglycemia. Therefore, AID systems could reduce the burden of glucose management compared with traditional insulin therapy [6,7].

AID systems in T1DM have attracted increasing attention in different populations of all age groups [8]. Several meta-analyses of AID systems uncovered promising efficacy [9-12]. Two large pooled analyses, including 24 studies with 585 participants in 2017 and 40 studies with 1,027 participants in 2018 [11,12], verified its favorable effect with increasing time in range (TIR) and decreasing time in either hyperglycemia or hypoglycemia in all age groups. But the maximum sample sizes for these analyses were only 54 and 75, respectively, and the longest follow-up duration was only 3 months. Since then there has been an upsurge in larger AID systems clinical trials, up to 326 cases, of longer duration, up to 24 months [13,14]. Recently, a meta-analysis conducted in 2023, including 25 studies with 1,345 participants, demonstrated the long-term effectiveness of AID systems in improving TIR, and the favorable effect on time below range (TBR) and time above range (TAR) [10]. However, that meta-analysis focused on children and adolescents and had potential methodological limitation, such as the handling of median values [15]. Moreover, updated artificial intelligence and science and technology have only since become available to allow FCL systems [16-19]. It is, therefore, timely we believe, to provide a comprehensive re-evaluation of both efficacy and safety of AID systems in patients with T1DM.

METHODS

The current study was conducted in accordance with the Pre-

ferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20] and registered with PROSPERO (CRD42023475763).

Data sources and searches

The literature published on PubMed, Embase, Web of Science, and Cochrane Library, and the grey literature from the ClinicalTrials.gov website was searched from database inception to August 31, 2023, using the keywords including 'type 1 diabetes mellitus', 'artificial pancreas', 'automated insulin delivery', and 'randomized controlled trial'. The detailed search strategy is shown in the Supplementary Methods (Search strategy). Our search was restricted to studies published in English.

Study selection

We included randomized controlled trial (RCT) that compared AID systems with insulin-based standard care in T1DM patients, irrespective of age, trial design (parallel or crossover), setting (outpatient or inpatient), or intervention duration. Studies involving non-T1DM participants and pregnant women were excluded. In addition, editorials, case reports, conference papers, and guidelines were excluded. The treatments in the control group included MDI, CSII, SAP, and SAP with LGS or PLGS.

Data extraction and quality assessment

Reference management software (Endnote X9, Clarivate, Philadelphia, PA, USA) was used to duplicate the identified literature. Three researchers (W.F., C.D., and R.X.) initially independently screened the title and abstract of the literature, then the full text, extracted data from each study using a standardized data extraction form in Excel as shown in the Supplementary Methods (Data extraction form) and evaluated the quality of each clinical trial using the Cochrane risk of bias tool that each study was classified as either high, low, or unclear risk of bias [21] and the certainty of evidence for all outcomes following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework with GRADEpro GDT software (<https://www.grade-pro.org>) [22], and disagreements were resolved by consensus or arbitrated by a fourth reviewer (X.L.).

The primary outcome was percentage of TIR (3.9 to 10.0 mmol/L [70 to 180 mg/dL] or 4.0 to 10.0 mmol/L [72 to 180 mg/dL] or 4.0 to 9.9 mmol/L [72 to 178 mg/dL], depending on the study). The secondary outcomes were other glucose met-

rics including the percentage of TAR (>10 mmol/L [180 mg/dL]) or TBR (<3.9 mmol/L [70 mg/dL] or <4.0 mmol/L [72 mg/dL], depending on the study), coefficient of variation (CV) of glucose, glycosylated hemoglobin (HbA1c) and insulin dose. In addition, the glycemia risk index (GRI) [23], a new composite CGM metric of glycemic risk, was also selected as a second outcome. Safety outcomes include diabetic ketoacidosis (DKA) and severe hypoglycemia.

Data synthesis and analysis

Review Manager version 5.3 (Cochrane, London, UK) and STATA version 14.0 (StataCorp., College Station, TX, USA) were used to perform statistical analyses. The 95% confidence intervals (CIs) were calculated for all results. Binary adverse outcomes were compared with the relative risk (RR). Continuous outcomes were compared with weighted mean differences, except for the insulin dose, which was compared with standardized mean differences (SMDs) owing to the different units in different studies. When the outcome medians and ranges were reported, appropriate formulae were selected to calculate the mean and variance [24]. We combined the study data from both parallel-group and crossover designs. Crossover trials were analyzed using group means and standard deviations as if they were parallel-group trials. Based on this assumption, the analysis was generally conservative [25]. In addition, we conducted a priori-decided subgroup analysis according to the timing of the intervention (24 hours vs. overnight), type of hormone (single vs. dual), age (adults vs. adolescents vs. mixed population), baseline HbA1c level ($<7.5\%$ vs. $\geq 7.5\%$), and remote monitoring (yes vs. no). We defined the Inreda artificial pancreas (AP), CamAPS HX, and bionic pancreas as the FCL and the other AID systems as the HCL, based on the consensus recommendations which defining no carbohydrate counting and manually initiated prandial boluses as FCL systems [26]. We also conducted a post hoc subgroup analysis based on type of closed-loop (dual-hormone FCL, single-hormone FCL, and HCL), time of follow-up (<3 months vs. ≥ 3 months), disease duration (<20 years vs. ≥ 20 years), type of algorithm and type of comparator.

The heterogeneity of the analysis was assessed by the I^2 and the chi-squared test based on the Cochran Q test. If $I^2 \geq 50\%$ or $P < 0.1$ for the chi-squared test, the random effects model was used by the DerSimonian and Laird estimation method; otherwise, a fixed-effects model was used. Sensitivity analysis was performed to estimate the robustness of the meta-analysis re-

sults, which was conducted using the leave-one-out strategy and repeating the meta-analyses, including studies with a parallel design. Publication bias was assessed using a funnel plot and Egger's test, where a P value less than 0.05 was considered the presence of publication bias. For all analyses, except for the Q test, statistical significance was set at $P < 0.05$.

Data and resource availability

The data sets generated during or analyzed in the current study are available from the corresponding author upon reasonable request.

RESULTS

Study selection

A total of 14,392 records were identified from the database search, and 79 records were identified from ClinicalTrials.gov. Two hundred and forty-one studies were assessed through a full-text review for eligibility and 65 studies were included in this analysis (Supplementary Fig. 1).

Characteristics of included studies

The baseline characteristics of the studies are summarized in Supplementary Table 1. Given the different populations, settings, and amounts of intervention hormones, each of eight studies were entered as two separate comparisons in the meta-analysis [27–34]. Thus, a total of 73 comparisons from 65 studies with 3,623 patients with T1DM (44 crossover and 21 parallel designs) were included in the analysis. There are 34 studies published in the last 5 years and the remaining 31 studies were published between 2013 and 2017. Seven studies used FCL systems and the remainder used HCL systems, with a wide variation in follow-up time ranging from one night to 24 months and in baseline HbA1c level ranging from 6.7% to 10.6%.

Risk of bias assessment

The Cochrane risk of bias tool was used to assess the methodological quality and bias of all included studies, as shown in Supplementary Fig. 2. Random sequence generation presented a low risk of bias in all studies because of the randomized control study design. Given the nature of the intervention, blinding of participants and personnel presented a high risk of bias in all studies, and blinding of outcome assessors presented a high risk of bias in most of the included studies except for

Table 1. Summary results of overall meta-analysis for all outcomes

Outcome	No. of comparisons	No. of patients		Mean difference or relative risk (95% CI)	P value	I ² , %
		Intervention	Control			
Time in range	62	2,292	2,008	11.74 (9.37 to 14.12)	<0.001	94.6
Time below range	60	2,242	1,958	-1.20 (-1.62 to -0.79)	<0.001	91.7
Time above range	54	1,979	1,684	-10.17 (-13.18 to -7.16)	<0.001	96.0
Coefficient of variation, %	41	1,682	1,402	-1.31 (-2.16 to -0.47)	0.002	83.1
HbA1c, %	25	1,453	1,171	-0.36 (-0.44 to -0.28)	<0.001	28.0
Glycemia risk index	6	139	139	-3.74 (-6.34 to -1.14)	0.005	99.3
Insulin dose	44	1,538	1,376	0.03 (-0.08 to 0.15)	0.577	57.2
Severe hypoglycemia	21	1,134	977	0.92 (0.65 to 1.31)	0.661	18.7
Diabetic ketoacidosis	9	554	445	1.15 (0.47 to 2.80)	0.766	0.0

CI, confidence interval; HbA1c, glycosylated hemoglobin.

three studies [35-37]. Allocation concealment presented a low risk of bias in 15 studies and an unclear risk of bias in other studies.

Primary outcomes

Sixty-two comparisons from 56 studies with 3,306 patients were pooled to analyze TIR. TIR was 11.74% (95% CI, 9.37 to 14.12; $P<0.001$; $I^2=94.6\%$, moderate certainty) of time per day (2 hours 49 minutes) higher with AID systems compared with other control treatments (Table 1, Fig. 1). The favorable effect of TIR was consistent in all subgroups (Table 2). Of note, AID systems had a greater improvement in TIR in dual-hormone FCL (19.64% of time per day [4 hours 43 minutes]; 95% CI, 13.74 to 25.55) compared with HCL (10.87% of time per day [2 hours 37 minutes]; 95% CI, 8.31 to 13.44) (Fig. 2). Additionally, the model predictive control (MPC)-based AID systems system revealed a similar improvement in TIR (11.41% of time per day [2 hours 44 minutes]; 95% CI, 8.74 to 14.09) compared with proportional integral derivative (PID)-based AID systems (11.60% of time per day [2 hours 47 minutes]; 95% CI, 7.65 to 15.54), and the patients with baseline HbA1c level of more than 7.5% showed a greater improvement in TIR (13.25% of time per day [3 hours 11 minutes]; 95% CI, 10.27 to 16.22) compare with the patients with baseline HbA1c level of less than 7.5% (8.84% of time per day [2 hours 7 minutes]; 95% CI, 5.91 to 11.78) with a significant subgroup difference ($P=0.039$). In addition, there was no difference in the subgroup of follow-up time (11.82% of time per day [2 hours 50 minutes] vs. 11.31% of time per day [2 hours 43 minutes], P value for subgroup difference=0.810).

Secondary outcome and safety outcome

Sixty comparisons with 3,253 patients were pooled for TBR. Compared to the control treatment, the period using AID systems was shortened by approximately 17 minutes per day (-1.20%; 95% CI, -1.62 to -0.79; $P<0.001$; $I^2=91.7\%$, moderate certainty) (Table 1, Supplementary Fig. 3). The favorable effects were consistent for all subgroups. However, differences in reduction in TBR were higher in studies with diabetes duration of more than 20 years (-1.80% of time per day [26 minutes]; 95% CI, -2.45 to -1.15) compared with diabetes duration of less than 20 years (-0.86% of time per day [12 minutes]; 95% CI, -1.41 to -0.31) with a significant subgroup difference ($P=0.031$). Use of AID systems was also associated with a significant reduction in studies with baseline HbA1c less than 7.5% compared with baseline HbA1c more than 7.5% (-1.93% of time per day [28 minutes] vs. -0.87% of time per day [13 minutes], $P=0.033$). There was no significant statistical difference in the subgroup of follow-up time (-1.57% of time per day [27 minutes] vs. -0.81% of time per day [12 minutes], $P=0.057$).

In total, 54 comparisons with 2,769 patients were pooled for TAR. TAR was 10.17% of time per day (95% CI, -13.18 to -7.16; $P<0.001$; $I^2=96.0\%$, moderate certainty) lower for AID systems compared to control treatment, equivalent to 2 hours 26 minutes per day (Table 1, Supplementary Fig. 4). Similarly, TAR improved in all subgroups. Results were more significantly favorable for dual-hormone FCL systems (-16.88% of time per day [4 hours 3 minutes]; 95% CI, -22.41 to -11.35) compared with HCL systems (-9.22% of time per day [2 hours 13 minutes]; 95% CI, -12.56 to -5.89). AID systems showed a re-

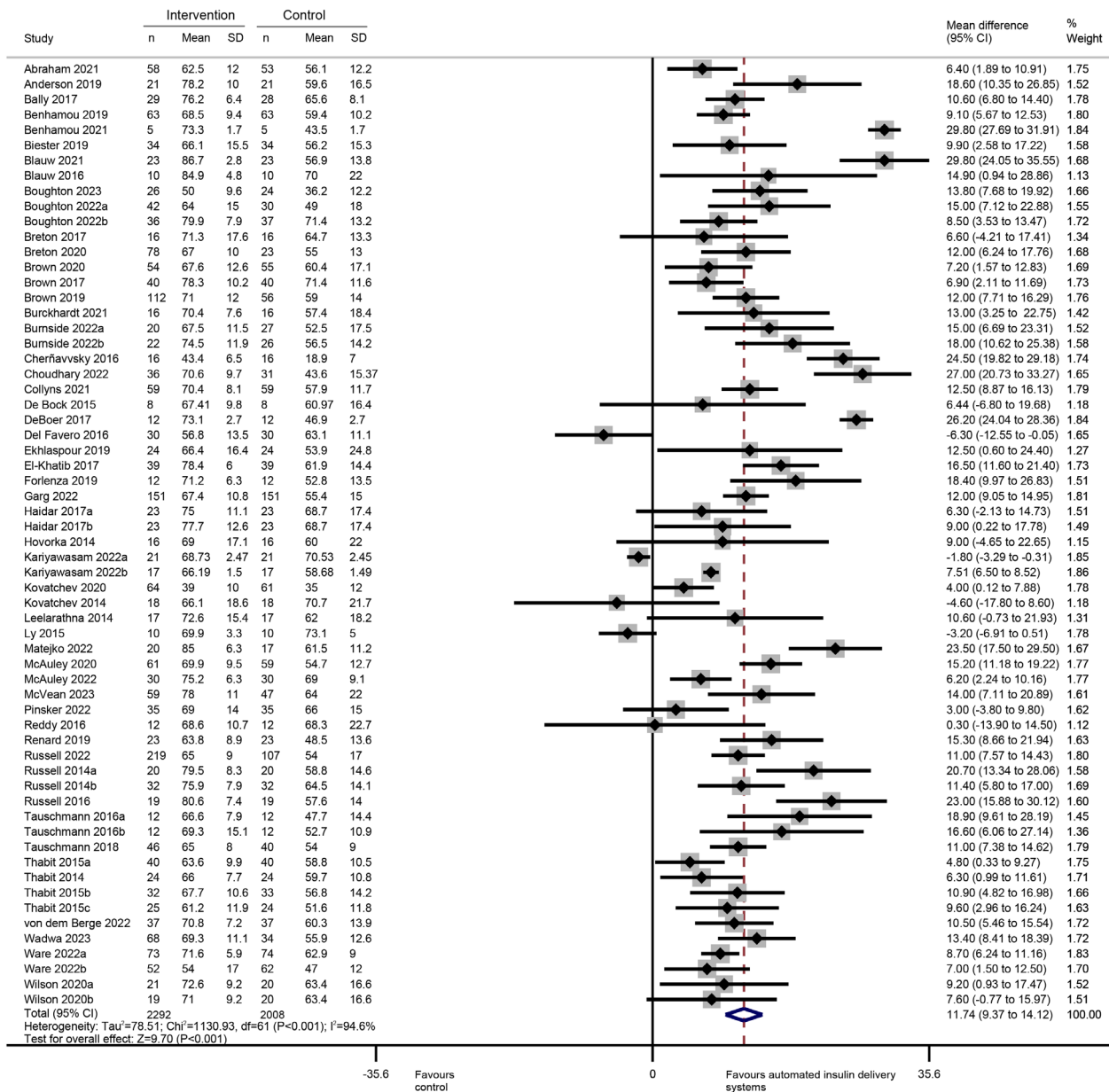


Fig. 1. Forest plot for time in range comparing automated insulin delivery systems with other insulin-based treatment. SD, standard deviation; CI, confidence interval.

duction in TAR in MPC-based systems (-10.96% of time per day [2 hours 39 minutes]; 95% CI, -14.09 to -7.83; $P<0.001$). There was almost no difference in the follow-up of less than 3 months compared to more than 3 months.

In terms of glucose variability, compared to control, treatment with AID systems demonstrated a favorable effect on CV (-1.31%; 95% CI, -2.16 to -0.47; $P=0.002$; $I^2=83.1\%$, moderate certainty) (Table 1, Supplementary Fig. 5). The favorable ef-

fect was greater in dual-hormone FCL systems than HCL systems both in CV (-4.34% vs. -1.11%). Significantly greater reductions were seen in the dual-hormone systems, in adult, with remote monitoring, and with diabetes duration of more than 20 years group for CV.

Considering the risk of hypoglycemia and hyperglycemia, we performed an additional pooled analysis of GRI. Use of AID systems was associated with the reduction in GRI (-3.74; 95%

Table 2. Summary results of prespecified subgroup meta-analyses for primary and secondary outcomes

Outcomes and subgroups	No. of comparisons	No. of patients		Mean difference between AID systems and other insulin therapy (95% CI), %	P value for overall effect	P value for subgroup differences	Weight, %	I ² , %
		Intervention	Control					
Time in range, %								
Total comparisons	62	2,292	2,008					
Timing of intervention								
24 hours	60	2,251	1,968	11.812 (9.396 to 14.229)	<0.001	0.479	97.22	94.8
Overnight	2	41	40	9.485 (3.516 to 15.454)	0.002		2.78	0.0
Hormone								
Single	54	2,107	1,822	11.021 (8.494 to 13.549)	<0.001	0.056	87.59	95.0
Dual	8	185	186	16.950 (11.412 to 22.488)	<0.001		12.41	79.6
Age								
Adults	23	814	713	13.107 (8.815 to 17.400)	<0.001	0.245	36.68	93.3
Children and adolescents	26	834	658	11.871 (8.191 to 15.551)	<0.001		41.68	95.5
Mixed population	13	644	637	8.933 (5.819 to 12.048)	<0.001		21.64	82.7
Follow-up, mo								
<3	38	1,456	1,175	11.816 (8.145 to 15.486)	<0.001	0.810	59.16	96.4
≥3	24	836	833	11.308 (9.408 to 13.208)	<0.001		40.48	74.4
Baseline HbA1c, %								
<7.5	21	660	661	8.844 (5.906 to 11.782)	<0.001	0.039	34.13	91.6
≥7.5	41	1,632	1,347	13.245 (10.270 to 16.220)	<0.001		65.87	92.9
Remote monitoring								
No	40	1,791	1,507	11.490 (9.555 to 13.424)	<0.001	0.904	64.96	81.1
Yes	22	501	501	11.825 (6.736 to 16.914)	<0.001		35.04	97.7
Diabetes duration, yr								
<20	38	1,543	1,258	11.217 (8.443 to 13.991)	<0.001	0.555	64.51	94.2
≥20	21	707	708	12.756 (8.470 to 17.041)	<0.001		35.49	93.7
Type of closed-loop								
Dual-hormone full closed-loop	6	143	143	19.643 (13.736 to 25.550)	<0.001	0.027	9.41	78.5
Single-hormone full closed-loop	2	245	131	11.671 (8.676 to 14.666)	<0.001		3.45	0.0
Hybrid closed-loop	54	1,904	1,734	10.873 (8.310 to 13.436)	<0.001		87.14	95.0
Type of algorithm								
MPC	37	1,261	1,105	11.411 (8.736 to 14.086)	<0.001	0.915	59.29	88.7
PID	15	595	568	11.595 (7.654 to 15.537)	<0.001		24.09	87.8
Other	10	436	335	13.091 (5.751 to 20.431)	<0.001		16.62	98.6
Type of comparator								
SAP	38	1,212	1,103	10.285 (7.622 to 12.948)	<0.001	0.304	60.69	93.3
CSII or MDI	10	425	424	13.293 (9.150 to 17.437)	<0.001		15.88	83.3
Mixed	14	655	481	14.547 (8.121 to 20.974)	<0.001		23.43	96.0
Time below range, %								
Total comparisons	60	2,242	1,958					
Timing of intervention								
24 hours	56	2,141	1,858	-1.221 (-1.653 to -0.790)	<0.001	0.470	94.01	92.2
Overnight	4	101	100	-0.933 (-1.587 to -0.279)	0.005		5.99	0.0
Hormone								
Single	53	2,096	1,811	-1.065 (-1.502 to -0.629)	<0.001	0.023	90.37	92.4
Dual	7	146	147	-2.310 (-3.289 to -1.331)	<0.001		9.63	53.0

(Continued to the next page)

Table 2. Continued

Outcomes and subgroups	No. of comparisons	No. of patients		Mean difference between AID systems and other insulin therapy (95% CI), %	P value for overall effect	P value for subgroup differences	Weight, %	I ² , %
		Intervention	Control					
Age								
Adults	22	619	612	−1.548 (−2.175 to 0.921)	<0.001	0.275	34.55	87.9
Children and adolescents	24	761	660	−0.912 (−1.769 to −0.056)	0.037		39.39	93.9
Mixed population	14	862	686	−0.927 (−1.429 to −0.424)	<0.001		26.01	82.6
Follow-up, mo								
<3	35	754	751	−1.567 (−2.233 to −0.900)	<0.001	0.057	53.32	92.8
≥3	25	1,488	1,207	−0.814 (−1.208 to −0.419)	<0.001		46.68	83.2
Baseline HbA1c, %								
<7.5	19	605	606	−1.927 (−2.823 to −1.031)	<0.001	0.033	31.69	94.6
≥7.5	41	1,637	1,352	−0.871 (−1.250 to −0.491)	<0.001		68.31	83.9
Remote monitoring								
No	39	1,754	1,470	−0.746 (−1.071 to −0.421)	<0.001	0.005	65.03	78.9
Yes	21	488	488	−1.911 (−2.646 to −1.175)	<0.001		34.97	90.6
Diabetes duration, yr								
<20	37	1,495	1,210	−0.861 (−1.414 to −0.308)	0.002	0.031	63.81	93.0
≥20	22	739	740	−1.799 (−2.448 to −1.150)	<0.001		36.19	89.3
Type of closed-loop								
Dual-hormone full closed-loop	5	104	104	−2.149 (−2.871 to −1.427)	0.009	<0.001	6.73	0.0
Single-hormone full closed-loop	2	245	131	0.141 (−0.162 to 0.442)	0.361		4.32	18.6
Hybrid closed-loop	53	1,893	1,723	−1.179 (−1.626 to −0.733)	<0.001		88.95	91.5
Type of algorithm								
MPC	35	1,220	1,064	−0.829 (−1.180 to −0.477)	<0.001	0.006	56.13	68.0
PID	15	586	559	−1.195 (−1.816 to −0.575)	<0.001		25.87	85.6
Fuzzy logic	1	34	34	1.300 (−0.239 to 2.839)	0.098		1.69	NA
Other	9	402	301	−2.206 (−3.533 to −0.879)	0.001		16.32	97.3
Type of comparator								
SAP	38	1,226	1,117	−1.212 (−1.759 to −0.665)	<0.001	0.001	64.53	92.3
CSII or MDI	9	409	408	−2.878 (−3.958 to −1.798)	<0.001		11.13	67.7
Mixed	13	607	433	−0.454 (−1.105 to 0.197)	0.171		24.35	90.2
Time above range, %								
Total comparisons	54	1,979	1,684					
Timing of intervention								
24 hours	52	1,938	1,644	−10.246 (−13.317 to −7.176)	<0.001	0.582	96.87	96.2
Overnight	2	41	40	−8.234 (−14.716 to −1.751)	0.013		3.13	0.0
Hormone								
Single	46	1,794	1,498	−9.612 (−12.897 to −6.327)	<0.001	0.233	85.64	96.5
Dual	8	185	186	−13.649 (−19.417 to −7.881)	<0.001		14.36	79.1
Age								
Adults	21	604	593	−9.909 (−14.788 to −5.030)	<0.001	0.546	39.06	93.9
Children and adolescents	22	732	624	−11.516 (−16.745 to −6.288)	<0.001		40.53	97.6
Mixed population	11	643	467	−8.050 (−11.648 to −4.452)	<0.001		20.41	79.9
Follow-up, mo								
<3	33	716	713	−10.006 (−14.590 to −5.421)	<0.001	0.952	59.52	97.5
≥3	21	1,263	971	−10.159 (−12.209 to −8.109)	<0.001		40.48	70.7

(Continued to the next page)

Table 2. Continued

Outcomes and subgroups	No. of comparisons	No. of patients		Mean difference between AID systems and other insulin therapy (95% CI), %	P value for overall effect	P value for subgroup differences	Weight, %	I ² , %
		Intervention	Control					
Baseline HbA1c, %								
<7.5	18	592	586	-6.938 (-10.806 to -3.070)	<0.001	0.060	34.19	94.4
≥7.5	36	1,387	1,098	-11.827 (-15.133 to -8.522)	<0.001		65.81	93.1
Remote monitoring								
No	36	1,558	1,263	-9.961 (-12.336 to -7.587)	<0.001	0.908	66.74	83.7
Yes	18	421	421	-10.366 (-16.813 to -3.918)	0.002		33.26	98.5
Diabetes duration, yr								
<20	35	1,477	1,185	-10.891 (-14.594 to -7.188)	<0.001	0.586	66.17	96.5
≥20	18	494	491	-9.072 (-14.468 to -3.677)	0.001		33.83	94.3
Type of closed-loop								
Dual-hormone full closed-loop	6	143	143	-16.879 (-22.411 to -11.348)	<0.001	0.066	10.85	72.3
Single-hormone full closed-loop	2	245	131	-11.715 (-14.851 to -8.579)	<0.001		3.90	0.0
Hybrid closed-loop	46	1,591	1,410	-9.224 (-12.562 to -5.886)	<0.001		85.25	96.5
Type of algorithm								
MPC	32	1,141	985	-10.958 (-14.085 to -7.830)	<0.001	0.894	58.83	90.1
PID	14	444	417	-9.916 (-14.206 to -5.626)	<0.001		25.44	85.6
Fuzzy logic	1	34	34	-9.300 (-17.219 to -1.381)	0.021		1.81	NA
Other	7	360	248	-7.396 (-17.027 to 2.235)	0.132		13.92	96.0
Type of comparator								
SAP	32	1,066	946	-9.403 (-13.281 to -5.525)	<0.001	0.206	58.78	96.5
CSII or MDI	8	258	257	-6.127 (-13.067 to 0.813)	0.084		14.54	89.5
Mixed	14	655	481	-14.046 (-19.835 to -8.256)	<0.001		26.68	94.5
Coefficient of variation, %								
Total comparisons	41	1,682	1,402					
Timing of intervention								
24 hours	39	1,641	1,362	-1.420 (-2.278 to -0.561)	0.001	0.020	96.37	83.4
Overnight	2	41	40	1.778 (-0.772 to 4.328)	0.172		3.63	0.0
Hormone								
Single	36	1,549	1,269	-0.974 (-1.848 to -0.099)	0.029	0.019	89.91	83.5
Dual	5	133	133	-4.337 (-7.016 to -1.658)	0.002		10.09	64.7
Age								
Adults	17	518	511	-2.487 (-3.867 to -1.107)	<0.001	0.005	43.66	87.1
Children and adolescents	16	598	501	0.277 (-0.758 to 1.312)	0.600		35.05	51.3
Mixed population	8	566	390	-1.368 (-2.623 to -0.114)	0.033		21.29	69.6
Follow-up, mo								
<3	18	381	378	-2.067 (-3.859 to -0.276)	0.024	0.243	37.63	85.9
≥3	23	1,301	1,024	-0.896 (-1.709 to -0.083)	0.031		62.37	74.9
Baseline HbA1c, %								
<7.5	12	445	446	-2.235 (-3.799 to -0.671)	0.005	0.169	29.84	82.0
≥7.5	29	1,237	956	-0.919 (-1.952 to 0.115)	0.081		70.16	84.1
Remote monitoring								
No	33	1,468	1,188	-0.996 (-1.881 to -0.111)	0.027	0.048	82.35	80.4
Yes	8	214	214	-2.841 (-4.440 to -1.242)	<0.001		17.65	68.5

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Table 2. Continued

Outcomes and subgroups	No. of comparisons	No. of patients		Mean difference between AID systems and other insulin therapy (95% CI), %	P value for overall effect	P value for subgroup differences	Weight, %	I ² , %
		Intervention	Control					
Diabetes duration, yr								
<20	27	1,274	993	−0.528 (−1.338 to 0.282)	0.201	0.014	63.63	65.3
≥20	14	408	409	−2.678 (−4.186 to −1.170)	<0.001		36.37	87.9
Type of closed-loop								
Dual-hormone full closed-loop	5	133	133	−4.337 (−7.016 to −1.658)	0.002	0.044	10.09	64.7
Single-hormone full closed-loop	2	245	131	1.063 (−3.240 to 5.367)	0.628		5.72	90.2
Hybrid closed-loop	34	1,304	1,138	−1.107 (−2.018 to −0.196)	0.017		84.19	83.1
Type of algorithm								
MPC	27	1,016	864	−0.485 (−1.307 to 0.337)	0.248	0.003	62.96	64.1
PID	7	280	253	−3.606 (−5.842 to −1.369)	0.002		17.76	85.3
Fuzzy logic	1	34	34	2.000 (−0.424 to 4.424)	0.106		2.61	NA
Other	6	352	251	−2.514 (−4.634 to −0.393)	0.020		16.68	90.6
Type of comparator								
SAP	26	905	796	−0.496 (−1.290 to 0.297)	0.220	0.021	61.12	62.9
CSII or MDI	6	232	235	−4.474 (−7.244 to −1.704)	0.002		14.50	85.3
Mixed	9	545	371	−1.448 (−3.388 to 0.491)	0.143		24.38	90.5
HbA1c, %								
Total comparisons	25	1,453	1,171					
Timing of intervention								
24 hours	24	1,428	1,147	−0.361 (−0.441 to −0.282)	<0.001	0.810	97.89	30.9
Overnight	1	25	24	−0.300 (−0.794 to 0.194)	0.233		2.11	NA
Age								
Adults	9	286	285	−0.330 (−0.473 to −0.187)	<0.001	0.371	29.87	23.6
Children and adolescents	10	522	418	−0.442 (−0.588 to −0.296)	<0.001		35.85	39.5
Mixed population	6	645	468	−0.314 (−0.426 to −0.202)	<0.001		34.28	16.1
Follow-up, mo								
<3	3	87	85	−0.304 (−0.546 to −0.062)	0.014	0.627	11.07	27.4
≥3	22	1,366	1,086	−0.367 (−0.450 to −0.284)	<0.001		88.93	30.2
Baseline HbA1c, %								
<7.5	9	399	400	−0.281 (−0.412 to −0.150)	<0.001	0.139	36.76	30.9
≥7.5	16	1,054	771	−0.402 (−0.495 to −0.309)	<0.001		63.24	21.3
Diabetes duration, yr								
<20	17	1,071	787	−0.365 (−0.469 to −0.260)	<0.001	0.903	67.27	40.1
≥20	8	382	384	−0.355 (−0.464 to −0.246)	<0.001		32.73	0.0
Type of closed-loop								
Single-hormone full closed-loop	2	245	131	−0.441 (−0.629 to −0.252)	<0.001	0.387	9.93	0.0
Hybrid closed-loop	23	1,208	1,040	−0.350 (−0.433 to −0.266)	<0.001		90.07	30.6
Type of algorithm								
MPC	15	776	616	−0.354 (−0.467 to −0.240)	<0.001	0.419	55.48	36.7
PID	7	416	395	−0.324 (−0.447 to −0.201)	<0.001		33.17	21.4
Other	3	261	160	−0.469 (−0.650 to −0.289)	<0.001		11.35	0.0
Type of comparator								
SAP	14	622	512	−0.311 (−0.415 to −0.208)	<0.001	0.369	53.34	23.5
CSII or MDI	5	347	342	−0.388 (−0.519 to −0.257)	<0.001		22.00	0.0
Mixed	6	484	317	−0.457 (−0.649 to −0.265)	<0.001		24.66	50.7

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Table 2. Continued

Outcomes and subgroups	No. of comparisons	No. of patients		Mean difference between AID systems and other insulin therapy (95% CI), %	P value for overall effect	P value for subgroup differences	Weight, %	I ² , %
		Intervention	Control					
Glycemia risk index								
Total comparisons	6	139	139					
Hormone								
Single	4	106	106	−2.910 (−5.958 to 0.138)	0.061	0.056	71.86	99.5
Dual	2	33	33	−6.336 (−8.088 to −4.585)	<0.001		28.14	0
Age								
Adults	4	101	101	−5.433 (−9.167 to −1.700)	0.004	0.046	63.85	97.5
Children and adolescents	2	38	38	−0.735 (−3.430 to 1.960)	0.593		36.15	99.4
Follow-up, mo								
<3	5	76	76	−4.082 (−7.106 to −1.057)	<0.001	0.240	82.22	99.4
≥3	1	63	63	−2.200 (−3.038 to −1.362)	<0.001		17.78	NA
Baseline HbA1c, %								
<7.5	2	38	38	−0.735 (−3.430 to 1.960)	0.593	0.046	36.15	99.4
≥7.5	4	101	101	−5.433 (−9.167 to −1.700)	0.004		63.85	97.5
Remote monitoring								
No	2	33	33	−6.336 (−8.088 to −4.585)	<0.001	0.056	28.14	0.0
Yes	4	106	106	−2.910 (−5.958 to 0.138)	0.061		71.86	99.5
Diabetes duration, yr								
<20	2	38	38	−0.735 (−3.430 to 1.960)	0.593	0.046	36.15	99.4
≥20	4	101	101	−5.433 (−9.167 to −1.700)	0.004		63.85	97.5
Type of closed-loop								
Dual-hormone full closed-loop	2	33	33	−6.336 (−8.088 to −4.585)	<0.001	0.056	28.14	0.0
Hybrid closed-loop	4	106	106	−2.910 (−5.958 to 0.138)	0.061		71.86	99.5
Type of algorithm								
PID	1	10	10	−4.800 (−9.376 to −0.224)	0.040	0.660	11.62	NA
Other	5	129	129	−3.600 (−6.374 to −0.827)	0.011		88.38	99.4
Type of comparator								
SAP	3	101	101	−1.209 (−3.313 to 0.896)	0.260	<0.001	53.93	98.9
CSII or MDI	1	10	10	−4.800 (−9.376 to −0.224)	0.040		11.62	NA
Mixed	2	28	28	−7.598 (−8.839 to −6.357)	<0.001		34.46	47.2
Insulin dose								
Total comparisons	44	1,538	1,376					
Timing of intervention								
24 hours	35	1,230	1,069	−0.041 (−0.159 to 0.078)	0.502	0.021	78.82	46.1
Overnight	9	308	307	0.322 (0.039 to 0.605)	0.026		21.18	65.5
Hormone								
Single	39	1,403	1,240	0.015 (−0.106 to 0.135)	0.813	0.485	88.92	54.8
Dual	5	135	136	0.184 (−0.277 to 0.646)	0.433		11.08	72.1
Age								
Adults	11	319	317	−0.147 (−0.308 to −0.014)	0.073	0.048	24.53	5.0
Children and adolescents	22	723	620	0.089 (−0.127 to 0.305)	0.420		47.51	71.7
Mixed population	11	496	439	0.103 (−0.027 to 0.233)	0.121		27.96	0.0

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Table 2. Continued

Outcomes and subgroups	No. of comparisons	No. of patients		Mean difference between AID systems and other insulin therapy (95% CI), %	P value for overall effect	P value for subgroup differences	Weight, %	I ² , %
		Intervention	Control					
Follow-up, mo								
<3	28	698	696	0.029 (−0.164 to 0.222)	0.768	0.978	56.41	67.5
≥3	16	840	680	0.026 (−0.085 to 0.137)	0.646		43.59	11.9
Baseline HbA1c, %								
<7.5	11	407	412	−0.158 (−0.357 to 0.042)	0.121	0.034	26.19	47.2
≥7.5	33	1,131	964	0.104 (−0.032 to 0.240)	0.135		73.81	55.3
Remote monitoring								
No	26	1,043	881	0.011 (−0.082 to 0.105)	0.811	0.624	61.97	3.4
Yes	18	495	495	0.083 (−0.187 to 0.353)	0.548		38.03	76.6
Diabetes duration, yr								
<20	33	1,215	1,055	0.060 (−0.072 to 0.192)	0.373	0.071	76.81	55.7
≥20	10	307	305	−0.137 (−0.304 to 0.031)	0.110		23.19	8.1
Type of closed-loop								
Dual-hormone full closed-loop	1	32	32	0.182 (−0.309 to 0.673)	0.468	0.683	2.44	NA
Single-hormone full closed-loop	1	26	24	0.216 (−0.341 to 0.772)	0.447		2.18	NA
Hybrid closed-loop	42	1,480	1,320	0.025 (−0.098 to 0.148)	0.692		95.39	68.9
Type of algorithm								
MPC	33	1,148	993	0.049 (−0.090 to 0.187)	0.490	0.063	74.68	58.0
PID	6	199	192	−0.089 (−0.357 to 0.179)	0.516		13.50	38.5
Fuzzy logic	4	179	179	0.217 (−0.107 to 0.540)	0.190		10.50	54.3
Other	1	12	12	−0.957 (−1.806 to −0.108)	0.027		1.32	NA
Type of comparator								
SAP	29	1,019	903	0.006 (−0.113 to 0.125)	0.919	0.269	65.88	37.2
CSII or MDI	9	306	305	0.275 (−0.138 to 0.689)	0.192		20.75	83.5
Mixed	6	213	168	−0.100 (−0.306 to 0.105)	0.339		13.37	0.0

AID, automated insulin delivery; CI, confidence interval; HbA1c, glycosylated hemoglobin; MPC, model predictive control; PID, proportional integral derivative; SAP, sensor-augmented pump; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; NA, not applicable.

CI, −6.34 to −1.14; $P=0.005$; $I^2=99.3\%$, moderate certainty) (Table 1, Supplementary Fig. 6).

Further pooled analyses of 25 comparisons with 2,375 patients for the long-term effect of AID systems on glycemic control exhibited that the HbA1c level was 0.36% (95% CI, −0.44 to −0.28; $P<0.001$; $I^2=28.0\%$, high certainty) lower in AID systems than control treatment. Finally, no difference between AID systems and other insulin-based treatments was seen in the insulin dose (SMD, 0.03; 95% CI, −0.08 to 0.15; $P=0.577$; $I^2=57.2\%$, moderate certainty) (Table 1, Supplementary Figs. 7 and 8).

For the safety outcomes, episodes of severe hypoglycemia were reported in 19 trials: 53 patients occurred during AID

systems treatment and 38 patients occurred during control use. Episodes of DKA were reported in nine trials: eight patients occurred during AID systems and five patients occurred in control therapy. Pooled effects were RR 0.92 (95% CI, 0.65 to 1.31; $P=0.616$; $I^2=18.7$, high certainty) for severe hypoglycemia and RR 1.15 (95% CI, 0.47 to 2.80; $P=0.766$; $I^2=0.0$, high certainty), indicating no differences between AID systems and control therapy (Table 1, Supplementary Figs. 9 and 10).

Sensitivity analyses

We further performed a sensitivity analysis for all outcomes to detect whether any single study could affect the reliability of the included studies by omitting studies one by one (Supple-

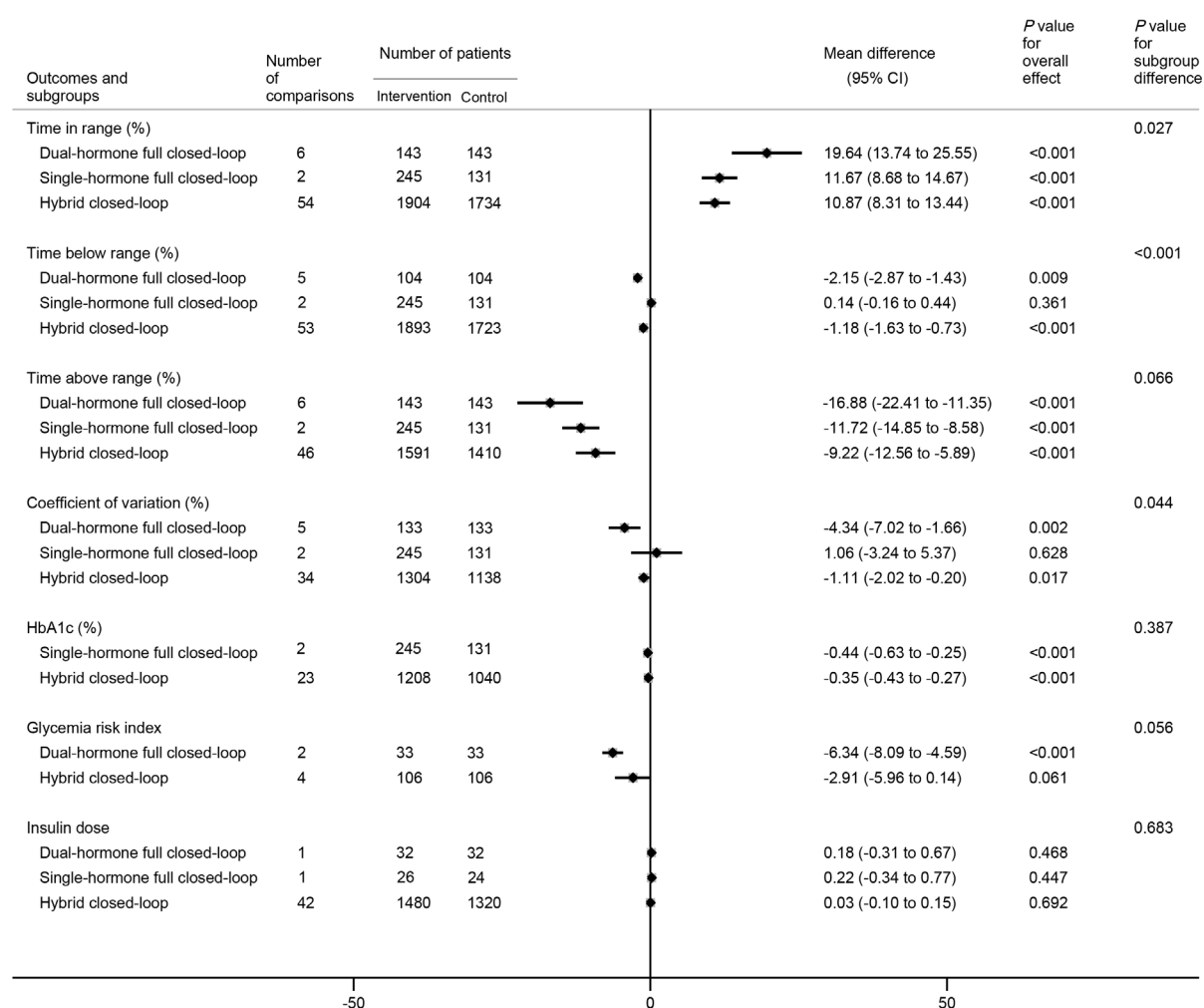


Fig. 2. Prespecified subgroup analyses for primary and secondary outcomes by the type of automated insulin delivery systems (dual-hormone full closed-loop systems, single-hormone full closed-loop, or hybrid closed-loop systems). CI, confidence interval; HbA1c, glycosylated hemoglobin.

mentary Figs. 11-19). When any single study was excluded, all outcomes showed that the point estimate of pooled effects still stayed within the 95% CI, indicating that our analysis results were stable.

We also repeated the meta-analysis for all outcomes using studies with a parallel design (Supplementary Table 2). The result also was consistent for TIR (12.29%; 95% CI, 9.44 to 15.14; $P<0.001$). Similar results were observed for all other secondary outcomes. In addition, despite the washout period in randomized crossover trials, considering possible within-person differences, we performed another sensitivity analysis for the primary outcome, adjusting for within-person differences in studies that did not report the mean and standard error of

paired differences [25]. The estimate for TIR was unchanged at 11.67% (95% CI, 9.85 to 13.50; $P<0.001$).

Publication bias and GRADE assessment

Publication bias was assessed for all outcomes by using a funnel plot (Supplementary Fig. 20) and Egger's test (Supplementary Table 3). We find symmetrical funnel plots and non-significant Egger's test results for TIR ($P=0.204$), TBR ($P=0.488$), TAR ($P=0.418$), CV ($P=0.178$), GRI ($P=0.373$), HbA1c ($P=0.128$), insulin dose ($P=0.264$), severe hypoglycemia ($P=0.072$), and DKA ($P=0.334$). Overall, the results for all outcomes were robust.

Considering that the nature of the intervention precludes

the blinding of patients and personnel, the certainty of the evidence was not rated down for risk of bias. There was substantial heterogeneity for primary and secondary outcomes except HbA1c, severe hypoglycemia, and DKA, resulting in a downgraded of the items of inconsistency. Therefore, the certainty of evidence was high for HbA1c, severe hypoglycemia and DKA, and moderate for other outcomes (Supplementary Table 4).

DISCUSSION

In this comprehensively systematic review and meta-analysis comparing AID systems with other conventional insulin-based treatments (non-AID systems), our data demonstrated that the application of AID systems therapy resulted in significant improvement in glycemic outcomes for individuals living with T1DM. Greater treatment effects favoring AID systems concerning GRI was observed in adults and patients with poorer glycemia control and longer diabetes duration. Importantly, use of dual-hormone FCL systems yielded superior glycemic control compared with HCL systems including increased time of TIR throughout the day. More benefits of hypoglycemia were also seen in patients on AID systems who were within target glycemic control and with longer diabetes duration. Also, using AID systems beyond 3 months up to 24 months showed better glycemic control in all age groups, supporting the recommendation of long-term use of AID systems even though in patients within target glycemic control.

Currently, landmark progress in insulin replacement therapy has shifted from SAP to HCL systems [38], and then to FCL. FCL system is a big step for lightening the burden of glycemia control, which relieving the hard work of carbohydrate counting. Despite FCL systems being developed recently there is no pooled analysis comparing the effects of FCL and HCL. In our study, users of dual-hormone FCL, not single-hormone FCL, showed greater benefits concerning glycemic control (increased TIR) potentially due to the joint result of insulin and glucagon. Regarding baseline HbA1c level that may affect the outcome, 88% (7/8) of comparisons in the FCL groups and 70% (45/65) of comparisons in the HCL groups were above 7.5%. Therefore, the high percentage of hyperglycemia in FCL groups at baseline may contribute to the benefit of FCL systems in terms of TIR and TAR. Indeed, a RCT found that both a new advanced HCL system, RocketAP, and an HCL system, Unified Safety System Virginia, were able to achieve greater glycemic control with announced meals compared to Rocket-

AP with unannounced meals [39]. More head-to-head trials comparing FCL with HCL systems in all age groups should be performed.

Another major concern with insulin therapy is the high risk of hypoglycemia, especially life-threatening nocturnal hypoglycemia [40]. To screen who would benefit the most from hypoglycemia risk, we performed subgroups analysis. Our data demonstrated that the beneficial effect of AID systems for hypoglycemia was more pronounced in patients within target glycemia control and longer diabetes duration, with AID systems reducing TBR by 1.93% and 1.80%. It is interesting that TBR reduced by less in children (down 0.91%) than in adolescents (down 1.55%), which is congruent with recent results that the benefits of TBR were less in children than adults [10]. Difference in improving TBR between different ages can be attributed, at least partially, to small insulin doses, unpredictable food intake, unscheduled exercise activities and rapid growth in children and adolescents [41]. This data adds to the need to pay more attention to young people when employing AID systems.

GRI, as a novel composite derived from CGM metrics, is recognized to be a promising tool for assessing glycemic quality in clinical practice [42] and has been proposed as a comprehensive index in the latest consensus on CGM metrics [43]. Recent real-world data revealed that HCL systems provided a significant improvement in GRI [44]. However, GRI was only available in 6 of our pooled comparisons, suggesting that this index is not widely used in clinical trials. In our analysis, the favorable effects of AID systems were reflected in the better index of GRI, underscoring the feasibility of using GRI as a measurable parameter to evaluate glycemic risk. In this sense, future studies might be recommended to provide the results of GRI, enabling a pooled analysis included more studies.

Encouragingly, these beneficial effects of AID systems appeared to be consistent over the long-term follow-up period, with an effect evident in the first 3 months. This result is in line with a recent meta-analysis focused on children and adolescents [10], though it included only nine trials of long-term intervention. Our larger meta-analysis (of 23 trials) included adults as well as children and adolescents, incorporated more evidence and estimated a broader variety of outcomes, supporting the robust extension of those previous results.

Another interesting finding is that beneficial glycemic effects were particularly prominent in the dual-hormone group compared with single-hormone group, findings suggested in previous meta-analysis [11]. Our present analysis further con-

firmed and expanded the generalizability of the results across various populations and settings. Beyond the benefits of reduced hypoglycemia offered by glucagon in dual-hormone AID systems, glycemic variability and hyperglycemia were also significantly lower in dual-hormone systems, suggesting the value of glucagon in mimicking physiologic glucose regulation. Additionally, with regard to algorithm, in congruent with previous meta-analysis [45] and a head-to-head comparison of MPC versus PID algorithms [46], our meta-analysis showed that both MPC- and PID-based AID systems performed well in glycemic control. However, in contrast to previous results supporting the superior performance of MPC algorithms in TIR whether meal was announced or not [45,46], we found that MPC-based AID systems did not present a significantly greater improvement in maintaining blood glucose in the target range over PID-based AID systems. In brief, the results from this meta-analysis could guide optimal use and selection of the AID systems to facilitate improvements in safe glycemic control.

Our study has several strengths. To our knowledge, this is the largest and the most comprehensive analysis of pooled RCTs, without restrictions of setting and age, ensuring more generalizability. Half of the studies included were published in the last 5 years when the technology of AID systems has shown rapid development. In particular, we compared the different effects of FCL and HCL, and found that dual-hormone FCL systems could achieve greater glycemic control, emphasizing the superiority of multi-hormonal combination [16,47]. Moreover, the value of GRI as the evaluation indicator for glycemic control in AID systems application as proposed illustrated a more favorable effect in AID systems for adult patients or with baseline HbA1c $\geq 7.5\%$, or with diabetes duration ≥ 20 years. Finally, we have demonstrated that improved glycemic control which occurs in the short-term can persist.

Nevertheless, we acknowledge several limitations in the meta-analysis. First, even though there are 11 studies (17%) with a sample size of more than 100, the sample size was relatively small in most studies, which may affect the accuracy of the effect estimated. Second, heterogeneity was high for glucose outcomes, which may be explained by different types and times of intervention or different baseline characteristics. Third, all studies were performed in an open-label manner due to the nature of the intervention. Lack of blinding leads to a high risk of performance bias. Fourth, we did not assess the impact of the AID systems intervention on sleep quality, quality of life,

and self-management burden for T1DM patients or the medical burden for the entire country.

In conclusion, AID systems significantly improve glucose control in patients with T1DM compared to other insulin-based treatments. Greater benefits of hypoglycemia were observed in patients within target glycemic control and longer diabetes duration. The favorable effect of TIR was more significant in the dual-hormone FCL systems than in the HCL systems.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at <https://doi.org/10.4093/dmj.2024.0130>.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

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Drafting the work or revising: W.F., C.D., Z.L., R.D.L., Z.Z., X.L.

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SUPPLEMENTARY METHODS

Search strategy (August 31, 2023)

Search strategy for PubMed (1,512 items)

#1. "Diabetes Mellitus, Type 1"[Mesh]
 #2. (((((((((((((((((((((((((((((((Diabetes Mellitus, Insulin-Dependent[Title/Abstract]) OR (Diabetes Mellitus, Insulin Dependent[Title/Abstract])) OR (Insulin-Dependent Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Juvenile-Onset [Title/Abstract])) OR (Diabetes Mellitus, Juvenile Onset [Title/Abstract])) OR (Juvenile-Onset Diabetes Mellitus[Title/Abstract])) OR (IDDM[Title/Abstract])) OR (Juvenile-Onset Diabetes[Title/Abstract])) OR (Diabetes, Juvenile-Onset[Title/Abstract])) OR (Juvenile Onset Diabetes [Title/Abstract])) OR (Diabetes Mellitus, Sudden-Onset[Title/Abstract])) OR (Diabetes Mellitus, Sudden Onset[Title/Abstract])) OR (Sudden-Onset Diabetes Mellitus[Title/Abstract])) OR (Type 1 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Insulin-Dependent, 1[Title/Abstract])) OR (Insulin-Dependent Diabetes Mellitus 1[Title/Abstract])) OR (Insulin Dependent Diabetes Mellitus 1[Title/Abstract])) OR (Type 1 Diabetes[Title/Abstract])) OR (Diabetes, Type 1[Title/Abstract])) OR (Diabetes Mellitus, Type I[Title/Abstract])) OR (Diabetes, Autoimmune [Title/Abstract])) OR (Autoimmune Diabetes[Title/Abstract])) OR (Diabetes Mellitus, Brittle[Title/Abstract])) OR (Brittle Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Ketosis-Prone[Title/Abstract])) OR (Diabetes Mellitus, Ketosis Prone[Title/Abstract])) OR (Ketosis-Prone Diabetes Mellitus [Title/Abstract])
 #3. #1 OR #2
 #4. "Insulin Infusion Systems"[Mesh]
 #5. (((((((((((((((((((((((((((Infusion System, Insulin[Title/Abstract]) OR (Infusion Systems, Insulin[Title/Abstract])) OR (Insulin Infusion System[Title/Abstract])) OR (System, Insulin Infusion[Title/Abstract])) OR (Systems, Insulin Infusion [Title/Abstract])) OR (Implantable Programmable Insulin Pump [Title/Abstract])) OR (Programmable Implantable Insulin Pump[Title/Abstract])) OR (Pump, Programmable Implantable Insulin[Title/Abstract])) OR (Insulin Pump, Programmable Implantable[Title/Abstract])) OR (Pancreas, Artificial Endocrine [Title/Abstract])) OR (Artificial Endocrine Pancreas[Title/Abstract])) OR (Endocrine Pancreas, Artificial [Title/Abstract])) OR (beta Cell, Artificial[Title/Abstract])) OR (Artificial beta Cell[Title/Abstract])) OR (Artificial beta Cells[Title/Abstract])) OR (Cell, Artificial beta[Title/Abstract])) OR

(Cells, Artificial beta[Title/Abstract])) OR (beta Cells, Artificial[Title/Abstract])) OR (bionic pancreas[Title/Abstract])) OR (synthetic pancreas[Title/Abstract])) OR (closed-loop[Title/Abstract])) OR (closed loop[Title/Abstract])) OR (Artificial pancreas[Title/Abstract])) OR (Pancreas, Artificial [Title/Abstract])) OR (automated insulin delivery[Title/Abstract])

#6. #4 OR #5

#7. (((((((((((randomized controlled trial[Publication Type])) OR (controlled clinical trial[Publication Type])) OR (randomized [Title/Abstract])) OR (placebo[Title/Abstract])) OR (randomly[Title/Abstract])) OR (controlled[Title/Abstract])) OR (trial[Title/Abstract])) OR (random[Title/Abstract])) OR (RCT[Title/Abstract])

#8. #3 AND #6 AND #7

Search strategy for Embase (1,335 items)

#1. ('diabetes'/exp OR diabetes) AND mellitus, AND type AND ('1'/exp OR 1)

#2. 'diabetes mellitus, insulin-dependent':ab,ti OR 'diabetes mellitus, insulin dependent':ab,ti OR 'insulin-dependent diabetes mellitus':ab,ti OR 'diabetes mellitus, juvenile-onset':ab,ti OR 'diabetes mellitus, juvenile onset':ab,ti OR 'juvenile-onset diabetes mellitus':ab,ti OR 'iddm':ab,ti OR 'juvenile-onset diabetes':ab,ti OR 'diabetes, juvenile-onset':ab,ti OR 'juvenile onset diabetes':ab,ti OR 'diabetes mellitus, sudden-onset':ab,ti OR 'diabetes mellitus, sudden onset':ab,ti OR 'sudden-onset diabetes mellitus':ab,ti OR 'type 1 diabetes mellitus':ab,ti OR 'diabetes mellitus, insulin-dependent, 1':ab,ti OR 'insulin-dependent diabetes mellitus 1':ab,ti OR 'insulin dependent diabetes mellitus 1':ab,ti OR 'type 1 diabetes':ab,ti OR 'diabetes, type 1':ab,ti OR 'diabetes mellitus, type i':ab,ti OR 'diabetes, autoimmune':ab,ti OR 'autoimmune diabetes':ab,ti OR 'diabetes mellitus, brittle':ab,ti OR 'brittle diabetes mellitus':ab,ti OR 'diabetes mellitus, ketosis-prone':ab,ti OR 'diabetes mellitus, ketosis prone':ab,ti OR 'ketosis-prone diabetes mellitus':ab,ti

#3. #1 OR #2

#4. insulin AND infusion AND systems

#5. 'infusion system, insulin':ab,ti OR 'infusion systems, insulin':ab,ti OR 'insulin infusion system':ab,ti OR 'system, insulin infusion':ab,ti OR 'systems, insulin infusion':ab,ti OR 'implantable programmable insulin pump':ab,ti OR 'programmable implantable insulin pump':ab,ti OR 'pump, programmable implantable insulin':ab,ti OR 'insulin pump, programmable implantable':ab,ti OR 'pancreas, artificial endocrine':ab,ti OR

'artificial endocrine pancreas':ab,ti OR 'endocrine pancreas, artificial':ab,ti OR 'beta cell, artificial':ab,ti OR 'artificial beta cell':ab,ti OR 'artificial beta cells':ab,ti OR 'cell, artificial beta':ab,ti OR 'cells, artificial beta':ab,ti OR 'beta cells, artificial':ab,ti OR 'bionic pancreas':ab,ti OR 'synthetic pancreas':ab,ti OR 'closed-loop':ab,ti OR 'closed loop':ab,ti OR 'artificial pancreas':ab,ti OR 'pancreas, artificial':ab,ti OR 'automated insulin delivery':ab,ti

#6. #4 OR #5

#7. 'randomized controlled trial':ab,ti OR 'controlled clinical trial':ab,ti OR 'randomized':ab,ti OR 'placebo':ab,ti OR 'randomly':ab,ti OR 'controlled':ab,ti OR 'trial':ab,ti OR 'random':ab,ti OR 'rct':ab,ti

#8. #3 AND #6 AND #7

Search strategy for Cochrane Library (1,750 items)

#1. Diabetes Mellitus, Type 1

#2. (Diabetes Mellitus, Insulin-Dependent):ab,ti,kw OR (Diabetes Mellitus, Insulin Dependent):ab,ti,kw OR (Insulin-Dependent Diabetes Mellitus):ab,ti,kw OR (Diabetes Mellitus, Juvenile-Onset):ab,ti,kw OR (Diabetes Mellitus, Juvenile Onset):ab,ti,kw OR (Juvenile-Onset Diabetes Mellitus):ab,ti,kw OR (IDDM):ab,ti,kw OR (Juvenile-Onset Diabetes):ab,ti,kw OR (Diabetes, Juvenile-Onset):ab,ti,kw OR (Juvenile Onset Diabetes):ab,ti,kw OR (Diabetes Mellitus, Sudden-Onset):ab,ti,kw OR (Diabetes Mellitus, Sudden Onset):ab,ti,kw OR (Sudden-Onset Diabetes Mellitus):ab,ti,kw OR (Type 1 Diabetes Mellitus):ab,ti,kw OR (Diabetes Mellitus, Insulin-Dependent, 1):ab,ti,kw OR (Insulin-Dependent Diabetes Mellitus 1):ab,ti,kw OR (Insulin Dependent Diabetes Mellitus 1):ab,ti,kw OR (Type 1 Diabetes):ab,ti,kw OR (Diabetes, Type 1):ab,ti,kw OR (Diabetes Mellitus, Type I):ab,ti,kw OR (Diabetes, Autoimmune):ab,ti,kw OR (Autoimmune Diabetes):ab,ti,kw OR (Diabetes Mellitus, Brittle):ab,ti,kw OR (Brittle Diabetes Mellitus):ab,ti,kw OR (Diabetes Mellitus, Ketosis-Prone):ab,ti,kw OR (Diabetes Mellitus, Ketosis Prone):ab,ti,kw OR (Ketosis-Prone Diabetes Mellitus):ab,ti,kw

#3. #1 or #2

#4. Insulin Infusion Systems

#5. (Infusion System, Insulin):ab,ti,kw OR (Infusion Systems, Insulin):ab,ti,kw OR (Insulin Infusion System):ab,ti,kw OR (System, Insulin Infusion):ab,ti,kw OR (Systems, Insulin Infusion):ab,ti,kw OR (Implantable Programmable Insulin Pump):ab,ti,kw OR (Programmable Implantable Insulin Pump):ab,ti,kw OR (Pump, Programmable Implantable Insulin):ab,ti,kw OR (Insulin Pump, Programmable Implantable):ab,ti,kw OR (Pan-

creas, Artificial Endocrine):ab,ti,kw OR (Artificial Endocrine Pancreas):ab,ti,kw OR (Endocrine Pancreas, Artificial):ab,ti,kw OR (beta Cell, Artificial):ab,ti,kw OR (Artificial beta Cell):ab,ti,kw OR (Artificial beta Cells):ab,ti,kw OR (Cell, Artificial beta):ab,ti,kw OR (Cells, Artificial beta):ab,ti,kw OR (beta Cells, Artificial):ab,ti,kw OR (bionic pancreas):ab,ti,kw OR (synthetic pancreas):ab,ti,kw OR (closed-loop):ab,ti,kw OR (closed loop):ab,ti,kw OR (Artificial pancreas):ab,ti,kw OR (Pancreas, Artificial):ab,ti,kw OR (automated insulin delivery):ab,ti,kw

#6. #4 or #5

#7. (randomized controlled trial):ab,ti,kw OR (controlled clinical trial):ab,ti,kw OR (randomized):ab,ti,kw OR (placebo):ab,ti,kw OR (randomly):ab,ti,kw OR (controlled):ab,ti,kw OR (trial):ab,ti,kw OR (random):ab,ti,kw OR (RCT):ab,ti,kw

#8. #3 and #6 and #7

Search strategy for Web of Science (9,795 items)

#1. TS=(Diabetes Mellitus, Type 1 OR Diabetes Mellitus, Insulin-Dependent OR Diabetes Mellitus, Insulin Dependent OR Insulin-Dependent Diabetes Mellitus OR Diabetes Mellitus, Juvenile-Onset OR Diabetes Mellitus, Juvenile Onset OR Juvenile-Onset Diabetes Mellitus OR IDDM OR Juvenile-Onset Diabetes OR Diabetes, Juvenile-Onset OR Juvenile Onset Diabetes OR Diabetes Mellitus, Sudden-Onset OR Diabetes Mellitus, Sudden Onset OR Sudden-Onset Diabetes Mellitus OR Type 1 Diabetes Mellitus OR Diabetes Mellitus, Insulin-Dependent, 1 OR Insulin-Dependent Diabetes Mellitus 1 OR Insulin Dependent Diabetes Mellitus 1 OR Type 1 Diabetes OR Diabetes, Type 1 OR Diabetes Mellitus, Type I OR Diabetes, Autoimmune OR Autoimmune Diabetes OR Diabetes Mellitus, Brittle OR Brittle Diabetes Mellitus OR Diabetes Mellitus, Ketosis-Prone OR Diabetes Mellitus, Ketosis Prone OR Ketosis-Prone Diabetes Mellitus) and Preprint Citation Index (Exclude – Database)

#2. TS=(Insulin Infusion Systems OR Infusion System, Insulin OR Infusion Systems, Insulin OR Insulin Infusion System OR System, Insulin Infusion OR Systems, Insulin Infusion OR Implantable Programmable Insulin Pump OR Programmable Implantable Insulin Pump OR Pump, Programmable Implantable Insulin OR Insulin Pump, Programmable Implantable OR Pancreas, Artificial Endocrine OR Artificial Endocrine Pancreas OR Endocrine Pancreas, Artificial OR beta Cell, Artificial OR Artificial beta Cell OR Artificial beta Cells OR Cell, Artificial beta OR Cells, Artificial beta OR beta Cells,

Artificial OR bionic pancreas OR synthetic pancreas OR closed-loop OR closed loop OR Artificial pancreas OR Pancreas, Artificial OR automated insulin delivery) and Preprint Citation Index (Exclude – Database)

#3. TS=(randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR controlled OR trial OR random OR RCT) and Preprint Citation Index (Exclude – Database)

#4. (#1 AND #2 AND #3)

Search strategy for ClinicalTrial.gov (79 items)

Closed loop AND Type 1 Diabetes

Data extraction form

For every trial we extracted following information.

Trial characteristics

1. Identifier (author years)
2. NCT
3. Design of the trial
4. Setting
5. Population

Intervention characteristics

1. Automated insulin delivery systems
2. Continuous glucose monitoring
3. Insulin pump
4. Algorithm
5. Type of closed-loop system
6. Hormone
7. Comparator
8. Time of intervention
9. Length of follow-up

10. Remote monitoring

Baseline characteristics

1. Patients (*n*)
2. Age (mean ± SD)
3. Male (*n*)
4. Weight (mean ± SD)
5. BMI (mean ± SD)
6. Diabetes duration (mean ± SD)
7. Pump duration (mean ± SD)
8. HbA1c (mean ± SD)
9. Insulin dose (mean ± SD)

Outcomes

1. Percentage of time in range (TIR) (mean ± SD)
2. Percentage of time below range (TBR) (mean ± SD)
3. Percentage of time above range (TAR) (mean ± SD)
4. Coefficient of variation (CV) (mean ± SD)
5. Glycaemia risk index (mean ± SD)
6. HbA1c (mean ± SD)
7. Insulin dose (mean ± SD)
8. Patients with severe hypoglycemia (*n*)
9. Patients with diabetic ketoacidosis (*n*)

Information for assessment of risk bias

1. Sequence generation (or randomized treatment order for cross-over studies)
2. Allocation concealment
3. Blinding
4. Incomplete outcome data
5. Selective outcome reporting
6. Other bias

Supplementary Table 1. Baseline characteristics of the included studies

Study	Trial registration	Study design	Setting	Population	Automated insulin delivery systems	Comparator	Single or dual hormone	24 hr or overnight	Follow-up	No. of patients	Type of closed-loop systems	Type of algorithm	HbA1c level at baseline, %	TIR	TBR
Abraham et al. (2021) [1]	ACTRN12616000753459	Parallel	Home	Children and adolescents	MiniMed 670G	CSII or MDI with or without CGM	Single	24 hours	26 weeks	135	HCL	PID	Intervention: 7.8±1.0 Control: 7.7±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Anderson et al. (2019) [2]	NCT02302963	Parallel	Home	Adolescents and adults	DAs	SAP	Single	24 hours	4 weeks	42	HCL	MPC	Intervention: 7.2±0.2 Control: 7.5±0.2	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Bally et al. (2017) [3]	NCT02772731	Crossover	Home	Adults	FlorenceD2A	CSII	Single	24 hours	4 weeks	29	HCL	MPC	Total: 6.9±0.5	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Benhamou et al. (2019) [4]	NCT02987556	Crossover	Home	Adults	DBLG1	SAP	Single	24 hours	12 weeks	63	HCL	Machine-learning	Total: 7.6±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Benhamou et al. (2021) [5]	NCT04042207	Crossover	hospital and home	Adults	DBLHU	PLGS	Single	24 hours	4 weeks	7	HCL	Machine-learning	Total: 8.3±1.2	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Biester et al. (2019) [6]	NCT01238406	Crossover	Home	Adolescents and adults	MD-Logic System	SAP	Single	24 hours	60 hours	39	HCL	Fuzzy logic	Total: 7.7±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Blauw et al. (2021) [7]	NCT03858062	Crossover	Home	Adults	Inreda AP	Usual care with CGM	Dual	24 hours	2 weeks	23	FCL	Self-learning	Total: 7.5±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Blauw et al. (2016) [8]	NCT02160275	Crossover	Home	Adults	Inreda AP	CSII	Dual	24 hours	4 days	10	FCL	PID	Total: 7.7±0.5	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Boughton et al. (2023) [9]	NCT04977908	Crossover	Home	Adults	CamAPS HX	SAP	Single	24 hours	8 weeks	26	FCL	MPC	Total: 9.2±1.1	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Boughton et al. (2022a) [10]	NCT02871089	Parallel	Home	Adolescents	Initial FlorenceM followed by the CamAPSFX	Standard insulin therapy	Single	24 hours	24 months	97	HCL	MPC	Intervention: 10.7±1.8 Control: 10.5±1.6	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Boughton et al. (2022b) [11]	NCT04025762	Crossover	Home	Adults	CamAPSFX	SAP	Single	24 hours	16 weeks	37	HCL	MPC	Total: 7.4±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Bretton et al. (2017) [12]	NCT02604524	Parallel	Winter camp	Adolescents	DAs	SAP	Single	24 hours	5 days	32	HCL	MPC	Intervention: 8.9±1.9 Control: 8.1±1.1	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Bretton et al. (2020) [13]	NCT03844789	Parallel	Home	Children	Control-IQ	SAP	Single	24 hours	16 weeks	101	HCL	MPC	Intervention: 7.6±1.0 Control: 7.9±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Brown et al. (2020) [14]	NCT03591354	Parallel	Home	Adolescents and adults	Control-IQ	PLGS	Single	24 hours	13 weeks	109	HCL	MPC	Intervention: 7.1±0.8 Control: 7.0±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Brown et al. (2017) [15]	NCT02131766, NCT02008188	Crossover	Hotel or research house (CLC session), home or usual environment (SAP session)	Adults	DAs	SAP	Single	24 hours	5 days	40	HCL	MPC	Total: 7.4±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Brown et al. (2019) [16]	NCT03563313	Parallel	Home	Adolescents and adults	Control-IQ	SAP	Single	24 hours	26 weeks	168	HCL	MPC	Intervention: 7.6±1.1 Control: 7.6±1.1	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Burckhardt et al. (2021) [17]	ACTRN12616000909426	Crossover	Home	Adolescents and adults	MiniMed 670G	CSII	Single	24 hours	8 weeks	16	HCL	PID	Total: 7.8±1.2	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Burnside et al. (2022a) [18]	ACTRN12620000034932	Parallel	Home	Children	AndroidAPS 2.8	SAP	Single	24 hours	24 weeks	48	HCL	OpenAPS	Intervention: 7.5 Control: 7.5	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)

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Supplementary Table 1. Continued

Study	Trial registration	Study design	Setting	Population	Automated insulin delivery systems	Comparator	Single or dual hormone	24-hr or overnight	Follow-up	No. of patients	Type of closed-loop systems	Type of algorithm	HbA1c level at baseline, %	TIR	TBR
Burnside et al. (2022b) [18]	ACTRN1262 000034952	Parallel	Home	Adults	AndroidAPS 2.8	SAP	Single	24 hours	24 weeks	49	HCL	OpenAPS	Intervention: 7.6 Control: 7.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Chernavsky et al. (2016) [19]	NCT01890954	Crossover	Research house	Adolescents	DIAs	CSII	Single	24 hours	1 day	16	HCL	MPC	Total: 8.2±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	NA
Choudhary et al. (2022) [20]	NCT04255504	Parallel	Home	Adults	MiniMed 670G 4.0	MDI+CGM	Single	24 hours	6 months	82	HCL	PID	Intervention: 9.0±1.0 Control: 9.1±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Collins et al. (2021) [21]	NCT04073576	Crossover	Home	Children, adolescents and adults	MiniMed 670G 4.0	SAP+PLGM	Single	24 hours	4 weeks	60	HCL	PID	Total: 7.6±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
De Bock et al. (2015) [22]	ACTRN1261 4001005640	Crossover	Home	Adolescents and adults	MiniMed 670G	SAP+LGS	Single	24 hours	5 days	8	HCL	PID	Total: 7.5±0.6	4.0–9.9 mmol/L (72–178 mg/dL)	<3.9 mmol/L (70 mg/dL)
DeBoer et al. (2017) [23]	NCT02750267	Crossover	Home (insulin pump therapy), hotel (AP therapy)	Children	DIAs	SAP	Single	24 hours	68 hours	12	HCL	MPC	Total: 7.5±0.6	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Del Favero et al. (2016) [24]	NCT02620878	Crossover	Summer camp	Children	DIAs	SAP	Single	24 hours	3 days	30	HCL	MPC	Total: 7.3±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Ekhlaspour et al. (2019) [25]	NCT03369067	Parallel	Ski camp	Children and adolescents	Control-IQ	SAP	Single	24 hours	48 hours	48	HCL	MPC	Intervention: 7.8±1.3 Control: 7.7±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
El-Khatib et al. (2017) [26]	NCT02092220	Crossover	Home	Adults	Bihormonal bionic pancreas	CSII or SAP	Dual	24 hours	11 days	39	FCL	MPC	Total: 7.7±1.2	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Fortenza et al. (2019) [27]	NCT03369067	Parallel	Home	Children	Control-IQ	SAP	Single	24 hours	3 days	24	HCL	MPC	Intervention: 7.4±0.7 Control: 7.4±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Garg et al. (2022) [28]	NCT02748018	Parallel	Home	Children, adolescents and adults	MiniMed 670G	CSII	Single	24 hours	6 months	302	HCL	PID	Intervention: 8.3±1.3 Control: 8.1±1.2	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Haidar et al. (2015a) [29]	NCT02189694	Crossover	Diabetes camp	Children and adolescents	Accu-Chek Combo	CSII	Single	Overnight	3 nights	33	HCL	MPC	Total: 8.3±0.8	4.0–10.0 mmol/L (72–180 mg/dL)	<4.0 mmol/L (72 mg/dL)
Haidar et al. (2015b) [29]	NCT02189694	Crossover	Diabetes camp	Children and adolescents	Accu-Chek Combo	CSII	Dual	Overnight	3 nights	33	HCL	MPC	Total: 8.3±0.8	4.0–10.0 mmol/L (72–180 mg/dL)	<4.0 mmol/L (72 mg/dL)
Haidar et al. (2017a) [30]	NCT01966393	Crossover	Home	Adults	Accu-Chek Combo	SAP	Single	24 hours	60 hours	23	HCL	MPC	Total: 7.5±0.8	4.0–10.0 mmol/L (72–180 mg/dL)	<4.0 mmol/L (72 mg/dL)
Haidar et al. (2017b) [30]	NCT01966393	Crossover	Home	Adults	Accu-Chek Combo	SAP	Dual	24 hours	60 hours	23	HCL	MPC	Total: 7.5±0.8	4.0–10.0 mmol/L (72–180 mg/dL)	<4.0 mmol/L (72 mg/dL)
Haidar et al. (2016a) [31]	NCT01905020	Crossover	Home	Adolescents and adults	Single hormone	CSII	Single	Overnight	2 nights	28	HCL	MPC	Total: 7.5±1.0	4.0–10.0 mmol/L (72–180 mg/dL)	<4.0 mmol/L (72 mg/dL)
Haidar et al. (2016b) [31]	NCT01905020	Crossover	Home	Adolescents and adults	Dual hormone	CSII	Dual	Overnight	2 nights	28	HCL	MPC	Total: 7.5±1.0	4.0–10.0 mmol/L (72–180 mg/dL)	<4.0 mmol/L (72 mg/dL)
Hovorka et al. (2014) [32]	NCT01221467	Crossover	Home	Adolescents	Florence	SAP	Single	Overnight	3 weeks	16	HCL	MPC	Total: 8.0±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Kariyawasam et al. (2022a) [33]	NCT03671915	Crossover	Hospital	Children	DiabeLoop DBL4K	SAP	Single	24 hours	72 hours	21	HCL	Machine learning	Total: 7.2±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Kariyawasam et al. (2022b) [33]	NCT03671915	Crossover	Home	Children	DiabeLoop DBL4K	SAP	Single	24 hours	6 weeks	21	HCL	Machine learning	Total: 7.2±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)

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Supplementary Table 1. Continued

Study	Trial registration	Study design	Setting	Population	Automated insulin delivery systems	Comparator	Single or dual hormone	24-hr or overnight	Follow-up	No. of patients	Type of closed-loop systems	Type of algorithm	HbA1c level at baseline, %	TIR	TBR
Kovatchev et al. (2020) [34]	NCT02985866	Parallel	Home	Adolescents and adults	inControl AP	SAP	Single	24 hours	13 weeks	127	HCL	MPC	Intervention: 7.4±0.9 Control: 7.4±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Kovatchev et al. (2014) [35]	NCT01714905, NCT01727817, NCT01742741	Crossover	Hotel or guest-house	Adults	DiAs	SAP	Single	24 hours	40 hours	20	HCL	MPC	Total: 7.4±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Kropff et al. (2015) [36]	NCT02153190	Crossover	Home	Adults	DiAs	SAP	Single	Overnight	2 months	32	HCL	MPC	Total: 8.2±0.6	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Ledarthna et al. (2014) [37]	NCT01666028	Crossover	Home (first day in clinical research facility)	Adults	Florence	SAP	Single	24 hours	8 days	17	HCL	MPC	Total: 7.6±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Ly et al. (2014) [38]	NCT01973413	Crossover	Diabetes camp	Adolescents and adults	DiAs	SAP	Single	Overnight	5–6 days	20	HCL	MPC	Total: 8.1±1.1	NA	NA
Ly et al. (2016) [39]	Not reported	Crossover	Diabetes camp	Children and adolescents	Medtronic PTD-IFB	SAP	Single	Overnight	5–6 days	21	HCL	PID	Total: 7.9±1.4	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Ly et al. (2015) [40]	NCT02366767	Parallel	Diabetes camp	Adolescents and adults	Medtronic PTD-IFB	SAP+LGS	Single	24 hours	6 days	20	HCL	PID	Total: 8.6±1.5	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Matejko et al. (2022) [41]	NCT04616391	Parallel	Home	Adults	MiniMed 780G	MDI	Single	24 hours	3 months	37	HCL	PID	Intervention: 7.1±0.8 Control: 7.4±1.2	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
McAuley et al. (2020) [42]	ACTRN1261 7000520336	Parallel	Home	Adults	MiniMed 670G	MDI or CSII	Single	24 hours	26 weeks	120	HCL	PID	Intervention: 7.4±0.9 Control: 7.5±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
McAuley et al. (2022) [43]	ACTRN1261 9000515190	Crossover	Home	Adults	MiniMed 670G	SAP	Single	24 hours	4 months	30	HCL	PID	7.6±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
McVean et al. (2023) [44]	NCT04233034	Parallel	Home	Children and adolescents	Control-IQ or MiniMed 670G 4.0 or subsequently the MiniMed 780G	MDI or CSII with or without PLGS	Single	24 hours	52 weeks	113	HCL	PID	Intervention: 10.3±1.3 Control: 10.2±1.6	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Nimri et al. (2017) [45]	NCT01726829	Crossover	Home	Children, adolescents and adults	MD-Logic system	SAP	Single	Overnight	4 nights	75	HCL	Fuzzy logic	Total: 7.8±0.7	NA	<3.9 mmol/L (70 mg/dL)
Nimri et al. (2014) [46]	NCT01238406	Crossover	Home	Adolescents and adults	MD-Logic system	SAP	Single	Overnight	6 weeks	24	HCL	Fuzzy logic	Total: 7.5±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Phillip et al. (2013) [47]	NCT01238406	Crossover	Diabetes Camp	Adolescents	MD-Logic system	SAP	Single	Overnight	1 night	56	HCL	Fuzzy logic	Total: 8.0±0.7	NA	<3.9 mmol/L (70 mg/dL)
Prisker et al. (2022) [48]	NCT04436796	Crossover	Home	Adults	iAPS	SAP	Single	24 hours	13 weeks	35	HCL	MPC	Total: 6.7±1.0	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Reddy et al. (2016) [49]	Not reported	Crossover	Clinical research facility	Adults	BiAP	CSII	Single	24 hours	24 hours	12	HCL	Bio-inspired control algorithm	Total: 7.4±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Renard et al. (2019) [50]	NCT02509429	Crossover	Hotel	Children	DiAs	TLGS	Single	24 hours	3 days	24	HCL	MPC	Total: 7.5±0.5	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Russell et al. (2022) [51]	NCT04200313	Parallel	Home	Children, adolescents and adults	iLet bionic pancreas	Any insulin-delivery method with CGM	Single	24 hours	13 weeks	326	FCL	Machine learning	Intervention: 7.9±1.2 Control: 7.7±1.1	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)

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Supplementary Table 1. Continued

Study	Trial registration	Study design	Setting	Population	Automated insulin delivery systems	Comparator	Single or dual hormone	24-hr or overnight	Follow-up	No. of patients	Type of closed-loop systems	Type of algorithm	HbA1c level at baseline, %	TIR	TBR
Russell et al. (2014a) [52]	NCT01762059	Crossover	Home (control), hotel (intervention)	Adults	Bionic pancreas	SAP	Dual	24 hours	5 days	20	FCL	MPC	Total: 7.1±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Russell et al. (2014b) [52]	NCT01833988	Crossover	Diabetes camps	Adolescents	Bionic pancreas	SAP	Dual	24 hours	5 days	32	FCL	MPC	Total: 8.2±1.0	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Russell et al. (2016) [53]	NCT02105324	Crossover	Diabetes camps	Children	Bionic pancreas	SAP	Dual	24 hours	5 days	19	FCL	MPC	Total: 7.8±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Sharifi et al. (2016) [54]	Not reported	Crossover	Home	Adolescents and adults	Android-HCL systems	SAP with LGS	Single	Overnight	4 nights	28	HCL	PID	Total: 7.5±0.6	NA	<4.0 mmol/L (72 mg/dL)
Tauschmann et al. (2016a) [55]	NCT01873066	Crossover	Home	Adolescents	FlorenceD2A	SAP	Single	24 hours	21 days	12	HCL	MPC	Total: 8.5±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Tauschmann et al. (2016b) [56]	NCT01873066	Crossover	Home	Adolescents	FlorenceD2A	SAP	Single	24 hours	7 days	12	HCL	MPC	Total: 8.3±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Tauschmann et al. (2018) [57]	NCT02523131	Parallel	Home	Children, adolescents and adults	FlorenceM	SAP	Single	24 hours	12 weeks	86	HCL	MPC	Total: 8.3±0.6	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Thabit et al. (2015a) [58]	NCT01440140, NCT01221467	Crossover	Home	Children and adults	Florence	SAP	Single	24 hours	4 weeks (adults), 3 weeks (children)	40	HCL	MPC	Adults: 8.1±0.8; Children: 8.0±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Thabit et al. (2014) [59]	NCT01440140	Crossover	Home	Adults	Florence	SAP	Single	24 hours	4 weeks	24	HCL	MPC	Total: 8.1±0.8	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Thabit et al. (2015b) [60]	NCT01961622	Crossover	Home	Adults	FlorenceD2A	SAP	Single	24 hours	12 weeks	33	HCL	MPC	Total: 8.5±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Thabit et al. (2015c) [60]	NCT01778348	Crossover	Home	Children and adolescents	FlorenceD2A	SAP	Single	Overnight	12 weeks	25	HCL	MPC	Total: 8.1±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
von dem Berge et al. (2022) [61]	NCT03815487	Crossover	Home	Children	MinMed 670G	PLGS	Single	24 hours	8 weeks	38	HCL	PID	Total: 7.4±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	NA
Wadwa et al. (2023) [62]	NCT04796779	Parallel	Home	Children	Control-IQ	CSII or MDI+CGM	Single	24 hours	13 weeks	102	HCL	MPC	Intervention: 7.5±1.2 Control: 7.7±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Ware et al. (2022a) [63]	NCT03784027	Crossover	Home	Children	CamAPS FX	SAP	Single	24 hours	16 weeks	74	HCL	MPC	Total: 7.3±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Ware et al. (2022b) [64]	NCT02925299	Parallel	Home	Children and adolescents	FlorenceM and CamAPS FX	CSII	Single	24 hours	6 months	133	HCL	MPC	Intervention: 8.2±0.7 Control: 8.3±0.7	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Wilson et al. (2020a) [65]	NCT03424044	Crossover	Home	Adults	Single hormone	PLGS	Single	24 hours	76 hours	23	HCL	PID	Total: 7.1±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)
Wilson et al. (2020b) [65]	NCT03424044	Crossover	Home	Adults	Dual hormone	PLGS	Dual	24 hours	76 hours	23	HCL	PID	Total: 7.1±0.9	3.9–10.0 mmol/L (70–180 mg/dL)	<3.9 mmol/L (70 mg/dL)

HbA1c, glycosylated hemoglobin; TIR, time in range; TBR, time below range; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; HCL, hybrid closed-loop; PID, proportional integral derivative; DiAs, diabetes assistant; SAP, sensor-augmented pump; MPC, model predictive control; DBLGI, Diaboloop Generation 1; DBLHU, Diaboloop for Highly Unstable Diabetes; PLGS, predictive low glucose suspend system; AP, artificial pancreas; CGM, continuous glucose monitor; FCL, full closed-loop; CLC, closed-loop control; NA, not applicable; PLGM, predictive low glucose monitoring; LGS, low glucose suspend; iAPS, inter-operable artificial pancreas system; BiAP, Bio-inspired Artificial Pancreas; TLGS, threshold-low-glucose-suspend.

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Supplementary Table 2. Summary of sensitivity analysis for studies with parallel design

Outcomes and subgroups	No. of comparisons	No. of patients		Mean difference between automated insulin delivery systems and other insulin therapy (95% CI), %	Z value for overall effect	P value for overall effect	I ² , %	Chi ²	df	P value	Tau ²
		Intervention	Control								
TIR	22	1,245	962	12.290 (9.441 to 15.139)	8.45	<0.001	84.7	136.86	21	<0.001	36.6519
TBR	22	1,245	962	-0.794 (-1.242 to -0.345)	-3.47	0.001	83.2	125.26	21	<0.001	0.7736
TAR	18	1,187	893	-11.495 (-14.708 to -8.282)	-7.012	<0.001	83.9	105.83	17	<0.001	38.5441
CV	19	1,064	785	-1.079 (-2.102 to -0.055)	-2.066	0.039	75.2	72.57	18	<0.001	3.5708
GRI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HbA1c	16	1,145	863	-0.413 (-0.516 to -0.311)	-7.907	<0.001	36.1	23.46	15	0.075	0.0147
Insulin dose	14	671	509	0.003 (-0.150 to 0.156)	0.037	0.970	36.8	20.55	13	0.082	0.0301

CI, confidence interval; TIR, time in range; TBR, time below range; TAR, time above range; CV, coefficient of variation; GRI, glycemia risk index; NA, not applicable; HbA1c, glycosylated hemoglobin.

Supplementary Table 3. Summary of publication bias for all outcomes by Egger's test

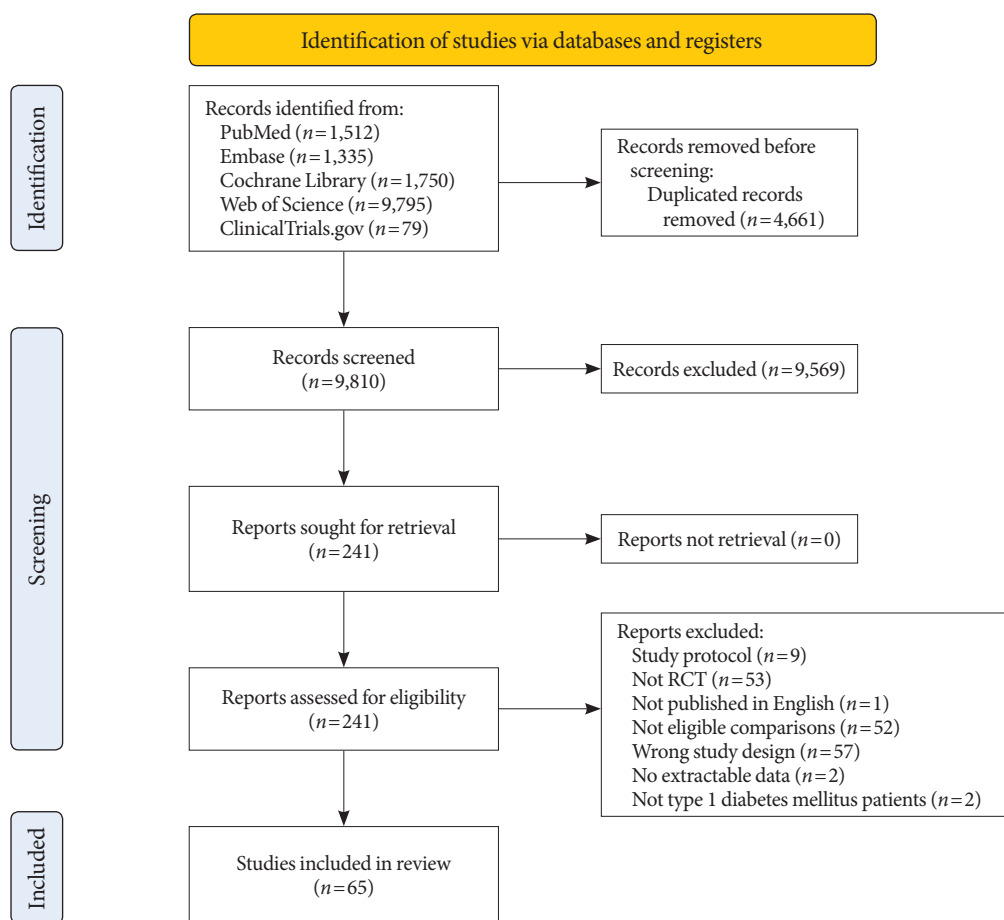
Outcome	T value	P value
TIR	1.28	0.204
TBR	-0.70	0.488
TAR	-0.82	0.418
CV	1.37	0.178
GRI	-1.00	0.373
HbA1c	-1.58	0.128
Insulin dose	-1.13	0.264
Severe hypoglycemia	1.91	0.072
Diabetic ketoacidosis	1.04	0.334

TIR, time in range; TBR, time below range; TAR, time above range; CV, coefficient of variation; GRI, glycemia risk index; HbA1c, glycosylated hemoglobin.

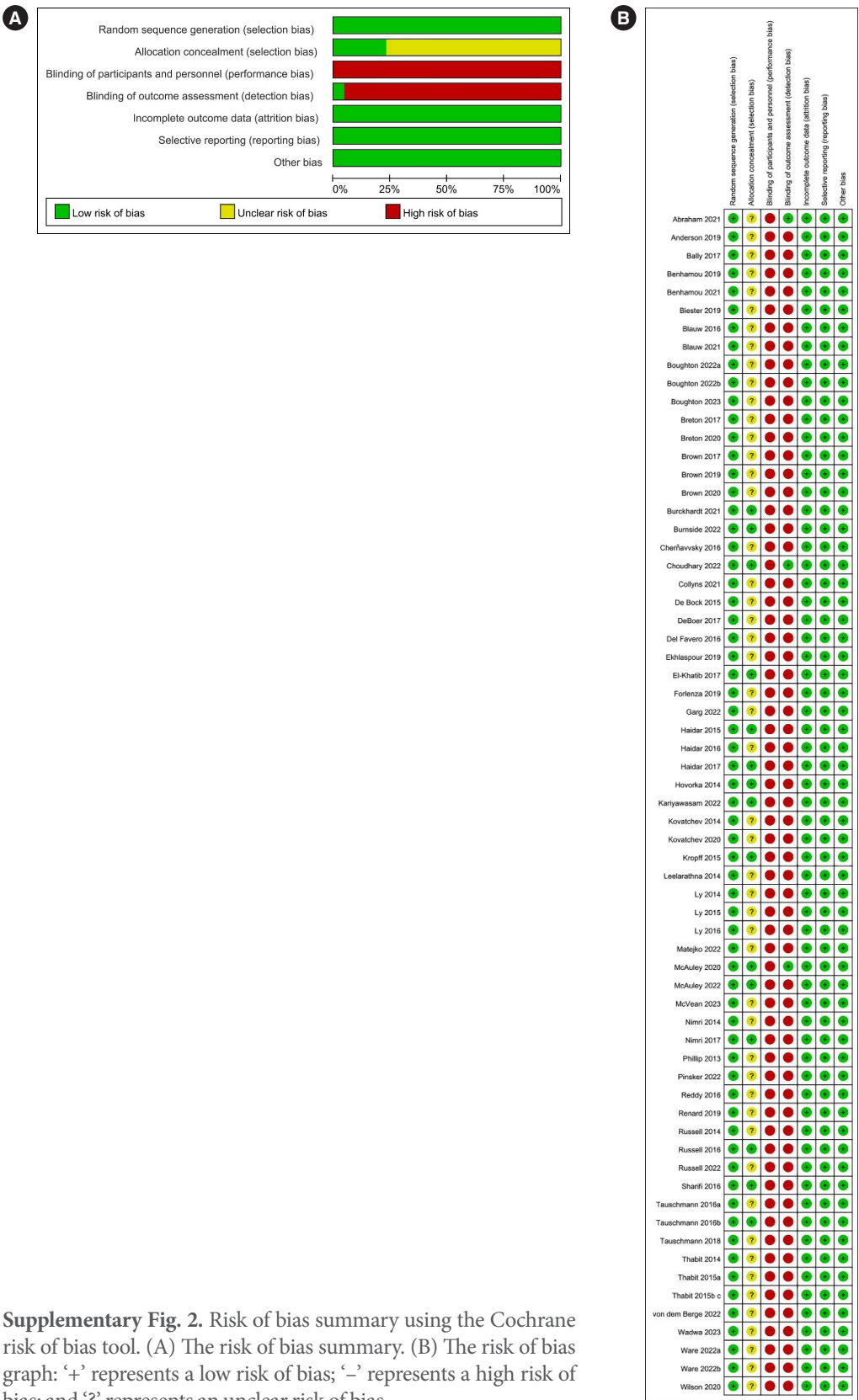
Supplementary Table 4. Summary of quality of evidence for all outcomes based on the GRADE

Outcomes	Certainty assessment					Number of patients		Effect		Certainty
	No. of comparisons	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Automated insulin delivery systems	Control treatment	
TIR	62	Randomized trials	Not serious ^a	Serious ^b	Not serious	Not serious ^c	None	2,292	2,008	⊕⊕⊕⊕ Moderate
TBR	60	Randomized trials	Not serious ^a	Serious ^b	Not serious	Not serious ^c	None	2,242	1,958	⊕⊕⊕⊕ Moderate
TAR	54	Randomized trials	Not serious ^a	Serious ^b	Not serious	Not serious ^c	None	1,979	1,684	⊕⊕⊕⊕ Moderate
CV	41	Randomized trials	Not serious ^a	Serious ^b	Not serious	Not serious ^c	None	1,682	1,402	⊕⊕⊕⊕ Moderate
HbA1c	25	Randomized trials	Not serious ^a	Not serious	Not serious	Not serious ^c	None	1,453	1,171	⊕⊕⊕⊕ High
GRI	6	Randomized trials	Not serious ^a	Serious ^b	Not serious	Not serious ^c	None	139	139	⊕⊕⊕⊕ Moderate
Insulin dose	44	Randomized trials	Not serious ^a	Serious ^b	Not serious	Not serious ^c	None	1,538	1,376	⊕⊕⊕⊕ Moderate
Severe hypoglycemia	21	Randomized trials	Not serious ^a	Not serious	Not serious	Not serious ^c	None	53/1,134 (4.7%)	48/977 (4.9%)	⊕⊕⊕⊕ High
Diabetic ketoacidosis	9	Randomized trials	Not serious ^a	Not serious	Not serious	Not serious ^c	None	8/554 (1.4%)	5/445 (1.1%)	⊕⊕⊕⊕ High

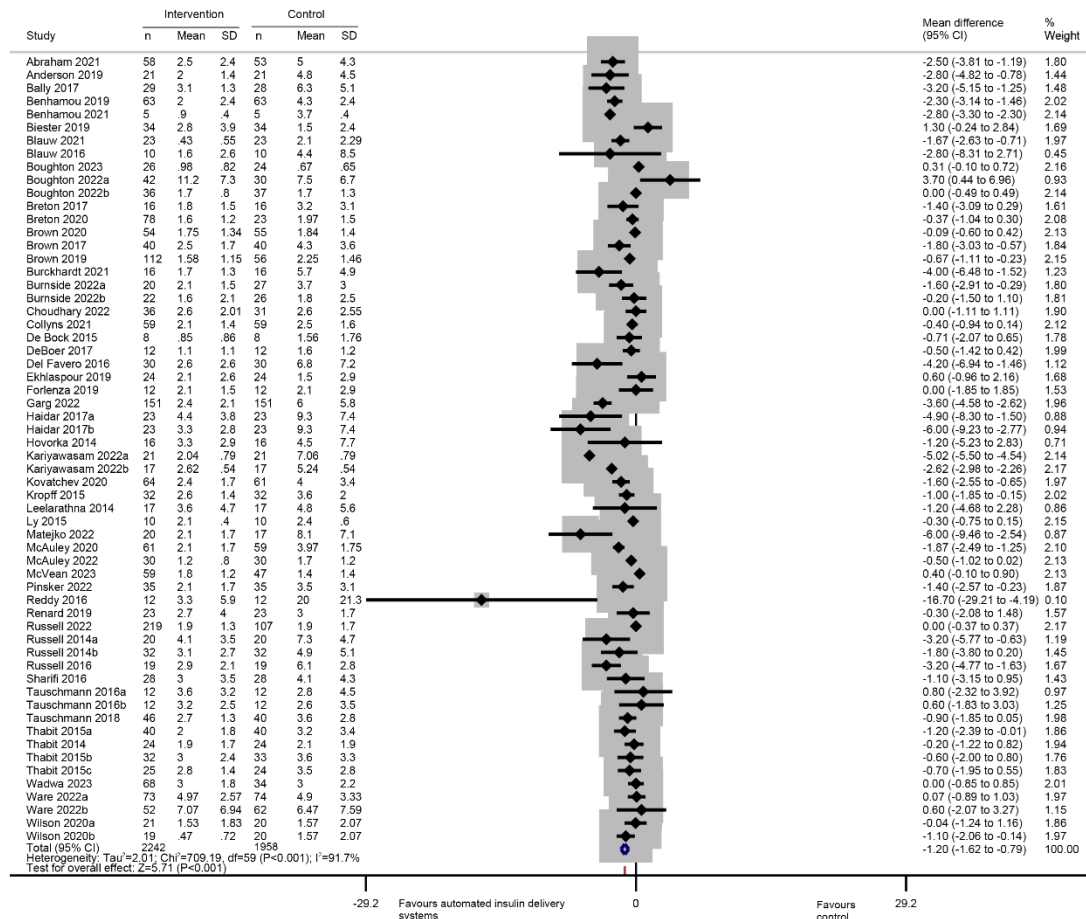
GRADE, Grading of Recommendations Assessment, Development, and Evaluation; CI, confidence interval; TIR, time in range; MD, mean difference; TBR, time below range; SD, standard deviation; TAR, time above range; CV, coefficient of variation; HbA1c, glycosylated hemoglobin; GRI, glycemia risk index; SMD, standardized mean difference; RR, relative risk.
^aAlthough all 65 studies were unblinded, the certainty of the evidence was not rated down for risk of bias because the nature of the intervention precludes blinding of patients and personnel, ^bThe *I*² was more than 50% indicating significant heterogeneity, ^cEffect size is precise enough not to warrant rating down and the 95% CI is narrow.



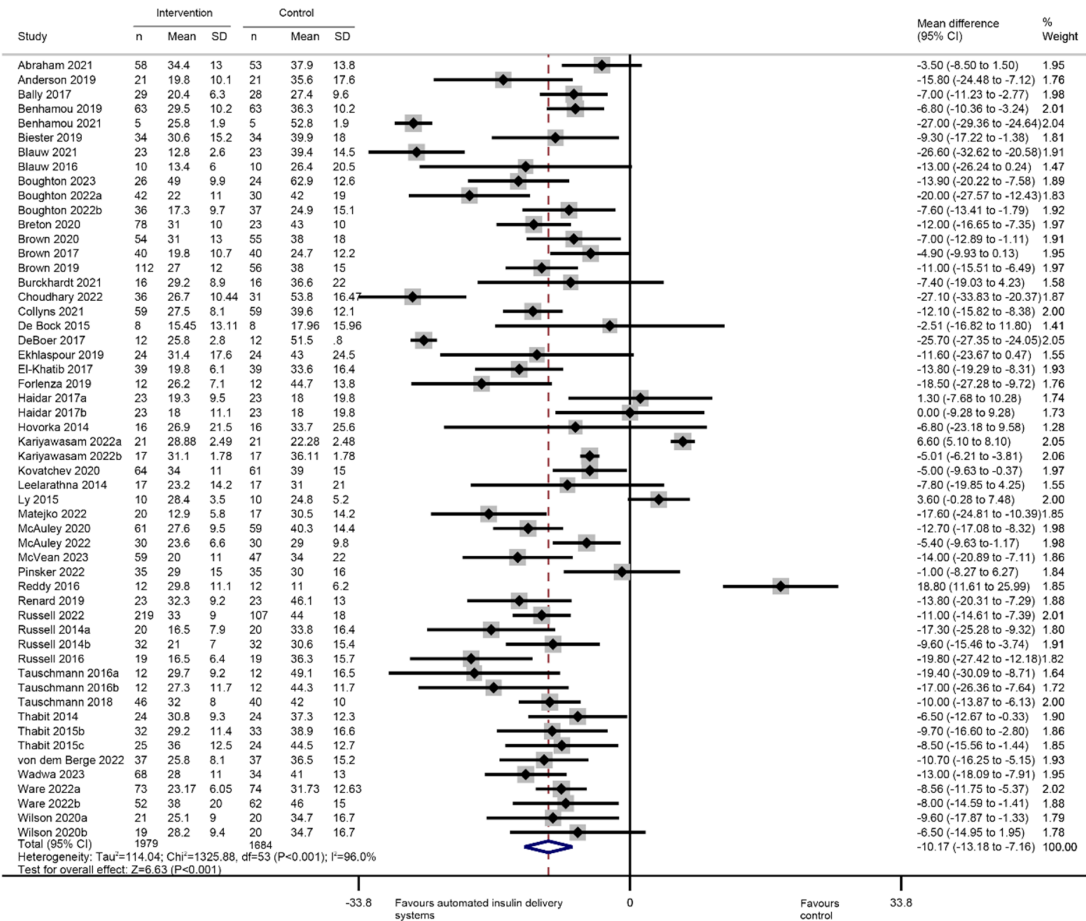
Supplementary Fig. 1. Flow diagram of study screening. RCT, randomized controlled trial.



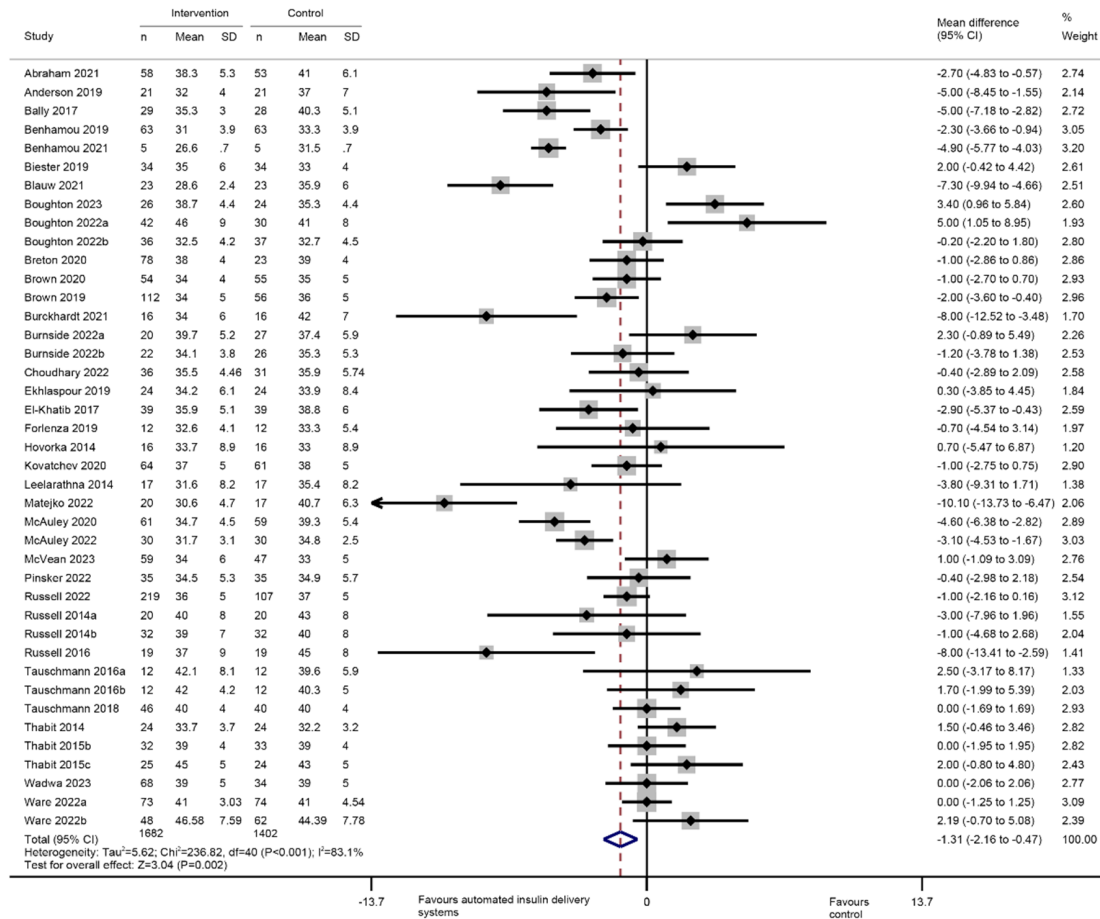
Supplementary Fig. 2. Risk of bias summary using the Cochrane risk of bias tool. (A) The risk of bias summary. (B) The risk of bias graph: ‘+’ represents a low risk of bias; ‘-’ represents a high risk of bias; and ‘?’ represents an unclear risk of bias.



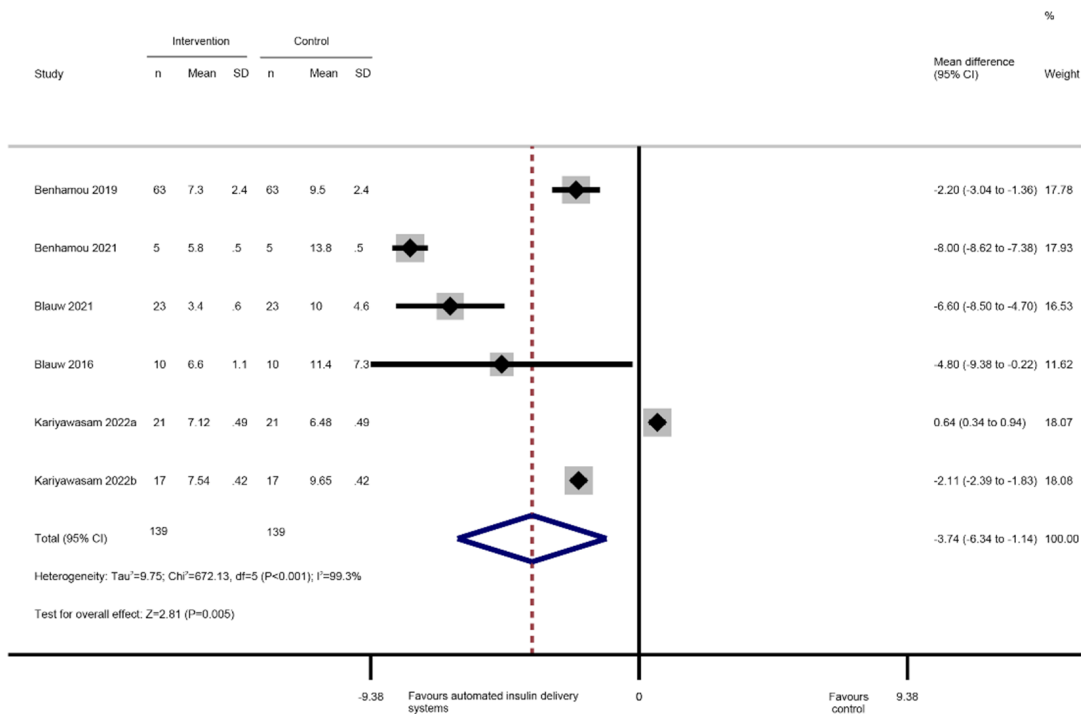
Supplementary Fig. 3. Forest plot for time below range comparing automated insulin delivery systems with other insulin-based treatment. SD, standard deviation; CI, confidence interval.



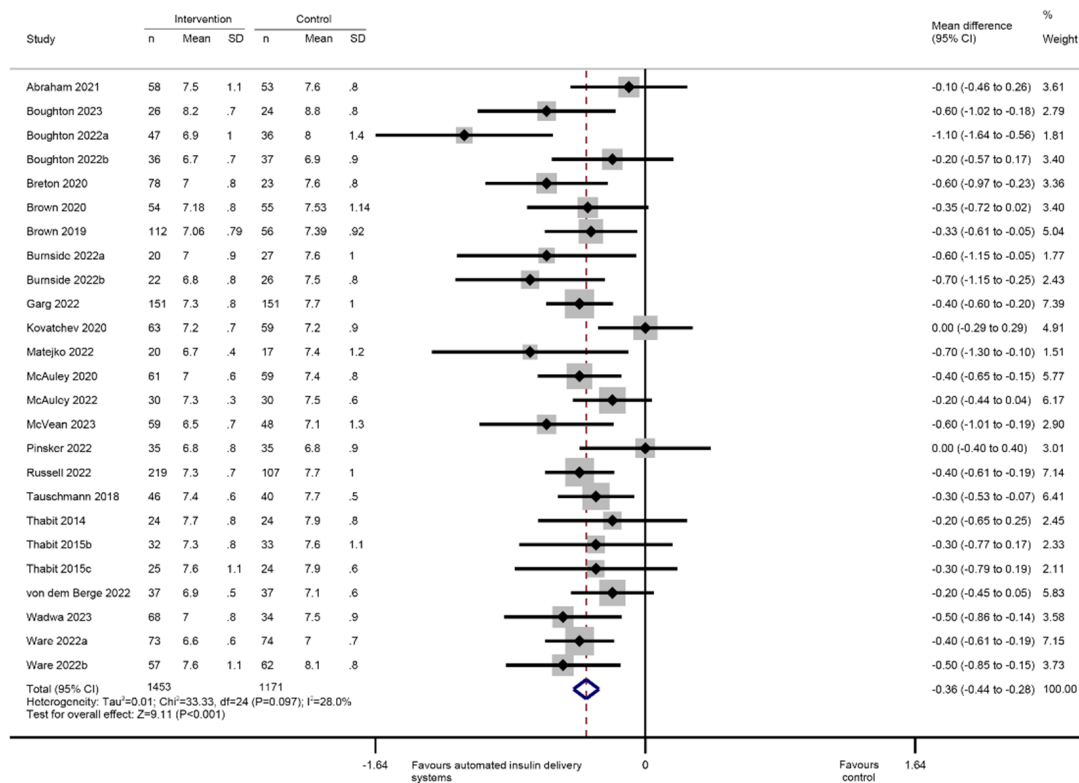
Supplementary Fig. 4. Forest plot for time above range comparing automated insulin delivery systems with other insulin-based treatment. SD, standard deviation; CI, confidence interval.



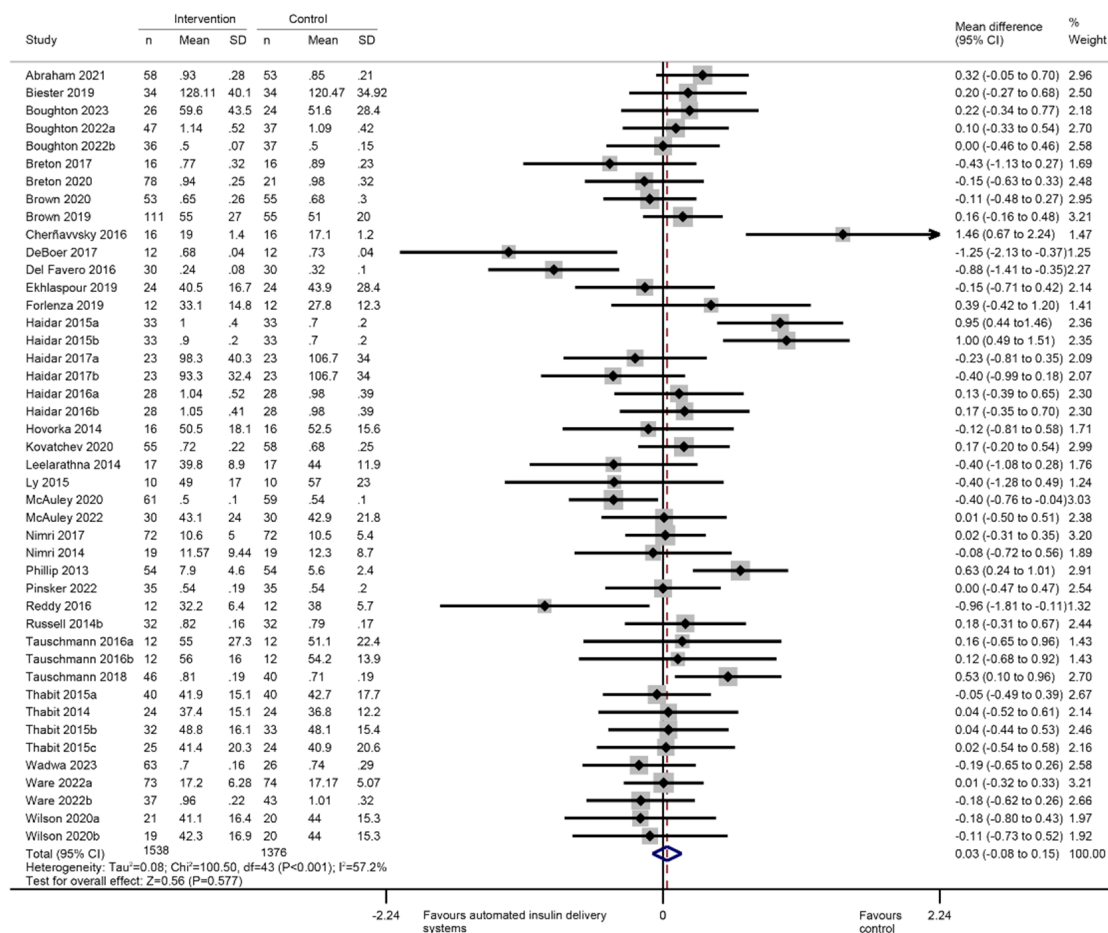
Supplementary Fig. 5. Forest plot for coefficient of variation comparing automated insulin delivery systems with other insulin-based treatment. SD, standard deviation; CI, confidence interval.



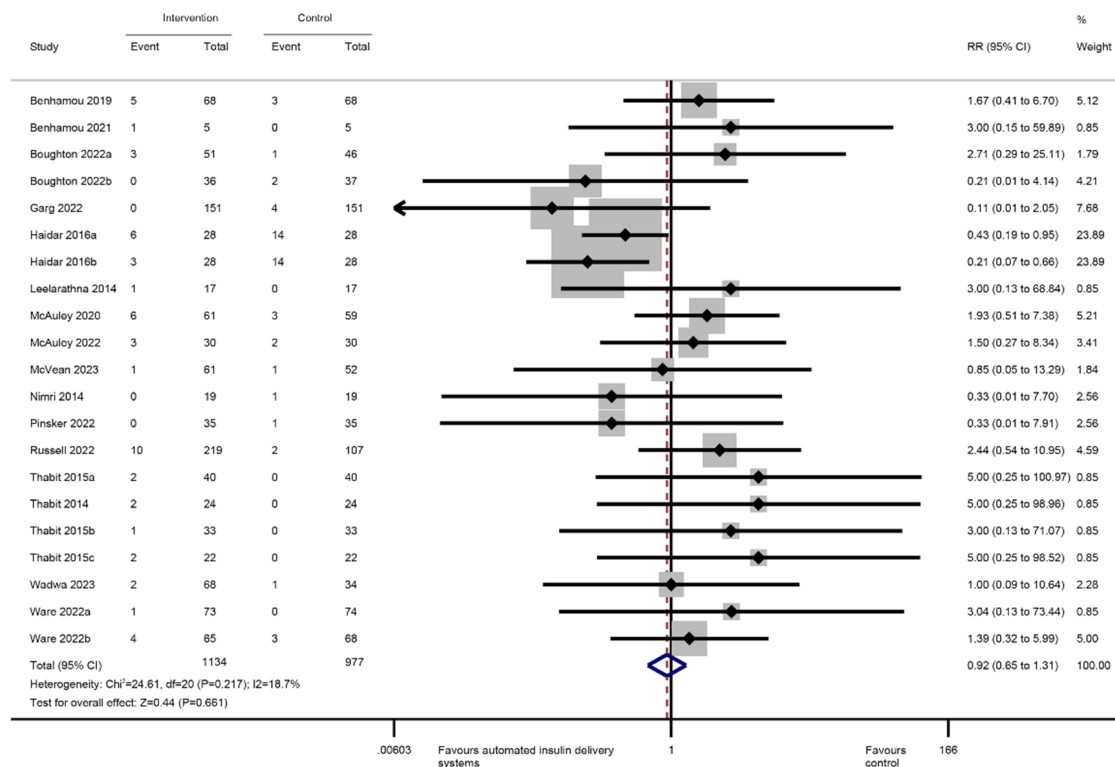
Supplementary Fig. 6. Forest plot for glycemia risk index comparing automated insulin delivery systems with other insulin-based treatment. SD, standard deviation; CI, confidence interval.



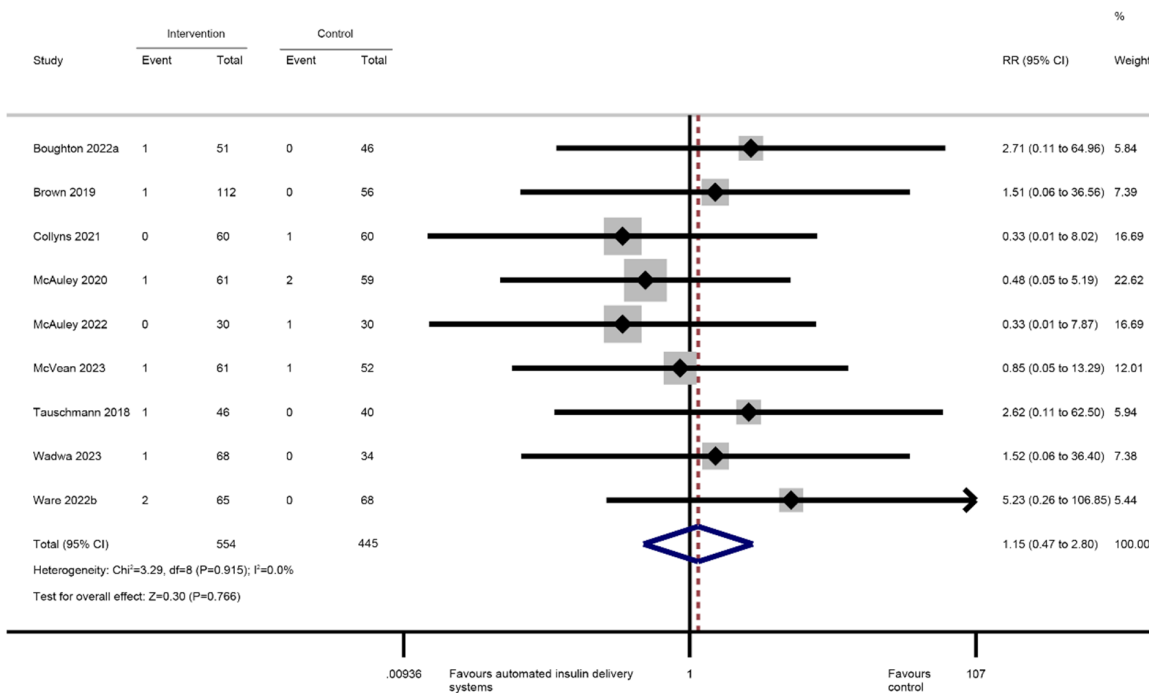
Supplementary Fig. 7. Forest plot for glycosylated hemoglobin comparing automated insulin delivery systems with other insulin-based treatment. SD, standard deviation; CI, confidence interval.



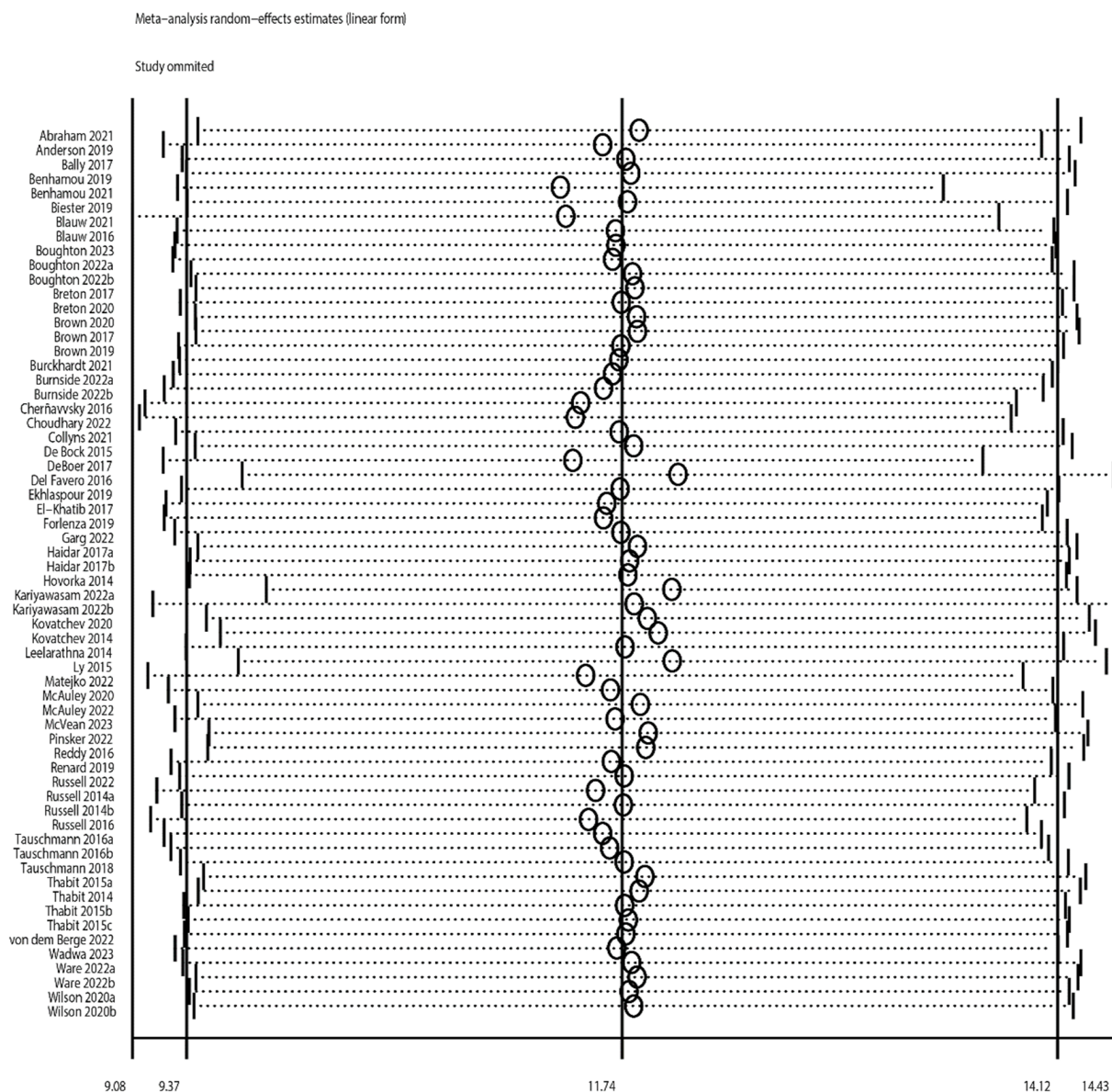
Supplementary Fig. 8. Forest plot for insulin dose comparing automated insulin delivery systems with other insulin-based treatment. SD, standard deviation; CI, confidence interval.



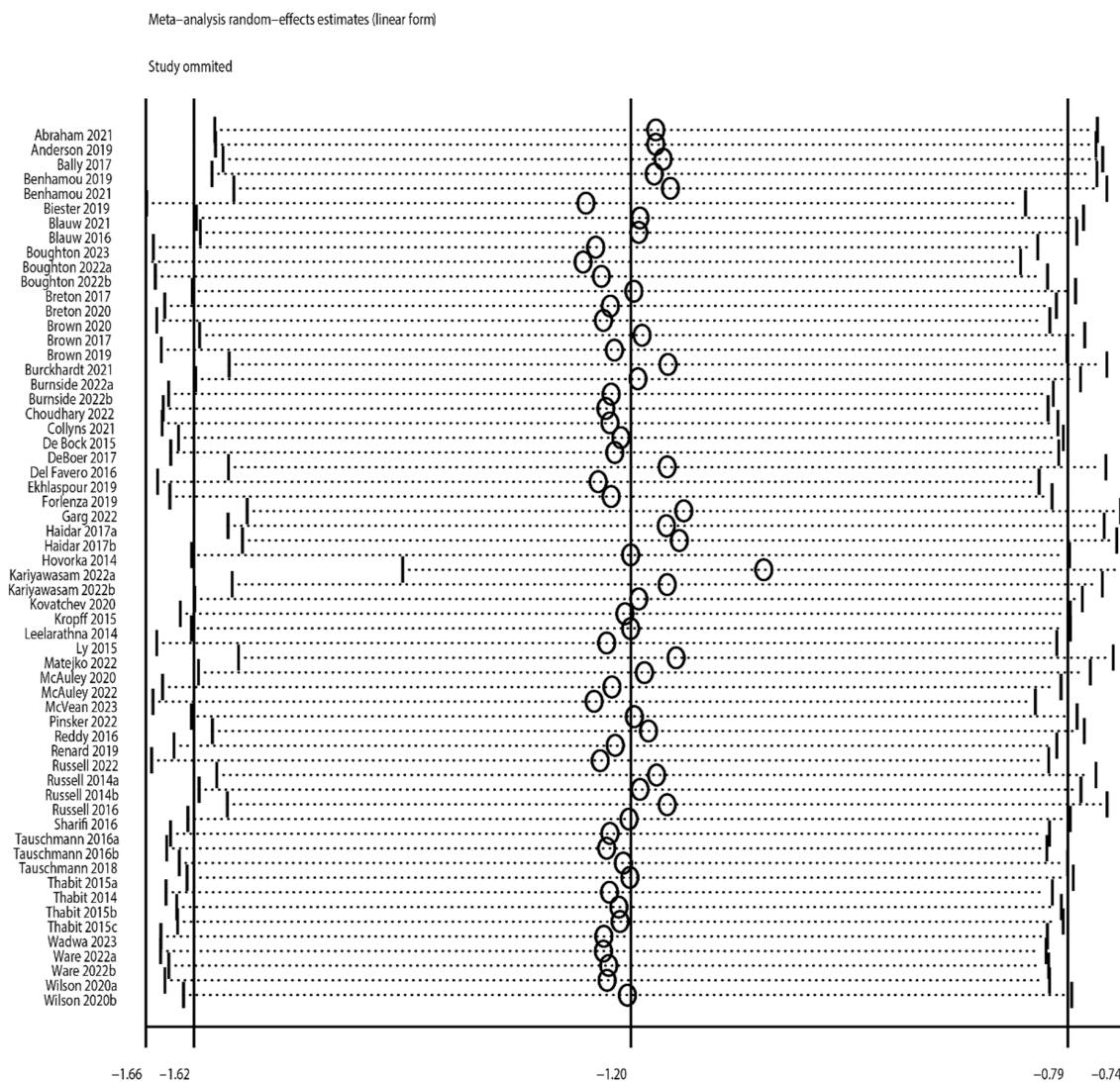
Supplementary Fig. 9. Forest plot for severe hypoglycemia comparing automated insulin delivery systems with other insulin-based treatment. RR, relative risk; CI, confidence interval.



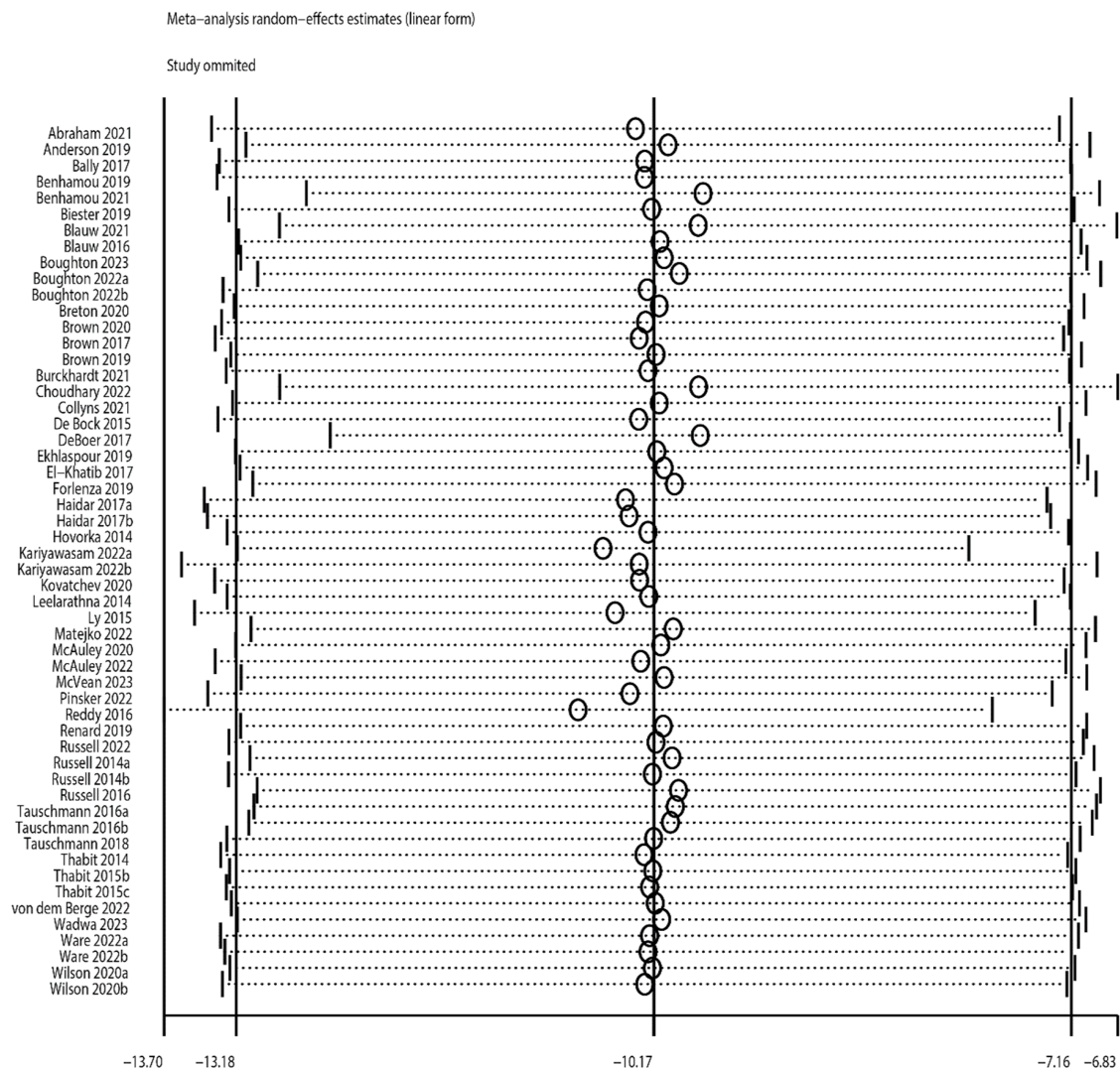
Supplementary Fig. 10. Forest plot for diabetic ketoacidosis comparing automated insulin delivery systems with other insulin-based treatment. RR, relative risk; CI, confidence interval.



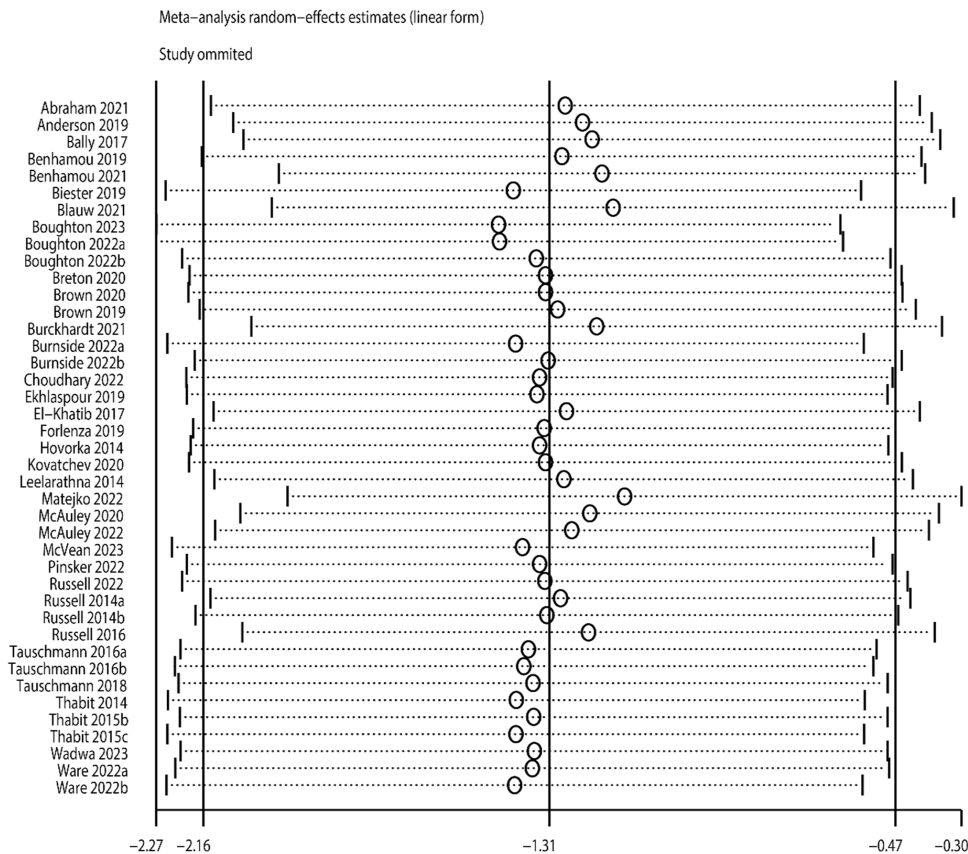
Supplementary Fig. 11. Sensitivity analysis for time in target range comparing automated insulin delivery systems with other insulin-based treatment.



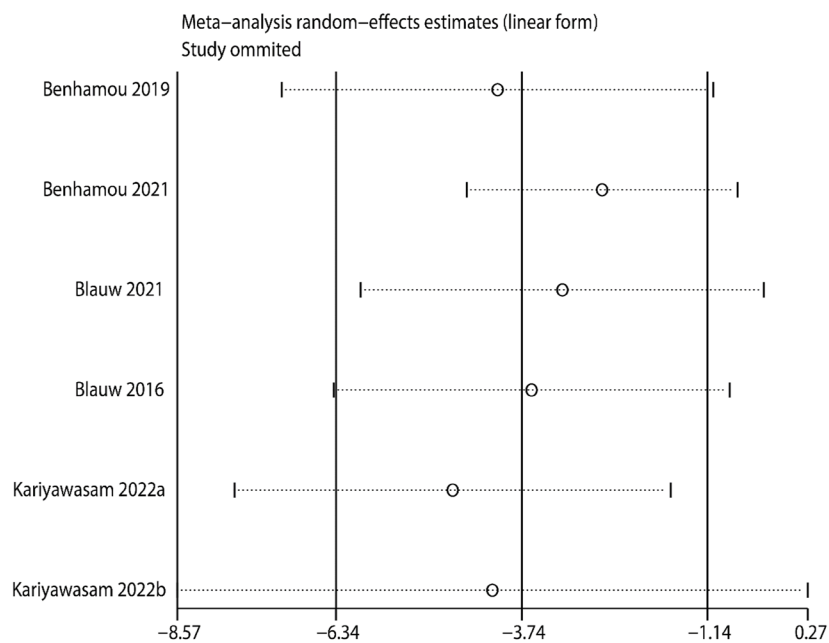
Supplementary Fig. 12. Sensitivity analysis for time below target range comparing automated insulin delivery systems with other insulin-based treatment.



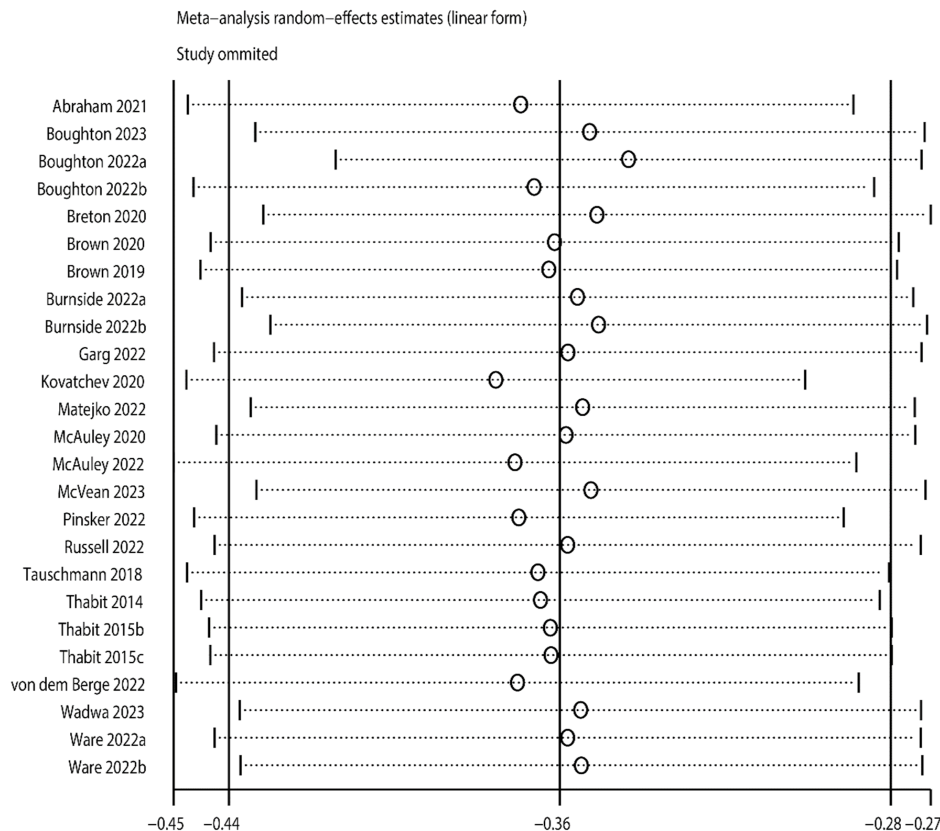
Supplementary Fig. 13. Sensitivity analysis for time above target range comparing automated insulin delivery systems with other insulin-based treatment.



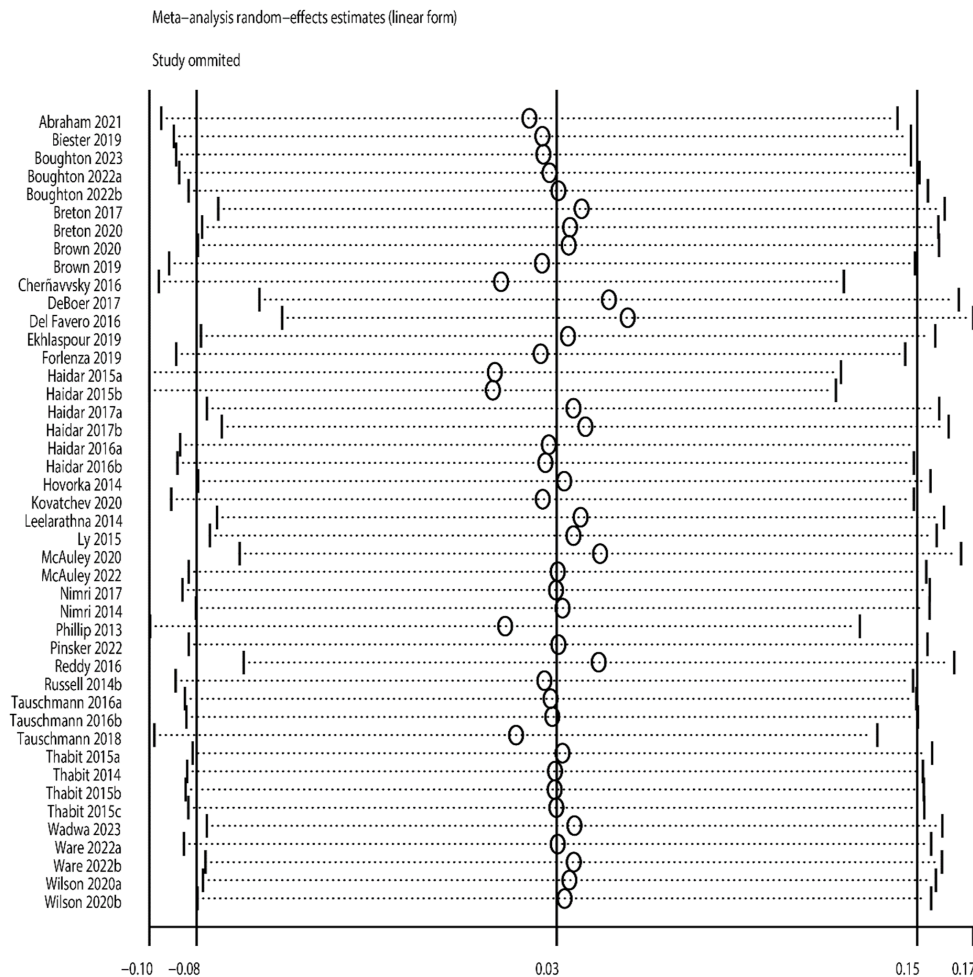
Supplementary Fig. 14. Sensitivity analysis for coefficient of variation comparing automated insulin delivery systems with other insulin-based treatment.



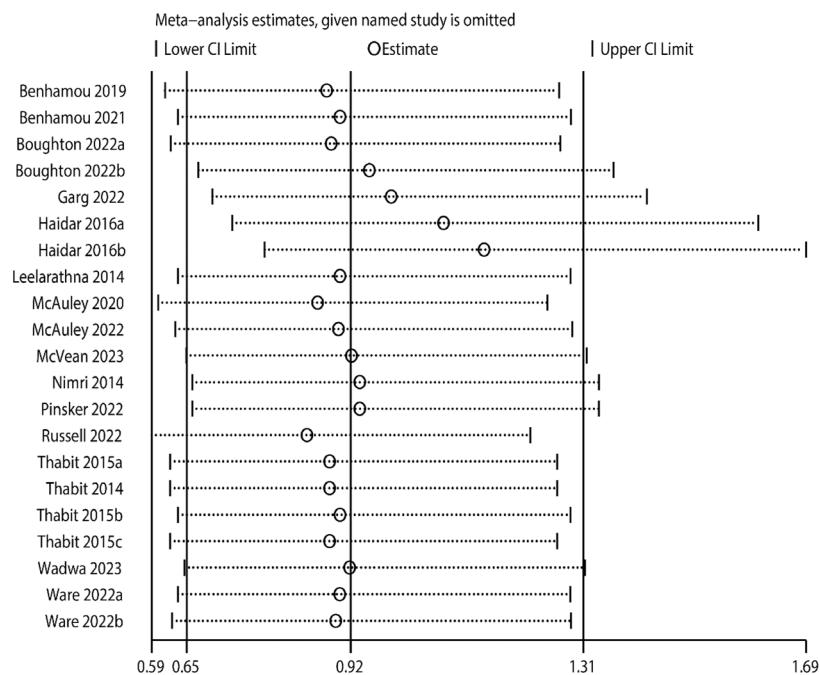
Supplementary Fig. 15. Sensitivity analysis for glycemia risk index comparing automated insulin delivery systems with other insulin-based treatment.



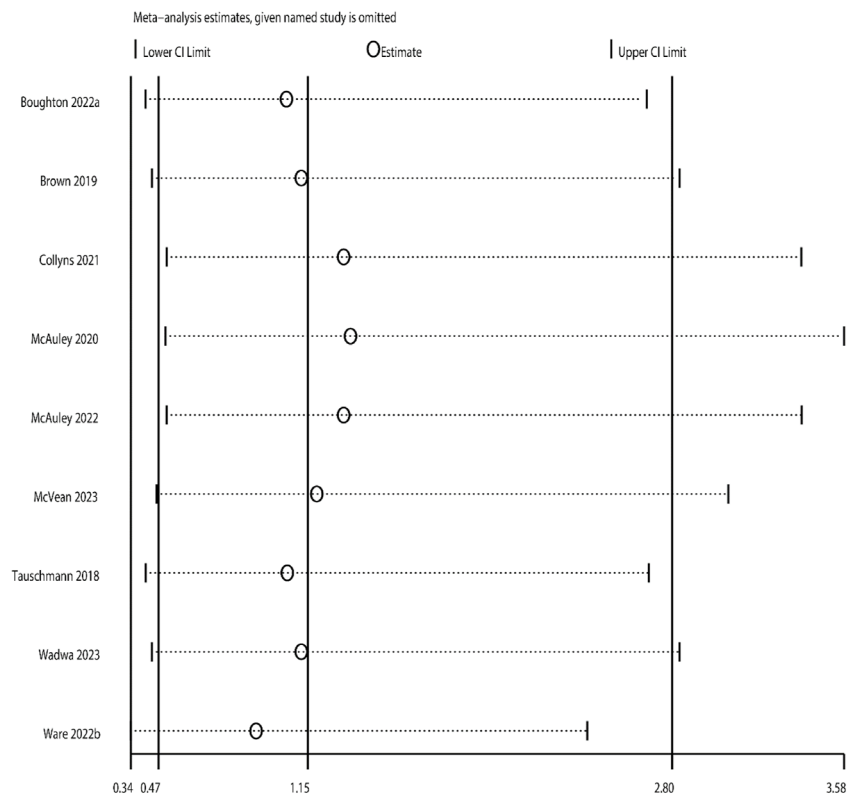
Supplementary Fig. 16. Sensitivity analysis for glycosylated hemoglobin comparing automated insulin delivery systems with other insulin-based treatment.



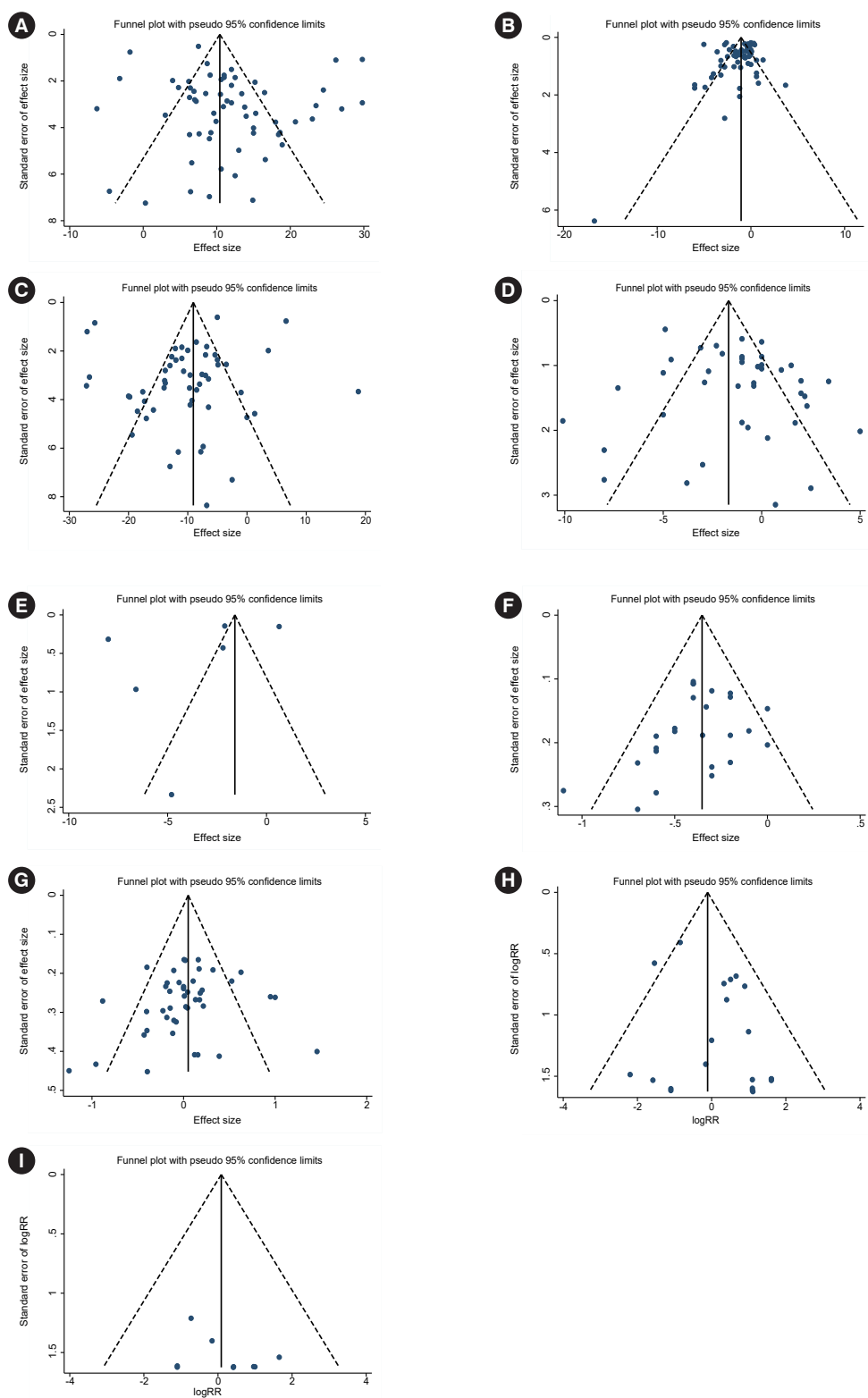
Supplementary Fig. 17. Sensitivity analysis for insulins dose comparing automated insulin delivery systems with other insulin-based treatment.



Supplementary Fig. 18. Sensitivity analysis for severe hypoglycemia comparing automated insulin delivery systems with other insulin-based treatment. CI, confidence interval.



Supplementary Fig. 19. Sensitivity analysis for diabetic ketoacidosis comparing automated insulin delivery systems with other insulin-based treatment. CI, confidence interval.



Supplementary Fig. 20. Funnel plot for all outcomes comparing automated insulin delivery systems with other insulin-based treatment. (A) Time in range, (B) time below range, (C) time above range, (D) coefficient of variation, (E) glycemia risk index, (F) glycosylated hemoglobin, (G) insulin dose, (H) severe hypoglycemia, and (I) diabetic ketoacidosis. RR, relative risk.