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Efficacy and Safety of Different Hybrid Closed Loop Systems for Automated Insulin Delivery in People With Type 1 Diabetes: A Systematic Review and Network Meta-Analysis

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Keywords: automated insulin delivery | hybrid closed loop | Time In Range | type 1 diabetes

ABSTRACT

Aims: To compare the efficacy and safety of different hybrid closed loop (HCL) systems in people with diabetes through a network meta-analysis.

Methods: We searched MEDLINE, EMBASE, CENTRAL and PubMed for randomised clinical trials (RCTs) enrolling children, adolescents and/or adults with type 1 or type 2 diabetes, evaluating Minimed 670G, Minimed 780G, Control-IQ, CamAPS Fx, DBLG-1, DBLHU, and Omnipod 5 HCL systems against other types of insulin therapy, and reporting time in target range (TIR) as outcome.

Results: A total of 28 RCTs, all enrolling people with type 1 diabetes, were included. HCL systems significantly increased TIR compared with subcutaneous insulin therapy without continuous glucose monitoring (SIT). Minimed 780G achieved the highest TIR ahead of Control IQ (mean difference (MD) 5.1%, 95% confidence interval (95% CI) [0.68; 9.52], low certainty), Minimed 670G (MD 7.48%, 95% CI [4.27; 10.7], moderate certainty), CamAPS Fx (MD 8.94%, 95% CI [4.35; 13.54], low certainty), and DBLG1 (MD 10.69%, 95% CI [5.73; 15.65], low certainty). All HCL systems decreased time below target range, with DBLG1 (MD −3.69%, 95% CI [−5.2; −2.19], high certainty), Minimed 670G (MD −2.9%, 95% CI [−3.77; −2.04], moderate certainty) and Minimed 780G (MD −2.79%, 95% CI [−3.94; −1.64], high certainty) exhibiting the largest reductions compared to SIT. The risk of severe hypoglycaemia and diabetic ketoacidosis was similar to other types of insulin therapy.

Sergio Di Molfetta, Ludovico Di Gioia, and Irene Caruso contributed equally to this work.

Conclusions: We show a hierarchy of efficacy among the different HCL systems in people with type 1 diabetes, thus providing support to clinical decision-making.
Trial Registration: PROSPERO CRD42023453717

1 | Introduction

Since its early beginning in the 1920s, insulin therapy has gone through extraordinary technological advances. In type 1 diabetes, continuous subcutaneous insulin infusion (CSII) has been shown to reduce both HbA1c and the rate of hypoglycaemic events when compared with multiple daily injections (MDI) therapy [1]. The advent of continuous glucose monitoring (CGM) has further revolutionised diabetes care, with additional benefits on glycaemic control, risk of hypoglycaemia, and quality of life [2–6]. In the last decade, the integration of CSII and CGM technology has allowed the development of increasingly sophisticated systems providing automated insulin delivery. Specifically, hybrid closed loop (HCL) systems provide algorithm-driven regulation (either increase or reduction) of insulin infusion through the insulin pump in response to changes in CGM-measured glucose levels, with the user being required to input data about meals and physical activity [7]. HCL systems have been shown to reduce HbA1c levels and increase time spent within target glucose range (TIR) without increasing time spent below range (TBR) and hypoglycaemic events, and in some studies to reduce hypoglycaemia [8–10]. Noteworthy, benefits of closed loop technology include improvements in psychosocial outcomes and quality of sleep [11].

Seven alternative HCL systems are currently commercially available: Minimed 670G (Medtronic, Northridge, CA, USA), Minimed 780G (Medtronic, Northridge, CA, USA), T:slim X2 with Control-IQ technology (Control-IQ) (Tandem Diabetes Care, San Diego, CA, USA), CamAPS Fx (CamDiab Ltd., Cambridge, UK), Diabeloop Generation 1 (DBLG-1) (Diabeloop, Grenoble, France), Diabeloop for highly unstable diabetes (DBLHU) (Diabeloop, Grenoble, France), and Omnipod 5 (Insulet Corporation, Acton, MA, USA) [12]. Although comparable in their overall structure, these HCL systems show meaningful differences in components, insulin dosing algorithms, modifiable settings, and additional features (Supporting Information S1: Section S1). Given the lack of head-to-head studies, this network meta-analysis aims to compare the performance of different HCL systems in people with diabetes.

2 | Materials and Methods

The study protocol was registered prior to conduct (PROSPERO CRD42023453717).

2.1 | Data Sources

We searched MEDLINE (via Ovid), EMBASE, and CENTRAL from inception to August 9, 2023 (Supporting Information S1: Section S2) and performed hand-searching in PubMed to identify online publications ahead of print.

2.2 | Ethics Approval

Analyses were performed on data extracted from published papers. Patient consent for publication was not required.

2.3 | Study Selection

We included randomised clinical trials (RCTs) enrolling children, adolescents and adults with type 1 or type 2 diabetes, evaluating a commercially available HCL system against other types of subcutaneous intensive insulin therapy, and reporting 24-h TIR (70–180 mg/dL) as an outcome.

Trials conducted in special populations of patients (pregnant women, patients with kidney or liver failure, hospitalised patients, or highly unstable diabetes) or evaluating HCL insulin delivery in response to experimentally induced stress challenges (physical exercise, gastronomic meals, etc.) were excluded as insulin therapy in these subgroups of patients and/or situations may be influenced by several factors not reflecting usual practice.

The primary review outcome was TIR at study end (mean difference [MD], 95% confidence interval [CI]). Secondary outcomes included TBR, time below 54 mg/dL (TBR <54 mg/dL), time above range (TAR), mean sensor glucose, coefficient of variation of mean glucose (CV), incidence of severe hypoglycaemic events, incidence of diabetic ketoacidosis (DKA), patients' satisfaction, and quality of life. All causes of death, occurrence of major adverse cardiovascular events, lower limb gangrene or lower limb amputation, development/worsening of diabetic retinopathy or nephropathy, and need for kidney replacement therapy were also collected.

2.4 | Data Extraction

Three reviewers (I.C., L.D.G. and S.D.M.) independently evaluated the retrieved citations based on predetermined inclusion and exclusion criteria. Disagreements were settled by discussion or by a third party (FG). The following data were collected from the included papers: study characteristics (study design, duration, year of publication, sample size), participants' characteristics (age, sex, HbA1c at baseline, and disease duration), HCL system under evaluation, comparator(s), TIR, TBR, TBR <54 mg/dL, 24-h mean sensor glucose, TAR, CV, patient-reported outcome measures (PROMs), prevalence of severe hypoglycaemic events and DKA, other severe adverse events.

For the purposes of our analysis, data were collected by pooling comparators as reported in the statistical analysis section.

Study investigators were contacted in case of missing data. If the mean was missing, it was calculated by dividing the sum of the median, first quartile, and third quartile by 3 [13]. If standard deviation (SD) was missing, it was calculated from the standard error (SE) by multiplying SE by the square root of the sample size; if none of this information was available, it was imputed based on the higher value within each group (Cochrane Handbook for Systematic Reviews of Interventions version 6.4).

Disagreements in data extraction were settled by debate or with the aid of a third party (FG).

2.5 | Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers (I.C. and L.D.G.) through the Cochrane Collaboration's tool (RoB version 2), evaluating the following domains: randomisation process, deviations from intended intervention, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias. Each domain was deemed low, with some concerns or high risk of bias. Any differences in assessment were resolved by consensus.

2.6 | Statistical Analysis

Data for continuous variables are expressed as mean (SD) or, if variables were not normally distributed, as median (interquartile range, IQR); categorical variables were represented as counts or frequencies.

Random-effects pairwise meta-analyses were conducted for direct comparisons. The transitivity assumption that a network meta-analysis approach is appropriate was assessed by comparing the distribution of potential effect modifiers across treatment comparisons (duration of intervention, year of publication, sample size, sex, duration of diabetes, age, HbA1c at baseline). Differences across studies in the above variables were explored in subgroup analyses.

We performed random-effects frequentist network meta-analyses [14], using MD and 95% CI for TIR, TBR, TBR <54 mg/dL, TAR, 24-h mean sensor glucose and CV, and odds ratio (OR) and 95% CI for the risk of severe hypoglycaemic events and diabetic ketoacidosis. Surface under the cumulative ranking curve (SUCRA) was also used to estimate the comparative efficacy of HCL systems.

As the comparators were diverse across the studies, for the purposes of our analysis, they were pooled as follows: *subcutaneous insulin therapy without CGM (SIT)*: MDI without CGM (one study), CSII without CGM (three studies), MDI or CSII without CGM (one study); *subcutaneous insulin therapy with CGM (SITCGM)*: MDI with real-time CGM (RT-CGM) (one study), MDI with intermittently scanned CGM (isCGM) (one study), MDI or CSII with CGM (one study), MDI or CSII with or without CGM (three studies), sensor-augmented pump therapy (SAPT) (nine studies); *LGSPLGS*: low glucose suspension (LGS) (one study), predictive lo glucose suspension (PLGS) (four studies), SAPT with or without LGS (one study), SAPT or PLGS (one study).

Heterogeneity was assessed by comparing the magnitude of the common between-study variance (τ^2) for each outcome with empirical distributions of heterogeneity variances [15]. Local consistency in networks was evaluated by comparing direct with indirect evidence [16] and global consistency with the design-by-treatment interaction model [17]. All analyses were performed using R packages meta [18] and netmeta [19]. We assessed confidence in network meta-analysis estimates using the CINeMA (Confidence In Network Meta-Analysis) framework and online application [20]. The evaluation of anticipated absolute effects of interventions was performed using the GRADEpro (McMaster University, 2020, Ontario, Canada) online tool. Prespecified subgroup analyses were conducted according to the duration of intervention (>13 or ≤13 weeks), duration of diabetes (≥10 or <10 years), age (≥18 or <18 years old), and HbA1c at baseline (≥8% or <8%).

3 | Results

3.1 | Study Characteristics

A total of 28 RCTs, enrolling 2446 patients with type 1 diabetes, were included in this systematic review and network meta-analysis (Figure 1). We found no eligible studies evaluating the efficacy and safety of DBLHU and Omnipod 5.

The characteristics of the studies and patients' baseline features are presented in Supporting Information S1: Section S2.1. Importantly, baseline HbA1c and age of participants were similar across studies with different HCL systems (Supporting Information S1: Section S2.2). The included studies were also comparable for year of publication, duration of intervention, sex of participants, and duration of diabetes. Twenty-four out of 28 studies were conducted in a multi-centre setting, and 18 were supported financially and/or with materials by companies.

The networks of trials used in the meta-analysis to evaluate TIR, TBR, TBR <54 mg/dL, TAR, CV, mean sensor glucose, and risk of severe hypoglycaemic events and diabetic ketoacidosis are shown in Figure 2a and Supporting Information S1: Sections S8–S14.

Overall risk of bias for the main outcome was deemed low for 18 trials, of some concern for 9 trials, and high for 1 trial (Supporting Information S1: Section S3). Comparison-adjusted funnel plots and Egger's test did not suggest the presence of publication bias for all outcomes (Supporting Information S1: Section S4). Evidence certainty was generally low for each of the main comparisons and is summarised in dedicated tables for mean change in TIR, TAR, TBR, CV, mean glucose and risk of severe hypoglycaemia and DKA in the Supporting Information S1: Sections S7.2, S8.2, S10.2, S11.2, S12.2, S13.2 and S14.2.

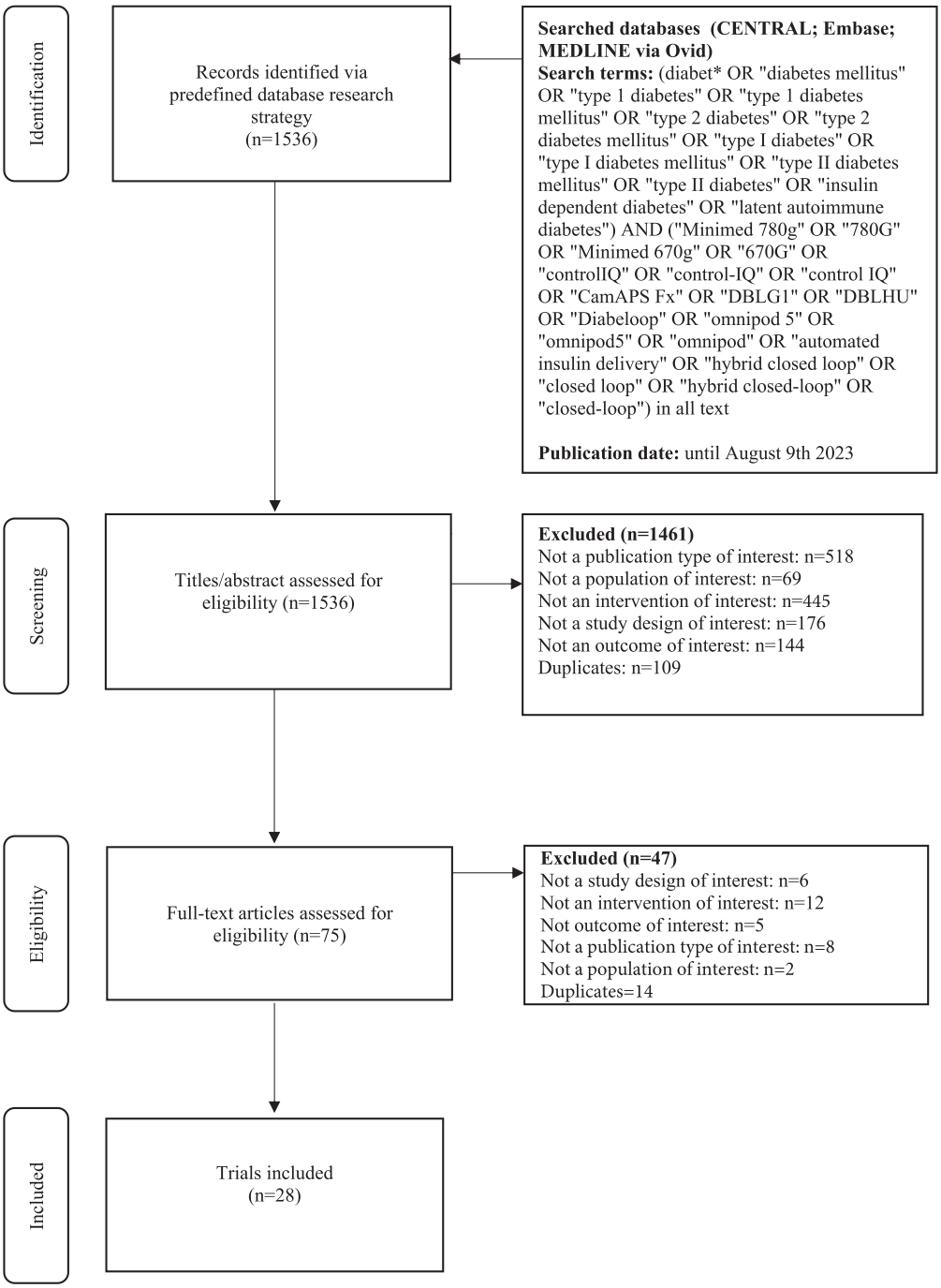

FIGURE 1 | PRISMA flowchart for study selection.

A substantial amount of network heterogeneity was detected for TBR, TAR, CV, and mean glucose; moderate heterogeneity was found for TIR and TBR <54 mg/dL; and heterogeneity was low for risk of severe hypoglycaemia and DKA. Global inconsistency in the design-by-treatment interaction model was high for all outcomes except for the risk of severe hypoglycaemia and DKA; however, local inconsistency was generally low (Supporting Information S1: Section S5).

3.2 | Time In Range

A total of 28 studies were included in the main analysis evaluating TIR. Pairwise meta-analysis results are presented in Supporting Information S1: Section S6.1. Network meta-analysis results are presented in Figure 2b and Table 1.

All HCL systems significantly increased TIR compared to SIT, with Minimed 780G exhibiting the largest improvement (1 study, 37 patients, MD 21.6%, 95% CI [17.6; 25.5], high certainty). Minimed 780G was superior to Control IQ (MD 5.1%, 95% CI [0.68; 9.52], low certainty), Minimed 670G (1 study, 224 patients, MD 7.48%, 95% CI [4.27; 10.7], moderate certainty), CamAPS Fx (MD 8.94%, 95% CI [4.35; 13.54], low certainty), and DBLG1 (MD 10.69%, 95% CI [5.73; 15.65], low certainty) (Figure 2b, Table 1). The efficacy of Control IQ, Minimed 670G and CamAPS Fx was comparable. DBLG1 was inferior to Control IQ, and comparable to Minimed 670G, CamAPS Fx,

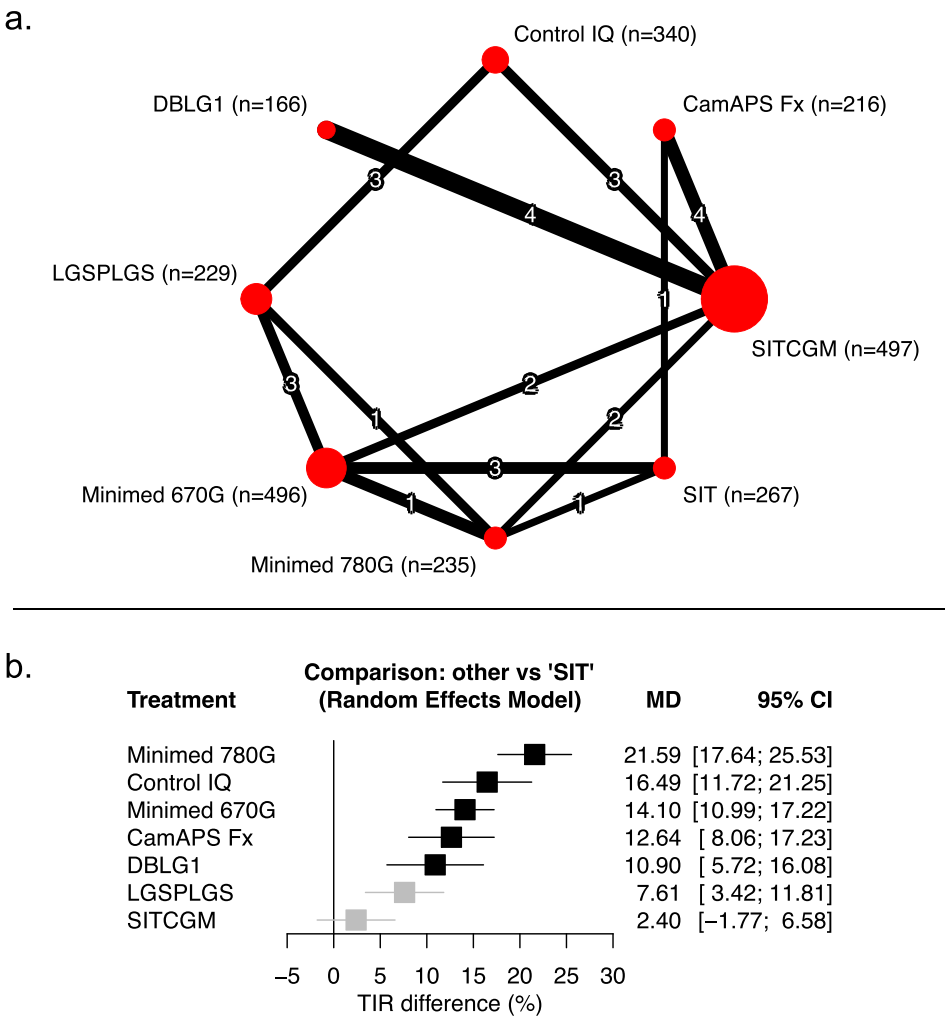

FIGURE 2 | (a) Meta-analysis network for Time In Range (TIR). Each circle indicates a treatment node, and its size is proportional to the number of trials evaluating each treatment (n = number of subjects). Lines connecting two nodes represent direct comparisons between two treatments; the thickness of the lines is proportional to the number of trials directly comparing the two connected treatments, as indicated. (b) Network meta-analysis results for Time In Range (TIR) compared with subcutaneous insulin therapy without CGM (SIT). Treatments are presented according to their effect estimates compared with SIT. Effect sizes are presented as mean difference (MD) and 95% confidence intervals (CI). HCL systems are highlighted in black, other treatments in grey. SIT: multiple daily injections (MDI) without continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII) without CGM, MDI or CSII without CGM; subcutaneous insulin therapy with CGM (SITCGM): MDI with real-time CGM (RT-CGM), MDI with intermittently scanned CGM (isCGM), MDI or CSII with CGM, MDI or CSII with or without CGM, sensor-augmented pump therapy (SAPT); LGSPLGS: low glucose suspension (LGS), predictive low glucose suspension (PLGS), SAPT with or without LGS, SAPT or PLGS.

and LGSPLGS (low certainty). All HCL systems besides DBLG1 were superior to LGSPLGS and SITCGM (Figure 2b, Table 1).

3.3 | Time Below Range

TBR was reported in 28 studies, while TBR <54 mg/dL was evaluated in 20 studies. Pairwise meta-analysis results are presented in Supporting Information S1: Sections S6.2 and S6.3 respectively. Network meta-analysis results are presented in Figure 3a and Supporting Information S1: Section S8 for TBR, and Supporting Information S1: Section S9 for TBR <54 mg/dL.

All HCL systems significantly decreased TBR and TBR <54 mg/dL compared to SIT. DBLG1, Minimed 670G and Minimed 780G achieved the largest reductions in TBR versus SIT (DBLG1: MD −3.69%, 95% CI [−5.2; −2.19], high certainty; Minimed 670G: MD −2.9%, 95% CI [−3.77; −2.04], moderate certainty; Minimed 780G: MD −2.79%, 95% CI [−3.94; −1.64], high certainty) with nonsignificant differences one with the others (Supporting Information S1: Section S8). Of note, DBLG1 was superior to both Control IQ (MD −1.19%, 95% CI [−2.33; −0.05], low certainty) and CamAPS Fx (MD −1.68%, 95% CI [−2.84; −0.52], moderate certainty) (Supporting Information S1: Section S8). The different HCL systems reduced TBR <54 mg/dL to the same extent, and their efficacy was comparable to LGSPLGS and SITCGM (Supporting Information S1: Section S9).

3.4 | Time Above Range

A total of 28 studies were included in the main analysis for TAR. Pairwise meta-analysis results are presented in Supporting Information S1: Section S6.4, while network meta-analysis results

TABLE 1 | Mean difference in Time In Range.

Minimed 780G	—	4.00 [−0.65; 8.65]	—	—	**12.50 [6.99; 18.01]**	**27.04 [20.31; 33.77]**	**23.50 [16.21; 30.79]**
5.10 [0.68; 9.52]	Control IQ	—	—	—	**9.39 [4.90; 13.88]**	**13.67 [9.69; 17.65]**	—
7.48 [4.27; 10.70]	2.38 [−1.67; 6.44]	Minimed 670G	—	—	**6.87 [2.79; 10.94]**	**8.25 [3.00; 13.49]**	**13.35 [9.75; 16.94]**
8.94 [4.35; 13.54]	3.84 [−0.51; 8.19]	1.46 [−2.73; 5.65]	CamAPS Fx	—	—	**10.04 [7.06; 13.02]**	**14.00 [6.21; 21.79]**
10.69 [5.73; 15.65]	**5.59 [0.99; 10.18]**	3.20 [−1.43; 7.84]	1.74 [−2.43; 5.92]	DBLG1	—	**8.49 [5.43; 11.56]**	—
13.97 [10.34; 17.60]	**8.87 [5.20; 12.54]**	**6.49 [3.31; 9.67]**	**5.03 [0.46; 9.60]**	3.29 [−1.62; 8.19]	LGSPLGS	—	—
19.18 [15.28; 23.08]	**14.08 [10.66; 17.50]**	**11.70 [8.22; 15.17]**	**10.24 [7.40; 13.07]**	**8.49 [5.43; 11.56]**	**5.21 [1.38; 9.04]**	SITCGM	—
21.59 [17.64; 25.53]	**16.49 [11.72; 21.25]**	**14.10 [10.99; 17.22]**	**12.64 [8.06; 17.23]**	**10.90 [5.72; 16.08]**	**7.61 [3.42; 11.81]**	2.40 [−1.77; 6.58]	SIT

Note: The lower half presents network meta-analysis results, while the upper half presents pairwise meta-analysis results. Treatments are reported in efficacy ranking order. Treatment estimates are expressed as mean difference and 95% confidence intervals of the column-defining treatment compared with the row-defining treatment for the Time In Range. Mean differences lower than 0 favour the column-defining treatment for network meta-analysis and the row-defining treatment for pairwise meta-analysis. Significant results are in bold. Subcutaneous insulin therapy without CGM (SIT): multiple daily injections (MDI) without continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII) without CGM, MDI or CSII without CGM; subcutaneous insulin therapy with CGM (SITCGM): MDI with real-time CGM (RT-CGM), MDI with intermittently scanned CGM (isCGM), MDI or CSII with CGM, MDI or CSII with or without CGM, sensor-augmented pump therapy (SAPT); LGSPLGS: low glucose suspension (LGS), predictive low glucose suspension (PLGS), SAPT with or without LGS, SAPT or PLGS.

are presented in Figure 3b and Supporting Information S1: Section S10.

All HCL systems significantly decreased TAR compared to SIT and SITCGM, with Minimed 780G and Control IQ achieving the largest reductions versus SIT (Minimed 780G: MD −18.82%, 95% CI [−24.3; −13.34], high certainty; Control IQ: MD −14.28%, 95% CI [−20.65; −7.91], low certainty). Moreover, as shown in Supporting Information S1: Section S10, Minimed 780G was superior to all other HCL systems but Control IQ in reducing TAR (MD 4.54 [−1.32; 10.40], low certainty). In turn, Control IQ had a similar efficacy in TAR reduction compared to CamAPS Fx and Minimed 670G (low certainty), while greater than DBLG1 (MD −6.7%, 95% CI [−13.20; −0.25], low certainty).

3.5 | Mean Glucose and Coefficient of Variation

A total of 26 and 23 studies were included in the main analyses for mean glucose and CV, respectively. Results of pairwise meta-analysis are presented in Supporting Information S1: Sections S6.5 and S6.6, and results of network meta-analysis are presented in Figure 3c,d and Supporting Information S1: Sections S11 and S12.

All HCL systems but DBLG1 significantly reduced mean glucose compared to SIT and SITCGM, with Minimed 780G achieving the largest reductions (MD −26 mg/dL, 95% CI [−36; −15.9], high certainty, and −26.1 mg/dL, 95% CI [−35.1; −17.2], moderate certainty, vs. SIT and SITCGM, respectively). Minimed 780G, Control IQ and CamAPS Fx significantly reduced mean glucose more than DBLG1, and Minimed 780G was also superior to Minimed 670G (MD −14.5 mg/dL, 95% CI [−22.3; −6.7], low certainty). In contrast, Control IQ, CampAPS Fx and Minimed 670G showed similar efficacy (Supporting Information S1: Section S11). DBLG1, Minimed 670G, Minimed 780G and Control IQ were found to be superior to SIT in reducing CV, with non-significant differences among the others. DBLG1 reduced CV significantly more than CamASP Fx (MD −4.77%, 95% CI [−7.65; −1.89], low certainty) (Supporting Information S1: Section S12).

3.6 | Adverse Events

A total of 25 studies reported the number of patients who experienced severe hypoglycaemia and DKA episodes. Results of pairwise meta-analysis are presented in Supporting Information S1: Sections S6.7 and S6.8, and results of network meta-analysis in Supporting Information S1: Sections S13 and S14.

The risk of severe hypoglycaemia and DKA was not statistically different with HCL systems compared with other types of subcutaneous intensive insulin therapy. The other severe adverse events are reported in Supporting Information S1: Section S15: due to the exiguous number of events detected throughout all 28 included studies, any comparison was unfeasible. Only 5 hard events in total were reported: 4 of them were in control groups, and only 1 in the HCL group. All these serious adverse events were not related to treatment.

3.7 | Subgroup and Sensitivity Analyses

Sensitivity analyses including only trials at low risk of bias (Supporting Information S1: Sections S7.7, S8.7, S9.6, S10.7,

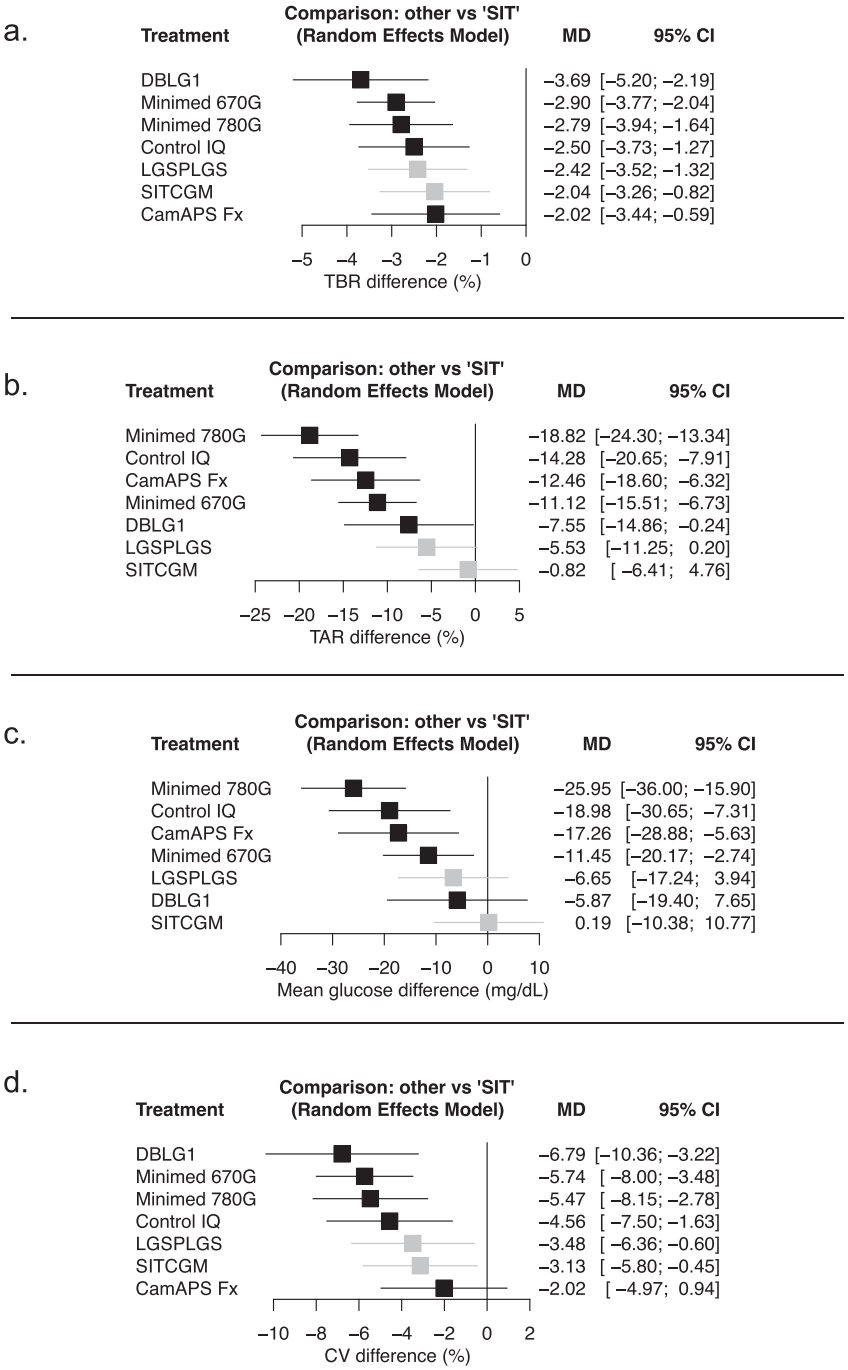

FIGURE 3 | Network meta-analysis results for (a) time below range (TBR), (b) time above range (TAR), (c) mean glucose, and (d) coefficient of variation (CV) compared with subcutaneous insulin therapy without CGM (SIT). Treatments are presented according to their effect estimates compared with SIT. Effect sizes are presented as mean difference (MD) and 95% confidence intervals (CI). HCL systems are highlighted in black, other treatments in grey. SIT: multiple daily injections (MDI) without continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII) without CGM, MDI or CSII without CGM; subcutaneous insulin therapy with CGM (SITCGM): MDI with real-time CGM (RT-CGM), MDI with intermittently scanned CGM (isCGM), MDI or CSII with CGM, MDI or CSII with or without CGM, sensor-augmented pump therapy (SAPT); LGSPLGS: low glucose suspension (LGS), predictive low glucose suspension (PLGS), SAPT with or without LGS, SAPT or PLGS.

S11.7, S12.7, S13.7, S14.7) or without imputed SDs (Supporting Information S1: Sections S7.8, S8.8, S9.7, S10.8, S11.8, S12.8) yielded similar results to the main analysis for all pre-specified outcomes.

In studies with baseline HbA1c ≥8.0%, Minimed 780G outperformed the other HCL systems in terms of achieved TIR, as indicated by larger differences than those observed in the overall analysis (e.g., MD 14.54%, 95% CI [6.43; 22.64] vs. CamAPS Fx; MD 18.64%, 95% CI [11.75; 25.53] vs. Minimed 670G) (Supporting Information S1: Section S7.6). Subgroup analyses in studies with ≥18 years of age or longer diabetes duration (≥10 years) similarly showed greater benefit with Minimed 780G (Supporting Information S1: Section S7.4 and S7.5). In contrast, in studies with

<13 weeks of duration, the superiority of Minimed 780G was confirmed only in comparison to Minimed 670G and DBLG1, while no significant difference emerged with respect to Control IQ and CamAPS Fx (Supporting Information S1: Section S7.3). Interestingly, Control-IQ, CamAPS Fx and DBLG1 achieved greater improvement in TIR versus SIT in subgroups with <18 years of age and disease duration <10 years compared to ≥18 years and ≥10 years, respectively, while Minimed 670G obtained similar improvements irrespective of age subgroup and greater improvement in studies with participants with disease duration >10 years compared to <10 years (Supporting Information S1: Sections S7.4 and S7.5).

Subgroup analyses for secondary outcomes were mostly in agreement with the main results. Different from the main results, since no study involving DBLG1 was included in the subgroup analysis for baseline HbA1c ≥8%, Minimed 780G and Minimed 670G emerged as superior to CamAPS Fx in reducing TBR (Supporting Information S1: Section S8.6). Furthermore, in studies lasting ≥13 weeks or conducted in patients with ≥18 years of age, disease duration ≥10 years, or baseline HbA1c ≥8%, Minimed 780G showed greater efficacy in reducing TAR and mean glucose than in the overall analysis (Supporting Information S1: Sections S10.3–S10.6 and S11.3–S11.6). None of the studies evaluating Minimed 780G included patients <18 years of age or with disease duration <10 years (Supporting Information S1: Section S7.4 and S7.5).

3.8 | Patient-Reported Outcome Measures (PROMs)

For 10 out of 28 studies, PROMs were reported in the main article or ancillary publications. Overall, HCL systems were found to be equal or better than comparators, except in the study by Abraham et al. where lower Diabetes Treatment Satisfaction Questionnaire (status) scores were obtained with Minimed 670G versus control group (Supporting Information S1: Section S16) [21].

4 | Discussion

In very recent years, HCL systems have revolutionised diabetes care by providing partially automated glucose-responsive insulin delivery, thus improving glycaemic control [7] and reducing the burden on patients [22], and have become the standard of care for type 1 diabetes in higher income countries [23].

The results of our analysis confirm that HCL users achieve higher TIR values than individuals on other types of subcutaneous intensive insulin treatment and for the first time show that Minimed 780G provides the best results with a MD ≥5% compared to other HCL systems (Figure 2b, Table 1). This difference is of interest, as international consensus identifies a difference ≥3% in mean TIR (absolute percentage points) to be clinically meaningful [24]. Our findings are consistent with real-life observations showing that TIR improvement is greater with Minimed 780G than with Minimed 670G [25] and Control-IQ [26, 27] and may be due to the peculiarities of the Minimed 780G algorithm, which combines elements from proportional-integral-derivative (PID), model predictive control (MPC) and fuzzy logic regulation [7], and delivers automatic correction insulin boluses up to one every 5 min. Importantly, subgroup analyses showed that the incremental benefit of Minimed 780G as opposed to other HCL systems is greater in studies with ≥18 years of age, ≥10 years of diabetes duration, or baseline HbA1c ≥8%, as indicated by larger mean differences than those observed in the overall analysis (Supporting Information S1: Sections S7.4–S7.6, respectively). Moreover, systems embedding a 'purely' predictive algorithm were found to perform at their best in studies with younger age and shorter diabetes duration of participants. While acknowledging the limitations of subgroup analyses, we believe that this finding may have a correlation with clinical practice.

Results in studies with mean age <18 years are noteworthy. While younger participants, irrespective of treatment, achieved lower TIR levels at study end than their adult counterparts, HCL systems, particularly those with predictive algorithms, were shown to reduce this gap unlike SIT or other CGM-enhanced technologies. However, with the exception of a single study evaluating the Minimed 670G system, all studies conducted in patients with mean age <18 years also had mean diabetes duration <10 years. Therefore, the encouraging results in younger participants might simply reflect the greater efficacy of certain systems in patients with short-standing diabetes who are possibly more prone to comply with algorithm-driven insulin delivery.

All HCL systems were associated with reduction of TBR compared to SIT, with the DBLG1 system achieving the largest reduction and significantly outranking Control-IQ, CamAPS Fx, and sensor-augmented pumps with LGS or PLGS function (Supporting Information S1: Section S8). This finding is not surprising when one considers that the Diabeloop algorithm allows a higher hypoglycaemia threshold to be set for insulin delivery and further recommends calibrated preventive sugaring when hypoglycaemia is predicted despite basal rate reduction; these two unique features may be potentially responsible for enhanced protection against hypoglycaemia. Of note, we did not find any significant difference between Minimed 780G and Control-IQ in terms of TBR reduction; however, in their retrospective cohort of 90 patients who had upgraded to Minimed 780G or Control-IQ, Bassi et al. found more favourable inverse probability-weighted change in TBR with the latter (−0.68% vs. +0.37%; $p = 0.010$) [26].

Serious adverse events, including severe hypoglycaemia and DKA, were low in all HCL systems (Supporting Information S1: Sections S13–S15). The reassuring safety profile of commercial HCL systems is supported by ever-growing observations from the real world [27, 28].

Patient-reported aspects, such as expectations, acceptance, and satisfaction, are important determinants of adherence and success with any regimen of insulin therapy, including modern approaches with CGM devices, insulin pumps and HCL systems. Indeed, psychological and physical barriers could compromise the achievement of desired glucose targets and/or lead to a drop from diabetes devices [29]. Apart from a single study, we found HCL systems to have comparable or more favourable effects on

the PROMs than other types of subcutaneous intensive insulin therapy (Supporting Information S1: Section S16). These findings are in line with those of a recent systematic review of studies in youth with type 1 diabetes and their parents [22]. Provision of high-quality training and support as well as development of realistic expectations may promote long-term usage and optimal outcomes in HCL users [30].

In the absence of direct comparisons, our analysis reveals that commercial HCL systems are not equally efficacious in achieving glycaemic control, and that differences may exist in specific subgroups of patients. When wondering which HCL system might suit the best in the individual patient, well-known factors to take into account involve pump (device size and/or burden, cannula options, insulin reservoir size, smartphone connectivity) and CGM features (duration, accuracy, need for calibration, ease of insertion, alarms), algorithm specifics (mark indications, flexibility of settings, special modes, insulin compatibility) and/or remote monitoring capability (shared function, automatic cloud uploads) [31]. In this scenario, our analysis may provide further insights to support patient-tailored decision-making, for example, orienting towards Minimed 780G and Control-IQ as first choices to achieve TIR goals in individuals with ≥18 years of age, higher baseline HbA1c and long-standing diabetes, and in those with <18 years of age and shorter duration of diabetes, respectively, or towards DBLG1 when reduction of TBR represents a priority.

However, the present analysis has some limitations. Firstly, since the included studies used different brands of sensors, comparisons of CGM outcomes should be interpreted with caution [24]. Secondly, for the purposes of our analysis, the results of MDI and CSII users, and of RT-CGM and is-CGM users, were pooled together in the SIT and SITCGM groups. While we acknowledge that MDI, CSII, RT-CGM and is-CGM users may achieve different outcomes, previous research has adopted the same approach as ours [31–34]. Thirdly, the certainty of evidence was low for many comparisons; hence, the results of this network meta-analysis should not be regarded as conclusive. Fourthly, all the included studies enrolled patients with type 1 diabetes, so the results cannot be applied to people with type 2 diabetes. Use of Control-IQ system has been evaluated in two retrospective studies recruiting mixed cohorts of patients with diabetes, of which a minority had type 2 diabetes; in both studies, type 2 patients shared with their type 1 counterparts meaningful improvements in TIR (~8%) with no change in level 1 hypoglycaemia and with a statistically significant, although overall minimal, increase in level 2 hypoglycaemia [35, 36]. More recently, in a 6-week prospective single arm trial [37], 30 adults with type 2 diabetes using the Control-IQ system achieved substantial glycaemic improvement (increase in TIR by 15% and reduction in mean glucose by 22 mg/dL) with no increase in hypoglycaemia. Given the preliminary indications of efficacy and safety in this population, a consensus of experts recommends considering the initiation of appropriate HCL systems in patients with type 2 diabetes [23]. Finally, the applicability of our results to special populations of patients, including pregnant women, hospitalised patients, and individuals with end-stage renal disease, liver failure, or highly unstable diabetes, is also not known, as these populations were excluded from the search criteria. Of note, an HCL system derived from DBLG1, the so-called DBLHU, has recently received the CE mark for the indication of unstable diabetes [38]. The use of commercial HCL systems in pregnancies complicated by type 1 diabetes warrants further investigation. For pregnant women with type 1 diabetes using CGM, the ADA guidelines suggest more stringent targets of TIR (>70% in the 63–140 mg/dL glucose range) compared to other populations with diabetes [39]. The CamAPS Fx algorithm has a target value as low as 80 mg/dL and is currently the only one approved for use during pregnancy. While information on neonatal outcomes is still lacking, its efficacy in improving maternal glycaemic control has been recently confirmed versus standard care in an RCT conducted at nine sites in the UK [40]. Moreover, expert guidance has been elicited with the intent to guide off-label use of the other commercial HCL systems throughout gestation [41, 42].

Very recently, a 'bionic pancreas' system with an increased level of automation of insulin delivery (insulin-only iLet bionic pancreas, Beta Bionics, Inc., Boston, MA, USA) has received FDA clearance for type 1 diabetes. In detail, this system does not use information about the patient's previous insulin regimen, is initialised only on the basis of body weight, and automates the delivery of all insulin doses with no warm-up period. Meal announcements consist of a qualitative estimate of carbohydrate intake, thus eliminating the need for carbohydrate counting [43]. The safety and efficacy of the bionic pancreas has been ascertained in 306 patients aged 6 to 79 years, of whom two-thirds were randomised to the bionic pancreas and the other third continued the usual care, including HCL systems in 30% of cases. Mean adjusted between-group differences in HbA1c and TIR at 13 weeks were −0.5% (95% CI [−0.6; −0.3]) and 11% (95% CI [9; 13]), respectively, in favour of the bionic pancreas, with non-significant differences in the time spent below 54 mg/dL [43].

In conclusion, HCL insulin delivery is associated with improved glycaemic control, reduced hypoglycaemia, reduced burden of disease, and increased satisfaction in people with type 1 diabetes. In the absence of direct comparisons, our analysis revealed that available HCL systems show a hierarchy of efficacy in achieving glycaemic control and that patient characteristics may impact glucose outcomes, thus providing insights for shared decision-making.

Author Contributions

Sergio Di Molfetta, Ludovico Di Gioia, Irene Caruso and Francesco Giorgino contributed to the study conception and design. Irene Caruso, Ludovico Di Gioia and Sergio Di Molfetta designed the statistical plan, performed the statistical search, collected the data, and performed the analysis. Suetonia C. Green and Patrizia Natale supervised the statistical analysis and the assessment of the certainty of evidence. Sergio Di Molfetta, Ludovico Di Gioia and Irene Caruso gave the major contribution in writing the manuscript. Ludovico Di Gioia created the figures. Sergio Di Molfetta, Ludovico Di Gioia, Irene Caruso, Angelo Cignarelli, Luigi Laviola, Sebastio Perrini, Patrizia Natale, Annalisa Natalicchio, Gian Pio Sorice, Giovanni F. M. Strippoli and Francesco Giorgino revised the article and contributed to the discussion. Francesco Giorgino supervised the project and finalised the manuscript. All authors have read and approved the final manuscript. Francesco Giorgino, Sergio Di Molfetta, Ludovico Di Gioia and Irene Caruso accessed and verified the underlying data. Francesco Giorgino is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

A.C.: AstraZeneca, Eli Lilly, Novo Nordisk, Roche Diagnostics, Sanofi Aventis (honoraria). A.N.: AstraZeneca, Novo Nordisk, and Sanofi Aventis (honoraria). F.G.: Eli Lilly, Roche Diabetes Care (grants); Eli Lilly, Novo Nordisk (consulting fees); AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Lifescan, Merck Sharp & Dohme, Medtronic, Novo Nordisk, Roche Diabetes Care, Sanofi Aventis; Eli Lilly, Sanofi Aventis (support for attending meetings/travel); AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Lifescan, Merck Sharp & Dohme, Medimmune, Medtronic, Novo Nordisk, Roche Diabetes Care, Sanofi Aventis (participation on Advisory Boards); EASD/EFSD, Società Italiana di Endocrinologia (SIE), Fo.Ri.SIE (unpaid leadership); AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi Aventis (support for medical writing and statistical analysis). G.P.S.: no competing interests. G.F.M.S.: no competing interests. I.C.: Eli Lilly, Novo Nordisk (honoraria); Eli Lilly, Novo Nordisk (support for attending meeting or travels). L.D.G.: Eli Lilly, MOVI SpA, Roche Diabetes Care (honoraria). L.L.: Abbott, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Merck Sharp & Dohme, Medtronic, Menarini, MOVI SpA, Mundipharma, Novo Nordisk, Roche Diabetes Care, Sanofi Aventis, Terumo (honoraria); Abbott, AstraZeneca, Boeringher-Ingelheim, Eli Lilly Italia, Medtronic, MOVI SpA, Novo Nordisk, Roche Diabetes Care, Sanofi Aventis, Terumo (participation on Advisory Boards). P.N.: no competing interests. S.D.M.: Ascensia, MOVI SpA, Roche Diabetes Care (honoraria); Ascensia, MOVI SpA, Roche Diabetes Care (participation on Advisory Boards). S.C.G.: no competing interests. S.P.: AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi Aventis (honoraria).

Data Availability Statement

All data relevant to the study are included in the article or uploaded as Supporting Information S1. Statistical code and data set: available on reasonable request from Prof. Francesco Giorgino (francesco.giorgino@uniba.it).

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3842.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.