HOW CAN WE BEST SUPPORT INSULIN SELF-TITRATION IN TYPE 2 DIABETES PATIENTS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

PANITAN PITAK

A Thesis Submitted to the Graduate school of Naresuan University
in Partial Fulfillment of the Requirements for the Master of Pharmacy
in Community Pharmacy
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Thesis entitled “How can we best support insulin self-titration in type 2 diabetes patients:
A systematic review and network meta-analysis”
By Miss Panitan Pitak
has been approved by the Graduate School as partial fulfillment of the requirements for the Master of Pharmacy Program in Community Pharmacy of Naresuan University

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ABSTRACT

Although insulin management is crucial, there is limited evidence on the best strategies to support insulin self-titration. This study aimed to evaluate the effects of various support strategies for insulin self-titration in patients with type 2 diabetes (T2D). A comprehensive search of PubMed, EMBASE, CENTRAL, and EBSCO Open Dissertations was conducted from inception to January 2023. Eligible studies included randomized controlled trials (RCTs) in patients with T2D that reported HbA1c reduction outcomes associated with insulin self-titration support strategies. Interventions were categorized based on the inclusion of components such as dosage guidance (DG), non-dosage guidance (NDG), and empowerment. Results were pooled using a random-effects model, with mean differences (MDs) and risk ratios (RRs) presented alongside 95% confidence intervals (CI). The certainty of evidence was assessed using the CINeMA online platform. The protocol of this study is registered on PROSPERO (CRD42023458307).

Seventeen RCTs involving 13,528 participants were included. Compared to usual care (UC), the greatest HbA1c reduction was observed with DG/Empowerment (MD-1.20; 95%CI: -2.33,-0.07), supported by moderate certainty evidence. Smaller reductions in HbA1c (MD [95%CI]) were observed with other strategies compared to UC: NDG/Empowerment (-0.97 [-1.24, -0.69]), DG (-0.42 [-0.60, -0.24]), and NDG (-0.31 [-0.58, -0.03]). No significant differences were found in the risk of severe hypoglycemia across all strategies, with very low certainty of evidence.

In summary, incorporating patient empowerment into insulin self-titration support strategies, whether paired with DG or NDG, is more effective in reducing HbA1c and should be prioritized in insulin self-titration management plans.

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Panitan Pitak

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ABBREVIATIONS

95%CI	=	95% confidence interval
ADA	=	American Diabetes Association
BMI	=	Body mass index
EPOC	=	Cochrane Effective Practice and Organization of Care Group
CINeMA	=	Confidence in Network Meta-Analysis
DSMS	=	Diabetes self-management support
DSME/S	=	Diabetes self-management education and support
DG	=	Dosage guidance
HbA1c	=	Glycated hemoglobin
MDs	=	Mean differences
MeSH	=	Medical Subject Heading
MCID	=	Minimal clinically important difference
NDG	=	Non-dosage guidance
OAD	=	Oral antidiabetic drugs
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	=	Randomized controlled trials
RRs	=	Risk ratios
SMBG	=	Self-monitoring of blood glucose
ST	=	Self-titration
SUCRA	=	Surface under the cumulative ranking
T2D	=	Type 2 diabetes
UC	=	Usual care

CHAPTER I

INTRODUCTION

Background and rationale

Diabetes is rapidly becoming one of the most pressing global health crises. In 2021, an estimated 537 million people were living with diabetes, and this number is expected to rise to 643 million by 2030, and 783 million by 2045.[1] Diabetes can lead to severe complications, including heart disease, kidney failure, and eye damage, which may result in blindness, as well as foot ulcers that could necessitate limb amputation. The four deadliest non-communicable diseases (NCDs) are cardiovascular diseases, causing 17.9 million deaths annually; cancers, responsible for 9.0 million deaths; respiratory diseases, leading to 3.9 million deaths; and diabetes, which results in 1.6 million deaths and ranks among the top 10 leading causes of death globally.[2, 3]

Diabetes is a chronic metabolic disorder marked by high blood glucose levels due to insulin resistance, inadequate insulin production, or both. There are two main types: in type 1 diabetes, the pancreas does not produce enough insulin; in T2D, the body's cells are resistant to insulin, leading to high blood sugar.[1, 4] T2D accounts for over 90% of diabetes cases globally and poses a significant health challenge, with rising prevalence worldwide.[3] Initially, insulin resistance leads to increased insulin production, but over time, pancreatic beta cells can fail to meet the body's needs, resulting in inadequate insulin levels.[5]

Insulin is a polypeptide hormone primarily secreted by β cells in the islets of Langerhans in the pancreas. It helps manage blood glucose by promoting its storage in the liver, muscles, and adipose tissue, which can lead to overall weight gain.[6] Given the rising use of insulin, it is crucial to support the adjustment of insulin dosage based on each patient's specific needs.[7] Nevertheless, achieving and maintaining glycemic control with insulin therapy in patients with T2D remains a persistent challenge.[8] Despite the development of advanced insulin analogs and insulin delivery devices, many patients with T2D still struggle with suboptimal glycemic control.[14] Current evidence indicates that only about 25% of patients with T2D who are treated with insulin have reached their target glycemic control.[9]

Insulin self-titration has been proposed as a potential solution to improve the achievement of target glycemic control.[19, 21] This approach improves insulin effectiveness by teaching patients to monitor their blood glucose levels and adjust their insulin dosage as accordingly to maintain optimal glycemic control. It is typically combined with follow-up physician visits every 3-4 months,[10, 11] and demonstrated that patient-led titration of basal insulin is as effective as physician-led titration for patients with uncontrolled T2D. Consequently, diabetes self-management education and supports for insulin self-titration should be implemented in clinical practice for patients to adjust their doses as needed.[12] Another randomized controlled trial found that the patient-preferred self-titration algorithm led to a higher success rate in achieving glucose targets and improved adherence.[13]

Diabetes self-management education and support (DSME/S) is essential for individuals with T2D. It provides the knowledge and skills necessary for effective self-care, while support mechanisms help sustain these behaviors long-term. Tailored to each patient's needs and circumstances, DSME/S encompasses health literacy, cultural factors, family support, and more.[18] The 2024 ADA guideline highlights the value of DSME/S in empowering patients to manage insulin, emphasizing its role in effective T2D management without raising hypoglycemia risk.[14-19] Various strategies, such as educational programs,[20] mobile decision-support tools,[21] and smartphone apps,[22] have been developed to aid insulin self-titration.[23] However, findings on the efficacy of different strategies for glycemic control vary, and it remains unclear which features best support insulin self-titration.[17, 23] Further studies comparing these strategies could help healthcare providers select the most effective approaches, ultimately enhancing diabetes care and patient outcomes.

Research question

What is the best strategy to support insulin self-titration in patients with T2D?

Research objective

To comprehensively compare the effects of various insulin self-titration support strategies in patients with T2D.

Operational definitions

Dosage guidance (DG) involves adjusting insulin dosage based on fasting blood sugar values from self-monitoring of blood glucose (SMBG) according to algorithms received via messages, apps, or other platforms.[24]

Empowerment encourages self-care and responsibility[25] through educational and motivational support from healthcare providers, equipping patients with essential elements such as knowledge, self-efficacy, consideration of health beliefs, and motivation.[26]

Non-dosage guidance (NDG) includes telephone reminders for insulin self-titration or instructions for patients to seek help from clinicians or investigators regarding insulin doses, without automatic dosage suggestions.

Physician titration is defined as a physician directly advising patients on dosage adjustments, often at frequent intervals such as every 3 days, weekly, or every 2 weeks.[27, 28]

Research significances

This network meta-analysis (NMA) aims to compare the effects of insulin self-titration supports by categorizing the interventions into different multicomponent strategies to assess their impact on HbA1c reduction. Considering the inconclusive results from current empirical studies and differences in support strategies, it remains uncertain which specific aspects of support improve the effectiveness of insulin self-titration in patients with T2D. Understanding the comparative impact of different self-titration support methods could help healthcare providers select the most suitable approach for improving diabetes care in eligible patients.

Academic implementation

The results of this study will serve as a foundation for future research on self-titration support based on a multicomponent model helping to determine which intervention component is the most effective feature. Identifying the optimal insulin self-titration support strategy to improve glycemic control could help establish evidence-based practice guidelines for managing T2D management in the future.

CHAPTER II

REVIEW OF RELATED LITERATURE AND RESEARCH

The following section provides an overview of significant literature and research studies: 1) type 2 diabetes mellitus, 2) insulin, 3) insulin self-titration, 4) insulin self-titration support, 5) evidence synthesis, 6) multicomponent model, and 7) quality of evidence from NMA

1. Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2D) is characterized by reduced sensitivity to insulin, known as insulin resistance.[5] In this condition, insulin becomes less effective, initially prompting the body to produce more insulin to maintain normal glucose levels. However, over time, insulin production declines, leading to the development of T2D.[5] Although T2D is typically diagnosed in individuals over 45, its prevalence is increasing among children, teenagers, and younger adults due to rising obesity rates, sedentary lifestyles, and high-calorie diets.[5]

Uncontrolled diabetes can lead to various complications, both acute and chronic. Diabetes is a major cause of cardiovascular disease (CVD), blindness, kidney failure, and lower limb amputations. Acute complications include hypoglycemia, diabetic ketoacidosis, hyperglycemic hyperosmolar state, and hyperglycemic diabetic coma. Chronic microvascular issues involve nephropathy, neuropathy, and retinopathy, while chronic macrovascular complications include coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease.[29] It is estimated that between 1.4% and 4.7% of middle-aged individuals with diabetes experience a cardiovascular disease (CVD) event annually.[5] Maintaining glycemic control is essential in diabetes management. Among various methods exist for monitoring glycemic levels, but HbA1c is widely considered the most reliable measure.

The American Diabetes Association (ADA) defines the diagnostic criteria for type 2 diabetes as one of the following[4]

- A fasting blood sugar (FBS) level of 126 mg/dL (7.0 mmol/L) or higher.
- A plasma glucose level of 200 mg/dL (11.1 mmol/L) or greater measured 2 hours after consuming a 75-gram oral glucose load during an oral glucose tolerance test (OGTT).
- A random plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher in a patient showing classic symptoms of hyperglycemia or a hyperglycemic crisis.
- A Glycated hemoglobin (HbA1c) level of 6.5% (48 mmol/mol) or above.

1.1 Glycated hemoglobin (HbA1c)

The evaluation by measuring HbA1c refers to the amount of sugar attached to red blood cells, measured in % and mmol/mol. This value is used for diagnosing, monitoring diabetes treatment, and in clinical trials. It reflects the accumulated blood sugar levels over the past 3 months. Diabetes treatment progress is monitored using this value every 4 months or at least twice a year if the patient can consistently maintain good blood sugar control.[30]

The target HbA1c levels vary according to different treatment guidelines. For example, the ADA 2021 guidelines state that the general target for patients is an HbA1c level of less than 7.0%.[30] The 2018 guidelines from the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) set a target of less than or equal to 6.5% for most patients.[31] Additionally, the updated 2020 guidelines from the National Institute for Health and Care Excellence (NICE) 2015 set a target of less than or equal to 6.5% for patients who are not at risk of hypoglycemia.[32]

1.2 Hypoglycemia definitions and severity

Hypoglycemia, or low blood sugar, is typically defined as having a blood glucose level under 70 mg/dL. Maintaining appropriate glucose levels in the bloodstream is essential, as hypoglycemia can lead to significant health risks. Hypoglycemia is categorized into three levels[33]:

Level 1 hypoglycemia is identified by a measurable blood glucose concentration of less than 70 mg/dL (3.9 mmol/L) but equal to or greater than 54 mg/dL (3.0 mmol/L). A glucose level of 70 mg/dL (3.9 mmol/L) is considered the point at which neuroendocrine responses to decreasing glucose levels start in individuals without diabetes. Common symptoms of hypoglycemia include shakiness, irritability, confusion, rapid heartbeat, sweating, and hunger.

Level 2 hypoglycemia is defined as a blood glucose concentration less than 54 mg/dL (3.0 mmol/L). This level is where neuroglycopenic symptoms typically appear and necessitates immediate intervention to correct the hypoglycemic state. If a person experiences level 2 hypoglycemia without any adrenergic or neuroglycopenic symptoms, they may have impaired awareness of hypoglycemia.

Level 3 hypoglycemia is characterized as a severe episode with significant changes in mental or physical function that necessitates assistance from another person to recover.

2. Insulin

When oral antidiabetic drugs (OAD) at maximum doses fail to achieve therapeutic targets for patients with T2D, the next step is to initiate insulin therapy.[34, 35] In certain situations, insulin or another injectable medication may be suggested as the first-line treatment. Insulin therapy is particularly recommended for patients with T2D who have an initial HbA1c level exceeding 9%. Prior studies found that the usage of insulin is expected to rise from 516·1 million vials per year in 2018 (1,000 units /bottle) to 633·7 million vials per year in 2030.[7]

Given this increasing use, supporting the administration and adjustment of insulin dosage according to each patient's needs is crucial.

For T2D, basal insulin is typically the starting choice, providing long-lasting blood sugar control. It is usually given once daily, either in the morning or at bedtime, with doses ranging from 2 to over 100 units depending on diet, activity, and insulin sensitivity.[36] Most patients begin with 10 to 20 units, gradually adjusting the dose. Combining insulin with oral medications often reduces the total insulin needed. Monitoring fasting blood sugar levels is crucial for dose adjustments, and consistently high levels may signal the need for a higher dose or multiple injections.[36]

Table 1: Types of insulin, classified based on their onset, peak, and duration of action[36]

Insulin	Onset	Peak	Duration
Rapid acting			
Insulin lispro	15-30 mins	0.5-2 hrs	2-5 hrs
Insulin aspart	15 mins	1-3 hrs	3-5 hrs
Insulin glulisine	12-30 mins	1.5 hrs	5-6 hrs
Short acting			
Regular	0.5-1 hrs	2-4 hrs	5-8 hrs
Intermediate acting			
Neutral protamine Hagedorn insulin (NPH)	2-4 hrs	4-10 hrs	8-16 hrs
Long acting			
Insulin glargine	2-4 hrs	None	24 hrs
Insulin detemir	1-2 hrs	6-12 hrs	20-24 hrs
Ultra-long acting			
Insulin degludec	0.5-1.5 hrs	none	42 hrs
Insulin glargine U300	6 hrs	none	24-36 hrs

Hrs = hours, mins = minutes

Risk factor and prevalence of insulin in glycemic control

According to findings from a previous systematic review and meta-analysis, only a quarter of T2D patients undergoing insulin therapy achieved glycemic control.[9] Although these proportions may vary slightly across studies with different characteristics, they still highlight the critical need for improved diabetes management by both patients and healthcare professionals. To improve diabetes management and glycemic control, public health initiatives should prioritize reducing socioeconomic disparities, optimizing insulin regimens, updating care practices, and strengthening primary care facilities.[9]

Patients with diabetes often have negative attitudes towards insulin therapy due to various social and psychological factors.[37] This highlights the need for a strategy to tackle issues related to reluctance in starting insulin. Such a strategy should focus on improving education and enhancing communication with the diabetes care team to address the stigma and fear associated with insulin use.[37]

Insulin titration, the process of adjusting insulin doses to maintain optimal blood glucose levels, can be managed through conventional (physician-led) or self-titration (patient-led) approaches. Conventional titration involves healthcare providers monitoring blood glucose levels and adjusting doses accordingly, which often requires regular follow-ups. This method offers professional oversight and structured guidance, reducing the risk of incorrect dosing. However, it limits patient autonomy, can delay dose adjustments, and is more time-consuming due to frequent appointments. In contrast, self-titration enables patients to follow a simplified algorithm, which is a structured guideline of step-by-step instructions that guides them to adjust their insulin dose by increasing or decreasing insulin units according to specific blood sugar thresholds. This approach empowers patients to take control of their diabetes, offering better glycemic control and more timely adjustments. However, it requires sufficient education and can place additional responsibility on patients, which may be challenging for some.[38]

Overall, self-titration offers patients greater flexibility and better glycemic control when supported by proper education, while conventional titration provides a structured, medically guided alternative.[39]

3. Insulin self-titration

Insulin self-titration is a patient-centered approach that enables individuals to independently manage their diabetes by adjusting insulin doses according to predefined protocols and regular blood glucose monitoring, reducing reliance on healthcare providers. The process involves consistent glucose monitoring, dose adjustments based on trends or protocol targets, and vigilance for adverse effects like hypoglycemia or glucose variability. With proper education and access to necessary resources, this method promotes patient autonomy and improves glycemic control, making it an effective and empowering strategy for diabetes management.[19]

Insulin self-titration empowers patients by fostering engagement, confidence, and control over diabetes management, allowing timely dose adjustments without relying on frequent healthcare visits. This approach reduces healthcare system burdens and improves glycemic outcomes through active patient involvement. However, barriers include the need for adequate health literacy to understand protocols, technological challenges with glucose monitoring tools, risks of dosing errors, psychological fears of incorrect adjustments, and financial constraints for necessary tools and education programs.[12, 19]

Managing blood sugar levels with insulin therapy in patients with T2D remains a continuous challenge, with insulin self-titration emerging as a recommended method to address this issue.[8] This method seeks to improve insulin effectiveness by educating patients to monitor their own blood glucose levels and adjust their insulin doses accordingly to achieve proper glycemic control,[40] while also incorporating follow-up visits with a physician every 3-4 months.[10, 11] Several diabetes practice guidelines have endorsed diabetes self-management support (DSMS) to enhance patient empowerment in diabetes care.[14, 40] Specifically, the 2024 ADA guideline has also emphasized that patient education and participation in insulin administration is beneficial.[15] Studies comparing these approaches have shown that self-titration can result in greater reductions in HbA1c and FBS without an increased risk of severe hypoglycemia,[20, 21, 41] while both approaches demonstrate similar patient satisfaction and quality of life scores.[17]

Insulin self-titration in patients with T2D emphasizes the importance of educating patients about insulin therapy and empowering them to manage their diabetes by adjusting their own insulin doses.[40] A number of insulin self-titration algorithms have been evaluated that aim to simplify insulin titration to effectively participate in the management of their disease by different life styles. These algorithms vary in their effectiveness for glycemic control and in their risk of hypoglycemia.[42] Several studies have demonstrated that patients can achieve glycemic control comparable to physician-directed titration by using simple basal insulin titration algorithms, such as increasing by 1 unit per day or every 3 days based on the average of three self-monitored FBS values.[17] The ATLAS, AT.LANTUS, and ATAS trials implemented insulin self-titration protocols that increased glargine doses by 2 or 4 units every three days.[13]

Additionally, simplified self-titration algorithms for prandial and basal-bolus insulin regimens have proven to be effective.[37] More complex titration algorithms, when combined with consistent support, can also help certain patients achieve optimal glycemic control, as shown in several studies.[40] Furthermore, a prior systematic review and meta-analysis found that patient-led basal insulin titration was not inferior to physician-led titration and was equally effective in patients with uncontrolled type 2 diabetes.[15] Therefore, integrating diabetes self-management education and support programs into clinical practice is essential to empower T2D patients using insulin to adjust their dosage as needed.

The insulin self-titration algorithm, which is established by a physician to allow patients to adjust their insulin dosage at home based on their blood sugar levels, varies depending on the type of insulin used. For example, the self-adjustment criteria for NPH every 3 days are based on the patient's blood sugar levels from the previous 3 days for those with T2D, as shown in the following table 2.[43]

Table 2: Self-titration of NPH based on fasting blood sugar (FBS)

FBS (mg/dl)	Dose (unit, u)
> 140	Increase 1 u
80-140	Do not adjust
< 80	Decrease 2 u

Insulin self-titration can be difficult to manage, and patients need ongoing support to safely and effectively adjust their insulin doses. However, when done correctly, it can improve treatment effectiveness without greatly increasing the risk of hypoglycemic side effects.[16, 17] To date, various strategies and programs have been developed to support insulin self-titration, including educational programs,[20] decision support of insulin dose and follow-up via mobile,[21] smartphone applications,[22] or via messaging.[23] However, assessments of various insulin self-titration support strategies have demonstrated mixed results in their effects on glycemic control.[17]

4. Insulin self-titration support

Educational programs for self-titrating patients produced comparable glycemic control to physician-led groups, though individual education required more time. There are various formats for supporting insulin self-titration, and there is no classification clearly. The following are examples of how others in the field of behavioral programs have categorized key components:[44]

1. Program component: This is categorized by the type of program offered, such as providing knowledge and skills for self-management of diabetes, offering knowledge and skills for self-management combined with support, or focusing on behavior programs aimed at dietary control and/or exercise. For example, providing empowerment and dosage guidance or dosage guidance alone as this study.

2. Intensity**:** This is categorized by the intensity, such as the number of hours spent in communication such as follow-up contacts lasting less than 1 hour or more during each session.[45]
3. Frequency of contacts: This is categorized by how often contact occurs such as contact patients less than 2-3 times a week or more.[46]
4. Method of communication: This is categorized by the method of communication, such as using only in-person interactions, a combination of in-person and technology, or using technology exclusively with minimal interaction with the provider. For example, patients with educational program compare to patients with educational program and mobile phone support.[21]

4.1 Studies of insulin self-titration support

Luo et al, 2023 performed a systematic review and meta-analysis of randomized controlled trials about device-supported, automated algorithms to titrate basal insulin in patients with T2D. The result showed that automated BI titration, compared to conventional care, was more likely to achieve the target HbA1c of <7.0% (RR, 1.82 [95% CI, 1.16-2.86]) and resulted in a lower mean HbA1c level (MD, -0.25% [95% CI, -0.43 to -0.06%]). However, no significant differences were observed between the two approaches regarding FBS levels, hypoglycemia incidence, severe or nocturnal hypoglycemia, or quality of life, with low to very low certainty in the evidence. Overall, automated BI titration was linked to modest reductions in HbA1c without increasing hypoglycemia risk.[17]

Zhang et al (2023) conducted a systematic review and meta-analysis to assess the length and efficacy of several E-health interventions in enhancing glycemic control in T2D patients in meta-analysis. The findings showed that glycemic control was improved by all types of e-health interventions. With an optimal intervention length of six months or less, SMS—a commonly used and easily accessible technology—proved to be the most efficient in lowering HbA1c.[47]

Additionally, a recent systematic review by Thomsen et al (2024) highlights that real-world studies on people with T2D reveal inadequate dose adjustments during basal insulin titration, resulting in suboptimal treatment and nearly 60% of patients not achieving glycemic targets. This systematic review of basal insulin dosage guidance

methods that support titration identified three categories: paper-based algorithms, telehealth solutions, and mathematical models. Overall, telehealth solutions seemed to have a better impact on reaching glycemic targets compared to paper-based methods, and the potential of machine learning is suggested as a future avenue for innovative research.[48]

Bonoto et al., 2017 evaluated the efficacy of mobile apps through a systematic review and meta-analysis to assist DM patients in treatment. In 6 RCTs, there was a statistically significant reduction of HbA1c at the end of studies in the intervention group, with the mean difference of -0.44; 95%CI: -0.59 to -0.29; I^2 = 32%). This indicates that the use of mobile apps by patients with diabetes could help improve the control of HbA1c.[25]

According to above review of literature, the current evidence has shown that different methods of insulin self-titration can lead to lower HbA1c levels, but no single method has yet been definitively recommended as the optimal approach.

4.2 Empowerment

Empowerment is a patient-centered, collaborative approach tailored to match the fundamental realities of diabetes care. Patient empowerment is the process of helping individuals recognize and develop their inherent ability to manage their own health and well-being. Since initially proposed in diabetes, there has been a growing recognition that, although health professionals are experts on diabetes care, patients are the experts on their own lives. This approach recognizes that knowing about an illness is not the same as knowing about a person's life and that, by default, patients are the primary decision-makers in control of the daily self-management of their diabetes.[49, 50]

Research has shown that patient-driven algorithms enabling individuals to initiate and adjust basal insulin can be effective compared to standard clinic-directed approaches.[51] However, while these strategies have been beneficial in improving psychosocial outcomes, a comprehensive review found that individual empowerment initiatives for diabetes mellitus (DM) did not lead to significant reductions in HbA1c. This highlights the need to refine and optimize these approaches to enhance their effectiveness in DM management. Further research is necessary to better understand the role of patient empowerment initiatives in managing T2D.[51]

5. Evidence synthesis

Evidence synthesis, through systematic reviews and meta-analyses, integrates findings from multiple studies to provide a comprehensive assessment of health intervention effectiveness. Below is an overview of evidence synthesis and key issues:

5.1 Systematic review and meta-analysis

A systematic review[52, 53]is a step-by-step method aimed at reducing bias, with a structured approach to searching, evaluating study quality, and synthesizing information to find answers. If statistical methods are used to pool findings from different studies, it is called a meta-analysis. Both systematic reviews and meta-analyses can be used to compare two options, while NMA is used to compare multiple options.

Meta-analysis[54-56] involves using statistics to combine the results of all studies reviewed in a systematic review to determine the pooled effect size. Results are often presented in a forest plot, showing the direction of the results and the heterogeneity of the study results. Heterogeneity can be assessed using statistics like the Cochrane Q-statistic and the percentage of inconsistency index (I^2). There are two models for calculating the effect size and 95% confidence intervals: the fixed-effect model and the random-effects model.

5.2 Network meta-analysis

Network meta-analysis (NMA)[57] compares three or more interventions by combining direct and indirect evidence from multiple studies, providing more precise estimates than using either type alone. It also allows comparisons between interventions that haven't been directly tested against each other. By analyzing all relevant interventions together, NMA ranks them for specific outcomes. A reference intervention is typically chosen, and other interventions are compared to it, with the remaining comparisons derived using coherence equations.[58]

Network map provides direct evidence for treatments that have been compared to one another. The map graphically illustrates the relationships and comparisons between different treatments, offering a clear representation of how they stack up against each other.[59] Nodes represent the different interventions within the network, while lines illustrate the available direct comparisons between pairs of interventions (Figure 1).[58]

Node size represents the different interventions being compared, with larger nodes indicating more evidence, such as more participants or trials for a given intervention. Smaller nodes reflect less data, helping to visualize which interventions have been more or less frequently studied.[57] Thicker lines indicate multiple studies comparing two interventions, while thinner lines suggest fewer direct comparisons.[60]

A closed loop in NMA occurs when three or more interventions are interconnected, enabling both direct and indirect comparisons. For example, if Intervention A is directly compared to Intervention B, B to C, and A to C, a closed loop is formed among A, B, and C.[58] Closed loops in NMA are essential for ensuring coherence and consistency by allowing comparisons between direct and indirect evidence, which helps identify inconsistencies or biases. They improve precision by combining these types of evidence, providing robust estimates of intervention effects, especially when direct comparisons are weak or unavailable. Additionally, closed loops facilitate the validation of the model by testing the coherence between different evidence types; high consistency enhances the reliability of NMA conclusions, while significant inconsistency may indicate problems with study quality or biases. Overall, closed loops strengthen NMA by confirming transitivity and consistency, thereby improving the accuracy of intervention effect estimates.[58]

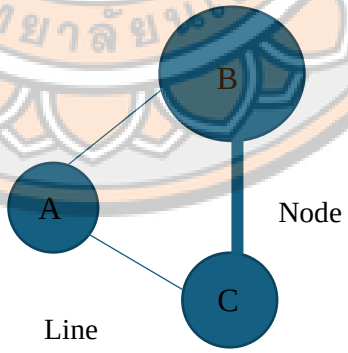


Figure 1: Example of network map of comparison for three groups

5.2.1 NMA assumption: heterogeneity, transitivity, and consistency

Key assumptions of NMA include heterogeneity**,** which represents the inherent differences between trials that directly compare the same pair of interventions. Additionally, transitivity ensures that indirect comparisons are valid by assuming comparability among treatment groups, while consistency ensures that direct and indirect evidence for each intervention are in agreement. These assumptions are crucial for the validity and reliability of NMA findings, as they help mitigate biases and discrepancies in the data from different studies.[58 60, 61]

Heterogeneity

Heterogeneity refers to variability in study results that impacts confidence in the treatment effect estimate. This variability can be due to true differences between studies or random variation. The GRADE system refers to this as "inconsistency." NMA considers variability between studies and discrepancies between direct and indirect evidence. Heterogeneity is measured using the variance of treatment effects (τ^2) and prediction intervals, which show where the true effect of a new study is likely to fall.

The chi-squared (χ^2) test is a statistical method used to assess heterogeneity in pairwise meta-analysis. It evaluates whether the observed differences in study results are consistent with what would be expected due to random chance alone. A low p value (or a large chi-squared statistic relative to its degrees of freedom) indicates significant heterogeneity, suggesting that the variation in intervention effects exceeds what can be attributed to chance.

This implies that even if a result is statistically significant, it might still reflect issues with heterogeneity. Conversely, a non-significant result should not be interpreted as evidence of the absence of heterogeneity. To quantify inconsistency effectively, a useful statistic is I^2, which can be calculated by the following formula:

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

where df is its degrees of freedom and Q is the chi-squared statistic. This statistic represents the percentage of variability in effect estimates attributed to heterogeneity rather than random sampling error.[58]

Interpreting I^2 can be tricky, as the significance of inconsistency varies depending on several factors. A general guide to interpretation is as follows:[58]

- 0% to 40%: This may indicate minimal importance;
- 30% to 60%: This may suggest moderate heterogeneity;
- 50% to 90%: This may indicate substantial heterogeneity;
- 75% to 100%: This signifies considerable heterogeneity.

The importance of I^2 is influenced by factors such as the size and direction of effects, as well as the strength of evidence for heterogeneity, including the p-value from the chi-squared test and the confidence interval for I^2.

The between-study variance, Tau^2, generally assumed to be constant across all comparisons within the network, serves as a measure of heterogeneity in a network of interventions. The level of heterogeneity in the estimated Tau^2 depends on the clinical outcome and the types of interventions being compared. Additional materials provide a more in-depth discussion of predicted Tau^2 values specific to various therapeutic contexts. Additionally, global incoherence is assessed using the p value from the Chi^2 statistic incoherence test and the I^2 statistic for incoherence.[58]

Transitivity

Transitivity assumes that the relative effect of treatment B vs. C can be inferred through treatment A, combining the effects of A vs. B and A vs. C. For valid indirect comparisons, the trials involved must be similar in key factors (except the intervention), such as patient characteristics and methodology.[58] Effect modifiers, which influence outcomes, can cause heterogeneity. If trials differ significantly in these modifiers, transitivity is violated, making indirect comparisons unreliable. Researchers must assess whether differences between studies are substantial enough to cause intransitivity, as this would affect the validity of results.[58] When both direct and indirect evidence are available, they can be combined into a mixed estimate, but transitivity must hold for this estimate to be reliable. Violations of transitivity or bias in direct effects can compromise the accuracy of the conclusions.[58]

Consistency

In NMA, coherence (or consistency) is the agreement between direct and indirect evidence for a comparison, based on the transitivity assumption that assumes minimal clinical and methodological differences across comparisons. Coherence is essential to ensure valid results, and a violation of this assumption leads to incoherence.[58]

Incoherence occurs when direct and indirect evidence disagree, and this can be quantified using the incoherence factor (IF), which measures the absolute difference between these estimates. Approaches for detecting incoherence include local methods, which examine specific regions of the network, and global methods, which assess the entire network for inconsistencies.[58]

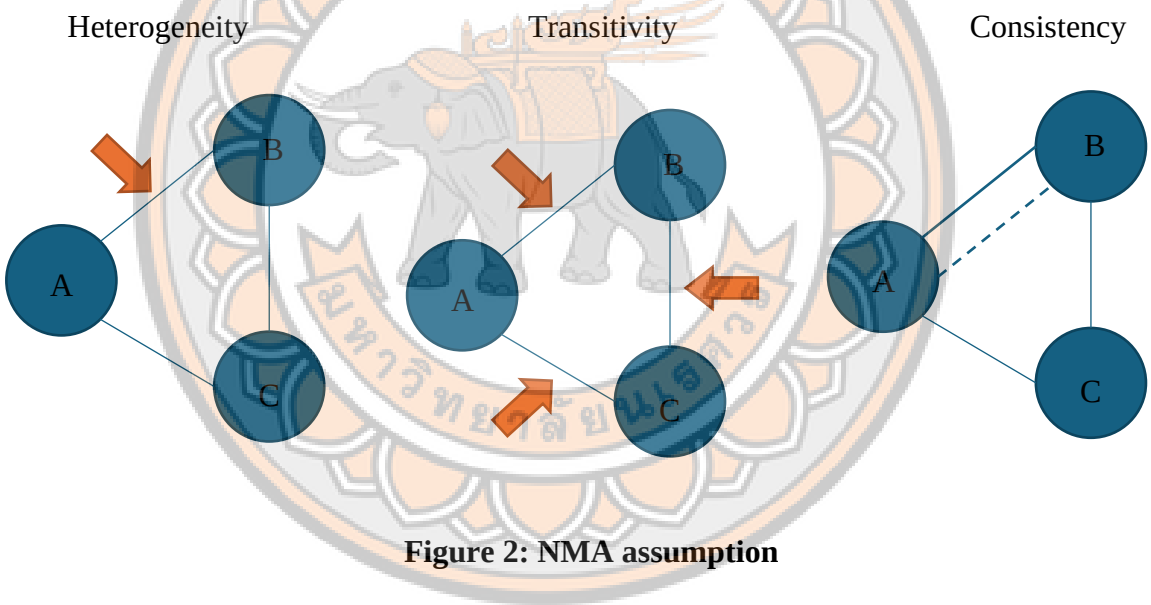


Figure 2: NMA assumption

5.2.2 Effect estimates

There are three types of comparisons of NMA[60]

1. Direct treatment comparison is the comparison of outcomes between two treatments that are directly compared.
2. Indirect treatment comparison is the comparison of treatment outcomes where there is no direct evidence available.
3. Mixed treatment comparison involves comparing the outcomes of interest by analyzing both direct and indirect evidence.

Effect estimates in NMA are central to understanding the relative effectiveness of multiple interventions. These estimates are visualized and interpreted through various tools, such as league tables, and cumulative ranking methods like SUCRA.

League table

A table displaying the relative effects between all treatments along with their corresponding uncertainties. A league table in NMA summarizes the relative effects of all treatments compared, including associated uncertainties like confidence or credible intervals. Each cell in the table represents the treatment effect between pairs of interventions, allowing for easy comparison of effectiveness. This format helps researchers identify treatments with strong evidence versus those with uncertain effects, facilitating informed decision-making regarding the most effective interventions.[58, 60]

Hierarchy of treatment effects: surface under the cumulative ranking (SUCRA)

The Surface Under the Cumulative Ranking (SUCRA) offers a streamlined, quantitative method to represent treatment efficacy in NMA by condensing ranking information into a single value between 0 and 1. This provides a straightforward interpretation, as higher SUCRA values indicate superior treatments, with 1 representing the best and 0 the worst.[62] However, SUCRA's meaningfulness depends on uniform preference differences between ranks; without this, the interpretation may be misleading. Another similar metric is the P-score, which, while derived differently within a frequentist framework, aligns with SUCRA values under the same conditions, ensuring consistency in treatment ranking interpretation across studies.[63, 64]

5.2.3 Additional analyses

Subgroup analyses divide participant data into smaller groups based on study characteristics, helping to identify variations in treatment effects across populations and informing tailored interventions.[65] However, such analyses are uncommon in systematic reviews due to limited detailed and consistent data across studies, which is necessary to conduct meaningful subgroup comparisons.[66]

When conducted, subgroup analyses are prone to risks, particularly the increased likelihood of misleading results. Small sample sizes, heterogeneity among studies, and the lack of predefined subgroups raise the risk of Type I (false positive) and Type II (false negative) errors, which can distort clinical conclusions.[67] These issues are compounded when multiple subgroups are tested without adjustments for multiple comparisons, potentially leading to spurious findings that influence clinical recommendations or misguide future research priorities. [65]

Sensitivity analysis tests the robustness of meta-analysis findings such as excluding studies with small sample sizes or high risk of bias. This method assesses how results change under different assumptions, providing insight into the reliability of conclusions. Unlike subgroup analyses, sensitivity analyses do not estimate effects for excluded studies but focus on comparing different analytical methods informally. Presenting results in summary tables is more effective than individual forest plots, aiding clearer interpretation of the findings.[65]

6. Multicomponent model

In standard NMA, each unique treatment or combination of treatments forms an individual node in the network. This approach allows for comparisons across both single and multicomponent interventions without distinguishing the effects of individual components within combined treatments. An alternative to this approach is to break down complex, multicomponent treatments into their components, analyzing the effect of each component separately. This component-based approach can help isolate the contributions of specific treatment elements within combined interventions.[68] (Table 3)

In some cases, instead of treating each combination uniquely, researchers may opt for a “clinically meaningful units” approach, which groups similar treatments (e.g., drugs within a specific class or similar psychotherapies) into a single node to simplify the analysis. Conversely, a “components and dismantling” approach seeks to identify the individual effects of common components across different treatments.[68]

Table 3: Example of multicomponent[68]

Component 1 (C1)	Component 2 (C2)	Component 3 (C3)	Feature
C1	-	-	C1
C1	C2	-	C1/C2
C1	C2	C3	C1/C2/C3
C1	-	C3	C1/C3
-	C2	-	C2
-	C2	C3	C2/C3
-	-	C3	C3

7. Quality of evidence from NMA

The diversity and strength of the NMA network depend on the number of interventions and comparisons available, as well as the quality of the evidence they provide. While NMA offers significant advantages over traditional pairwise meta-analysis, it also inherits common challenges, including issues of heterogeneity, consistency, and precision, which can lead to inconsistency or incoherence in the results.

To evaluate confidence in the results of NMA, tools such as Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) and Confidence in Network Meta-Analysis (CINeMA) framework are commonly used.

7.1 Grading of Recommendation, Assessment, Development, and Evaluations (GRADE)

The GRADE approach is a comprehensive and widely adopted framework for evaluating evidence quality and the strength of recommendations in healthcare. Created by the GRADE Working Group and initially developed at McMaster University, GRADE addresses the limitations of earlier systems by providing a transparent, structured, and consistent method for assessing evidence and making recommendations.[69-71]

Once evidence is gathered, its quality is assessed using the GRADE framework, which evaluates studies across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on these factors, evidence is rated into four levels: high, moderate, low, or very low, reflecting the confidence in the estimates. The

strength of recommendations is then determined by balancing the benefits and harms of an intervention, the certainty of the evidence, patient values, and resource use. GRADE categorizes recommendations as strong or weak/conditional, with strong recommendations indicating that most patients would opt for the intervention, and weak recommendations reflecting variability in individual preferences and circumstances. Ultimately, these steps help ensure that guidelines are based on the best available evidence while considering the unique context and needs of patients.

The GRADE approach to contextualization

In 2017, GRADE refined its definition of "certainty of evidence," framing it as the confidence that the true effect lies on one side of a threshold or within a specified range. GRADE offers three levels of "contextualization" to apply evidence based on specific needs:[72]

1. Minimally Contextualized: Used mainly in systematic reviews, focusing on a single outcome compared against a simple threshold, like "no effect" or the minimal clinically important different (MCID).
2. Partially Contextualized: Expands to consider a range of effect sizes (e.g., small, moderate, large) for one outcome, allowing more nuanced judgments.
3. Fully Contextualized: Primarily applied in guidelines, weighing the overall net benefits across multiple outcomes, including patient values and preferences.

For example, in evaluating antidepressants for major depressive disorder, if the confidence interval (CI) of an effect estimate doesn't overlap with "no effect," the certainty remains high. However, if it crosses MCID, certainty may be downgraded due to imprecision.

Where exact thresholds aren't feasible, implicit thresholds (judging effects as "important" or not based on collective insight) may be used. This adds flexibility but can introduce biases, so predefined thresholds are encouraged for consistency.

In summary, GRADE enhances clarity and confidence in healthcare decision-making by offering a systematic, adaptable, and patient-centered framework for evaluating evidence and developing recommendations. This ensures that guidelines are relevant, reliable, and responsive to real-world needs.

7.2 Confidence in Network Meta-Analysis

Despite the growing use of NMA in evidence synthesis, many studies still fail to adequately report treatment comparisons or illustrate the underlying comparison structures clearly. Typically, these treatment networks present only direct evidence, which overlooks the broader evidence that could be gained by incorporating indirect comparisons. This limits the insights that could be derived from NMA and diminishes its value. CINeMA framework addresses this gap by evaluating the credibility of NMA results across six key domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. CINeMA framework allows researchers to quantify the overall strength of the evidence, making it easier for audiences to assess the value of NMAs compared to pairwise meta-analyses, which rely solely on direct evidence.[73, 74]

By providing a systematic evaluation of NMA results, CINeMA framework enhances transparency and improves the interpretation of treatment networks. Through case studies, CINeMA framework has demonstrated that the structure of treatment networks can vary significantly depending on factors such as sample size, precision, and the measures used to report evidence. These insights encourage researchers to report comprehensive evidence across both direct and indirect comparisons, improving the quality of NMAs. CINeMA framework's structured approach contributes to a more rigorous and transparent evidence synthesis process, ultimately ensuring that conclusions drawn from NMAs are more reliable.[73, 74]

CINeMA framework evaluates six domains to assess the credibility of the evidence in NMAs. These domains are:[73, 74]

1. **Within-Study Bias**: Flaws in the design or conduct of individual studies that can lead to systematic errors in estimating treatment effects. Tools like the Cochrane Risk of Bias Tool assess risks such as random sequence generation and allocation concealment. Studies with low risk of bias are considered more reliable.
2. **Reporting Bias**: Occurs when certain results, typically those showing favorable effects, are selectively published or emphasized. CINeMA framework helps identify whether reporting bias is suspected or undetected, ensuring that all results are considered in the analysis.

3. **Indirectness**: Refers to the relevance of study participants, interventions, outcomes, or settings to the research question. For example, if a study includes elderly patients in a review intended for a general adult population, the evidence may be considered indirect and less applicable to the broader question.
4. **Imprecision**: Refers to the precision of the effect estimates. CINeMA framework evaluates whether the NMA provides sufficiently precise estimates to inform clinical decisions. By combining both direct and indirect evidence, NMAs can increase precision and provide more reliable treatment comparisons.
5. **Heterogeneity**: Refers to the variability in treatment effects across studies. High heterogeneity can reduce the confidence in the findings, while low heterogeneity suggests that the studies are consistent and the results are more reliable. CINeMA framework helps assess whether the variation between studies is due to real differences or random chance.
6. **Incoherence**: Occurs when direct and indirect comparisons in a network disagree, suggesting a problem with the transitivity assumption. CINeMA framework evaluates whether discrepancies between direct and indirect evidence reduce confidence in the overall conclusions.

Once these six domains are assessed, CINeMA framework provides a final summary that rates the confidence in the evidence for each relative treatment effect. This rating follows the GRADE system, assigning confidence levels as very low, low, moderate, or high. The initial confidence level starts high and is downgraded based on concerns identified in the domains. Minor concerns lead to a one-step downgrade, while major concerns lead to a two-step downgrade. Because the domains are interconnected, issues in one area (such as indirectness) may impact others (such as incoherence), and these interactions must be considered to avoid multiple downgrades.[73, 74]

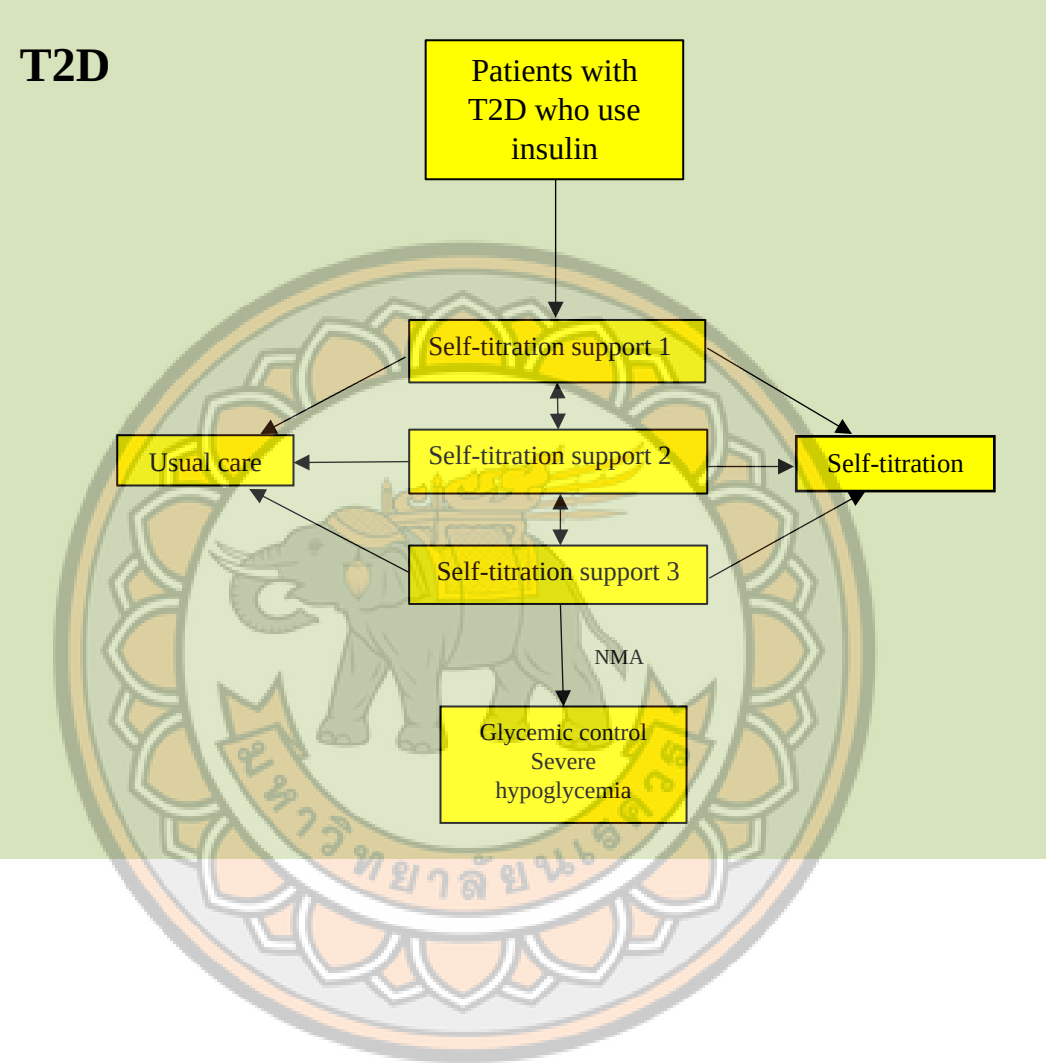
For example, high heterogeneity can increase imprecision and complicate the detection of incoherence, further reducing confidence in the results. Therefore, evaluating all six domains together is crucial for an accurate assessment of the evidence. CINeMA framework ’s approach ensures that the overall confidence in NMA results is based on a comprehensive evaluation of all relevant factors, leading to more reliable conclusions and better-informed healthcare decisions.

In summary, CINeMA framework provides a structured, transparent framework for assessing the credibility of NMA results. By considering within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence, CINeMA framework helps identify weaknesses in the evidence base and improves the reliability of systematic reviews. This comprehensive evaluation supports more informed decision-making, ensuring that clinical guidelines and recommendations are based on the most robust evidence available. CINeMA framework's systematic and transparent approach contributes to the overall rigor of the evidence synthesis process, improving the quality and usefulness of NMAs in guiding healthcare decisions.[89]

Both GRADE and CINeMA framework provide systematic frameworks for evaluating evidence quality, but they are designed for different purposes. GRADE is a more general framework applicable to all types of evidence synthesis, while CINeMA framework is specifically tailored for NMA. Both frameworks use similar domains (risk of bias, imprecision, indirectness, etc.) but CINeMA framework introduces heterogeneity and incoherence as additional critical aspects, particularly relevant for NMAs. Both systems assign confidence levels (high, moderate, low, very low) to indicate the quality of evidence, but GRADE also uses this to generate clinical recommendations, whereas CINeMA framework's primary goal is to ensure transparent and rigorous evidence synthesis in NMAs.

Additionally, the GRADE process is applied independently to both direct estimate and indirect estimate, with the indirect rating being the lowest of the two direct components. The certainty rating for an NMA estimate is then the higher of the direct and indirect ratings. This separation is particularly important in cases where direct and indirect estimates differ substantially, as researchers are advised to prioritize the estimate with the highest certainty. However, this approach can lead to incoherent rankings and adds significant complexity, especially in large networks with numerous indirect comparisons.[75]

Research framework



CHAPTER III

RESEARCH METHODOLOGY

1. Research design

This NMA was conducted by following the methods suggested in the Cochrane Handbook.[58] The study protocol was registered on PROSPERO (CRD42023458307) and amendments to initial protocol registered on PROSPERO as shown in Appendix 1. Reporting in this thesis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting of systematic reviews incorporating the NMA of healthcare interventions.[76] Given the complexity of the supporting strategies for insulin self-titration, which consist of several interacting components, the interventions were classified based on a multicomponent model.[68]

2. Search strategy and selection criteria

The following bibliographic databases were searched from their inception to January 2023 to identify relevant articles: PubMed, EMBASE, Cochrane CENTRAL, and CINAHL. Gray literature was identified by searching EBSCO Open Dissertations. Other search techniques were also used, including a snowballing search of references from the included studies and citation tracking via Scopus in November 2023, to ensure that relevant articles not captured via database search were well covered and up to date.

Search terms included Medical Subject Heading (MeSH) terms and modified keywords from previous studies,[12, 77-80] which included five domains: 1) T2D, 2) insulin, 3) titration/adjustment, 4) self-management, and 5) HbA1c. The full search terms and search results of the search strategy for all databases are detailed in Appendix 2.

3. Study selection

Randomized controlled trials were included if they met the following inclusion criteria: 1) studied in patients with T2D aged 18 years or over without pregnancy; 2) compared self-titration support strategies with other interventions; and 3) reported HbA1c reduction at least 3 months post-intervention. PP and Kansak Boonpattharatthiti (KB) independently determined study eligibility by screening the titles and abstracts to assess whether they met the inclusion criteria. Subsequently, the full manuscript of

articles that passed the title/abstract screening were reviewed independently by the same reviewers. When disagreements and uncertainties regarding eligibility occur, they were resolved by discussions with the third reviewer (TD).

4. Data extraction and quality assessment

Two reviewers (PP and KB) extracted each included study independently using a data extraction form modified from the Cochrane Effective Practice and Organization of Care Group (EPOC) data extraction form.[81] The following information was extracted: population characteristics (age, gender, body mass index (BMI), duration of T2D, type of insulin, medicine regimen), study characteristics (number of participants, country, duration of study), interventions (detail of self-titration support), comparator (self-titration and usual care), outcome (HbA1c reduction, the number of severe hypoglycemia cases; defined by each included study).

Two independent reviewers (PP and KB) used the Cochrane Effective Practice and Organization of Care Group (EPOC) risk of bias tool to assess the methodological quality of included studies, which evaluates the following domains: sequence generation; adequacy of allocation concealment; baseline outcome measurements; comparable baseline characteristics of providers; completeness of outcome data; protection against contamination; non-selective outcome reporting; and other risks of bias.[82] The overall risk of bias within a study was determined based on key domains, including baseline outcome measurements, incomplete outcome data, and protection against contamination. Low risk (low risk of bias for all key domains), high risk (high risk of bias for one or more key domains), and unclear risk (unclear risk of bias for one or more key domains) were the classifications given to each study. The third reviewer (TD) arbitrated disagreements between the first two reviewers.

5. Classification of insulin self-titration support

After a careful discussion among researchers and clinicians, informed by relevant literature, interventions supporting insulin self-titration were classified based on the existence of two main components: dosage guidance (DG) and patient empowerment. DG involves adjusting insulin dosage based on fasting blood sugar values from SMBG according to algorithms received via messages, apps, or other platforms.[24] Non-dosage guidance (NDG) includes telephone reminders for insulin self-titration or instructions for

patients to seek help from clinicians or investigators regarding insulin doses, without automatic dosage suggestions. Empowerment encourages self-care and responsibility[25] through educational and motivational support from healthcare providers, equipping patients with essential elements such as knowledge, self-efficacy, consideration of health beliefs, and motivation.[26]

According to the classification based on the multicomponent approach there were 4 possible comparative features of interventions in this study: 1) DG with empowerment (DG/Empowerment); 2) NDG with empowerment (NDG/Empowerment); 3) DG Only; and 4) NDG Only.

Self-titration is defined as the process in which patients adjust their own insulin doses based on their blood glucose measurements, typically using SMBG.[19] Self-titration support includes any interventions designed to help patients perform insulin self-titration more effectively. For comparators, usual care refers to the standard, conventional care typically provided to patients with T2D in clinical settings. Patients rely on routine visits to their healthcare provider for adjustments to their treatment.[10]

6. Data analysis

The Chi-squared test and I^2 were applied to determine statistical heterogeneity and assessed the clinical heterogeneity based on the variation in population characteristics and detail For each comparable outcome, i.e. HbA1c and severe hypoglycemia, a network geometry was drawn to investigate the interaction of direct evidence among various forms of insulin self-titration support and other interventions (self-titration and usual care). Mean differences (MDs) was used to determine the pooled effects of change in HbA1c and the effect on severe hypoglycemia was presented using risk ratios (RRs). All effect estimates were presented along with their respective 95% confidence interval (95%CI). The effects of self-titration support strategies were ranked by the surface under the cumulative ranking (SUCRA).[83,84]

The Chi-squared test and I^2 were applied to determine statistical heterogeneity and assessed the clinical heterogeneity based on the variation in population characteristics and detail of interventions across studies.[85, 86] The assessment of global network inconsistency was performed using the consistency-inconsistency model by Q statistic and the Chi-squared test.[87] Transitivity was evaluated by examining the distribution of

clinical and methodological factors that could influence the outcomes of interest. A comparison-adjusted funnel plot was utilized to evaluate small study effects, serving as an indicator of publication bias.[88]

A p-value <0.05 was considered as a statistically significant. A sensitivity analysis to investigate the robustness of the main findings was performed by excluding trials with small sample sizes, as well as those categorized as having a high risk of bias or unclear risk of bias. Subgroup analyses was also conducted using the following criteria: baseline of HbA1c, BMI, T2D duration, and study duration. All analyses were carried out using R-studio Version 2022.02.0, Build 443 (netmeta package).

The certainty of evidence was assessed using the Confidence in Network Meta-Analysis (CINeMA) online platform[73, 74] which considers the following six domains:1) within-study bias; 2) reporting bias; 3) indirectness; 4) imprecision from MCID (MCID = 0.5% for HbA1c[89, 90] and MCID = 0.75 of relative risk for severe hypoglycemia[91, 92]); 5) heterogeneity; and 6) incoherence. Each domain is rated as having "major concerns", "some concerns", or "no concerns". Four levels of confidence—very low, low, moderate, or high—were assigned to each relative treatment effect, corresponding to the GRADE assessment. These levels were determined by summarizing judgments across domains.[73]

CHAPTER IV

RESEARCH RESULTS

1. Search results

The literature search yielded 8,365 articles after duplicates were removed. Following the screening of titles and abstracts, 8,276 articles were excluded for being irrelevant to self-titration support or not being RCT. The remaining 89 articles underwent a full-text review for eligibility, resulting in 74 papers being excluded for the reasons detailed in Figure 3 and Appendix 3. Additionally, two more articles were identified through citation tracking and snowball searching. In total, the identified 17 trials[93-109] met the inclusion criteria for quantitative synthesis.

2. Study characteristics

Four of the seventeen trials were conducted in the US.[95, 101, 104, 107] Two trials were conducted in Taiwan[96, 106] and one trial was conducted in each of the following countries: Brazil,[109] Canada,[93] China,[102] France,[98] Germany,[100] Japan,[103] Korea,[105] and Singapore.[94] Three trials were conducted in more than two countries.[97, 99, 108] Seven trials compared the effect of insulin self-titration support with self-titration without additional support.[93, 94, 96, 98, 100, 104, 105] Five trials studied the effect of insulin self-titration support versus usual care,[95, 97, 101, 102, 106] whereas the remaining five trials focused on self-titration without additional support and usual care.[99, 103, 107-109]

A total of 13,528 participants (55.9% male) were included in the 17 trials, with mean ages ranging from 48.4 to 62.6 years, BMIs between 23.7 and 34.7 kg/m², and durations of T2D from 7.1 to 16.9 years. Basal insulin was used in nearly all trials, with the exception of two that examined both basal and prandial insulin.[95, 109] OAD used in the majority of included trials were metformin and sulfonylurea. The target HbA1c goal varied across the included trials, ranging from <6.5% to <7.5%. The study duration among included trials was between 3 and 7 months. (Table 4)

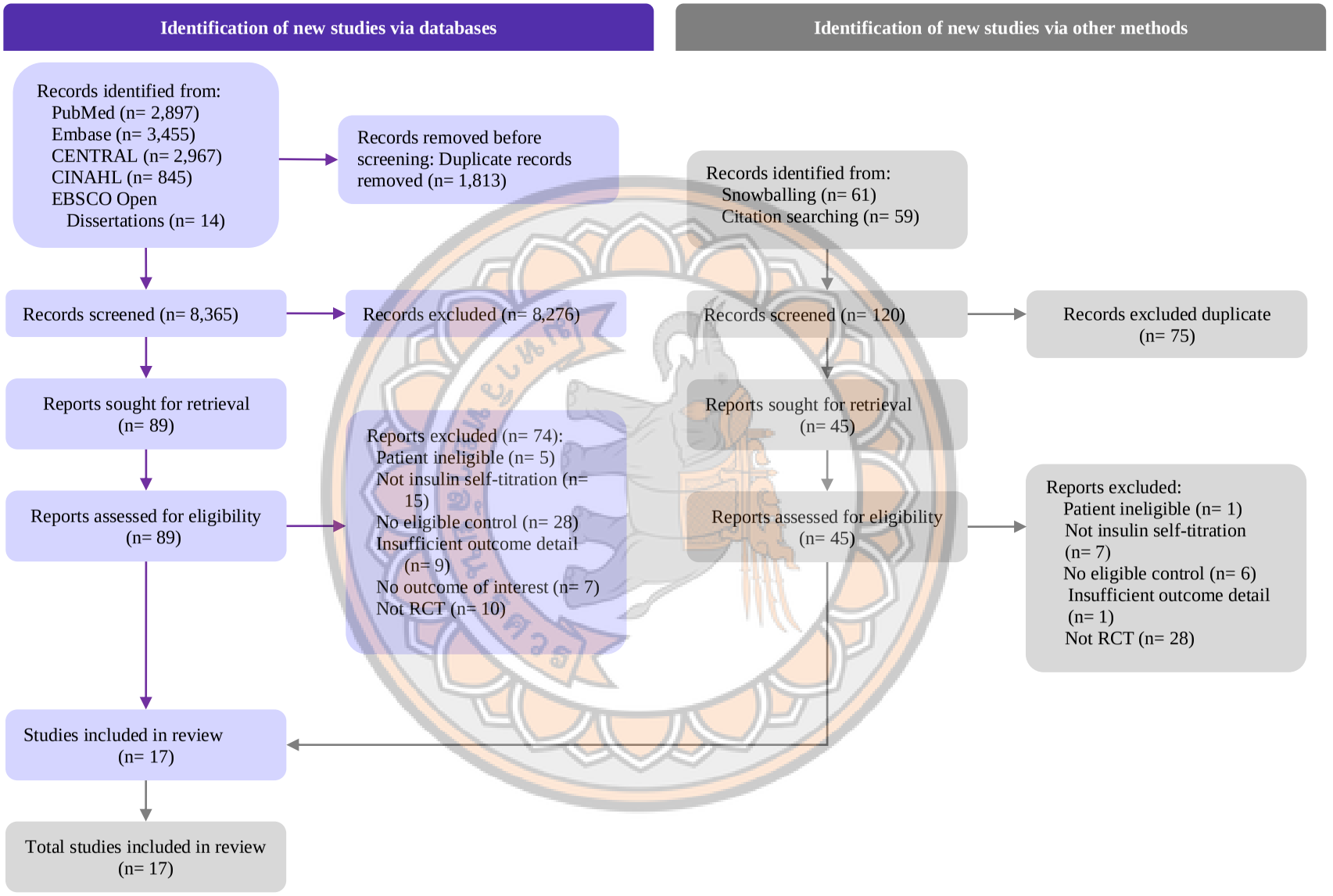


Figure 3: PRISMA diagram

Table 4: Characteristics of included studies

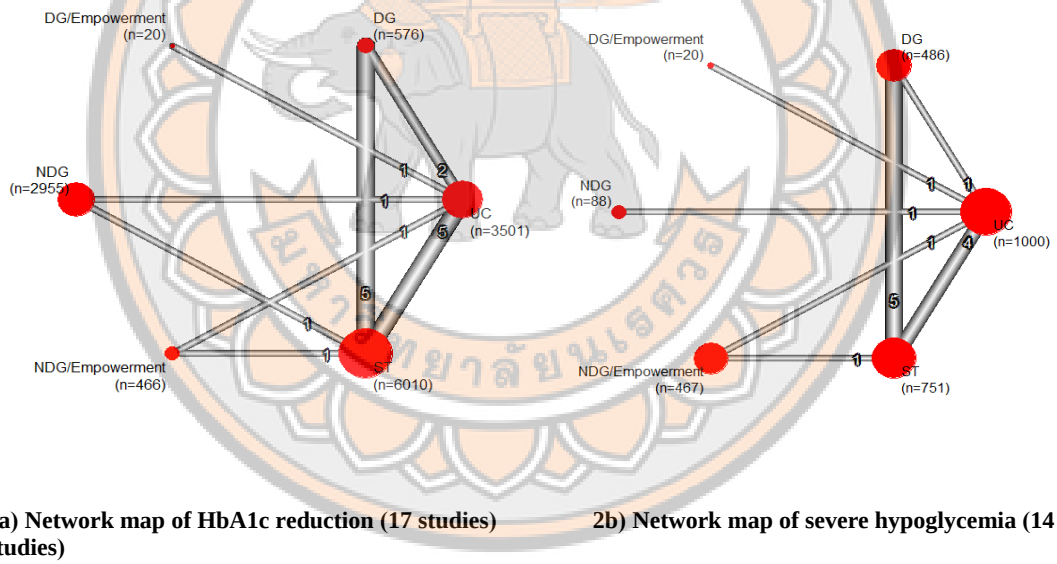
Author	Country	Duration of study, month	Number of participants	Age, year (Mean ±SD)	BMI, kg/m2 (Mean ±SD	Gender (%male)	Duration of diabetes, year (Mean ±SD)	Baseline HbA1c, % (Mean ±SD)	Type of insulin	Goal HbA1c, %	Severe hypoglycemia definition
Bajaj, et al. (2016)[93]	Canada	3	139	56.4 ± 8.2	32.9 ± 5.9	NA	12.0 ± 6.8	8.8 ± 1.2	Glargine	<7.0	NA
Bee, et al. (2016)[94]	Singapore	6	66	53.3 ± 7.4	27.5 ± 4.7	66.7	12 ± 8	9.9 ± 1.8	Detemir	<7.5	NA
Bergenstal, et al. (2019)[95]	USA	6	181	60.3 ± 7.8	34.7 ± 5.0	51.6	15.7 ± 6.7	8.6 ± 0.8	Basal and bolus insulin	<7.0	Requiring help from another person
Chen, et al. (2008)[96]	Taiwan	7	78	58.7 ± 10.6	25.8 ± 4.5	44	12.7 ± 4.4	9.55 ± 1.8	NPH	< 6.5 or <7.0	Requiring help with blood glucose <50 mg/dL or quick recovery after carbohydrate, intravenous glucose, or glucagon.
Davies, et al. (2019)[97]	19 study centers in European countries	4	151	62.1 ± 9.5	33.2 ± 6.9	68.9	NA	NA	Glargine	<7.0	Requiring help from another person and receiving treatment with an intravenous injection of glucose or glucagon
Franc, et al. (2019)[98]	France	4	191	58.7 ± 9.6	29.7 ± 5.1	64.6	13.1 ± 7.6	8.9 ± 1.1	Glargine and detemir	<7.0	Requiring help from another person
Garg, et al. (2015)[99]	6 countries	6	552	57.2 ± 8.6	27.4 ± 4.7	51.6	9.7 ± 6.2	8.7 ± 1.0	Glargine	<7.0	Requiring help with blood glucose <36 mg/dL or quick recovery after carbohydrate, intravenous glucose, or glucagon.
Hermanns,et al. (2023)[100]	Germany	3	251	59.7 ± 10.1	31.5 ± 5.7	63.6	10.3 ± 7.0	8.2 ± 0.9	Basal insulin	<7.0 or <7.5	Requiring help from another person
Hsu, et al. (2016)[101]	USA	3 months ± 2 weeks	40	53.6	30.7	NA	NA	10.8 ± 1.2	Basal insulin	<7.0	NA
Hu, et al. (2021)[102]	China	3	849	54.2 ± 13.9	23.7 ± 2.5	58.8	7.1 ± 5.9	9.3 ± 1.9	Glargine	≤ 6.5 or <7.0	A hypoglycemic event that necessitates help from another person to administer carbohydrates, glucagon, or other emergency resuscitation interventions

Author	Country	Duration of study, month	Number of participants	Age, year (Mean ±SD)	BMI, kg/m2 (Mean ±SD	Gender (%male)	Duration of diabetes, year (Mean ±SD)	Baseline HbA1c, % (Mean ±SD)	Type of insulin	Goal HbA1c, %	Severe hypoglycemia definition
Ishii, et al. (2021)[103]	Japan	6	120	62.6 ± 11.6	NA	70.8	13.5 ± 8.0	NA	Glargine	<7.0	NA
Kennedy, et al. (2006)[104]	USA	6	5,721	57 ± 12	34.3 ± 7.5	51	8.5 ± 6.4	8.6 ± 1.6	Glargine	<7.0	Requiring help with blood glucose <36 mg/dL or quick recovery after carbohydrate, intravenous glucose, or glucagon.
Kim et al. (2010)[105]	Korea	3	92	48.4 ± 10.1	23.9 ± 3.0	49.9	8.5 ± 6.3	9.8 ± 1.2	Glargine	<7.0	Requiring help with blood glucose <50 mg/dL or quick recovery after carbohydrate, intravenous glucose, or glucagon.
Liu, et al. (2022)[106]	Taiwan	6	181	59.6 ± 12.3	26.6 ± 4.5	46.9	10.3 ± 5.5	9.12 ± 1.1	Detemir	<7.0	Requiring help with blood glucose <50 mg/dL or quick recovery after carbohydrate, intravenous glucose, or glucagon.
Meneghini, et al. (2007)[107]	USA	6.5	4,825	58.6 ± 11.9	33.8 ± 6.3	51.6	11.4 ± 8.3	8.5 ± 1.6	Detemir	<7.0	Any circumstance that required third-party assistance for recovery
Misra, et al. (2019)[108]	6 Asian countries including 7 centers in India	6	69	51.9 ± 7.1	27.9 ± 3.6	62.7	8.5 ± 5.3	9.2 ± 1.2	Glargine	<7.0	NA
Silva, et al. (2015)[109]	Brazil	3	22	57.5 ± 11.9	29.4 ± 6.1	32.5	16.9 ± 8.2	9.3 ± 1.3	Basal and prandial insulin	<7.5	A hypoglycemic crisis that necessitates help from another person and intravenous injections of glucagon or glucose

Abbreviations: BMI = body mass index, HbA1c = glycated hemoglobin, NPH = Neutral protamine Hagedorn, NA = Not applicable

3. Intervention characteristics

Five trials compared DG, which utilized tools such as web-based applications, mobile apps, telephones, and devices, with self-titration (ST), detailed in Table 5.[93, 94, 98, 100, 105] Two trials compared DG with usual care (UC).[95, 97] In one trial, NDG was compared to UC,[106] while another trial compared it to ST.[104] In a trial focusing on DG/Empowerment, the empowerment component utilized cloud-based approaches aimed at fostering greater confidence and self-efficacy among participants.[101] One trial on NDG/Empowerment included coaching sessions conducted over the telephone to empower patients,[102] while Another trial used telephone reminders and a structured education package to enhance patient empowerment.[96] Patients in five trials comparing self-titration (ST) to usual care (UC) did not receive any additional support.[99, 103, 107-109] (Figure 4)



2a) Network map of HbA1c reduction (17 studies) **2b) Network map of severe hypoglycemia (14 studies)**

Figure 4: Network map

Abbreviations: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care

The numbers along the connection lines in each network geometry indicate the number of studies for each direct comparison.

4. Quality of included studies

Based on the evaluation of three key risk of bias domains, 15 trials were classified as having an overall low risk of bias. However, one trial each was identified as having a high risk of bias [97] and an unclear risk of bias[103] (Appendix 4).

Table 5: Characteristics of insulin self-titration supports among included studies

Study	Intervention detail	Control detail
Bajaj, et al.(2016)[93]	DG: Delegated non-healthcare professionals gave instructions on how to utilize the web-based LTHome program, administer insulin, and handle dosage.	ST: The INSIGHT protocol recommended that patients increase their insulin dosage by 1 unit per day until their FBS was less than 7.0 mmol/L. Specialist HCP-driven diabetes education program (enhanced usual therapy [EUT], insulin dosing, and titration instructions) were given by certified diabetes educators (CDE) in accordance with a standard protocol.
Bee, et al. (2016)[94]	DG: The app suggested an insulin dosage based on the FBS measurements that patients entered each day.	ST: Patients used written instructions and paper logbooks.
Bergenstal, et al. (2019)[95]	DG: The d-Nav device in conjunction with committed health care professionals' (HCP-S) assistance. Based on glucose readings, the diabetic navigator, or d-Nav®, automatically adjusts the dosage of insulin. Prior to each injection, patients utilized the device to determine their blood glucose level and receive a recommended dosage of insulin.	UC: Only using health care professionals (HCP-S) to manage insulin therapy.
Chen, et al. (2008)[96]	NDG/Empowerment: Patients changed their insulin dosage before bed, and research nurses called them once a week to remind them. In addition, our structured education package gave these subjects health beliefs, self-efficacy, and knowledge. Once these obstacles were removed, our participants were able to use SMBG to modify their insulin and enhance their glycaemic control. As previously mentioned, our phone reminder also gave these participants desire to enhance their glycaemic management, self-efficacy, and health beliefs.	ST: Every three days, patients were urged to self-manage dose adjustments, and the researchers checked up with them at clinical visits spaced four weeks apart. By themselves, the patients were able to adjust their insulin dosage before bed.
Davies, et al. (2019)[97]	DG: MyStar Dose Coach® is a blood glucose meter and titration device that offers automated dosing recommendations to help individuals with type 2 diabetes self-titrate insulin glargine.	UC: The researchers, who were diabetic specialists, advised routine titration (with the device's titration capability disabled) based on prior insulin use (insulin naïve vs. insulin treated).
Franc, et al. (2019)[98]	DG: IVRS, along with brief phone consultations (~5 minutes), and Diabeo-BI, along with brief phone consultations (~5 minutes), plus an in-person visit of approximately 30 minutes at the fourth month.	ST: A face-to-face visit in the fourth month (about 30 minutes) and an optional visit at the first month are standard treatment.

Study	Intervention detail	Control detail
Garg, et al. (2015)[99]	ST: Patients received instructions on how to adjust their own insulin dosage twice a week.	UC: At every appointment, the doctor performed titration, which is standard procedure in Asia.
Hermanns,et al. (2023)[100]	DG: Patients received instructions for utilizing the titration program through the My Dose Coach app on their phone. At least one FBS measurement had to be completed daily by participants, and the results had to be entered into the application. The application used the settings saved in the online platform to determine a basal insulin dose and computed the median of three consecutive FBS levels.	ST: The control group participants were given a printed titration chart to use in order to titrate their basal insulin levels.
Hsu, et al. (2016)[101]	DG/Empowerment: The cloud-based diabetes management program shows the three most recent blood glucose readings, computes and shows the mean in relation to thresholds for decision-making, and indicates the dose change that is advised according to the protocol. The app's integrated communication tools, which highlight data patterns and decision-making events, facilitate prompt learning and therapeutic support. Efficiency is provided via secure text communications, while deeper data analysis and cooperative decision-making are made possible by virtual visits (audio, video, and screen sharing). Virtual visits are typically utilized more often in the beginning by both patients and medical professionals until the patients become more self-efficacy and capable.	UC: As directed by their HCPs, patients in the control group got routine clinic care for starting and titrating insulin, with follow-up in-person visits and phone/fax correspondence with doctors and educators.
Hu, et al. (2021)[102]	NDG/Empowerment: In order to assist self-adjustment, participants attended a baseline in-person session for dosage setting and choice coaching. The same nurse then conducted five coaching calls at weeks 1, 2, 4, 8, and 12. The diabetes specialist nurses in the intervention group conducted telephone follow-ups at designated weeks, offering continuous encouragement, guidance, and support to enhance treatment effectiveness and empower patients in making treatment-related decisions.	UC: In this group, patients only changed their insulin dosages when prescribed by their physicians. They received five coaching calls from the same nurse at weeks 1, 2, 4, 8, and 12 of the 12-week follow-up. However, the nurses did not offer any advice on insulin dose titration; instead, they only gathered information on insulin dosages and side effects.
Ishii, et al. (2021)[103]	ST: Insulin self-titration by patients	UC: Insulin titration by physicians
Kennedy, et al. (2006)[104]	NDG: In addition to training at study visits every six weeks, active titration was defined as weekly patient contact (by phone, email, or fax) to assess overall health, check glucose levels, and reinforce the insulin titration and follow-up appointment schedule.	ST: "Usual titration" was defined as patient education during research visits, which occur every six weeks, but without any uninvited patient interaction in between sessions.

Study	Intervention detail	Control detail
Kim et al. (2010)[105]	DG: A specific gadget (model AMM-2200, All Medicus Co., Ltd., Anyang, Republic of Korea) with glucometer capabilities was employed. It immediately sent glucose levels to the patient's personal data sheet on the internet when the patient's mobile device was connected. The patient received automatic notifications from the system every day at 5 p.m.	ST: Using glucometers, patients self-monitored their FBS every day and titrated their basal insulin accordingly.
Liu, et al. (2022)[106]	NDG: Patients in the active titration algorithm group were instructed to call the investigator weekly for guidance on self-adjusting their insulin dose until the fasting blood sugar target was reached.	UC: The investigator's interactions with patients in the conventional titration algorithm group were limited to regular visits at weeks 4, 12, and 24.
Meneghini, et al. (2007)[107]	ST: Patients were guided to adjust their insulin dosage every three days according to the average of three self-monitored fasting capillary blood glucose readings.	UC: The investigator adjusted the standard-of-care group sites based on standard practice guidelines.
Misra, et al. (2019)[108]	ST: Patients self-adjusted their basal insulin dose every 3 days using the middle value of the previous three consecutive FBS readings.	UC: During each appointment, the physician adjusted the basal insulin dose.
Silva, et al. (2015)[109]	ST: Patients were advised to independently adjust their basal and prandial insulin doses and make bolus corrections using regular or ultra-rapid-acting insulins, based on the knowledge gained from learning workshops.	UC: Treatment was modified solely by the assistant physician during regular medical appointments.

Abbreviations: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care

5. Impact on HbA1c (glycemic control)

Seventeen trials involving 13,528 patients were included in NMA to evaluate HbA1c reduction across different insulin self-titration support strategies. All interventions led to significant reductions in HbA1c compared to usual care (Table 6). The highest effect estimates were seen in patients receiving DG/Empowerment, with a MD of -1.20 (95% CI: -2.33, -0.07), followed by NDG/Empowerment (MD: -0.97; 95% CI: -1.24, -0.69), both supported by moderate-certainty evidence (Appendix 6.1). Indirect comparisons showed no significant difference between DG/Empowerment and NDG/Empowerment (MD: -0.23; 95% CI: -1.40, 0.93), though the certainty of this evidence was very low.

When compared to usual care, the interventions without empowerment component showed approximately half the effect of their counterparts, with MDs [95% CI] of -0.42 [-0.60, -0.24] for DG and -0.31 [-0.58, -0.03] for NDG, rated as very low and moderate certainty, respectively. Insulin self-titration without additional support showed only a minimal reduction in HbA1c compared to usual care (MD: -0.16; 95% CI: -0.31, -0.02), with low-certainty evidence.

These findings were further supported by SUCRA results (Appendix 5.1), indicating that DG/Empowerment (88%) and NDG/Empowerment (87%) had the highest probabilities of being the most effective interventions, followed by DG (59%) and NDG (42%).

6. Effects on severe hypoglycemia

The definitions of severe hypoglycemia varied significantly among the included studies. Several studies defined severe hypoglycemia simply as requiring assistance from another person.[95, 98, 100, 102, 107] Others biochemical thresholds (e.g., blood sugar <36[99, 104] or <50 mg/dL[96, 105, 106]) or specified recovery after treatment with oral carbohydrates, intravenous glucose, or glucagon. Two studies emphasized the requirement for intravenous glucose or glucagon injections from another person with no blood sugar cut point in their definitions.[97, 109] Some studies did not provide explicit definitions.[93, 94, 101, 103, 108]

A comparison of 14 trials (involving 2,801 patients) that reported severe hypoglycemic events found no significant difference in the risk of severe hypoglycemia across all interventions (Table 6). However, the certainty of this evidence was rated as very low for all comparisons, primarily due to significant concerns regarding imprecision (Appendix 6.2). Consequently, the SUCRA rankings showed less variation among the different interventions (Appendix 5.2). It is also noteworthy that the incidence of severe hypoglycemia was low across all trials, ranging from 0% to 0.7%.

Table 6: League table of the effects on HbA1c reduction (lower triangle) and severe hypoglycemia (upper triangle)

DG/Empowerment	0.96 [0.01; 117.26] ⊕◯◯◯	0.70 [0.01; 50.30] ⊕◯◯◯	2.11 [0.01; 361.11] ⊕◯◯◯	0.98 [0.01; 58.83] ⊕◯◯◯	1.00 [0.02; 48.03] ⊕◯◯◯
-0.23 [-1.40; 0.93] ⊕◯◯◯	**NDG/Empowerment**	0.73 [0.03; 16.91] ⊕◯◯◯	2.19 [0.03; 182.04] ⊕◯◯◯	1.02 [0.06; 17.46] ⊕◯◯◯	1.03 [0.62; 17.82] ⊕◯◯◯
-0.78 [-1.92; 0.37] ⊕⊕◯◯	-0.55 [-0.86; -0.23]* ⊕⊕◯◯	**DG**	3.00 [0.06; 139.13] ⊕◯◯◯	1.39 [0.32; 6.02] ⊕◯◯◯	1.42 [0.23; 8.66] ⊕◯◯◯
-0.89 [-2.06; 0.27] ⊕⊕◯◯	-0.66 [-1.04; -0.28]* ⊕⊕⊕◯	-0.12 [-0.42; 0.18] ⊕⊕⊕◯	**NDG**	0.46 [0.01; 17.58] ⊕◯◯◯	0.47 [0.01; 13.93] ⊕◯◯◯
-1.04 [-2.18; 0.10] ⊕⊕◯◯	-0.80 [-1.10; -0.51]* ⊕⊕◯◯	-0.26 [-0.42; -0.09]* ⊕⊕⊕◯	-0.14 [-0.40; 0.11] ⊕⊕⊕◯	**ST**	1.02 [0.27; 3.84] ⊕◯◯◯
-1.20 [-2.33; -0.07]* ⊕⊕⊕◯	-0.97 [-1.24; -0.69]* ⊕⊕⊕◯	-0.42 [-0.60; -0.24]* ⊕◯◯◯	-0.31 [-0.58; -0.03]* ⊕⊕⊕◯	-0.16 [-0.31; -0.02]* ⊕⊕◯◯	**UC**

*Statistically Significant

Certainty of evidence: ⊕◯◯◯=Very low; ⊕⊕◯◯=Low; ⊕⊕⊕◯=Moderate; ⊕⊕⊕⊕=High

Abbreviations: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care

7. Assessment of heterogeneity, inconsistency, transitivity, and publication bias

The majority of direct evidence on HbA1c reduction showed low to moderate heterogeneity, while all comparisons of severe hypoglycemia had low heterogeneity (Appendix 5). No inconsistency was detected between direct and indirect evidence across all outcomes (p = 0.78 for HbA1c reduction, and p = 0.98 for severe hypoglycemia). The patient characteristics and baseline HbA1c levels in the included trials were generally similar to those of the broader population.[9, 110] No evidence of intransitivity was found, as the distributions of potential effect modifiers—such as insulin types, diabetes duration, study duration, and the proportion of insulin-naïve patients—were consistent across all comparisons (Appendix 8). Additionally, the funnel plots for HbA1c reduction and severe hypoglycemia appeared symmetrical (Appendix 9.1 and 9.2), indicating a low risk of publication bias for both outcomes.

8. Subgroup and sensitivity analyses

A criteria for a BMI subgroup analysis was based on the previous meta-analysis that showed a significantly increased risk of inadequate glycemic control in obese patients (BMI ≥30 kg/m^2).[111] Patients with a history of more than 10 years of diabetes had poor glycemic control so this timeframe was used as a cut-off point for a subgroup analysis based on T2D duration (<10 and ≥10 years).[112] The study duration of 6 months was used as a cut-off point for a subgroup analysis based on study duration since a previous study indicated that patients achieved considerable reductions in HbA1c levels 6 months after intensifying their treatment.[113] Baseline HbA1c level of 9.0% was chosen as the cut-off of a subgroup analysis based on different levels of glycemic control.[114]

Findings from a subgroup of studies on patients with average BMI <30 kg/m² appeared similar to findings from studies on patients with BMI ≥30 kg/m². A consistent trend of no distinct differences between groups was observed in subgroup analyses based on T2D duration and study duration. None of the included trials incorporating patients focused on patients with HbA1c less than or equal to 9.0%. Hence, comparisons between groups with different baseline glycemic control levels could not be made. However, findings from non-empowerments interventions indicated similar results between subgroups of different baseline HbA1c levels. In summary, none of the factors tested in subgroup analyses acted as effect modifiers in this NMA. (Table 7)

In the first sensitivity analysis, studies with small sample size were excluded based on a cut-off of the lowest 25% quartiles of all studies,[115] resulting in the exclusion of four studies.[94, 101, 108, 109] After removing these studies, the outcomes showed a similar trend to the main analysis, indicating the robustness of the results (details are presented in table 8 and Appendix 7.1). Furthermore, two studies[97, 103] were excluded from the analysis due to their high risk of bias and unclear risk of bias respectively. After excluding these studies, the mean HbA1c reduction for 15 studies remained same as the full analysis of 17 studies and the mean difference of league table also remained similarly (details are presented in table 9 and Appendix 7.2).

Table 7: Subgroup analysis and treatment pairs

Subgroup (MD, 95%CI)	BMI (kg/m^2)		T2D duration (year)		Study duration (month)		Baseline HbA1c (%)	
	<30	≥30	<10	≥10	<6	≥6	≤9	>9
DG/Empowerment VS NDG/Empowerment	NA	NA	NA	NA	-0.22 [-1.50; 1.06]	NA	NA	-0.21 [-1.32; 0.90]
DG/Empowerment VS DG	NA	-0.87 [-2.11; 0.37]	NA	NA	-0.83 [-2.06; 0.40]	NA	NA	-0.54 [-1.70; 0.62]
DG/Empowerment VS NDG	NA	-0.85 [-2.19; 0.50]	NA	NA	-1.00 [-2.35; 0.35]	NA	NA	-1.07 [-2.25; 0.11]
DG/Empowerment VS ST	NA	-1.05 [-2.30; 0.21]	NA	NA	-1.04 [-2.26; 0.19]	NA	NA	-0.90 [-2.03; 0.23]
DG/Empowerment VS UC	NA	-1.20 [-2.40; 0.00]	NA	NA	-1.20 [-2.39; -0.01]	NA	NA	-1.20 [-2.30; -0.10]
NDG/Empowerment VS DG	-0.34 [-0.64; -0.04]	NA	-0.42 [-0.85; 0.00]	-0.47 [-1.07; 0.14]	-0.61 [-1.20; -0.03]	-0.28 [-0.79; 0.24]	NA	-0.34 [-0.73; 0.06]
NDG/Empowerment VS NDG	-0.85 [-1.31; -0.39]	NA	-0.62 [-0.90; -0.35]	-0.93 [-1.75; -0.10]	-0.78 [-1.58; 0.02]	-0.59 [-1.05; -0.12]	NA	-0.86 [-1.32; -0.40]
NDG/Empowerment VS ST	-0.77 [-0.98; -0.56]	NA	-0.82 [-1.08; -0.56]	-0.77 [-1.33; -0.21]	-0.82 [-1.38; -0.25]	-0.77 [-1.22; -0.32]	NA	-0.69 [-0.97; -0.41]
NDG/Empowerment VS UC	-0.98 [-1.14; -0.82]	NA	-0.98 [-1.15; -0.81]	-1.06 [-1.66; -0.45]	-0.98 [-1.46; -0.50]	-0.89 [-1.35; -0.44]	NA	-0.99 [-1.15; -0.83]
DG VS NDG	-0.51 [-1.02; 0.00]	0.02 [-0.57; 0.62]	-0.20 [-0.55; 0.15]	-0.46 [-1.08; 0.16]	-0.17 [-0.89; 0.55]	-0.31 [-0.59; -0.03]	-0.06 [-0.50; 0.38]	-0.53 [-1.10; 0.05]
DG VS ST	-0.43 [-0.64; -0.22]	-0.18 [-0.51; 0.16]	-0.40 [-0.74; -0.06]	-0.30 [-0.52; -0.08]	-0.20 [-0.46; 0.05]	-0.49 [-0.74; -0.24]	-0.26 [-0.49; -0.03]	-0.35 [-0.63; -0.08]
DG VS UC	-0.64 [-0.91; -0.37]	-0.33 [-0.66; 0.00]	-0.56 [-0.95; -0.16]	-0.59 [-0.86; -0.31]	-0.37 [-0.70; -0.04]	-0.62 [-0.86; -0.37]	-0.37 [-0.61; -0.13]	-0.66 [-1.04; -0.28]
NDG VS ST	0.08 [-0.38; 0.54	-0.20 [-0.70; 0.30]	-0.20 [-0.30; -0.10]	0.16 [-0.44; 0.76]	-0.04 [-0.74; 0.67]	-0.18 [-0.31; -0.06]	-0.20 [-0.57; 0.17]	0.17 [-0.33; 0.68]
NDG VS UC	-0.13 [-0.56; 0.30	-0.35 [-0.97; 0.26]	-0.36 [-0.58; -0.13]	-0.13 [-0.69; 0.43]	-0.20 [-0.84; 0.44]	-0.31 [-0.45; -0.16]	-0.31 [-0.75; 0.13]	-0.13 [-0.56; 0.30]
ST VS UC	-0.21 [-0.37; -0.04]	-0.15 [-0.52; 0.21]	-0.16 [-0.35; 0.04]	-0.29 [-0.51; -0.06]	-0.16 [-0.46; 0.13]	-0.12 [-0.20; -0.05]	-0.11 [-0.34; 0.12]	-0.30 [-0.57; -0.04]

NA = not applicable

In the subgroup analysis, the pooled HbA1c reduction of self-titration supports was from BMI <30 and ≥30 kg/m^{2}since the previous meta-analysis showed a significantly increased risk of inadequate glycemic control in obese patients (BMI ≥30 kg/m2).[1] Patients with more than 10 years of diabetes had poor glycemic control so subgroup of T2D duration <10 and ≥10 years was conducted.[2] From these data, study duration was divided to two groups and the study indicated that patients achieved considerable reductions in HbA1c levels 6 months after intensifying their treatment.[3] Baseline HbA1c was analyze as a baseline HbA1c level of 9.0% was chosen as the cut-off for poor glycemic control.[4]

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Table 8: League table of sensitivity analyses from excluding trials with the small sample size

8.1 HbA1c reduction (13 studies)
League table

NDG/Empowerment				
-0.55 [-0.89; -0.21]*	DG			
-0.68 [-1.08; -0.27]*	-0.12 [-0.44; 0.20]	NDG		
-0.82 [-1.13; -0.51]*	-0.27 [-0.45; -0.09]*	-0.15 [-0.42; 0.13]	ST	
-0.96 [-1.25; -0.67]*	-0.41 [-0.60; -0.21]*	-0.28 [-0.58; 0.01]	-0.14 [-0.30; 0.03]	UC

*statistically significant

8.2 Severe hypoglycemia (11 studies)
League table

NDG/Empowerment				
1.45 [0.06; 35.41]	DG			
0.45 [0.01; 37.70]	0.31 [0.01; 15.14]	NDG		
0.99 [0.06; 17.11]	0.68 [0.14; 3.30]	2.19 [0.06; 85.84]	ST	
0.95 [0.06; 16.54]	0.66 [0.10; 4.45]	2.11 [0.07; 62.20]	0.96 [0.23; 3.99]	UC

Table 9: League table of sensitivity analyses from excluding trials with high and unclear risk of bias

9.1 HbA1c reduction (15 studies)
League table

DG/Empowerment					
-0.23 [-1.36; 0.90]	NDG/Empowerment				
-0.69 [-1.81; 0.43]	-0.46 [-0.72; -0.19]*	DG			
-0.87 [-2.00; 0.26]	-0.64 [-0.93; -0.36]*	-0.18 [-0.42; 0.05]	NDG		
-1.04 [-2.15; 0.08]	-0.81 [-1.04; -0.58]*	-0.35 [-0.50; -0.20]*	-0.16 [-0.34; 0.01]	ST	
-1.20 [-2.31; -0.09]*	-0.97 [-1.18; -0.76]*	-0.51 [-0.69; -0.34]*	-0.33 [-0.53; -0.12]*	-0.16 [-0.28; -0.05]*	UC

*statistically significant

9.2 Severe hypoglycemia (12 studies)
League table

DG/Empowerment					
1.01 [0.01; 124.79]	NDG/Empowerment				
1.25 [0.01; 107.62]	1.24 [0.05; 32.81]	DG			
0.47 [0.00; 80.88]	0.47 [0.01; 39.52]	0.38 [0.01; 21.49]	NDG		
0.96 [0.01; 61.69]	0.95 [0.05; 16.71]	0.77 [0.16; 3.78]	2.03 [0.05; 83.03]	ST	
1.00 [0.02; 48.03]	0.99 [0.06; 17.43]	0.80 [0.09; 7.27]	2.11 [0.07; 62.20]	1.04 [0.23; 4.79]	UC

CHAPTER V

DISCUSSION

Discussion

The findings of this study demonstrated that integrating patient empowerment into the support program, either with DG or NDG, is more effective in reducing HbA1c than supporting strategies without patient empowerment. Although the optimal strategy still remains unclear, these approaches should be considered in clinical practice.

The effect of DG on HbA1c reduction was consistent with the previous meta-analysis on device-supported automated basal titration, which showed a slight improvement in reducing HbA1c levels by -0.25% [0.43, -0.06%].[17] However, the effects of patient empowerment on HbA1c reduction in this study were found to differ from those reported in a prior meta-analysis by Aquino et al., which showed that patient empowerment did not lead to a reduction in HbA1c levels.[116] A plausible explanation for the differences between this study and Aquino et al. is that patient empowerment in this study was an add-on component to either DG or NDG, which may have resulted in synergistic effects. Additionally, this study focused on patients with insulin self-titration, which, when performed appropriately, can have a substantial impact on glycemic control.[17]

Empowerment serves as one of the main components of the support strategy. Findings in my study highlight the significant impact of incorporating empowerment into the strategy to support insulin self-titration. This aligns well with findings from previous self- care studies on chronic medical conditions, which consistently showed that patient empowerment was associated with improved health outcomes.[117] Through empowerment related to self-efficacy,[118] patients gain both knowledge and confidence to accept and adhere to insulin therapy and to make effective self-management decisions based on their own priorities and goals for chronic disease, including T2D.[26, 119, 120]

In addition to empowerment, dosage guidance of insulin self-titration support from apps, devices, tools, or websites has been shown to enhance patients' confidence in adjusting their insulin dosage and has made them feel more comfortable with self-

managing their treatment.[41] Moreover, DG as apps can be synchronized to enable clinicians to remotely monitor individuals with diabetes.[121] However, a previous study found that the effect of DG by smartphone application on HbA1c reduction was not significantly different from self-titration by conventional paper-and-pencil calculations.[94] Additionally, it is important to note that not all individuals with T2D have access to smartphone devices in a real-world clinical setting. According to the current evidence that did not show the effects of different DG platforms, the choice of DG supportive method can be decided based on patient's preference and affordability.

A previous study by Luo et. al., suggested that the risk of severe hypoglycemia was not significantly different between device-supported automated basal insulin titration and conventional care.[17] This coincides with findings from this study, which also showed that none of the insulin support strategies were associated with an increased risk of severe hypoglycemia. This indicates that supporting insulin self-titration appears to be a safe approach. However, for some comparisons, such as DG versus NDG, the result was 3.00 [0.06, 139.13]. Although this was not statistically significant, the confidence interval was extremely wide, indicating considerable uncertainty. Therefore, incorporating data from future studies is essential to strengthen the evidence base and enable a more reliable and precise analysis.

Due to the limited number of included studies, most pairwise comparisons involved only a single study, making it impractical to classify interventions using the detailed criteria outlined in the TIP framework.[122] Instead, treatment classification was based on emerging themes identified during data extraction, particularly focusing on DG and patient empowerment These categories were selected because they consistently appeared across studies and were seen as key components influencing glycemic outcomes.. However, in several cases, intervention details were not clearly reported, requiring subjective interpretation to determine whether DG or empowerment components were present. This reliance on subjective judgment may affect the validity of the classification approach, highlighting the need for cautious interpretation of the study findings.

The treatment classification based on the multicomponent concept offers distinct advantages over the traditional lumping classification by enabling a detailed examination key component interventions. Unlike the traditional lumping classification approach, which classified interventions as single entities, this model assesses the effects of individual components, leading to more precise estimates of treatment efficacy. This component-based approach allows for the exploration of interventions that share certain elements while differing in others, thus providing valuable insights for designing future interventions and reducing between-study heterogeneity.[68]

However, the presence of only a single study in certain comparisons may affect the results. For example, the comparison between DG-Empowerment and DG was not statistically significant (-0.78% [-1.92, 0.37]), whereas NDG-Empowerment compared with DG was statistically significant (-0.55% [-0.86, -0.23]).Subgroup analyses were conducted based on baseline HbA1c levels, BMI, T2D duration, and study duration. None of these criteria were identified as significant effect modifiers, as the findings across groups were similar. Baseline HbA1c appeared to influence the degree of reduction, with interventions targeting DG and empowerment consistently showing the greatest effectiveness in reducing HbA1c levels. However, these groups were not statistically different as the effect modifier. In this study, sensitivity analyses were crucial in confirming the robustness of the findings by excluding trials with small sample sizes, as well as those with a high or unclear risk of bias.

R program offers significant advantages for conducting NMAs, particularly due to its open-source, free accessibility, and a strong support community of sharing resources and insights. It provides powerful and flexible tools for advanced analyses and multiple treatment comparisons. R's customizable graphical capabilities allow for tailored visualizations, such as forest plots and funnel plots, which enhance the presentation of results. With over 20 meta-analytic packages available on CRAN, R supports a wide range of functions, from assessing publication bias. In R, the netmeta package supports frequentist NMA, while gemtc and BUGSnet are popular for Bayesian analyses. The choice between these approaches depends on the context, with Bayesian methods being beneficial when prior information is available and frequentist methods offering simplicity when no priors are needed. Frequentist methods are appropriate for scenarios where computational simplicity and established methodologies are

preferred.[124, 125] In this study, the frequentist approach was used for analysis. This method relies solely on observed data, avoiding the need for prior information, which simplifies the analysis. This flexibility makes R an ideal choice for more complex NMAs.[126, 127]

The certainty of evidence varies across different strategies, with empowerment-based approaches generally associated with higher confidence due to more consistent and robust results. The wide range in certainty reflects several challenges. Some comparisons provided very low or low certainty of evidence, primarily due to significant concerns regarding heterogeneity and imprecision, as well as reporting bias indicated across comparisons. These biases impacted the confidence in the overall findings. Additionally, assessing the impact on severe hypoglycemia remains difficult due to the low incidence of these events and the lack of data, resulting in very low certainty in comparative risk assessments.[73]

More head-to-head studies are needed to compare self-titration with self-titration support interventions. These studies are crucial to understanding the impact of providing support versus no support during insulin self-titration. Additionally, previous research has compared different methods of grouping self-support to determine the most effective way to implement it. If future analyses include sufficient studies to address this question, they could provide practical guidance for improving insulin self-titration practice. Including a greater number of studies for each comparison of insulin self-titration support will allow for the separation of individual components to better understand what was done and how it was implemented. For example, by examining the components of DG in detail, it would be possible to determine the appropriate frequency for insulin dose adjustments when applying it in practice.

Implications in practice

All support strategies demonstrated greater effectiveness in reducing HbA1c compared to insulin self-titration alone and usual care. Therefore, patients with T2D performing insulin self-titration, particularly basal insulin, should receive additional support, with emphasis on DG/Empowerment and NDG/Empowerment. These two interventions resulted in a clinically meaningful reduction in HbA1c, exceeding MCID of 0.5%, without a significant increase in the risk of severe hypoglycemia.

There may also be additional components involved, such as telemedicine, which is defined as the delivery of healthcare services via remote communication and technology. The inclusion of telemedicine in some interventions may affect the generalizability of the findings, as access to technology, digital literacy, and healthcare infrastructure can vary widely across different populations and settings. As a result, outcomes observed in trials incorporating telemedicine might not be directly applicable to settings where such resources are limited or where patient preferences and healthcare delivery models differ.[123]

Furthermore, DG and NDG demonstrate variations in components such as the frequency of insulin titration and types of healthcare providers. Additionally, the diversity of empowerment strategies could not be consistently classified, representing a limitation in the generalizability and applicability of the findings. Based on these findings, incorporating patient empowerment was recommend into all support strategies, while DG or NDG can be tailored to suit individual patients' needs and abilities.

Strengths and limitations

The strength of my study lies in the use of NMA approach, which incorporates both direct and indirect evidence to provide more accurate effect estimates. This method helped address the knowledge gap regarding the inconclusive effects of interventions supporting insulin self-titration and identify the most effective intervention component. Although multicomponent model was used in the categorized insulin self-titration strategies, the specific implementation of each component (such as dose guidance and empowerment) and the titration algorithms differed across trials within the same group, potentially influencing the results.

Further research is needed to explore the impact of these variations on treatment outcomes. Another limitation is the inconsistent definition of severe hypoglycemia across trials, as varying blood glucose thresholds may have influenced the number of reported cases. However, these differences are unlikely to have significant clinical implications, since the severity of hypoglycemia is more influenced by the presence of symptoms and the need for assistance than by the exact glucose value.[128] Additionally, the short follow-up periods of 3 to 6 months limits the ability to draw conclusions about the long-term impact on glycemic control and hypoglycemia risk .

Conclusion

Current evidence indicates that supportive strategies for insulin self-titration lead to improved glycemic control in T2D patients without increasing the risk of severe hypoglycemia. Patient empowerment is a key factor in boosting the effectiveness of these strategies in reducing HbA1c compared to other approaches. Additionally, DG or NDG (such as reminders and consultations) can be customized to align with each patient's specific needs and skills. Further studies are needed to identify the factors that influence the successful implementation of additional supportive measures for patients with T2D who practice insulin self-titration.

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APPENDICES

Appendix 1: Amendments to initial protocol registered on PROSPERO (CRD42023458307)

Original protocol	Amendment	Rationale
The comparator(s)/control was indicated as usual care.	The comparator(s)/control is indicated as usual care and self-titration.	This study focused on the effect of strategies that support insulin self-titration. However, the included RCT compared support strategies against usual care (physician titration) and self-titration was found without additional support. Since these two interventions differ, it was deemed more appropriate to distinguish between them in this study.
Types of study to be included were randomized controlled trial (RCT) , cohort study, and quasi-experimental study (with a control group).	Types of study to be included are RCT.	The initial search included various study designs, such as cohort studies and quasi-experimental studies (with a control group), in addition to randomized controlled trials (RCTs). However, it was later decided to focus exclusively on RCTs to ensure the highest level of evidence for the network meta-analysis (NMA), thereby strengthening the validity of the findings regarding the comparative effects of different support strategies.

Appendix 2: Search strategies (from the establishment of the database to Jan 2023)

2.1 PubMed

Search number	Query	Results
1	"diabetes type 2"[Title/Abstract]	1,735
2	"type 2 diabetes"[Title/Abstract]	160,172
3	"diabetes mellitus, type 2"[MeSH Terms]	165,144
4	insulin[Title/Abstract]	399,874
5	insulin[MeSH Terms]	197,024
6	titrat*[Title/Abstract]	69,324
7	adjust*[Title/Abstract]	774,017
8	"self management"[Title/Abstract]	25,521
9	"self management"[MeSH Terms]	5,025
10	"self regulation"[Title/Abstract]	10,656
11	"self control"[MeSH Terms]	5,316
12	a1c[Title/Abstract]	20,209
13	HbA1c[Title/Abstract]	48,398
14	"Glycated Hemoglobin"[MeSH Terms]	41,791
15	OR/1-3	221,038
16	OR/4-5	435,244
17	OR/6-11	878,664
18	OR/12-14	75,642
19	15 AND 16	79,544
20	17 AND 18 AND 19	2,897

2.2 Embase

Search number	Query	Results
1	'diabetes type 2':ab,ti	2,741
2	'type 2 diabetes':ab,ti	236,141
3	'non insulin dependent diabetes mellitus'/exp	319,285
4	'insulin':ab,ti	538,963
5	'insulin'/exp	387,093
6	'titrat*':ab,ti	93,011
7	'adjust*':ab,ti	1,107,770
8	'self management':ab,ti	34,294
9	'self management'/exp	98,975
10	'self regulation':ab,ti	11,363
11	'self regulation'/exp	19,748
12	'a1c':ab,ti	29,022
13	'hba1c':ab,ti	77,080
14	'glycosylated hemoglobin'/exp	162,221
15	#1 OR #2 OR #3	360,562
16	#4 OR #5	641,480
17	#6 OR #7 OR #8 OR #9 OR #10 OR #11	1,322,675
18	#12 OR #13 OR #14	164,426
19	#15 AND #16	137,670
20	#17 AND #18 AND #19	7,207
21	#20 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	3,455

2.3 CENTRAL

Search number	Query	Results
1	(“diabetes type 2”):ti,ab,kw	679
2	(“type 2 diabetes”):ti,ab,kw	41,137
3	MeSH descriptor: [Diabetes Mellitus, type 2] explode all trees	20,469
4	(“insulin”):ti,ab,kw	69,411
5	MeSH descriptor: [insulins] explode all trees	15,470
6	(titrat*):ti,ab,kw	17,450
7	(adjust*):ti,ab,kw	93,154
8	(“self management”):ti,ab,kw	10,065
9	MeSH descriptor: [Self-Management] explode all trees	741
10	(“self regulation”):ti,ab,kw	2,362
11	MeSH descriptor: [Self-Control] explode all trees	409
12	(A1c):ti,ab,kw	26,759
13	(HbA1c):ti,ab,kw	21,749
14	MeSH descriptor: [Glycated hemoglobin A] explode all trees	6,469
15	OR/1-3	45,661
16	OR/4-5	69,479
17	OR/6-11	119,828
18	OR/12-14	29,332
19	15 AND 16	27,706
20	17 AND 18 AND 19	2,967

2.4 CINAHL

Search number	Query	Results
1	TI “diabetes type 2” OR AB “diabetes type 2”	393
2	TI “type 2 diabetes” OR AB “type 2 diabetes”	58,887
3	(MH "Diabetes Mellitus, Type 2")	70,596
4	TI insulin OR AB insulin	69,620
5	(MH "insulin+")	36,147
6	TI titrat* OR AB titrat*	7,635
7	TI adjust* OR AB adjust*	256,523
8	TI “self management”OR AB “self management”	17,342
9	(MH "Self-Management")	2,576
10	TI “self regulation” OR AB “self regulation”	4,833
11	(MH "Self Regulation+")	8,393
12	TI a1c OR AB a1c	8,161
13	TI HbA1c OR AB HbA1c	15,063
14	(MH "Hemoglobin A, Glycosylated")	3,838
15	OR/1-3	87,988
16	OR/4-5	79,255
17	OR/6-11	291,112
18	OR/12-14	20,708
19	15 AND 16	22,157
20	17 AND 18 AND 19	845

2.5 EBSCO Open Dissertation

Search number	Query	Results
1	TI “diabetes type 2” OR AB “diabetes type 2”	41
2	TI “type 2 diabetes” OR AB “type 2 diabetes”	2,978
3	(MH "Diabetes Mellitus, Type 2")	-
4	TI insulin OR AB insulin	6,606
5	(MH "insulin+")	-
6	TI titrat* OR AB titrat*	2,156
7	TI adjust* OR AB adjust*	29,524
8	TI “self management” OR AB “self management”	1,334
9	(MH "Self-Management")	-
10	TI “self regulation” OR AB “self regulation”	1,728
11	(MH "Self Regulation+")	-
12	TI a1c OR AB a1c	237
13	TI HbA1c OR AB HbA1c	508
14	(MH "Hemoglobin A, Glycosylated")	-
15	OR/1-3	3,000
16	OR/4-5	6,606
17	OR/6-11	34,507
18	OR/12-14	680
19	15 AND 16	1,082
20	17 AND 18 AND 19	14

Appendix 3: List of excluded articles and reasons for exclusion

No.	Reference
1. No eligible control (28 studies)	
1.	Bonadonna RC, Giaccari A, Buzzetti R, Perseghin G, Cucinotta D, Avogaro A, et al. Comparable efficacy with similarly low risk of hypoglycaemia in patient- vs physician-managed basal insulin initiation and titration in insulin-naïve type 2 diabetic subjects: the Italian titration approach study. Diabetes Metab Res Rev. 2020;36:e3304.
2.	Chraibi A, Al-Herz S, Nguyen BD, Soeatmadji DW, Shinde A, Lakshmivenkataraman B, et al. An RCT investigating patient-driven versus physician-driven titration of BIAsp 30 in patients with type 2 diabetes uncontrolled using NPH insulin. Diabetes Ther. 2017;8:767-80.
3.	Cook CB, Mann LJ, King EC, New KM, Vaughn PS, Dames FD, Dunbar VG, Caudle JM, Tsui C, George CD, McMichael JP. Management of insulin therapy in urban diabetes patients is facilitated by use of an intelligent dosing system. Diabetes Technol Ther. 2004 Jun;6:326-35.
4.	Dailey G, Aurand L, Stewart J, Ameer B, Zhou R. Comparison of three algorithms for initiation and titration of insulin glargine in insulin-naive patients with type 2 diabetes mellitus. J Diabetes. 2014 Mar;6:176-83.
5.	Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. Diabetes Care. 2005;28:1282-8.
6.	Del Prato S, Nicolucci A, Lovagnini-Scher AC, Turco S, Leotta S, Vespasiani G, et al. Telecare provides comparable efficacy to conventional self-monitored blood glucose in patients with type 2 diabetes titrating one injection of insulin glulisine-the ELEONOR study. Diabetes Technol Ther. 2012;14:175-82.
7.	Edelman SV, Liu R, Johnson J, Glass LC. AUTONOMY: the first randomized trial comparing two patient-driven approaches to initiate and titrate prandial insulin lispro in type 2 diabetes. Diabetes Care. 2014;37:2132-40.
8.	Gao Y, Luquez C, Lynggaard H, Andersen H, Saboo B. The SimpleMix study with biphasic insulin aspart 30: a randomized controlled trial investigating patient-driven titration versus investigator-driven titration. Curr Med Res Opin. 2014;30:2483-92.
9.	Gerety G, Bebakar WM, Chaykin L, Ozkaya M, Macura S, Hersløv ML, et al. Treatment intensification with insulin degludec/insulin aspart twice daily: randomized study to compare simple and step-wise titration algorithms. Endocr Pract. 2016;22:546-54.
10.	Giaccari A, Bonadonna RC, Buzzetti R, Perseghin G, Cucinotta D, Fanelli C, et al. Similar glycaemic control and risk of hypoglycaemia with patient- versus physician-managed titration of insulin glargine 300 U/mL across subgroups of patients with T2DM: a post hoc analysis of ITAS. Acta Diabetol. 2021;58:789-96.

No.	Reference
11.	Harris SB, Yale JF, Berard L, Stewart J, Abbaszadeh B, Webster-Bogaert S, et al. Does a patient-managed insulin intensification strategy with insulin glargine and insulin glulisine provide similar glycemic control as a physician-managed strategy? results of the START (self-titration with apidra to reach target) study: a randomized noninferiority trial. Diabetes Care. 2014;37:604-10.
12.	Hramiak I, Gerstein HC, Leiter LA, Yale JF, Bajaj HS, Stewart J, et al. Comparing a daily versus weekly titration algorithm in people with type 2 diabetes switching from basal insulin to iGlarLixi in the LixiLan ONE CAN randomized trial. Diabetes Obes Metab. 2022;24:1998-2007.
13.	Kramer G, Kuniss N, Kloos C, Lehmann T, Müller N, Sanow B, Lorkowski S, Wolf G, Müller UA. Principles of self-adjustment of insulin dose in people with diabetes type 2 and flexible insulin therapy. Diabetes Res Clin Pract. 2016 Jun;116:165-70.
14.	Krnić M, Marolt I, Skelin M, Grulović N, Rahelić D. An observational, multicentre study on different insulin glargine U100 titration algorithms used in patients with type 2 diabetes in daily medical practice in Adriatic countries: The ADRESA study. Diabetes Res Clin Pract. 2019;150:144-9.
15.	Labajo HRV, Dampil OAC. The efficacy of daily compared to twice weekly basal insulin titration algorithms among patients with type II diabetes mellitus: A 12-week randomized controlled trial. Phillippine J Intern Med. 2018;56:148-52.
16.	Ligthelm RJ. Self-titration of biphasic insulin aspart 30/70 improves glycaemic control and allows easy intensification in a Dutch clinical practice. Prim Care Diabetes. 2009;3:97-102.
17.	Ma X, Chien JY, Johnson J, Malone J, Sinha V. Simulation-based evaluation of dose-titration algorithms for rapid-acting insulin in subjects with type 2 diabetes mellitus inadequately controlled on basal insulin and oral antihyperglycemic medications. Diabetes Technol Ther. 2017;19:483-90.
18.	Park SW, Bebakar WM, Hernandez PG, Macura S, Hersløv ML, de la Rosa R. Insulin degludec/insulin aspart once daily in Type 2 diabetes: a comparison of simple or stepwise titration algorithms (BOOST® : SIMPLE USE). Diabet Med. 2017;34:174-9.
19.	Russell-Jones D, Dauchy A, Delgado E, Dimitriadis G, Frandsen HA, Popescu L, et al. Take Control: a randomized trial evaluating the efficacy and safety of self- versus physician-managed titration of insulin glargine 300 U/mL in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2019;21:1615-24.
20.	Seufert J, Fritsche A, Pscherer S, Anderten H, Borck A, Pegelow K, et al. Titration and optimization trial for the initiation of insulin glargine 100 U/mL in patients with inadequately controlled type 2 diabetes on oral antidiabetic drugs. Diabetes Obes Metab. 2019;21:439-43.
21.	Yang W, Zhu L, Meng B, Liu Y, Wang W, Ye S, et al. Subject-driven titration of biphasic insulin aspart 30 twice daily is non-inferior to investigator-driven titration in Chinese patients with type 2 diabetes inadequately controlled with premixed human insulin: a randomized, open-label, parallel-group, multicenter trial. J Diabetes Investig. 2016;7:85-93.

No.	Reference
22.	Kalweit KL, Van Zyl DG, Rheeder P. Titrating insulin in patients with type 2 diabetes using a structured self-monitoring blood glucose regimen. S Afr Med J. 2018;108:654-9.
23.	Lee JY, Tsou K, Lim J, Koh F, Ong S, Wong S. "Symptom-based insulin adjustment for glucose normalization" (SIGN) algorithm: a pilot study. Diabetes Technol Ther. 2012;14:1145-8.
24.	Levy NK, Orzeck-Byrnes NA, Aidasani SR, Moloney DN, Nguyen LH, Park A, et al. Transition of a text-based insulin titration program from a randomized controlled trial into real-world settings: implementation study. J Med Internet Res. 2018;20:e93.
25.	Tamez-Pérez HE, Cantú-Santos OM, Gutierrez-González D, González-Facio R, Romero-Ibarguengoitia ME. Effect of digital-tool-supported basal insulin titration algorithm in reaching glycemic control in patients with type 2 diabetes in Mexico. J Diabetes Sci Technol. 2022;16:1513-20.
26.	Tews D, Gouveri E, Simon J, Marck C. A smartphone-based application to assist insulin titration in patients undergoing basal insulin-supported oral antidiabetic treatment. J Diabetes Sci Technol. 2023;17:988-97.
27.	Ulrich H, Bowen M. The clinical utility of professional continuous glucose monitoring by pharmacists for patients with type 2 diabetes. J Am Pharm Assoc. 2021;61:e76-82.
28.	Watson AJ, Kvedar JC, Rahman B, Pelletier AC, Salber G, Grant RW. Diabetes connected health: a pilot study of a patient- and provider-shared glucose monitoring web application. J Diabetes Sci Technol. 2009;3:345-52.
2. No outcome of interest (7 studies)	
1.	Bonadonna RC, Giaccari A, Buzzetti R, Aimaretti G, Cucinotta D, Avogaro A, et al. Italian titration approach study (ITAS) with insulin glargine 300 U/mL in insulin-naïve type 2 diabetes: design and population. NutrMetab Cardiovasc Dis. 2019;29:496-503.
2.	Farmer A, Wade A, French DP, Goyder E, Kinmonth AL, Neil A. The DiGEM trial protocol - a randomised controlled trial to determine the effect on glycaemic control of different strategies of blood glucose self-monitoring in people with type 2 diabetes. BMC Fam Pract. 2005;6.
3.	Hermanns N, Ehrmann D, Finke-Gröne K, Roos T, Freckmann G, Kulzer B. Evaluation of a digital health tool for titration of basal insulin in people with type 2 diabetes: rationale and design of a randomized controlled trial. J Diabetes Sci Technol. 2023:19322968221148756.
4.	Menon A, Gray L, Fatehi F, Bird D, Darssan D, Karunanithi M, et al. Mobile-based insulin dose adjustment for type 2 diabetes in community and rural populations: study protocol for a pilot randomized controlled trial. Ther Adv Endocrinol Metab. 2019;10:2042018819836647.
5.	Ng'ang'a L, Ngoga G, Dusabeyezu S, Hedt-Gauthier BL, Ngamije P, Habiyaremye M, et al. Implementation of blood glucose self-monitoring among

No.	Reference
	insulin-dependent patients with type 2 diabetes in three rural districts in Rwanda: 6 months open randomised controlled trial. BMJ Open. 2020;10:e036202.
6.	Odawara M, Misra A, Shestakova M, Pan CY, Jabbar A, Freemantle N, et al. Titration of insulin glargine in patients with type 2 diabetes mellitus in Asia: physician-versus patient-led? rationale of the Asian treat to target Lantus study (ATLAS). Diabetes Technol Ther. 2011;13:67-72.
7.	Oyer DS, Shepherd MD, Coulter FC, Bhargava A, Deluzio AJ, Chu PL, et al. Efficacy and tolerability of self-titrated biphasic insulin aspart 70/30 in patients aged >65 years with type 2 diabetes: an exploratory post hoc subanalysis of the INITIATEplus trial. Clin Ther. 2011;33:874-83.
3. Not RCT (10 studies)	
1.	Beluchin E, Bäz L, Müller N, Lehmann T, Kloos C, Wolf G, et al. Frequency of self-adjustment of insulin dose and metabolic control in type 2 diabetes is there an association? Diabet Med. 2013;30:e91-4.
2.	Bramwell SE, Meyerowitz-Katz G, Ferguson C, Jayaballa R, McLean M, Maberly G. The effect of an mHealth intervention for titration of insulin for type 2 diabetes: a pilot study. Eur J Cardiovasc Nurs. 2020;19:386-92.
3.	Brown NN, Carrara BE, Watts SA, Lucatorto MA. RN diabetes virtual case management: a new model for providing chronic care management. Nurs Adm Q. 2016;40:60-7.
4.	Davies M, Evans R, Storms F, Gomis R, Khunti K. Initiation of insulin glargine in suboptimally controlled patients with type 2 diabetes: sub-analysis of the AT LANTUS trial comparing treatment outcomes in subjects from primary and secondary care in the UK. Diabetes ObesMetab. 2007;9:706-13.
5.	Davies M, Sinnassamy P, Storms F, Gomis R. Insulin glargine-based therapy improves glycemic control in patients with type 2 diabetes sub-optimally controlled on premixed insulin therapies. Diabetes Res Clin Pract. 2008;79:368-75.
6.	Deerochanawong C, Leelawattana R, Kosachunhanun N, Tantiwong P. Basal insulin dose titration for glycemic control in patients with type 2 diabetes mellitus in Thailand: results of the REWARDS Real-World Study. Clin Med Insights Endocrinol Diabetes. 2020;13:1179551420935930.
7.	Seamon G, Caron O, Jiang A, Farrar M, Hughes P, Lugo B, et al. Pharmacist-led phone call initiative targeting hemoglobin A1c levels in patients with uncontrolled diabetes. J Am Coll Clin Pharm. 2021;4:1267-73
8.	Siegmund T, Pfohl M, Forst T, Pscherer S, Bramlage P, Foersch J, et al. Titration of basal insulin or immediate addition of rapid acting insulin in patients not at target using basal insulin supported oral antidiabetic treatment - a prospective observational study in 2,202 patients. Diabetes MetabSyndr. 2017;11:51-7.
9.	Stockton K, Deas C. Evaluation of outcomes of a pharmacist-run, outpatient insulin titration telepharmacy service. Innov Pharm. 2019;10.
10.	Vogt L, Thomas A, Fritzsche G, Heinke P, Kohnert KD, Salzsieder E. Model-based tool for personalized adjustment of basal insulin supply in patients with

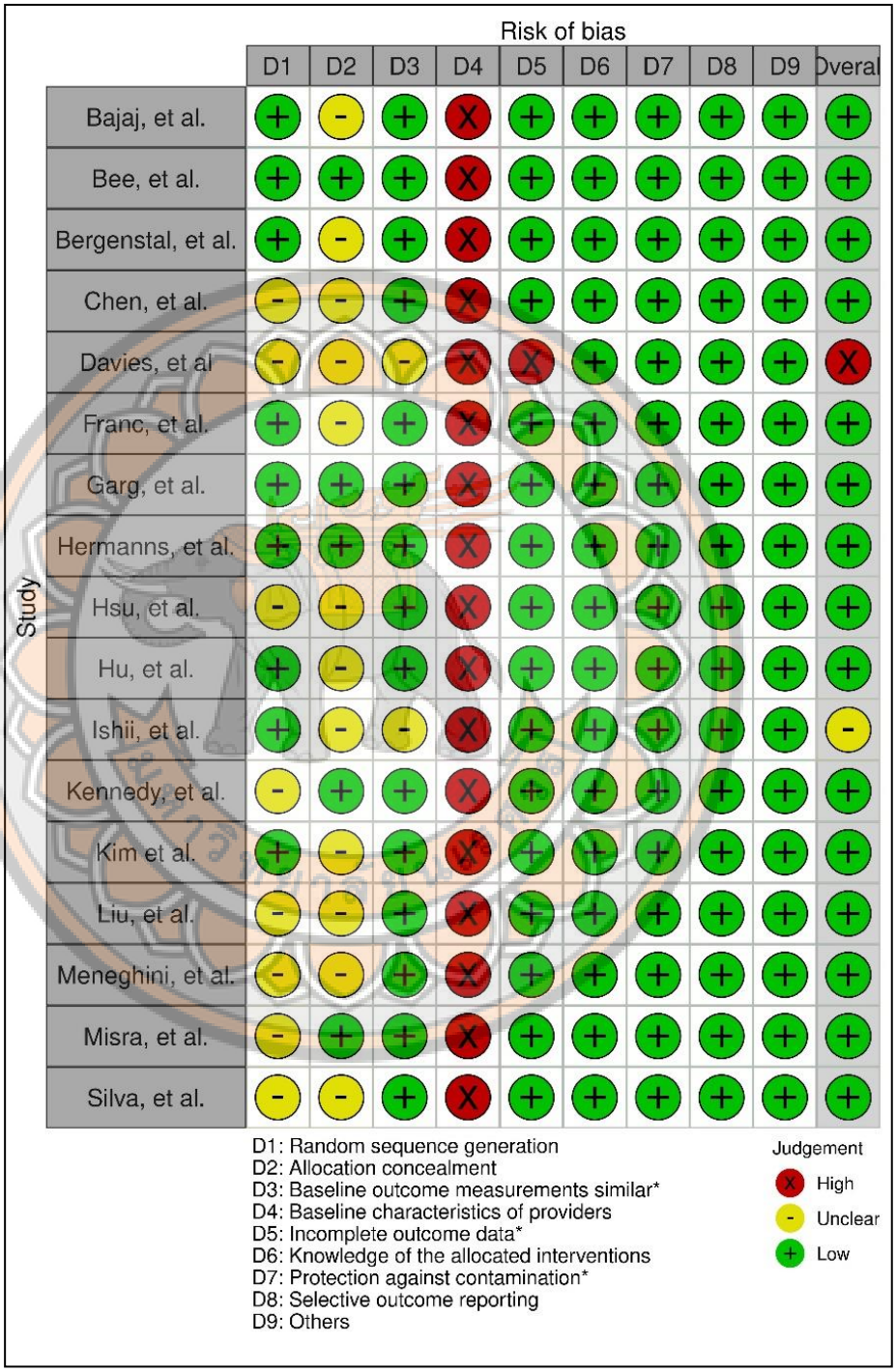
No.	Reference
	intensified conventional insulin therapy. J Diabetes Sci Technol. 2019;13:928-34.
4. Insufficient outcome detail (9 studies)	
1.	Bellido V, Bellido D, Tejera C, Carral F, Goicolea I, Soto A, et al. Effect of telephone-delivered interventions on glycemic control in type 2 diabetes treated with glargine insulin. Telemed J E Health. 2019;25:471-6.
2.	Boels A, Vos RC, Dijkhorst-Oei LT, Rutten GEH. Smartphone triggered diabetes self-management education and support in insulin treated type 2 diabetes patients: results of the randomised TRIGGER study. Diabetologia. 2018;61:S403-4.
3.	Chen J, Chen YL, Ji LN, Zhang PH, Zhu DS, Li X, Ji JC, Zhao F, Zhang H. Dose titration model and correlative factors analysis in Chinese patients with type-2 diabetes on basal insulin - results from an observational registry of basal insulin treatment study. Endokrynol Pol. 2018;69(4):395-402.
4.	Chen SY, Chang YH, Hsu HC, Lee YJ, Hung YJ, Hsieh CH. One-year efficacy and safety of the telehealth system in poorly controlled type 2 diabetic patients receiving insulin therapy. Telemed J E Health. 2011 Nov;17:683-7.
5.	Crowley MJ, Tarkington PE, Bosworth HB, Jeffreys AS, Coffman CJ, Maciejewski ML, et al. Effect of a comprehensive telehealth intervention vs telemonitoring and care coordination in patients with persistently poor type 2 diabetes control: a randomized clinical trial. JAMA Intern Med. 2022;182:943-52.
6.	David EA, Soremekun RO, Abah IO, Aderemi-Williams RI. Impact of pharmacist-led care on glycaemic control of patients with uncontrolled type 2 diabetes: a randomised controlled trial in Nigeria. Pharm Pract (Granada). 2021;19:2402.
7.	Gómez AM, Henao DC, Vargas FL, Muñoz OM, Lucero OD, Jaramillo MG, et al. Efficacy of the mHealth application in patients with type 2 diabetes transitioning from inpatient to outpatient care: a randomized controlled clinical trial. Diabetes Res Clin Pract. 2022;189:109948.
8.	Lashkari T, Borhani F, Sabzevari S, Abbaszadeh A. Effect of telenursing (telephone follow-up) on glycemic control and body mass index (BMI) of type 2 diabetes patients. Iran J Nurs Midwifery Res. 2013;18:451-6.
9.	Philis-Tsimikas A, Fortmann AL, Bastian A, Kanchi A, Abad R, Sheng T, et al. 202-OR: basal insulin digital titration app vs. enhanced paper titration tool: a randomized control study. Diabetes. 2020;69.
5. Not insulin self-titration (15 studies)	
1.	Bergenstal RM, Johnson M, Powers MA, Wynne A, Vlajnic A, Hollander P, et al. Adjust to target in type 2 diabetes: comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. Diabetes Care. 2008;31:1305-10.
2.	Boels AM, Rutten G, Zuithoff N, de Wit A, Vos R. Effectiveness of diabetes self-management education via a smartphone application in insulin treated type 2

No.	Reference
	diabetes patients - design of a randomised controlled trial ('TRIGGER study'). BMC EndocrDisord. 2018;18:74.
3.	Boels AM, Vos RC, Dijkhorst-Oei LT, Rutten GEHM. Effectiveness of diabetes self-management education and support via a smartphone application in insulin-treated patients with type 2 diabetes: results of a randomized controlled trial (TRIGGER study). BMJ Open Diabetes Res Care. 2019;7.
4.	Cani CG, Lopes Lda S, Queiroz M, Nery M. Improvement in medication adherence and self-management of diabetes with a clinical pharmacy program: a randomized controlled trial in patients with type 2 diabetes undergoing insulin therapy at a teaching hospital. Clinics (Sao Paulo). 2015;70:102-6.
5.	Dong Y, Ren T, Hao S, Zhou Y, Li W. Analysis of proportionality of continuous nursing and insulin on the compliance of elderly diabetic patients: a perspective of holistic health management. Lat Am J Pharm. 2021;40:279-84.
6.	Gong E, Baptista S, Russell A, Scuffham P, Riddell M, Speight J, et al. My diabetes coach, a mobile app-based Interactive conversational agent to support type 2 diabetes self-management: randomized effectiveness-implementation trial. J Med Internet Res. 2020;22:e20322.
7.	Grady M, Campbell D, MacLeod K, Srinivasan A. Evaluation of a blood glucose monitoring system with automatic high- and low-pattern recognition software in insulin-using patients: pattern detection and patient-reported insights. J Diabetes Sci Technol. 2013;7:970-8.
8.	Ilany J, Bhandari H, Nabriski D, Toledano Y, Konvalina N, Cohen O. Effect of prandial treatment timing adjustment, based on continuous glucose monitoring, in patients with type 2 diabetes uncontrolled with once-daily basal insulin: a randomized, phase IV study. Diabetes Obes Metab. 2018;20:1186-92.
9.	Kim EK, Kwak SH, Jung HS, Koo BK, Moon MK, Lim S, et al. The effect of a smartphone-based, patient-centered diabetes care system in patients with type 2 diabetes: a randomized, controlled trial for 24 Weeks. Diabetes Care. 2019;42:3-9.
10.	Lee JY, Chan CKY, Chua SS, Ng CJ, Paraidathathu T, Lee KKC, et al. Telemonitoring and team-based management of glycemic control on people with type 2 diabetes: a cluster-randomized controlled trial. J Gen Intern Med. 2020;35:87-94.
11.	Lum ZK, Chang KL, Tsou KY, Tan JY, Wong CSM, Kok ZY, et al. Enhancing diabetes care with community pharmacist-involved collaborative care model: A multi-centrerandomised controlled trial. Diabetes Res Clin Pract. 2022;185:109238.
12.	Oyer DS, Shepherd MD, Coulter FC, Bhargava A, Brett J, Chu PL, et al. A(1c) control in a primary care setting: self-titrating an insulin analog pre-mix (INITIATEplus trial). Am J Med. 2009;122:1043-9.
13.	Yaron M, Roitman E, Aharon-Hananel G, Landau Z, Ganz T, Yanuv I, et al. Effect of flash glucose monitoring technology on glycemic control and treatment satisfaction in patients with type 2 diabetes. Diabetes Care. 2019;42:1178-84.

No.	Reference
14.	Yki-Järvinen H, Juurinen L, Alvarsson M, Bystedt T, Caldwell I, Davies M, et al. Initiate insulin by aggressive titration and education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. Diabetes Care. 2007;30:1364-9.
15.	Yong YM, Shin KM, Lee KM, Cho JY, Ko SH, Yoon MH, et al. Intensive individualized reinforcement education is important for the prevention of hypoglycemia in patients with type 2 diabetes. Diabetes Metab J. 2015;39:154-63.
6. Patient ineligible (5 studies)	
1.	Di Molfetta S, Patruno P, Cormio S, Cignarelli A, Paleari R, Mosca A, et al. A telemedicine-based approach with real-time transmission of blood glucose data improves metabolic control in insulin-treated diabetes: the DIAMONDS randomized clinical trial. J Endocrinol Invest. 2022;45:1663-71.
2.	Egede LE, Williams JS, Voronca DC, Knapp RG, Fernandes JK. Randomized controlled trial of technology-assisted case management in low income adults with type 2 diabetes. Diabetes Technol Ther. 2017;19:476-82.
3.	Harris S, Yale JF, Dempsey E, Gerstein H. Can family physicians help patients initiate basal insulin therapy successfully?: randomized trial of patient-titrated insulin glargine compared with standard oral therapy: lessons for family practice from the Canadian INSIGHT trial. Can Fam Physician. 2008;54:550-8.
4.	Salvo MC, Brooks AM. Glycemic control and preventive care measures of indigent diabetes patients within a pharmacist-managed insulin titration program vs standard care. Ann Pharmacother. 2012;46:29-34.
5.	Yong A, Power E, Gill G. Improving glycaemic control of insulin-treated diabetic patients--a structured audit of specialist nurse intervention. J Clin Nurs. 20021;11:773-6.

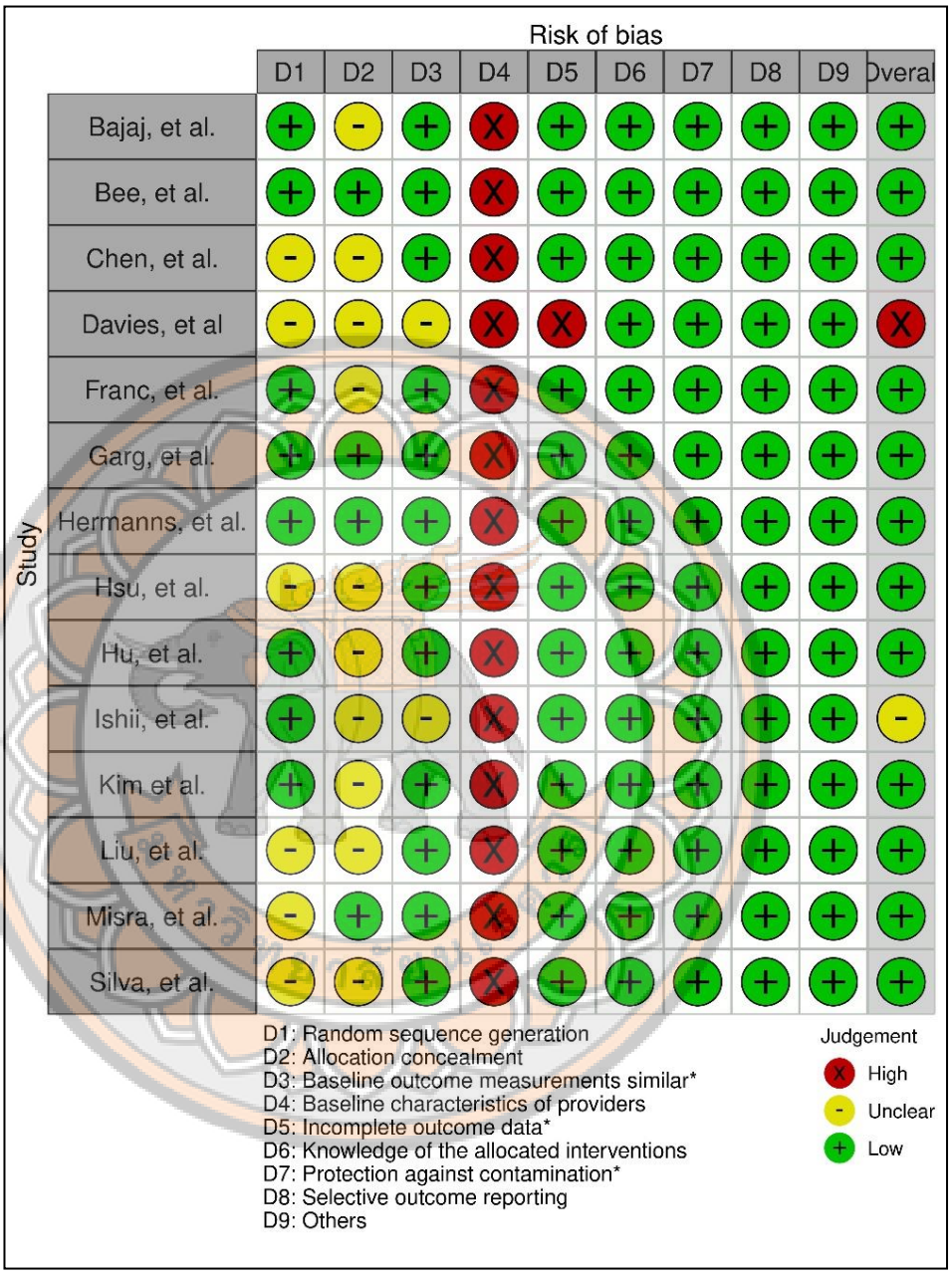
Appendix 4: Risk of bias among included trials based on each specific outcome

4.1 HbA1c reduction (17 studies)



*Key domains

4.2 Severe hypoglycemia (14 studies)



*Key domains

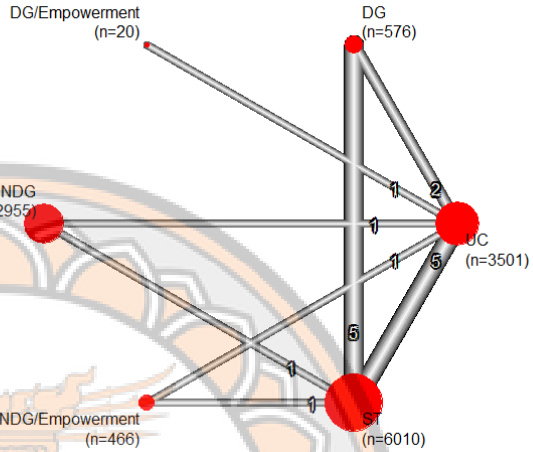
List of included trials

No.	Study
1.	Bajaj HS, Venn K, Ye C, Aronson R. Randomized trial of long-acting insulin glargine titrationweb tool (LTHome) versus enhanced usual therapy of glargine titration (INNOVATE Trial). DiabetesTechnol Ther. 2016;18:610-15.
2.	Bee YM, Batcagan-Abueg AP, Chei CL, Do YK, Haaland B, Goh SY, et al. A smartphoneapplication to deliver a treat-to-target insulin titration algorithm in insulin-naive patients with type 2diabetes: a pilot randomized controlled trial. Diabetes Care. 2016;39:e174-6.
3.	Bergenstal RM, Johnson M, Passi R, Bhargava A, Young N, Kruger DF, et al. Automated insulindosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre,randomised controlled trial. Lancet (London, England). 2019;393:1138-48.
4.	Chen HS, Wu TE, Jap TS, Lin SH, Hsiao LC, Lin HD. Improvement of glycaemia control insubjects with type 2 diabetes by self-monitoring of blood glucose: comparison of two managementprograms adjusting bedtime insulin dosage. Diabetes Obes Metab. 2008;10:34-40.
5.	Davies M, Bain S, Charpentier G, Flacke F, Goyeau H, Woloschak M, et al. A randomizedcontrolled, treat-to-target study evaluating the efficacy and safety of insulin glargine 300 U/mL (Gla-300) administered using either device-supported or routine titration in people with type 2 diabetes. JDiabetes Sci Technol. 2019;13:881-9.
6.	Franc S, Joubert M, Daoudi A, Fagour C, Benhamou PY, Rodier M, et al. Efficacy of twotelemonitoring systems to improve glycaemic control during basal insulin initiation in patients withtype 2 diabetes: The TeleDiab-2 randomized controlled trial. Diabetes Obes Metab. 2019;21:2327-32.
7.	Garg SK, Admane K, Freemantle N, Odawara M, Pan C-Y, Misra A, et al. Patient-led versusphysician-led titration of insulin glargine in patients with uncontrolled type 2 diabetes: a randomizedmultinational ATLAS study. Endocr Pract. 2015;21:143-57.
8.	Hermanns N, Ehrmann D, Finke-Groene K, Krichbaum M, Roos T, Haak T, et al. Use ofsmartphone application versus written titration charts for basal insulin titration in adults with type 2diabetes and suboptimal glycaemic control (My Dose Coach): multicentre, open-label, parallel,randomised controlled trial. Lancet Reg Health Eur. 2023;33:100702.
9.	Hsu WC, Lau KHK, Huang R, Ghiloni S, Le H, Gilroy S, et al. Utilization of a cloud-baseddiabetes management program for insulin initiation and titration enables collaborative decisionmaking between healthcare providers and patients. Diabetes Technol Ther. 2016;18:59-67.
10.	Hu X, Deng H, Zhang Y, Guo X, Cai M, Ling C, et al. Efficacy and safety of a decision supportintervention for basal insulin self-titration assisted by the nurse in outpatients with T2DM: arandomized controlled trial. Diabetes Metab Syndr Obes. 2021:1315-27.
11.	Ishii H, Nakajima H, Kamei N, Uchida D, Suzuki D, Ono Y, et al. Comparison of patient-led andphysician-led insulin titration in Japanese type 2 diabetes mellitus patients based on treatmentdistress, satisfaction, and self-efficacy: the COMMIT-patient study. Diabetes Ther. 2021;12:595-611.
12.	Kennedy L, Herman WH, Strange P, Harris A, Team GAC. Impact of active versus usualalgorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA1c onglycemic control in patients with type 2 diabetes: the glycemic optimization with algorithms and labsat point of care (GOAL A1C) trial. Diabetes Care. 2006;29:1-8.
13.	Kim CS, Park SY, Kang JG, Lee SJ, Ihm SH, Choi MG, et al. Insulin dose titration system indiabetes patients using a short messaging service automatically produced by a knowledge matrix.Diabetes Technol Ther. 2010;12:663-9.
14.	Liu SC, Chuang SM, Wang CH, Chien MN, Lee CC, Chen WC, et al. Comparison of two titrationprogrammes for adding insulin detemir to oral antidiabetic drugs in patients with poorly controlledtype 2 diabetes mellitus. Diabetes Obes Metab. 2023;25:700-6.
15.	Meneghini L, Koenen C, Weng W, Selam JL. The usage of a simplified self-titration dosingguideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes–results of therandomized, controlled PREDICTIVE™ 303 study. Diabetes Obes Metab. 2007;9:902-13.
16.	Misra A, Patel M, Agarwal P, Lodha S, Tandon N, Magdum M, et al. Effectiveness and safetyof physician-led versus patient-led titration of insulin glargine in Indian patients with type 2 diabetesmellitus: a subanalysis of the Asian Treat to Target Lantus Study (ATLAS). Diabetes Technol Ther.2019;21:656-64.
17.	Silva DDR, Bosco AA. An educational program for insulin self-adjustment associated withstructured self-monitoring of blood glucose significantly improves glycemic control in patients withtype 2 diabetes mellitus after 12 weeks: a randomized, controlled pilot study. Diabetol Metab Syndr.2015;7:1-9.

Appendix 5: Main analysis
Abbreviation: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care

5.1 HbA1c reduction (17 studies)

Network map



Heterogeneity

Comparison	Network meta-analysis	Pairwise meta-analysis		
	MD [95% CI]	MD [95% CI]	I^2, p-value	No. studies
DG/Empowerment:DG:	-0.78 [-1.92; 0.37]	NA	NA	0
DG:NDG	-0.12 [-0.42; 0.18]	NA	NA	0
NDG/Empowerment:DG	-0.55 [-0.86; -0.23]*	NA	NA	0
DG:ST	-0.26 [-0.42; -0.09]*	-0.30 [-0.49; -.10]*	44.7%, 0.12	5
DG:UC	-0.42 [-0.60; -0.24]*	-0.35 [-0.61; -.08]*	91.9%, 0.00	2
DG/Empowerment:NDG	-0.89 [-2.06; 0.27]	NA	NA	0
DG/Empowerment:NDG/Empowerment	-0.23 [-1.40; 0.93]	NA	NA	0
DG/Empowerment:ST	-1.04 [-2.18; 0.10]	NA	NA	0
DG/Empowerment:UC	-1.20 [-2.33; -0.07]*	-1.20 [-2.33; -.07]*	NA	1
NDG/Empowerment:NDG	-0.66 [-1.04; -0.28]*	NA	NA	0
NDG:ST	-0.14 [-0.40; 0.11]	-0.20 [-0.49; 0.09]	NA	1
NDG:UC	-0.31 [-0.58; -0.03]*	-0.13 [-0.64; 0.38]	NA	1
NDG/Empowerment:ST	-0.80 [-1.10; -0.51]*	-0.77 [-1.30; -.25]*	NA	1
NDG/Empowerment:UC	-0.97 [-1.24; -0.69]*	-0.98 [-1.30; -.66]*	NA	1
ST:UC	-0.16 [-0.31; -0.02]*	-0.21 [-0.38; -.04]*	34.9%, 0.19	5

statistically significant
Abbreviations: CI=Confidence interval; NA=Not applicable; MD = Mean difference

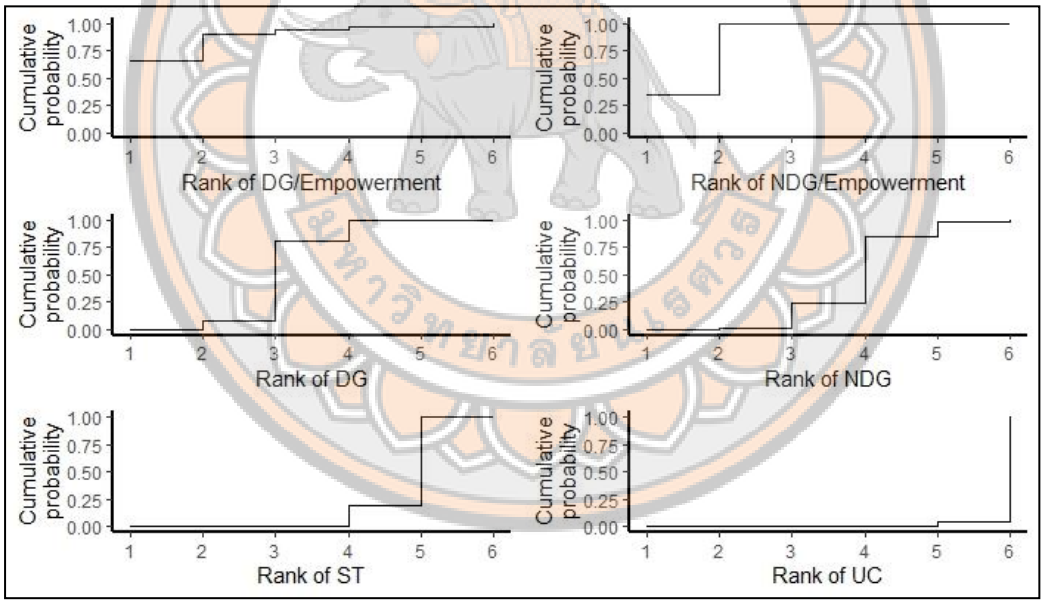
Inconsistency test

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model

Test	Q	df	p-value	tau.within	tau2.within
Between designs	1.09	3	0.78	0.18	0.03

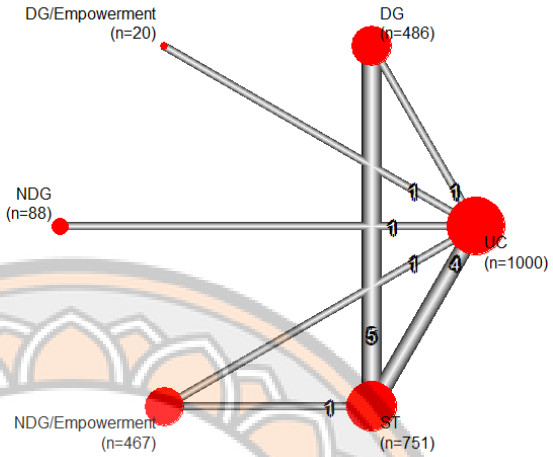
SUCRA

Treatment	SUCRA
DG/Empowerment	0.88
NDG/Empowerment	0.87
DG	0.59
NDG	0.42
ST	0.24
UC	0.01
based on 1000 simulations	



5.2 Severe hypoglycemia (14 studies)

Network map



Heterogeneity

Comparison	Network meta-analysis	Pairwise meta-analysis		
	MD [95% CI]	MD [95% CI]	I^2, p-value	No. studies
DG/Empowerment:DG:	1.42 [0.02; 102.05]	NA	NA	0
DG:NDG	0.33 [0.01; 15.36]	NA	NA	0
NDG/Empowerment:DG	1.37 [0.06; 31.77]	NA	NA	0
DG:ST	0.72 [0.17; 3.08]	0.77 [0.16; 3.78]	0.0%, 0.99	5
DG:UC	0.70 [0.12; 4.27]	0.50 [0.02; 14.78]	NA	1
DG/Empowerment:NDG	0.47 [0.00; 80.88]	NA	NA	0
DG/Empowerment:NDG/Empowerment	1.04 [0.01; 126.63]	NA	NA	0
DG/Empowerment:ST	1.02 [0.02; 61.09]	NA	NA	0
DG/Empowerment:UC	1.00 [0.02; 48.03]	1.00 [0.02; 48.03]	NA	1
NDG/Empowerment:NDG	0.46 [0.01; 37.76]	NA	NA	0
NDG:ST	2.15 [0.06; 81.52]	NA	NA	0
NDG:UC	2.11 [0.07; 62.20]	2.11 [0.07; 62.20]	NA	1
NDG/Empowerment:ST	0.98 [0.06; 16.78]	0.95 [0.02; 46.73]	NA	1
NDG/Empowerment:UC	0.96 [0.06; 16.50]	0.99 [0.02; 49.93]	NA	1
ST:UC	0.98 [0.26; 3.71]	1.04 [0.24; 4.53]	0.0%, 0.99	4

Abbreviations: CI=Confidence interval; NA=Not applicable; MD = Risk ratio

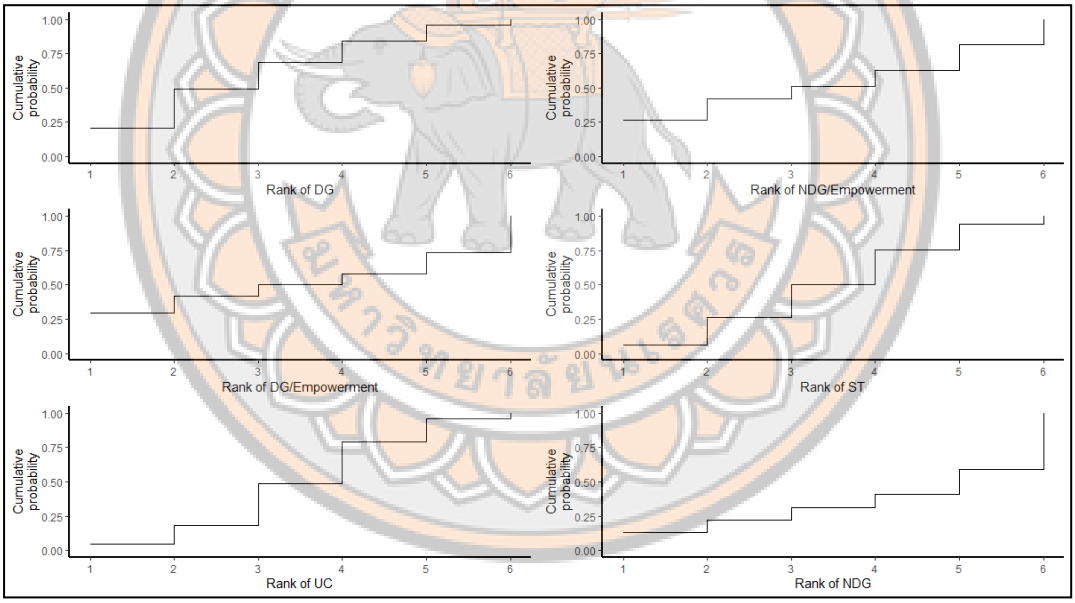
Inconsistency test

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model

Test	Q	df	p-value	tau.within	tau2.within
Between designs	0.05	2	0.98	0	0

SUCRA

Treatment	SUCRA
DG	0.64
NDG/Empowerment	0.53
DG/Empowerment	0.51
ST	0.50
UC	0.49
NDG	0.33
based on 1000 simulations	

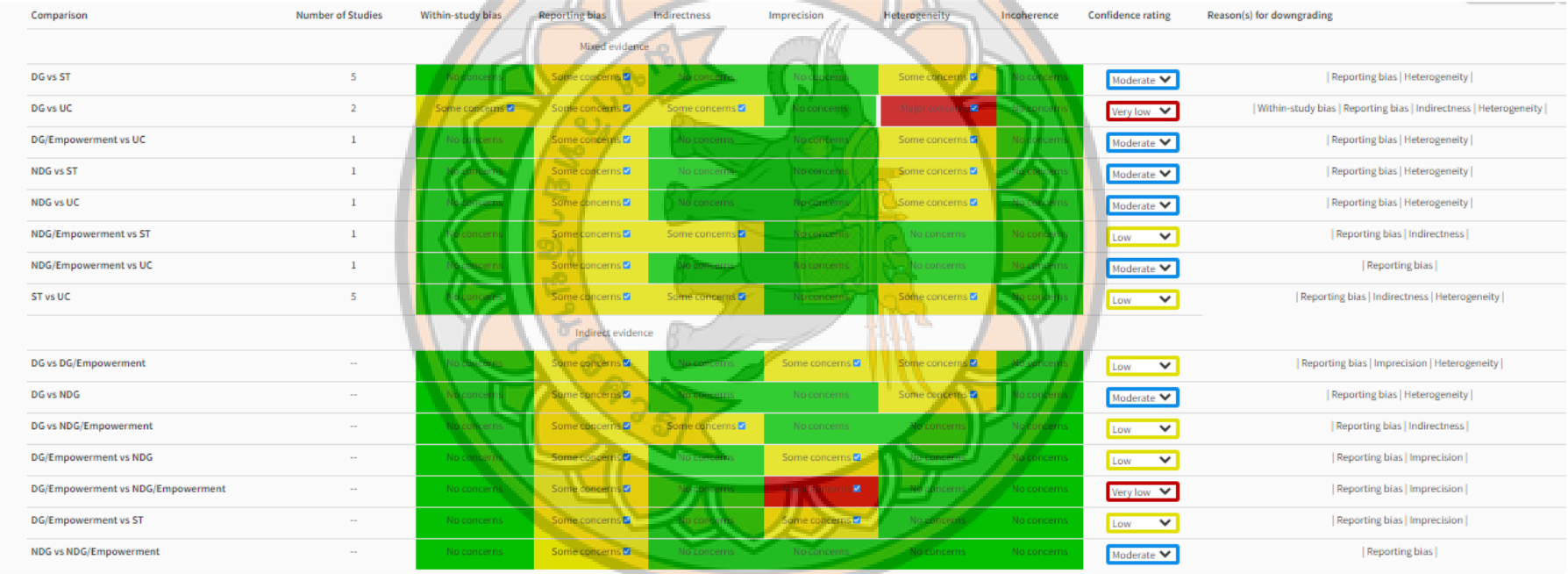


Appendix 6: Grading for certainty of evidence

The certainty (quality) of evidence for each comparison was assessed using the Confidence in Network Meta-Analysis (CINeMA) online platform. The CINeMA approach considers 6 domains, i.e., within-study bias, reporting bias, indirectness, imprecision (considering the confidence interval in conjunction with the minimal clinically important difference, MCID), heterogeneity, and incoherence. The level of confidence was decreased by a single level for any domain that had "some concerns", and two levels for any domain that had "high concerns". Domains that were closely related were considered jointly ("Indirectness" and "Incoherence") and ("Imprecision" and "Heterogeneity"). If only direct or indirect evidence was available for comparisons, this NMA was assigned low risk to the incoherence domain based on the global inconsistency test.

6.1 HbA1c reduction

Used MCID of 0.5%[5, 6]



Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Mixed evidence									
DG vs ST	5	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate	| Reporting bias | Heterogeneity |
DG vs UC	2	Some concerns	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Very low	| Within-study bias | Reporting bias | Indirectness | Heterogeneity |
DG/Empowerment vs UC	1	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate	| Reporting bias | Heterogeneity |
NDG vs ST	1	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate	| Reporting bias | Heterogeneity |
NDG vs UC	1	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate	| Reporting bias | Heterogeneity |
NDG/Empowerment vs ST	1	No concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	Low	| Reporting bias | Indirectness |
NDG/Empowerment vs UC	1	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate	| Reporting bias |
ST vs UC	5	No concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Low	| Reporting bias | Indirectness | Heterogeneity |
Indirect evidence									
DG vs DG/Empowerment	--	No concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low	| Reporting bias | Imprecision | Heterogeneity |
DG vs NDG	--	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate	| Reporting bias | Heterogeneity |
DG vs NDG/Empowerment	--	No concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	Low	| Reporting bias | Indirectness |
DG/Empowerment vs NDG	--	No concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	Low	| Reporting bias | Imprecision |
DG/Empowerment vs NDG/Empowerment	--	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
DG/Empowerment vs ST	--	No concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	Low	| Reporting bias | Imprecision |
NDG vs NDG/Empowerment	--	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate	| Reporting bias |

Abbreviation: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care

[5] Lenters-Westra E, Schindhelm R, Bilo H, Groenier K, Slingerland R. Differences in interpretation of haemoglobin A1c values among diabetes care professionals. J Neth J Med. 2014;72:462-6.

[6] Jayedi A, Emadi A, Shab-Bidar S. Dose-dependent effect of supervised aerobic exercise on HbA1c in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Sports medicine (Auckland, NZ). 2022;52:1919-38.

6.2 Severe hypoglycemia

Used MCID (Relative risk) of 0.75[7, 8]

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
			Mixed evidence						
DG vs ST	5	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
DG vs UC	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Within-study bias | Reporting bias | Imprecision |
DG/Empowerment vs UC	1	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
NDG vs UC	1	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
NDG/Empowerment vs ST	1	No concerns	Some concerns	Some concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Indirectness | Imprecision |
NDG/Empowerment vs UC	1	No concerns	Some concerns	Some concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Indirectness | Imprecision |
ST vs UC	4	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
			Indirect evidence						
DG vs DG/Empowerment	--	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
DG vs NDG	--	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
DG vs NDG/Empowerment	--	No concerns	Some concerns	Some concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Indirectness | Imprecision |
DG/Empowerment vs NDG	--	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
DG/Empowerment vs NDG/Empowerment	--	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
DG/Empowerment vs ST	--	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
NDG vs NDG/Empowerment	--	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |
NDG vs ST	--	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low	| Reporting bias | Imprecision |

Abbreviation: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care

[7]Dankers M, Nelissen-Vrancken M, Hart BH, Lambooij AC, van Dijk L, Mantel-Teeuwisse AK. Alignment between outcomes and minimal clinically important differences in the Dutch type 2 diabetes mellitus guideline and healthcare professionals' preferences. Pharmacol Res Perspect. 2021;9:e00750.

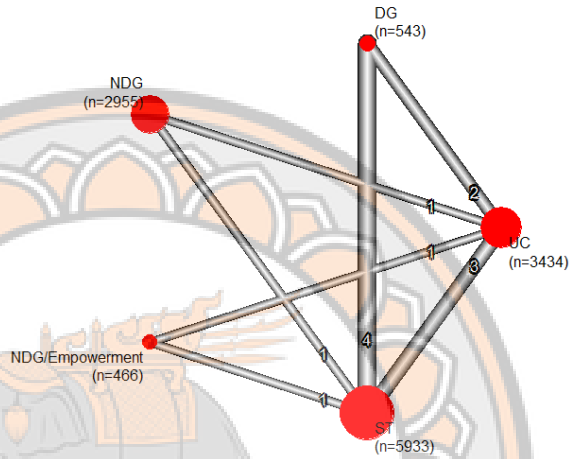
[8]Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Interpreting results and drawing conclusions. Cochrane handbook for systematic reviews of interventions version. 2019:403-31.

Appendix 7: Sensitivity analyses
Abbreviation: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care

7.1 Excluding trials with small sample size (<25th percentile)

7.1.1 HbA1c reduction (13 studies)

Network map



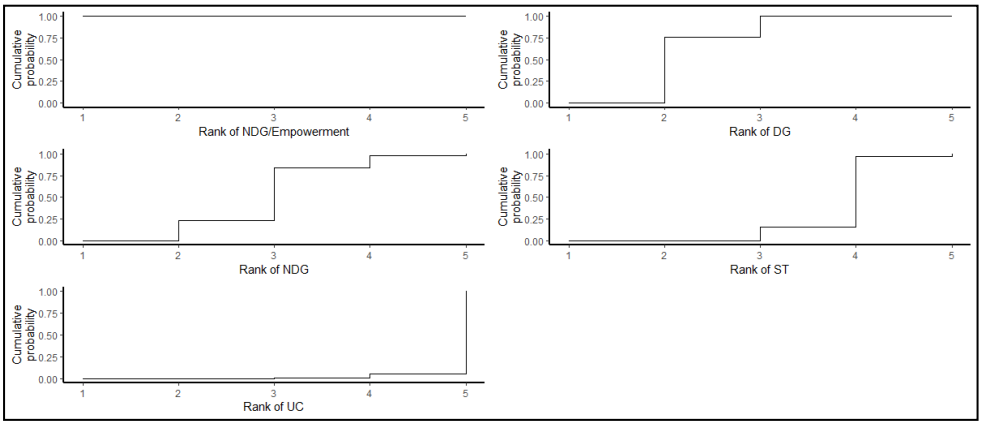
Inconsistency test

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model

Test	Q	df	p-value	tau.within	tau2.within
Between designs	0.68	3	0.88	0.20	0.04

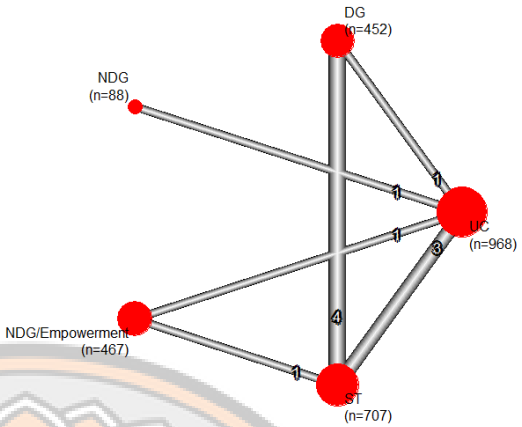
SUCRA

Treatment	SUCRA
NDG/Empowerment	1.00
DG	0.69
NDG	0.51
ST	0.28
UC	0.01
based on 1000 simulations	



7.1.2 Severe hypoglycemia (11 studies)

Network map



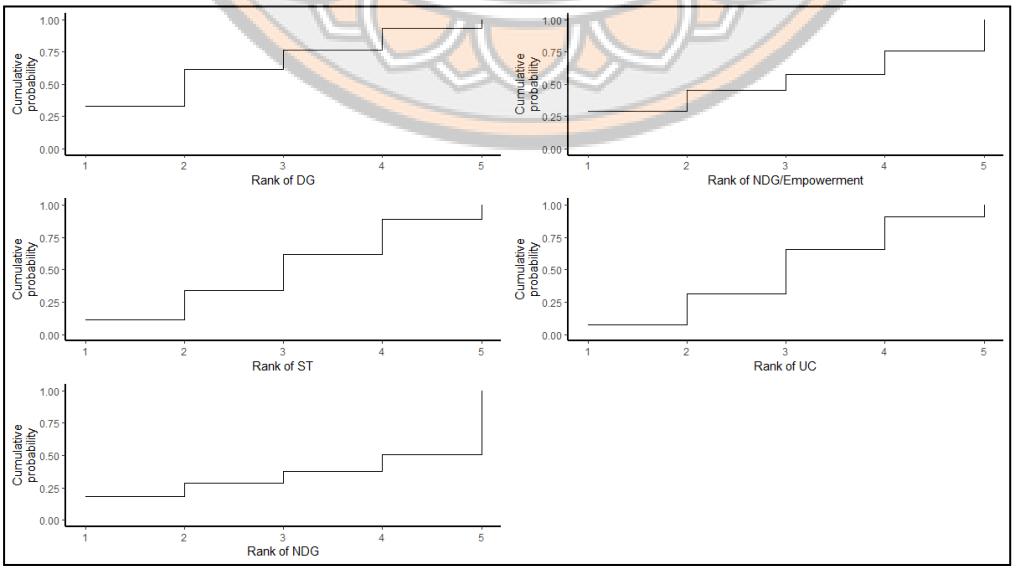
Inconsistency test

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model

Test	Q	df	p-value	tau.within	tau2.within
Between designs	0.03	2	0.98	0	0

SUCRA

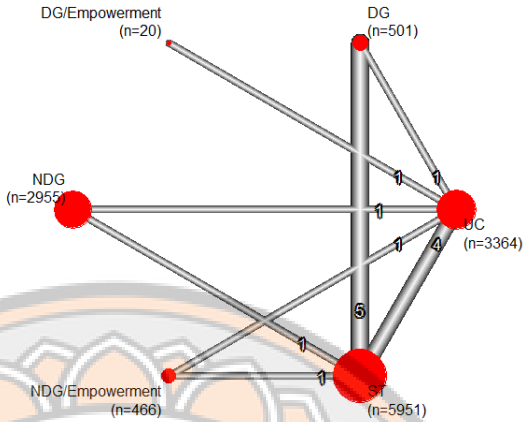
Treatment	SUCRA
DG	0.66
NDG/Empowerment	0.52
ST	0.49
UC	0.49
NDG	0.34
based on 1000 simulations	



7.2 Excluding trials with high risk of bias and unclear risk of bias

7.2.1 HbA1c reduction (15 studies)

Network map



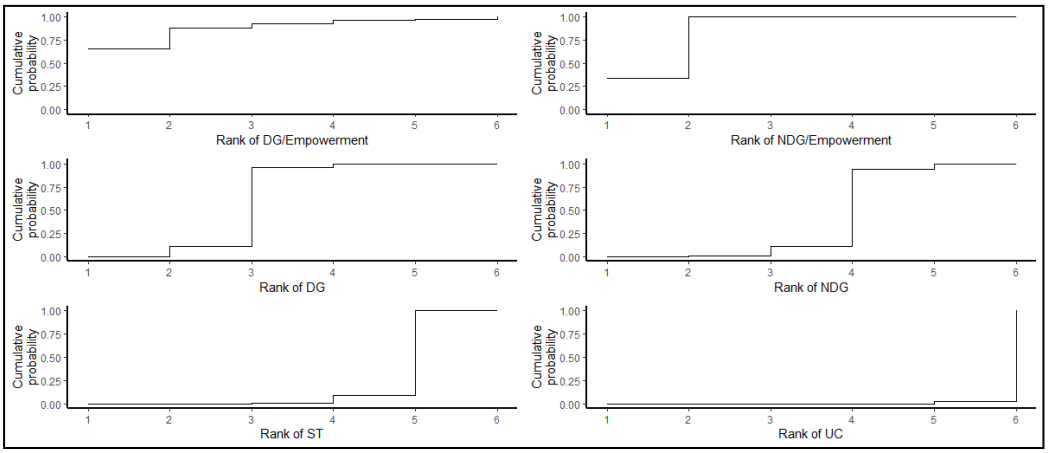
Inconsistency test

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model

Test	Q	df	p-value	tau.within	tau2.within
Between designs	2.50	3	0.47	0.09	0.01

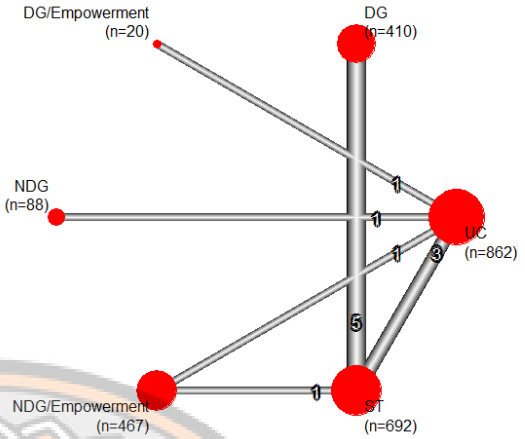
SUCRA

Treatment	SUCRA
DG/Empowerment	0.88
NDG/Empowerment	0.87
DG	0.61
NDG	0.41
ST	0.22
UC	0.01
based on 1000 simulations	



7.2.2 Severe hypoglycemia (12 studies)

Network map



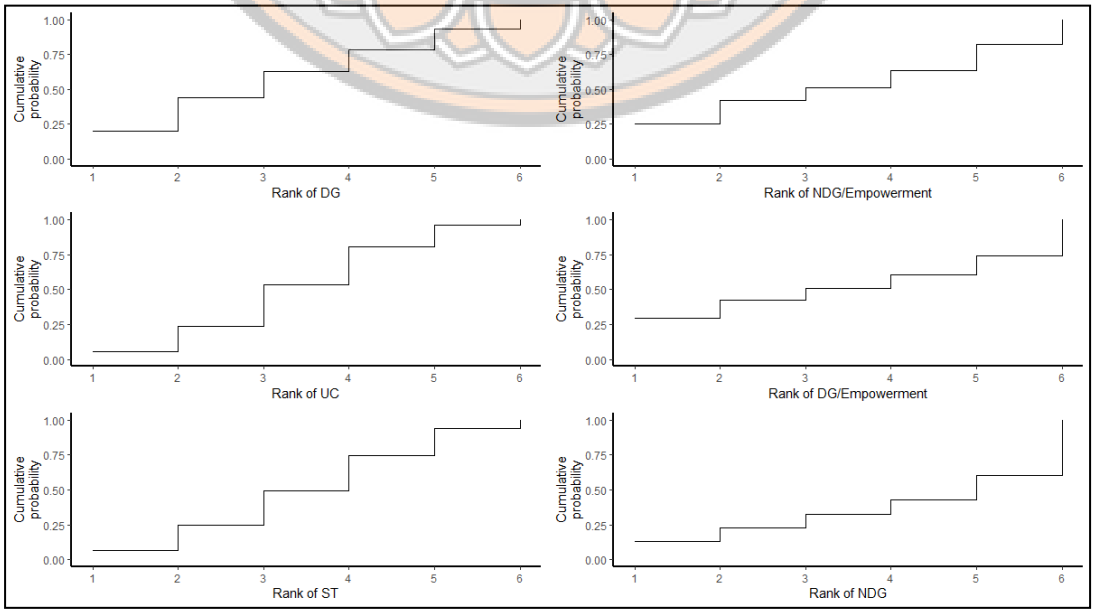
Inconsistency test

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model

Test	Q	df	p-value	tau.within	tau2.within
Between designs	0.00	1	0.99	0	0

SUCRA

Treatment	SUCRA
DG	0.60
NDG/Empowerment	0.53
UC	0.52
DG/Empowerment	0.51
ST	0.49
based on 1000 simulations	



Appendix 8: Assessment of transitivity assumption

8.1 HbA1c reduction

Treatment comparison	No. of studies	No. of subjects	Age, year (Mean ±SD)	Gender (%male)	BMI, kg/m2 (Mean ±SD	Baseline HbA1c (%)	Duration of diabetes, year (Mean ±SD)	Type of insulin	Duration of study, month	Naïve insulin user (%)	Studies
DG/Empowerment VS UC	1	40	53.3-53.8	NA	30.8-31.7	10.8-10.9	NA	100% basal insulin	3 months ± 2 weeks	100	Hsu
DG VS UC	2	332	60.3-62.1	51.6-68.9	33.2-34.7	8.5-8.7 (Bergenstal)	15.3-16.1 (Bergenstal)	100% basal insulin	4-6	0-39.7	Bergenstal, Davies
DG VS ST	5	739	48.4-59.7	49.9-66.7 (Bee, Franc, Hermanns, Kim)	23.9-32.9	8.2-9.9	8.5-13.1	100% basal insulin	3-6	32.4-100 (100% from Bee, Franc, Hermanns)	Bajaj, Bee, Franc, Hermanns, Kim
NDG/Empowerment VS UC	1	849	53.6-54.8	57.0-60.6	23.5-23.8	9.2-9.4	6.4-7.9	100% basal insulin	3	100	Hu
NDG/Empowerment VS ST	1	78	57.9-59.6	39.3-48.4	25.6-26.2	9.5-9.7	9.2-9.4	100% basal insulin	7	0	Chen
NDG VS UC	1	181	59.0-60.2	44.3-49.5	26.5-26.7	9.1-9.2	9.1-9.2	100% basal insulin	6	100	Liu
NDG VS ST	1	5,721	57 ± 12	49.0-53.0	34.2-34.5	8.8-8.9	8.4-8.7	100% basal insulin	6	100	Kennedy
ST VS UC	5	5,588	51.9-62.6	32.5-70.8	27.4-33.8 (Garg, Meneghini, Misra, Silva)	8.5-9.3 (Garg, Meneghini, Misra, Silva)	8.5-16.9	99.61% basal insulin	3-6.5	0-100 (100% from Garg, Misra, Ishii)	Garg, Ishii, Meneghini, Misra, Silva

Abbreviation: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care; NA = not applicable

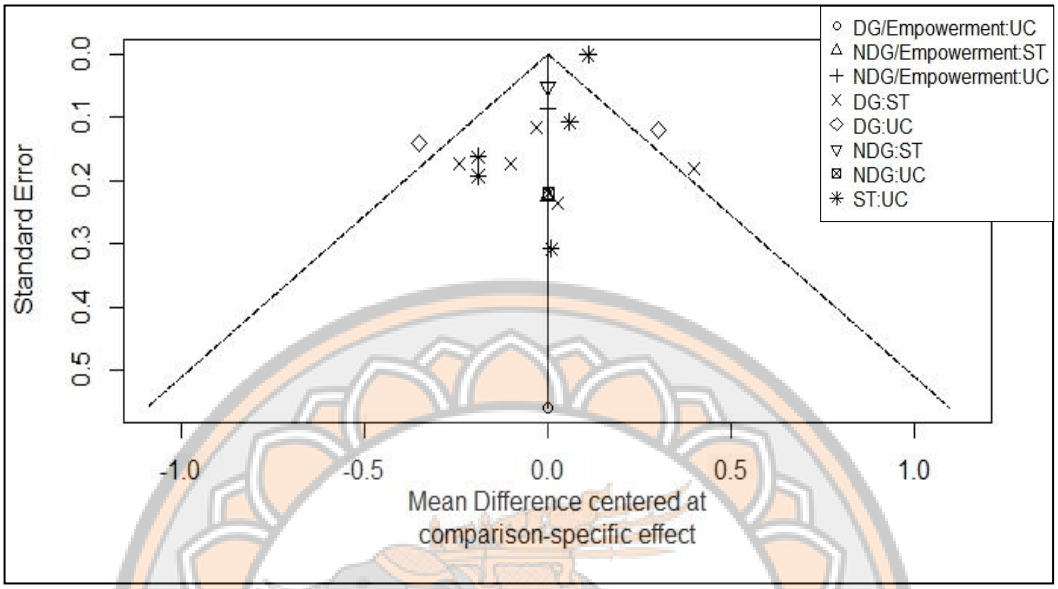
8.2 Severe hypoglycemia

Treatment comparison	No. of studies	No. of subjects	Age, year (Mean ±SD)	Gender (%male)	BMI, kg/m2 (Mean ±SD	Baseline HbA1c (%)	Duration of diabetes, year (Mean ±SD)	Type of insulin	Duration of study, month	Naïve insulin user (%)	Studies
DG/Empowerment VS UC	1	40	53.3-53.8	NA	30.8-31.7	10.8-10.9	NA	100% basal insulin	3 months ± 2 weeks	100	Hsu
DG VS UC	1	151	61.2-62.9	64.0-73.7	33.2-33.3	NA	NA	100% basal insulin	4	39.7	Davies
DG VS ST	5	739	48.4-59.7	49.9-66.7 (Bee, Franc, Hermanns, Kim)	23.9-32.9	8.2-9.9	8.5-13.1	100% basal insulin	3-6	32.4-100 (100% from Bee, Franc, Hermanns)	Bajaj, Bee, Franc, Hermanns, Kim
NDG/Empowerment VS UC	1	849	53.6-54.8	57.0-60.6	23.5-23.8	9.2-9.4	6.4-7.9	100% basal insulin	3	100	Hu
NDG/Empowerment VS ST	1	78	57.9-59.6	39.3-48.4	25.6-26.2	9.5-9.7	9.2-9.4	100% basal insulin	7	0	Chen
NDG VS UC	1	181	59.0-60.2	44.3-49.5	26.5-26.7	9.1-9.2	9.1-9.2	100% basal insulin	6	100	Liu
ST VS UC	4	763	51.9-62.6	32.5-62.7	27.4-29.4 (Garg, Misra, Silva)	8.7-9.3 (Garg, Misra, Silva)	8.5-16.9	99.61% basal insulin	3-6	0-100 (100% from Garg, Ishii, Misra)	Garg, Ishii, Misra, Silva

Abbreviation: DG/Empowerment = dosage guidance with empowerment; NDG/Empowerment = Non-dosage guidance with empowerment; DG = dosage guidance; NDG = Non-dosage guidance; ST = Self-titration; UC = usual care; NA = not applicable

Appendix 9: Assessment of publication bias using comparison-adjusted funnel plot

9.1 HbA1c reduction



9.2 Severe hypoglycemia