Device-supported automated basal insulin titration in adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials

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Summary

Background **Technological advances make it possible to use device-supported, automated algorithms to aid basal insulin (BI) dosing titration in patients with type 2 diabetes.**

Methods **A systematic review and meta-analysis of randomized controlled trials were performed to evaluate the efficacy, safety, and quality of life of automated BI titration versus conventional care. The literature in Medline, Embase, Web of Science, and the Cochrane databases from January 2000 to February 2022 were searched to identify relevant studies. Risk ratios (RRs), mean differences (MDs), and their 95% confidence intervals (CIs)**

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were calculated using random-effect meta-analyses. Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Findings Six of the 7 eligible studies (889 patients) were included in meta-analyses. Low- to moderate-quality evidence suggests that patients who use automated BI titration versus conventional care may have a higher probability of reaching a target of HbA_{1c} <7.0% (RR, 1.82 [95% CI, 1.16–2.86]); and a lower level of HbA_{1c} (MD, −0.25% [95% CI, −0.43 to −0.06%]). No statistically significant differences were detected between the two groups in fasting glucose results, incidences of hypoglycemia, severe or nocturnal hypoglycemia, and quality of life, with low to very low certainty for all the evidence.

Interpretation Automated BI titration is associated with small benefits in reducing HbA_{1c} without increasing the risk of hypoglycemia. Future studies should explore patient attitudes and the cost-effectiveness of this approach.

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Keywords: Type 2 diabetes; Basal insulin; Automated titration; Glucose control; HbA_{1c} level; Hypoglycemia; Systematic review

Research in context

Evidence before this study

Basal insulin (BI) initiation can be challenging for both people with diabetes and clinicians alike. Thus, patients may find it helpful to use a device-supported titration integrated with the automated algorithm that directly provides patients with BI dosing suggestions calculated according to prior dose, real-time fasting blood glucose level, and incidental hypoglycemia episodes. Medline, Embase, Web of Science, and the Cochrane databases were searched for randomized controlled trials published between January 1, 2000 and February 17, 2022. Six studies (889 patients) were identified to be adequate for meta-analyses.

Added value of this study

Two long-acting BI agents (insulin glargine or insulin detemir) and their comparison outcome data at follow-up of 3–4 months were reported by the included studies. A greater proportion of patients treated with automated titration reached a target of HbA_{1c} <7.0% compared to conventional care. Statistically significant differences were not found between the two groups in the proportion of patients achieving fasting glucose targets, the level of fasting glucose, incidences of hypoglycemia, severe or nocturnal hypoglycemia, and quality of life. Two studies showed a shorter timeframe to achieve the target glucose level or algorithm endpoint in the automated titration group compared to the control.

Implications of all the available evidence

Automated BI titration may be associated with small benefits in reducing HbA_{1c} and appears to be a safe strategy for patient self-management in people with type 2 diabetes. The tool is easy to use and convenient for the healthcare system, can enhance patient self-efficacy, and may be associated with increased quality of life and satisfaction by reducing complexity in the BI initiation. The tool may also have a good application value in the Western Pacific Region to non-communicable diseases managed in community settings. Future studies with larger sample sizes, longer follow-up duration and different age groups are needed and should consider using real-world data, and explore patient attitudes and the cost-effectiveness of automated titration.

Introduction

Type 2 diabetes (T2DM) is a chronic health condition that affects approximately 1 in 16 people and it is ranked the ninth leading cause of mortality worldwide. The prevalence of T2DM has grown and is estimated to reach 7079 per 100,000 in 2030 and 7862 per 100,000 population in 2040.[1] Risk of micro- and macrovascular complications, and death is significantly increased when T2DM patient glucose levels are inadequately controlled.[2]

Lifetime care focusing on optimal glycemic control and avoidance of hypoglycemia is essential in preventing T2DM complications and improving patients' quality of life. Treatment usually starts with diet and exercise therapies, and oral glucose-lowering drugs are later added. As the disease progresses, beta-cell function declines gradually which can lead to progressive hyperglycemia, and initiation of insulin will be required in the majority of patients. For patients who cannot achieve or maintain optimal glycemic control with non-injectable or injectable

glucose-lowering medications, insulin therapy is usually recommended to increase metabolism.[3,4]

During insulin initiation and routine insulin dosing, gradual adjustment of insulin dose based on glycemic response, also called "dosing algorithms" is required to improve glycemic control without increasing the risk of hypoglycemia.[3,5,6] However, unsatisfactory patient outcomes are commonly seen both in programs primarily self-led by patients, and healthcare providers (HCPs).[3,7] A study in China found that 43% of T2DM patients were not able to adjust their doses properly 6 months after basal insulin (BI) initiation.[8] While some patients may have needed meal-time insulin added, only one-quarter of patients achieved a target of HbA_{1c} ≤7.0% 1 year after BI therapy initiation.[9] A large study using multi-national registry data in Asia reported suboptimal glycemic control in T2DM patients on all insulin treatments (basal only, basal-bolus, bolus only, and pre-mixed), with HbA_{1c} of 8.74 ± 1.95%.[10]

Delay in the initiation and dose optimization of BI can be associated with factors of limited healthcare resources and from a patient's perspective, fear of undesired adverse effects, e.g., hypoglycemia and weight gain,[6,11] insufficient confidence in insulin efficacy and adhering to a long-term, complex management process.[11]

Telemedicine using computer-assisted, algorithmic insulin titration guidance for patients through advanced information technology (internet, phone, short messaging service [SMS], and applications [apps]) is playing an increasingly important role with various advantages and has demonstrated noninferior or even superior effects on patient outcomes.[5,6,12,13] On a self-management basis, patients receive automated dosing suggestions based on the measured glucose level which they manually input or automatically upload to the device/app which functions as a "glucose meter" or "basal calculator".[7,12,13]

Previous studies found these automated titration tools to be simple, efficient in knowledge dissemination and practice. More patients can be managed with less resources in terms of HCPs and education programs, reducing medical expenses, as well as enhancing patient satisfaction.[5,6,12] These benefits can reduce delays in achieving optimal glycemic control in more individuals, which is crucial for those starting to use a BI by injection. It is meaningful to synthesize and appraise the evidence on this approach. Therefore, a systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to assess glycemic reduction efficacy, safety, and quality of life of the device-supported automated BI titration compared to conventional care among T2DM patients receiving a BI.

Methods

A systematic review of RCTs was conducted in accordance with the Cochrane handbook.[14] The results were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[15] (PROSPERO registration number: CRD42022330753). One modification was made to the protocol by conducting a subgroup analysis by RCTs either enrolled insulin-naïve patients alone or mixed patients of insulin-naïve and pre-treated with insulin at baseline. The prespecified primary outcomes of interest were HbA_{1c} control, and adverse events (hypoglycemia, severe hypoglycemia, and nocturnal hypoglycemia). Secondary outcomes were fasting glucose control, health-related quality of life, and time to reach the optimal level of glucose control or algorithm endpoint.

Data sources and study selection

Medline (via Ovid), Embase, Web of Science, the Cochrane Central Registry of Controlled Trials (CENTRAL), and the Cochrane database of systematic reviews from January 1, 2000 to February 17, 2022 were searched to identify relevant studies. Available time of both newer BIs (BIs other than NHP became available after January 2000) and smartphone applications (late 2000s) was considered to determine the literature search duration. Structured, database-specific search strategies were developed using terms related to "diabetes mellitus, type 2", "insulin degludec", "glargine" "detemir", "neutral protamine hagedorn (NPH) insulin" AND "e health", "telehealth", "web based", "mobile based" and "internet-based intervention". Medical Subject Heading terms were utilized wherever possible. The full search strategy was included in the Supplementary Materials. The reference lists of previously published systematic reviews and included RCTs were searched. The search was restricted to English studies, and human participants.

Eligible RCTs included the following characteristics: (1) adult patients (≥18 years of age) with T2DM who required basal insulin therapy defined as: patients with inadequately controlled glucose (HbA_{1c} ≥ 7%) when treated with non-insulin glucose-lowering agents (undertaking ≥1 oral glucose-lowering drug), (2) basal insulin including degludec, glargine U-300, glargine U-100, detemir, and NPH, (3) an electronic, remote patient titration system was compared against conventional titration managed by health-care providers, and (4) glycemic control, the incidence of hypoglycemia, quality of life, or cost outcomes were reported as the clinical outcomes. Both peer-reviewed publications and conference abstracts were included. Studies investigating a device-supported insulin dose advice system for non-BI therapies were excluded.

Two reviewers (ZZ and CX), working in pairs, screened titles/abstracts and full texts independently and in duplicate for eligible articles. Reviewers resolved disagreement by discussion and when necessary, consulting other two methodological arbitrators (XY and YC) and clinical professionals (LJ and YL).

Data extraction

Two reviewers (ZZ and CX) extracted study characteristics and outcomes from included studies using a piloted electronic data extraction form. A third reviewer (YC) subsequently checked all the data for accuracy. The authors of included studies were contacted when the necessary data in the articles were not found. The required data from graphical representations were extracted using an online application (Web Plot Digitizer, Austin, Texas, USA).

Methodological quality assessment

The risk of bias for each outcome in each included study was assessed using the Cochrane Risk of Bias tool 2.0 for RCTs by considering low, uncertain, or high risk of bias for domains of bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results.[16] Two reviewers (ZZ and CX) resolved discrepancies through discussion or by consulting two methodological reviewers (XY and YC) when needed.

The Grading of Recommendations, Assessment, Development, and Evaluations ("GRADE") approach was utilized to evaluate and present the certainty of the evidence by the outcome.[17–20] According to "GRADE" methodology, data from RCTs begin as high certainty of evidence and depending on the assessment of the risk of bias,[14] imprecision,[21] inconsistency,[22] indirectness,[23] and publication bias,[14] the certainty of evidence can be rated down as moderate, low, or very low. The minimal important difference (MID) thresholds, if known, were used in the assessment of imprecision.[21] Funnel plots were planned to be used to address publication bias whenever there were 10 or more studies in a meta-analysis.[14]

Statistical analysis

Random-effects model was used as the primary analysis approach, and intervention effects of automated basal insulin titration were pooled on similar outcomes across eligible RCTs, focusing on intention-to-treat analysis. Fixed-effects model is another approach in combining studies and is based on an assumption that 'between study variability is 0', thus privileges (assigning more weight to) data from larger studies over smaller studies. Random-effects model is based on an assumption that 'between study variability is not 0', and attempts to estimate the mean of a distribution of effects in calculation, thus assigning more weight to data from smaller studies compared to the fixed-effects model. When potential variability exists, the random-effects model tends to generate more conservative results (less likely to show statistical significance) than the fixed-effects model.[14] In this systematic review, a fixed-effects model was also performed as a sensitivity analysis.

For dichotomous outcomes, the relative effects using risk ratios (RRs) (point estimate of effect) and 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method. For a favourable outcome, for example, the proportion of patients reaching a satisfactory level of HbA_{1c}, RR and 95% CI values greater than 1 indicates the intervention group has a beneficial effect. On the contrary, for an unfavorable outcome, for example, incidence of hypoglycemia, RR and 95% CI values smaller than 1 indicate the intervention group has a beneficial effect. When 95% CI of RR includes the no effect threshold of 1, it means that there is no statistically significant difference in effect between intervention and control groups. For continuous outcomes, the units (% for HbA_{1c} and mmol/L for fasting glucose measures) were first unified, and mean difference (MD) (point estimate of effect) and 95% CI with the inverse-variance method were used. When 95% CI of MD includes the no effect threshold of 0, there is no difference in effect between intervention and control groups.

When a meta-analysis was not possible, the outcome data were presented using narrative summaries. For trials with more than 2 intervention groups, the method recommended by the Cochrane review group was followed by dividing the numerator and denominator in the control group by the number of intervention groups to avoid double counting for studies.[14] For example, if an RCT has one intervention, group A with 1 event of 30 patients, another intervention, group B, with 1 event of 32 patients, and a control group with 4 events of 30 patients, then the event and patient numbers in the control group could be divided by 2 (the number of the intervention groups). Data entered into the meta-analysis would be 1 out of 30 for the intervention group A against 2 out of 15 for the control group, and 1 out of 32 for the intervention group B against 2 out of 15 for the control group.

Two subgroup analyses were prespecified if the analyzable data were available: patient age (≥60 years versus <60 years) and patient education level ('below high school graduation' versus 'high school graduation and above'). Sensitivity analysis was not pre-specified. All statistical analyses were performed using Review Manager 5.4 (The Cochrane Collaboration, 2020, Copenhagen, Denmark).

Role of the funding source

The project was sponsored by the Chinese Geriatric Endocrine Society. The funding body had no role in study design, data collection, data analysis, data representation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed the final manuscript before submission for publication.

Results

Search results

Following the removal of duplicates, 1291 potential eligible studies were identified, of which 85 (81 RCTs and 4 systematic reviews) proved potentially relevant based on title and abstract screening, and 6 RCTs (859 patients) proved eligible on the full-text review (Fig. 1).[5–7,13,24,25] Only the abstract was found for one RCT (242 patients) that was reported at the American Diabetes Association (ADA) Scientific Sessions in 2020.[26] No ongoing studies were identified.

Study characteristics

Table 1 presents the study characteristics. Five RCTs with two-arm parallel comparisons[5–7,24,26] and one with three-arm outcomes[13] provided data suitable for meta-analysis that compared automated patient self-titration and conventional care which reported glycemic and safety outcomes up to 12 weeks[5,6,24,25] or 16 weeks.[7,13,26] Of these, two studies only enrolled patients who started to receive basal insulin using automated titration or conventional care,[13,24] and four studies included both patients who were insulin naïve and those were pre-treated with insulin at enrollment.[5–7,26] One study (TITRATION trial) compared patient self-titration according to the INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) algorithm to a previously tested EDITION algorithm managed by investigators among T2DM patients who took glargine U-300, and found similar effects in reducing fasting plasma glucose (FPG) and safety in both groups.[25] This study was included in quantitative synthesis as a post hoc sensitivity analysis because it was slightly different from other studies, as the patients in the treatment group (INSIGHT) increased the basal insulin by 1 unit per day until the target fasting self-monitored blood glucose (FSMBG) was reached without using an automated device during their self-titration.[25]

Risk of bias of included studies

The risk of bias assessment results were presented in Supplementary e-Table S1. Five RCTs were assessed to have some concerns about the overall bias.[5,6,13,24,25] One RCT was rated as high risk.[7] Due to insufficient information, the risk of bias was unable to be assessed for one study that was published as an abstract.[26]

Relative effects of the intervention

Glycemic control

HbA_{1c}. Three RCTs (402 patients) reported a proportion of people who reached target of HbA_{1c} <7.0% at 3–4 months.[5,6,13] The meta-analysis showed a higher proportion of people achieving an optimal HbA_{1c} target with automated basal insulin titration versus conventional care (RR, 1.82 [95% CI, 1.16–2.86], Fig. 2A, Table 2). The certainty of the evidence was moderate due to serious imprecision. Low quality of evidence

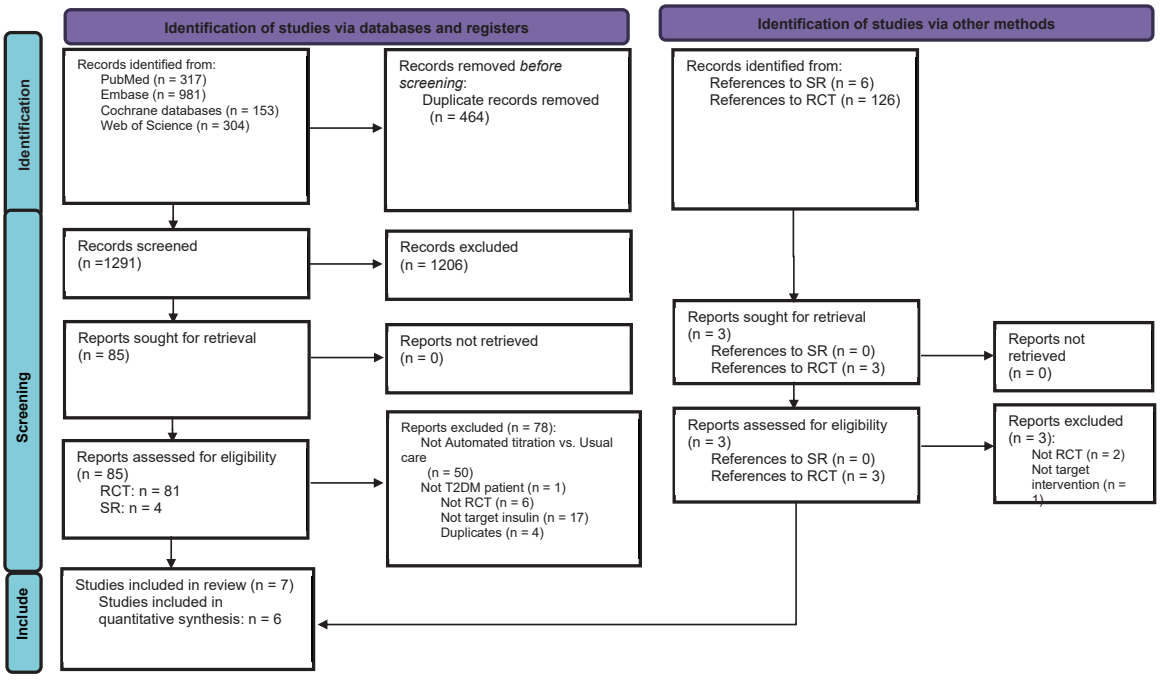

Fig. 1: Eligibility assessment flow diagram according to PRISMA guidelines (https://doi.org/10.1371/journal.pmed1000097). RCT, randomized controlled trial; SR, systematic review.

Author (year); countries	Randomized/ analyzed	Age (year)	Insulin-naive, n (%)	Duration of T2DM (year)	Baseline blood glucose level	BW (kg) and/ or BMI (kg/m2)	Insulin	Intervention	Comparator
Bajaj et al. (2016)[5]; Canada	139/139	56.4 (8.22)	45 (32.37)	12 (6.8)	HbA_{1c} 8.8 (1.34) %	BW, NR; BMI 32.9 (5.94)	Glargine U-100 administered at bedtime; initial dose, 10–20 units/ day; final dose at 12 weeks, 26.2 (21.6) units in Group I, 28.5 (26.2) units in Group C	LTHome (MyStarWebCoach), a long-acting insulin glargine titration web tool containing a rules engine-based algorithm for glargine titration and maintenance	Enhanced usual therapy (EUT), a diabetes education program; patients were advised to increase by 1 unit every day until their FBG <7.0 mmol/L
Bee et al. (2016)[24]; Singapore	66/66	53.3 (7.4)	66 (100)	12 (8)	HbA_{1c} 9.9 (1.8) %	BW, NR; BMI 27.5 (4.69)	Detemir administered at bedtime; initial dose, 10 units/day; final dose at 24 weeks, 33 units in Group I, 28 units in Group C	Diabetes Pal, a smartphone app developed by authors' institute that could suggest insulin dose based on FBG readings entered by patients and allow remote monitoring FBG to flag issues to the endocrinologists	Conventional care with paper logbooks and written instructions
Davies et al. (2019)[7]; UK, France, Germany, US and Italy	151/151	62.1 (9.5)	60 (39.74)	NR	FPG 10.5 (2.4) mmol/L	BW 98.5 (23.8); BMI 33.2 (6.9)	Glargine U-300 administration time NR; initial dose, 0.20 units/ kg/day; final dose at 16 weeks, NR	MyStarDoseCoach, an integrated titration device/blood glucose meter to assist self-titrate insulin glargine by providing automated dosing suggestions	Routine titration as recommended by diabetes specialists; titration feature of the device turned off
Kim et al. (2010)[6]; Korea	100/92	48.4 (10.11)	89 (96.74)	8.5 (6.27)	HbA_{1c} 9.8 (1.25) %; FBG 11.0 (2.8) mmol/L	BW 63.9 (9.88); BMI 24 (3.04)	Glargine U-100 administered at bedtime; initial dose, 0.2 units/kg/ day; final dose at 12 weeks, 32.6 units/day in Group I, 32.2 units/day in Group C	Specialized system producing an automatic adjustment of insulin dose based on the mean FBG for 3 consecutive days; FBG data could be monitored on the website	Conventional care with diabetes notebook and glucometer
Franc et al. (2019)[13]; French	191/189	58.7 (9.6)	189 (100)	13.1 (7.6)	HbA_{1c} 8.9 (11.1) %	BW, NR; BMI 29.7 (5.1)	Detemir administered at bedtime; initial dose, 10 units/day; final dose at 16 weeks, 0.54 units/kg/day in Group I1, 0.49 units/kg/ day in Group I2, 0.40 units/kg/day in Group C	1. Diabeo-BI app running in a smartphone 2. Interactive voice response system (IVRS) that instructed patients with 4-digit identification codes to call daily before insulin injection and follow the steps suggested by the IVRS	Conventional care; patient education and visits
Philis-Tsimikas et al. (2020),[26] US	242/237	61 (53–69)[a]	27 (11.4)	11 (7–18)[a]	HbA_{1c} 8.7 (8.0–9.6) %	NR	Basal insulin; drug not specified	Mobile Insulin Dosing System (MIDS), an app-based self-titration tool	Enhanced paper-based tool based on a stepped down titration algorithm, with diabetes educator support

(Table 1 continues on next page)

Author (year); countries	Randomized/ analyzed	Age (year)	Insulin-naive, n (%)	Duration of T2DM (year)	Baseline blood glucose level	BW (kg) and/ or BMI (kg/m2)	Insulin	Intervention	Comparator
(Continued from previous page)									
Yale et al. (2017);[25] Canada	212/212	62.3 (10.9)	74 (34.91)	NR	FPG 8.6 (3.0) mmol/L	BW 96.6 (21.7); BMI, NR	Glargine U-300 administered at bedtime; initial dose: 0.20 units/ kg/day; final dose at 12 weeks, 0.7 units/kg/day	Patient self-titration according to INSIGHT algorithm; insulin dosage increased by 1 unit/day to reach a FSMBG in the target range of 4.4 to 5.6 mmol/L; patients could call healthcare staff if hypoglycemia occurred	EDITION algorithm: investigator adjusted dose 1–3 times weekly, based on median FSMBG values of the last 3 days, to achieve the target range of 4.4–5.6 mmol/L; weekly contacts with healthcare staff were scheduled

Continuous variables are presented with mean (standard deviation) unless otherwise indicated; categorical variables are presented as numbers (percent). BMI, body mass index; BW, body weight; FBG, fasting blood glucose; FSMBG, fasting self-monitored blood glucose; (Group) I, intervention, refers to the automated basal insulin titration; (Group) C, comparator, refers to the conventional care; HbA_{1c}, hemoglobin A1C; INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment; NR, not reported; T2DM, type 2 diabetes; UK, United Kingdom; USA, United States. [a]Median (interquartile range).

Table 1: **Characteristics of included studies.**

based on 856 patients in 6 RCTs[5–7,13,24,26] showed that automated titration significantly reduced HbA_{1c} versus conventional care at 3–4 months of follow-up (MD, –0.25% [95% CI, –0.43 to –0.06%], Fig. 2B, Table 2). Nevertheless, the effect and 95% CI did not exceed the ADA and the National Institute for Health and Care Excellence recommended MID of 0.5% for HbA_{1c} level.4.[27,28]

Fasting glucose level. Four RCTs (698 patients) reported a proportion of people who reached the fasting glucose target at 3–4 months with a prespecified level of fasting blood glucose (FBG) target within the ranges of FBG 4.0–6.0,[13] or 3.9–10.0,[26] and target FPG ranging 5.0–7.2 mmol/L.[5,7] The meta-analysis showed that the point estimate favoured automated titration but the between-group difference did not reach statistical significance, with 95% CI of the RR included the no effect value of 1 (RR, 1.18, [95% CI, 0.83–1.66], Supplementary e-Fig. S1, Table 2). The pooled results from 480 patients in 4 RCTs (two reported FPG[7,24] and two reported FBG[6,13]) did not present a statistically significant difference between the two groups in terms of fasting glucose level at 3–4 months (MD, –0.40 mmol/L [95% CI, –0.91 to 0.11 mmol/L], Supplementary e-Fig. S2, Table 2).

Safety

Hypoglycemia. Four RCTs (441 patients) reported the outcome of hypoglycemia at 3–4 months.[5–7,24] The point estimate of the pooled results favoured automated titration, but the between-group difference did not show statistical significance (RR, 0.91 [95% CI, 0.68–1.22], Fig. 3, Table 2). The certainty of the evidence was low due to the serious risk of bias and imprecision.

Severe hypoglycemia. In 4 of the 5 RCTs (612 patients) that investigated this outcome, no episodes of severe hypoglycemia were reported.[5,6,13,24] One RCT reported severe hypoglycemia in one patient in the conventional care group.[7] The certainty of the evidence (RR, 0.34 [95% CI, 0.01–8.16], Supplementary e-Fig. S3, Table 2) was very low due to a serious risk of bias and very serious imprecision.

Nocturnal hypoglycemia. The meta-analysis of 3 RCTs (382 insulin-naïve patients)[5–7] did not show statistically significant difference between the two groups (RR, 0.99 [95% CI, 0.52–1.89], Supplementary e-Fig. S4, Table 2), with very low certainty of evidence due to serious risk of bias, and very serious imprecision.

Quality of life

Two RCTs (290 insulin-naïve patients) assessed the quality of life using the World Health Organization (WHO)-5 well-being index at 3–4 months.[5,7] The pooled result did not present a statistically significant difference between the two groups (MD, –2.73 points [95% CI –8.56 to

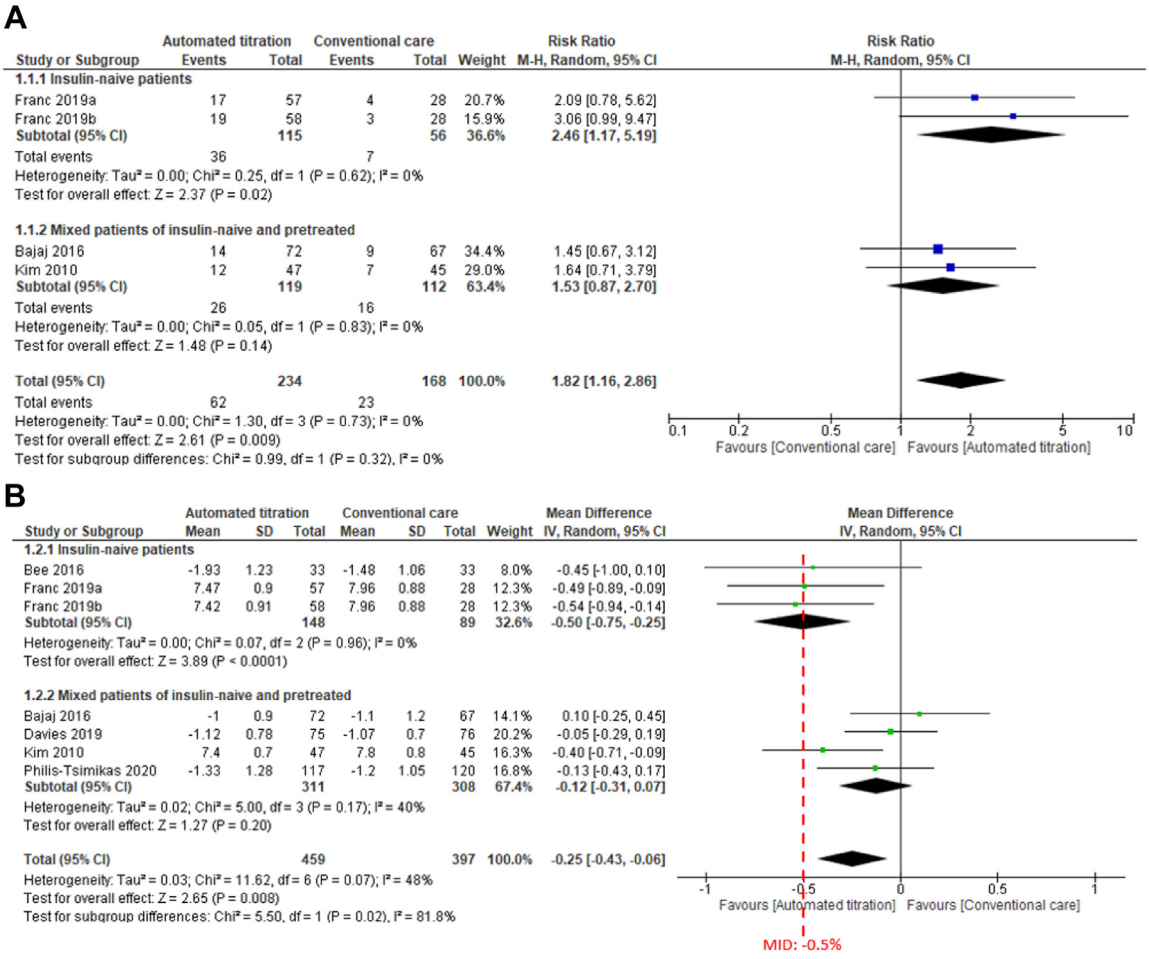

Fig. 2: A) HbA_{1c} control assessed with proportion of people reached target of HbA_{1c} <7.0% at 3–4 months; B) HbA_{1c} control assessed with level of HbA_{1c} (%) at 3–4 months, random-effects model.

3.10], Supplementary e-Fig. S5, Table 2), with very low certainty of evidence due to serious risk of bias, and very serious inconsistency and imprecision.

Time to reach the target glucose control or algorithm endpoint

A pooled estimate was not possible. Two RCTs (217 patients) reported this outcome, both favouring automated titration. The difference in time to achieve the fasting glucose level or algorithm endpoint was 3 weeks shorter (mean, 10 weeks versus 13 weeks for 50% of patients reached glycemic target)[7] and 12 days shorter (median, 27 days versus 39 days)[24] when patients received a device-supported, automated titration compared to conventional care in these two studies, accordingly.

Subgroup analyses results

Insufficient data from the included RCTs precluded us from conducting the prespecified subgroup analysis for patients by different age or education level groups. In a post hoc subgroup analysis comparing RCTs with insulin-naïve patients alone or otherwise, significant differences in treatment effects were found in terms of two outcomes of glycemic control: level of HbA_{1c} (%) (interaction P = 0.02, Fig. 2B) and the proportion of people achieving the target fasting glucose level (interaction P = 0.0004, Supplementary e-Table S2, Supplementary e-Fig. S1). Both indicated a larger effect in insulin-naïve patients than in patients who were a mixture of both insulin-naïve and pre-treated.

Sensitivity analyses results

One outcome, fasting glucose level demonstrated statistical significance favouring automated BI titration (MD, –0.37 mmol/L [95% CI, –0.63 to –0.11 mmol/L], Supplementary e-Fig. S6, Supplementary e-Table S3). For the rest of the outcomes, results by the fixed-effects model were similar to those by the random-effects model (Supplementary e-Table S3).

Outcomes	Relative effects (95% CI) and source of evidence	Absolute effect estimates		Point estimate favours	Statistical significance	Certainty/quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)				
Proportion of people reached target of HbA_{1c} <7.0% at 3–4 months	RR 1.82 (1.16–2.86) Based on data from 402 patients in 3 RCTs (Bajaj 2016, Franc 2019, Kim 2010)	137[a]	112 (22–255)	Group I	Yes	Moderate ⨁⨁⨁◯ (Serious imprecision)[b]	Automated titration likely increases proportion of patients reached target HbA_{1c} <7.0%.
HbA_{1c} (%) at 3–4 months	MD 0.25% lower (0.06 lower to 0.43 lower) Based on data from 856 patients in 6 RCTs (Bajaj 2016, Bee 2016, Davies 2019, Franc 2019, Kim 2010, Philis-Tsimikas 2020)	–	–	Group I	Yes	Low ⨁⨁◯◯ (Serious risk of bias and inconsistency)[c]	Automated titration may reduce the level of HbA_{1c}.
Proportion of people reached target FPG or FBG at 3–4 months[d]	RR 1.18 (0.83–1.66) Based on data from 698 patients in 4 RCTs (Bajaj 2016, Davies 2019, Franc 2019, Philis-Tsimikas 2020)	552[a]	99 (−94 to 364)	Group I	No	Very low ⨁◯◯◯ (Serious risk of bias, very serious inconsistency and serious imprecision)[e]	The evidence is very uncertain about the effect of automated titration on the proportion of people who reached target FPG.
Fasting glucose level (mmol/L) at 3–4 months	MD 0.40 mmol/L lower (0.91 lower to 0.11 higher) Based on data from 480 patients in 4 RCTs (Bee 2016, Davies 2019, Franc 2019, Kim 2010)	–	–	Group I	No	Very low ⨁◯◯◯ (Serious risk of bias, serious inconsistency and imprecision)[f]	We areThe evidence is very uncertain about the effect of automated titration on FPG.
Hypoglycemia at 3–4 months	RR 0.91 (0.68–1.22) Based on data from 441 patients in 4 RCTs (Bajaj 2016, Bee 2016, Davies 2019, Kim 2010)	298[a]	−27 (−95 to 66)	Group I	No	Low ⨁⨁◯◯ (Serious risk of bias and imprecision)[g]	The evidence suggests that automated titration results in no difference in risk of hypoglycemia.
Severe hypoglycemia at 3–4 months	RR 0.34 (0.01–8.16) Based on data from 612 patients in 5 RCTs (Bajaj 2016, Bee 2016, Davies 2019, Franc 2019, Kim 2010)	4[a]	−2 (−4 to 26)	Group I	No	Very low ⨁◯◯◯ (Serious risk of bias and very serious imprecision)[h]	The evidence is very uncertain about the effect of automated titration on risk of severe hypoglycemia.
Nocturnal hypoglycemia at 3–4 months	RR 0.99 (0.52–1.89) Based on data from 382 patients in 3 RCTs (Bajaj 2016, Davies 2019, Kim 2010)	90[a]	−1 (−43 to 80)	Group I	No	Very low ⨁◯◯◯ (Serious risk of bias and very serious imprecision)[h]	The evidence is very uncertain about the effect of automated titration on risk of nocturnal hypoglycemia.
Quality of life assessed with WHO-5 well-being index score (0–100) at 3–4 months	MD 2.73 points lower (8.56 lower to 3.10 higher) Based on data from 290 patients in 2 RCTs (Bajaj 2016, Davies 2019)	–	–	Group C	No	Very low ⨁◯◯◯ (Serious risk of bias, very serious inconsistency and imprecision)[i]	The evidence is very uncertain about the effect of automated titration on quality of life.

CI, confidence interval; FBG, fasting blood glucose; FPG, fasting plasma glucose; "GRADE", grading quality of evidence and strength of recommendations; Group C, comparator, refers to the conventional care; Group I, intervention, refers to the automated basal insulin titration; HbA_{1c}, hemoglobin A1C; MD, mean difference; RCT, randomized controlled trial; RR, risk ratio; T2DM, Type 2 diabetes; WHO, World Health Organization. [a]The event rate from the conventional care was used as baseline risk.[14] [b]One level was rated down for imprecision (wide CI). [c]Two levels were rated down: 0.5 level for risk of bias (some concerns in 4 domains), and 1.5 for inconsistency (I^2 = 81.8%). [d]Two studies prespecified a FPG target within the range of 5.0–7.2 mmol/L, one study prespecified a FBG target within the range of 4.0–6.0 mmol/L and one study a FBG target within the range of 3.9–10.0 mmol/L. [e]Three levels were rated: 0.5 level for risk of bias (some concerns in 4 domains), 1.5 for inconsistency (I^2 = 91.9%), and one for imprecision (wide CI includes important benefit and harm). [f]Two levels were rated down: 0.5 level for risk of bias (some concerns in 4 domains), 0.5 for inconsistency (I^2 = 52.2%), and one for imprecision (wide CI includes important benefit and harm). [g]One point five levels were rated down: 0.5 level for risk of bias (some concerns in 4 domains), and one for imprecision (wide CI includes important benefit and harm). [h]Two point five levels were rated down: 0.5 level for risk of bias (some concerns in 4 domains), and two for imprecision (very wide CI includes important benefit and harm). [i]Three levels were rated down: 0.5 level for risk of bias (some concerns in 4 domains), 1.5 for inconsistency (I^2 = 82%), and one for imprecision (wide CI includes important benefit and harm).

Table 2: **"GRADE" summary of findings: automated basal insulin titration versus conventional care among adults with T2DM, evidence from RCTs, random-effects model.**

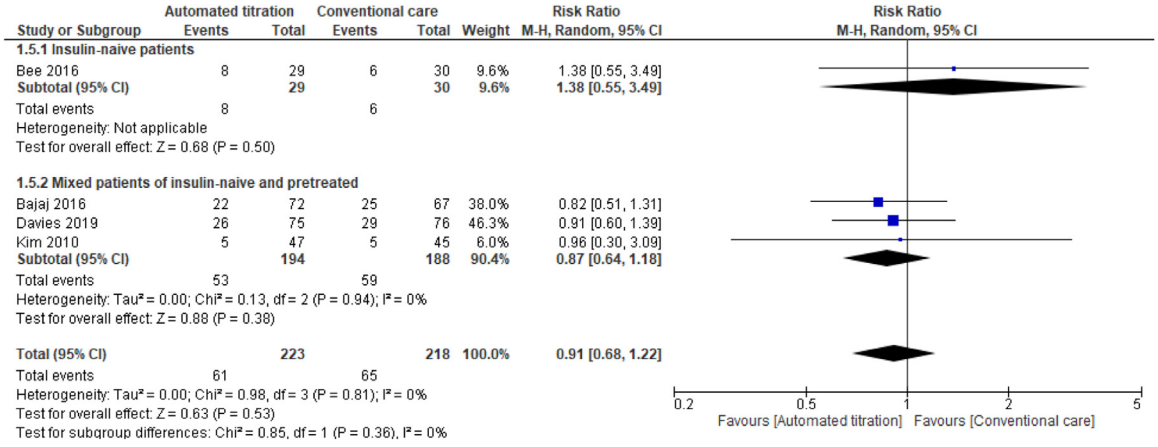

Fig. 3: Hypoglycemia at 3–4 months, random-effects model.

The sensitivity analysis by including the TITRATION trial showed similar results except for one outcome, i.e., there was no statistically significant difference between the two groups for the proportion of people reached the target of HbA_{1c} <7.0% (RR, 1.43 [95% CI, 0.95–2.17], Supplementary e-Fig. S7, Table 3).

Another post hoc sensitivity analysis excluding the study rated as high risk of bias did not impact the results in this study except for one outcome, i.e., fasting glucose level demonstrated statistical significance favouring automated BI titration (MD, –0.56 mmol/L [95% CI, –1.10 to –0.03 mmol/L], Supplementary e-Table S4).

Cost

Data for cost of the automated BI titration system were sought in the eligible RCTs and were not found.

Discussion

Insulin initiation, titration, and persistence are key therapeutic challenges that require different strategies and tools. Starting BI to achieve and maintain the optimal glycemic targets while minimizing the risk of hypoglycemia presents considerable challenges. Device-supported titration integrated with an automated algorithm that provides patients with BI dosing suggestions may greatly assist the process. Interventions used in the included studies of this systematic review were automated titration systems through an internet-based platform, or smartphone SMS that provided dosing suggestions directly to the patients. The BI dosing calculation was based on three variables: prior dose, real-time fasting blood glucose level, and incidental hypoglycemia episodes entered by the patient.[5–7,13,24] Included studies investigated glargine U-300 (long-acting insulin),[7,25] glargine U-100 (long-acting insulin),[5,6] and detemir (long-acting insulin).[13,24]

Low to moderate quality evidence showed glycemic reduction effects assessed with the proportion of patients achieving target of HbA_{1c} <7.0% (RR, 1.82 [95% CI, 1.16–2.86]) and level of HbA_{1c} (MD, –0.25% [95% CI, –0.43 to –0.06%]) with automated BI titration versus conventional patient care at 3–4 months of follow-up (Fig. 2A and B, Table 2). The proportion of people who reached the target of HbA_{1c} <7.0% is more useful than the degree of HbA_{1c} decrease because the former takes into account patients' baseline HbA_{1c} level and reflects a relative change in patients in an individual RCT. No statistically significant differences were detected between the two groups in fasting glucose results, incidences of hypoglycemia, severe or nocturnal hypoglycemia, and quality of life, all with low to very low certainty of evidence (Fig. 3, Supplementary e-Figs. S1–S5, Supplementary e-Table S2). Of note, the level of HbA_{1c} had a significant reduction in automated BI titration than that in conventional care but the level of FPG did not show a significant between-group difference in reduction because the RCTs providing the results for HbA_{1c} and those providing the results for FPG are not the same. Four RCTs[4,6,13,24] reported both HbA_{1c} and FPG outcomes, and the other 2 RCTs[5,26] only reported HbA_{1c} data (Fig. 2B, Supplementary e-Fig. S2, Table 2). In the sensitivity analysis by fixed-effects model and the sensitivity analysis excluding the study rated as high risk of bias, the level of FPG showed a significant difference in favour of automated BI titration (Supplementary e-Fig. S6, Supplementary e-Tables S3 and S4).

A previously published narrative review reported benefits and development of potential novel digital health technologies usage to assist insulin initiation and dosing optimization in people with T2DM.[12] Findings of the current review are consistent with this article and other previously published studies[6,7,12,29,30] indicating automated titration improves glycemic control, and is a

Outcomes (at 3–4 months)	Number of studies	Sample size	Effect	95% CI
Proportion of people reached target of HbA_{1c} <7.0%	4	614	RR 1.43	0.95–2.17[a]
HbA_{1c} (%)	7	1068	MD −0.21	−0.37 to −0.04[b]
Proportion of people reached target fasting glucose	4	910	RR 1.16	0.85–1.57[a]
Fasting glucose level (mmol/L)	5	692	MD −0.34	−0.80 to 0.12[a]
Hypoglycemia	5	654	RR 1.04	0.86–1.27[a]
Severe hypoglycemia	4	594	RR 0.33	0.05–2.05[a]
Nocturnal hypoglycemia[c]	4	594	RR 0.99	0.71–1.37[a]

Quality of life was not presented in the current sensitivity analysis because the TITRATION study did not report this outcome. CI, confidence interval; HbA_{1c}, hemoglobin A1C; MD, mean difference; RCT, randomized controlled trial; RR, risk ratio; T2DM, Type 2 diabetes. [a]The between-group difference did not show statistical significance. [b]The point estimate of pooled result favoured automated titration with the statistical significance in between-group comparison. [c]The TITRATION study 25 reported incidences of nocturnal hypoglycemia before 6:00 AM, before 8:00 AM, and before the first self-monitored blood glucose. Data before 6:00 AM was extracted for this meta-analysis.

Table 3: **Sensitivity analysis results by including the TITRATION study 25: automated basal insulin titration versus conventional care among adults with T2DM, evidence from RCTs, random-effects model.**

safe treatment. Furthermore, subgroup effects were found in the level of HbA_{1c} and the proportion of people who reached the target fasting glucose level (Fig. 2B, Supplementary e-Fig. S1, Supplementary e-Table S3) which indicated a larger effect of the intervention in patients who were insulin-naïve at baseline than the studies enrolling both insulin-naïve and those pre-treated. A possible explanation can be that insulin-naïve patients might have a greater engagement in utilizing the device and automated tools in dosing titration while they learn to start BI therapy. Patients who have been treated with insulin for a period (pre-treated patients) might have enough confidence to maintain or adjust the doses on their own, and possibly did not use the device every time; secondly, those who were already on insulin treatment might have a longer duration of disease and a worse beta cell function, therefore, insulin titration needed higher accuracy and might be more difficult to perform. Thus, the difference in HbA_{1c} or status of reaching the fasting glucose target in the studies enrolling both insulin-naïve and those pre-treated was smaller than the difference in studies enrolling the insulin-naïve patients alone.

Previous studies and this systematic review found the following advantages of automated BI titration. (1) The devices and systems/platforms described in most studies are easy to use.[5,6] Patients found them simple and had a compliance rate as high as 96%.[6] (2) Based on its self-regulation manner, the automated titration with a timely response mechanism enhances patient confidence and self-efficacy by providing additional verification of reasoning in suggesting doses. Patients gain a sense of "autonomy" and "empowerment" instead of being tied with HCPs.[7,12,13,31] It can promote patient adherence to the pre-uploaded instructions of apps and knowledge in order to understand BI, regimen options, and the importance of disease management (including exercise, diet, and glucose monitoring).[24,31] (3) Individual studies found an increased quality of life in patients using automated titration.[6,7] The system is convenient to use.[6] Patients can manage the BI titration at home, and may reduce distress.[7] These technologies can facilitate patient-centred care, and improve informed shared decision-making by providing an individualized option incorporating patient values and preferences.[5,30,31] (4) The system can reduce resources related to HCP personnel and the use of conventional diabetes education. Patients using automated titration may start with more frequent (than conventional care) contacts with HCPs and medical technicians for both medical advice and technological questions or algorithm adjustments. After they are familiar with the apps or system, they will have much fewer visits.[5] Moreover, it saves HCPs' efforts and time on reading glycemic and dosing data, which potentially leads to a good cost-effectiveness feature although this point needs high-quality studies to confirm in future research.[6] (5) The automated system reduces the complexity of BI titration with an immediate and sensible response.[5,7] Patients can receive medical feedback based on their real-time data which may adjust the dose more quickly and continuously promote patients to monitor their blood glucose in a steady manner.[6] It may shorten the time needed to achieve an individualised glucose control target.[6,7,24] (6) Automated BI titration is a remote care model customized with automation components. It is especially important for patients who need BI initiation during lockdowns in the COVID-19 pandemic.[12]

The potential benefits of device-driven BI titration algorithms have to be considered under a few premises that are more fundamental and crucial to play effects in patient management. Previous evidence has shown that patient self-titration is more effective than practitioner-led titration, in part due to less clinical inertia by healthcare providers, as well as better empowerment and engagement of the patient.[11,29,32] Indeed, using digitalization or web-based platform to standardize information may already improve knowledge in both

providers and patients resulting in better patient-provider communication and decision making. For example, it is possible that the initial time spent on teaching the patients how to use the devices and the underlying principles of insulin titration may have major impacts on patient empowerment and engagement that influence the outcomes, and such time is often unreported or under-evaluated. It is against this background that devices are largely enabling tools. The devices themselves should not be considered as the only or the most important factor that mediate favourable patient outcomes. Also, digital solutions often attempt to install too much information aiming to 'automate' human decision-making without taking into consideration many human factors which are often unpredictable and highly variable. The sensitivity analysis by including the RCT of a simple and user-friendly INSIGHT algorithm in the meta-analyses showed similar effects. Certainly, the digitalization of a simple BI titration algorithm like the INSIGHT (patient self-titration, insulin dosage increased by 1 unit/day to reach a FSMBG in the target range of 4.4–5.6 mmol/L) can be helpful in increasing access for implementation.

A rigorous systematic review was conducted in this study by following the Cochrane handbook.[14] Explicit eligibility criteria were developed and a pre-tested, comprehensive search was conducted. Multiple independent reviewers completed study selection, data abstraction and risk of bias evaluation in duplicate. Optimal methodologies were used to avoid double counting studies with multiple study groups and provided the certainty of the evidence for each outcome using the "GRADE" approach.[17,18]

This systematic review has some weaknesses that are related to limitations in the evidence. First, the included studies in this study focused on the BI initiation process and meta-analysis results could only be presented at a follow-up of up to 16 weeks based on the available data. A longer follow-up duration, e.g., 1 year, would be valuable to assess the tool efficacy, safety, and patient attitudes. One possibility with longer-term intervention could be that with more detailed BI dose adjustment and relatively steady blood glucose monitoring, there could be an effect of maintaining optimal glycemic control with good safety compared to conventional care. The other possibility would be that patients become tired of using the device over time and reduce adherence to it; and the significant difference between the two groups would be diminished.

Second, in RCTs or real-world scenarios, there is a potential that some patients need more than just a BI. Some may have over-titrated the BI and are never going to attain a goal without the addition of bolus insulin at meals. According to the ADA recommendations, once a patient has titrated basal insulin to 0.5 units/kg/day, bolus doses should be added.[4] If patients were over this dosage, failure to attain an optimal goal might happen due to adding bolus doses instead of an inappropriate titration scheme. Such a fact was not able to be analysed in this systematic review due to a lack of detailed patient management data.

Third, statistical significance may be easier to be obtained in a meta-analysis synthesizing total data of multiple studies than those in individual studies. Evidence from a large individual trial that meets the optimal sample size would be superior to the results from a systematic review of a similar total sample size to detect the effects of treatment. When large trials are absent, which is often the case in clinical studies, systematic reviews of RCTs may serve the role of providing evidence.[14,15] Furthermore, one of the major concerns during the evidence quality assessment in this systematic review was imprecision due to the relatively small sample size and event numbers. As a result, the limited number of eligible studies and sample size attributes to the small benefits of the automated BI titration strategy with moderate to very low quality of evidence. Also, publication bias was unable to be assessed because there were fewer than 10 studies.[14] With an increased sample size, and more detailed data collected and reported, it would be possible to conduct additional analyses of hypoglycemia frequencies, other subgroups, and meta-regressions.

Fourth, this systematic review intended to synthesize results from RCTs, the study design that is considered as high on the hierarchy of evidence, hence did not include the non-RCTs depending on the study protocol. High-quality observational studies, especially with large sample sizes and optimal conduction, for example, control of selection bias and use of adjustment in analysis, are valuable to be considered in future systematic reviews on this research question.

Fifth, a cost-effectiveness analysis would be valuable, but relevant data were not collected in the included studies. Patients may choose mobile health (mHealth) apps from free to download up to different levels of cost by monthly or yearly subscription, or by item charging.[33] A report published in 2018 estimated that the average cost to develop an mHealth app was U.S. $425,000.[34] A cross-sectional study in India reported an average score of 4.6 (standard deviation 0.5) on a scale of 1–5 (the higher, the more favorable assessment) for cost-effectiveness assessment for smartphone and internet-based mHealth usage among 200 patients with diabetes.[35] No cost information specifically on the automated BI titration was found. Uncertainties and issues remain surrounding investment, maintenance, implementation, and evaluation costs in terms of the applications. These costs may vary a lot by geography. Time spent with the healthcare providers, for example, the length of time on training about apps, as well as the subsequent remote monitoring or counselling has not been formally evaluated in comparison with the conventional care.

Sixth, the available data did not allow us to conduct the prespecified subgroup analysis by age and education level. There might be barriers for people who are less technologically proficient such as seniors, less educated or those with cognitive impairments to use the automated titration independently and accurately.[5,7] Therefore, the generalizability of the findings of this study may be limited.

Lastly, some software or device-related problems might have weakened the effects of the intervention. The problems reported by the included studies include misunderstanding of the app or device function, mistakes in device use, device malfunctions, and some design pitfalls of the app.[7,24]

Even though this systematic review was based on global evidence, the study findings can be applied to the World Health Organization's Western Pacific Region (WPR). One-third of the RCTs in quantitative analysis in this study was conducted in the countries of the WPR (Korea[6] and Singapore[24]). Mobile health techniques have been widely used in management of non-communicable diseases including diabetes and pre-diabetes in the WPR.[32] These approaches may play an important role in healthcare systems and disease management focusing on community settings.[32]

Additional future studies with larger sample sizes, longer follow-ups, and different age groups are required to comprehensively evaluate the clinical outcomes by subgroups of device/technology proficiency, and verify the findings of the current meta-analysis results. Researchers may also consider conducting studies with a qualitative design to investigate attitudes toward automated titration, and cost-effectiveness research, including real-world data with more variables in wider settings. Overall, the focus on digital tools should not underplay the importance of patient empowerment and algorithm simplicity which are essential components for effective insulin titration to achieve early glycemic control.

Contributors

LJ, YL, YC, JX, and XY conceived and designed this study. ZZ and CX conducted the database search and reviewed the reference lists of articles included in the screening. ZZ and CX performed initial screening and review of full texts for eligibility. ZZ, CX and YC extracted the data and completed the quality assessment. XY resolved any conflicts in quality assessment. YC and ZZ prepared the tables and figures and conducted the data analysis. YL, YC, XY, and LJ conducted data interpretation and drafted the first draft of the manuscript. All authors approved the project plan and reviewed and revised the final manuscript before submission.

Data sharing statement

Data is available upon reasonable request to the corresponding authors.

Declaration of interests

Within the past 4 years, Yong Mong Bee and Daisuke Yabe have received consulting remuneration from a commercial entity or other organization with an interest related to the subjectiveness of the meeting or work; Siew Pheng Chan, Margaret McGill, Daisuke Yabe or their research teams have received support from a commercial entity or other organization with an interest related to the subjectiveness of the meeting or work respectively; Siew Pheng Chan also has received non-monetary support valued at more than US $1000 (including equipment, facilities, research assistants, paid travel meetings, etc.). Ketut Suastika received honoraria for scientific symposium or webinar on basal insulin from several pharmaceutical companies, almost the events collaborated with Indonesia Society of Endocrinology. Alice Pik Shan Kong received research grants and/or speaker honoraria from Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli-Lilly, Kyowa Kirin, Merck Serono, Nestle, Novo-Nordisk, Pfizer and Sanofi. Khue Nguyen Thy received an honorarium for the chair in scientific meetings from Servier, Boehringer Ingelheim and Eisai. Soo Lim received research funding from MSD and CKD, and honoraria for lectures from Novo Nordisk, Sanofi, Boehringer Ingelheim, AstraZeneca and MSD. Linong Ji has received consulting and lecture fees from Eli Lilly, Novo Nordisk, Merck, Bayer, Sanofi-Aventis, Roche, MSD, Metronics AstraZeneca, Boehinger Ingelheim, and Abbott. Other authors declare no competing interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100746.

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