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## Time for using Machine Learning for Dose Guidance in Titration of People with Type 2 Diabetes? A Systematic Review of Basal Insulin Dose Guidance

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**Abbreviations:** (T2D) Type 2 diabetes, (PROSPERO) International Prospective Register of Systematic Reviews, (PRISMA) Preferred Reporting Items for Systematic Reviews and Meta-analyses, (JBI) Joanna Briggs Institute, (RCT) randomized controlled trial, (HCP) healthcare professional, (DTSQ) Diabetes Treatment Satisfaction Questionnaire

**Keywords:** Basal insulin, dose guidance, glycemic control, insulin titration, type 2 diabetes, systematic review

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**Figure and table count:** 4 figures, 6 tables

1 **Abstract:**

2 **Background:** Real-world studies of people with Type 2 Diabetes (T2D) have shown  
3 insufficient dose adjustment during basal insulin titration in clinical practice leading  
4 to suboptimal treatment. Thus, 60% of people with T2D treated with insulin do not  
5 reach glycemic targets. This emphasizes a need for methods supporting efficient  
6 and individualized basal insulin titration of people with T2D. However, no  
7 systematic review of basal insulin dose guidance for people with T2D has been  
8 found.

9 **Objective:** To provide an overview of basal insulin dose guidance methods that  
10 support titration of people with T2D and categorize these methods by  
11 characteristics, effect, and user experience.

12 **Methods:** The review was conducted according to the Preferred Reporting Items for  
13 Systematic Review and Meta-Analysis (PRISMA) guidelines. Studies about basal  
14 insulin dose guidance, including adults with T2D on basal insulin analogs published  
15 before 07/09/2022, were included. Joanna Briggs Institute critical appraisal  
16 checklist was applied to assess risk of bias.

17 **Results:** In total, 35 studies were included, and three categories of dose guidance  
18 were identified: paper-based titration algorithms, telehealth solutions, and  
19 mathematical models. Heterogeneous reporting of glycemic outcomes challenged  
20 comparison of effect between the three categories. Few studies assessed user  
21 experience.

22 **Conclusions:** Studies mainly used titration algorithms to titrate basal insulin as  
23 telehealth or in paper format, except for studies using mathematical models. A  
24 numerically larger proportion of participants seemed to reach target using

- 25 telehealth solutions compared to paper-based titration algorithms. Exploring
- 26 capabilities of machine learning may provide insights that could pioneer future
- 27 research while focusing on holistic development.

28 **1. Introduction**

29 Initiation of basal insulin is a complex and time-consuming task associated with  
30 clinical inertia<sup>(1-5)</sup>. Thus, approximately 60% of people with T2D treated with insulin  
31 do not reach glycemic targets<sup>(4,6-8)</sup>. Insulin titration is used when determining the  
32 optimal dose for an individual<sup>(2,4,9)</sup>. This is necessary since people with T2D vary in  
33 pancreatic insulin production and insulin resistance<sup>(9,10)</sup>. Hence, the optimal dose of  
34 basal insulin differs among people with T2D and may change over time due to, e.g.,  
35 stress levels, lifestyle changes, and sickness.

36 Suboptimal treatment is partly caused by non-adherence to treatment and failure  
37 to initiate or intensify treatment promptly<sup>(9,11)</sup>. Lack of adjustment to insulin  
38 treatment is mainly caused by the complexity of the titration process<sup>(5)</sup>. This causes  
39 people with T2D to remain on suboptimal insulin doses, leading to less  
40 improvement in glycemic control than what could have been accomplished with an  
41 optimal dose<sup>(5,12,13)</sup>. In addition, studies based on real-world data have shown both a  
42 delay in the initiation of basal insulin and insufficient dose adjustment during  
43 titration<sup>(1,14,15)</sup>. Suboptimal insulin titration has been shown in the range of 3-12  
44 months after initiation of active titration in clinical practice<sup>(3,6,16-19)</sup>. This elucidates  
45 that people with T2D, in some cases, have not reached glycemic target after 3+  
46 months of active titration. Failure to achieve glycemic targets during the initial three  
47 months of titration is associated with a higher risk of failure to reach glycemic  
48 targets two years after the initiation<sup>(15)</sup>. This emphasizes the need for dose guidance  
49 supporting efficient and individualized basal insulin titration of people with T2D to  
50 provide optimal and timely treatment.

51 In recent years, basal insulin dose guidance has been of rapidly growing interest  
52 within international research, emphasized by increased publications on the subject.

53 Despite this interest and the fact that it has been a research field for several  
54 decades, a preliminary search of the Cochrane Database of Systematic Reviews and  
55 Reviews, the International Prospective Register of Systematic Reviews (PROSPERO),  
56 and Joanna Briggs Institute (JBI) Evidence Synthesis revealed no systematic review  
57 of basal insulin dose guidance for people with T2D. Therefore, this systematic review  
58 aims to provide an overview of methods used for basal insulin dose guidance  
59 supporting titration of people with T2D and categorize these methods by  
60 characteristics, effect, and user experience.

## 61 **2. Methods**

### 62 **2.1 Study Design**

63 The systematic review was conducted according to the Preferred Reporting Items  
64 for Systematic Reviews and Meta-analyses (PRISMA) guidelines<sup>(20)</sup>. Therefore, a  
65 protocol was registered in PROSPERO on 19/12/2021 (CRD42021289364), forming  
66 the review's basis<sup>(21)</sup>.

### 67 **2.2 Eligibility Criteria**

68 Studies evaluating dose guidance methods supporting basal insulin titration of  
69 people with T2D in any setting, including participants ( $\leq 18$  years) diagnosed with  
70 T2D, were considered. Studies investigating populations of mixed diabetes types  
71 without a transparent subgroup analysis or without a clear statement of diabetes  
72 types were excluded.

73 Studies including participants on basal-bolus regimens, human or intermediate  
74 insulin, or other injectable antidiabetic treatment were excluded.

75 Primary studies reporting any glycemic outcome published in English, Danish,  
76 Norwegian, or Swedish before 07/09/2022, as peer-reviewed full-text, were

77 included. All study designs except study protocols, animal research, expert opinions,  
78 and case studies were considered.

### 79 **2.3 Information sources and search strategy**

80 A comprehensive systematic search was performed in PubMed, Embase, and IEEE  
81 by one author (C.H.N.T) with assistance from a research librarian. Citation and  
82 reference searches were conducted in Google Scholar. Authors of relevant studies  
83 were contacted if additional information was needed.

84 Unstructured searches in PubMed and Google Scholar were performed to identify  
85 relevant search terms. The search was adjusted to each database. Search terms  
86 included different synonyms and spellings. Search functions were applied, including  
87 thesaurus, Boolean operators, phrase, truncation, free text, and advanced search  
88 (Supplementary material).

### 89 **2.4 Selection process**

90 First, studies identified through the systematic search were uploaded to RefWorks  
91 (version 2.1.0.1). Second, duplicates were removed using the functions *Exact*  
92 *duplicates* and *Close duplicates*. Third, one reviewer (C.H.N.T.) screened the title  
93 and abstract of the remaining studies. Fourth, studies deemed eligible were  
94 retrieved in full text and assessed by one reviewer (C.H.N.T.). Doubt about the  
95 studies' eligibility was resolved through discussion with co-authors. Reason for  
96 exclusion of studies was recorded during full-text assessment (Supplementary  
97 material). The final sample consisted of studies deemed eligible after full-text  
98 assessment.

### 99 **2.5 Data extraction and synthesis**



100 One author (C.H.N.T.) extracted data using a sheet in Microsoft Excel (2016).  
101 Extracted data included study characteristics (title, author, publication year, study  
102 design, country, sample size, and duration of study), participant characteristics (age,  
103 sex, BMI, insulin-naïve, and initial HbA1c), characteristics of the dose guidance  
104 method (setting, description of the method, and type of insulin used), and glycemic  
105 outcomes.

106 A narrative synthesis of extracted data was conducted, and characteristics of  
107 studies and populations were described. The narrative synthesis focused on  
108 categorizing dose guidance methods and assessing effect of the interventions and  
109 user experience according to the categorization.

## 110 **2.6 Risk of bias assessment**

111 Critical appraisal tools from JBI were applied by study design of the studies to assess  
112 risk of bias<sup>(22)</sup>. Study design was determined using Andrews and Likis, 2015<sup>(23)</sup>. One  
113 author (C.H.N.T.) assessed included studies with support from co-authors.

114 Before critical appraisal was performed, authors agreed on a scoring system and  
115 cut-off points per the JBI reviewers manual<sup>(24)</sup>. Studies were judged as described in  
116 Melo et al., 2018<sup>(25)</sup>.

117 A suitable tool for simulation studies was not found from JBI; therefore, the critical  
118 appraisal tool from Fone et al., 2003<sup>(26)</sup> was used.

## 119 **3. Results**

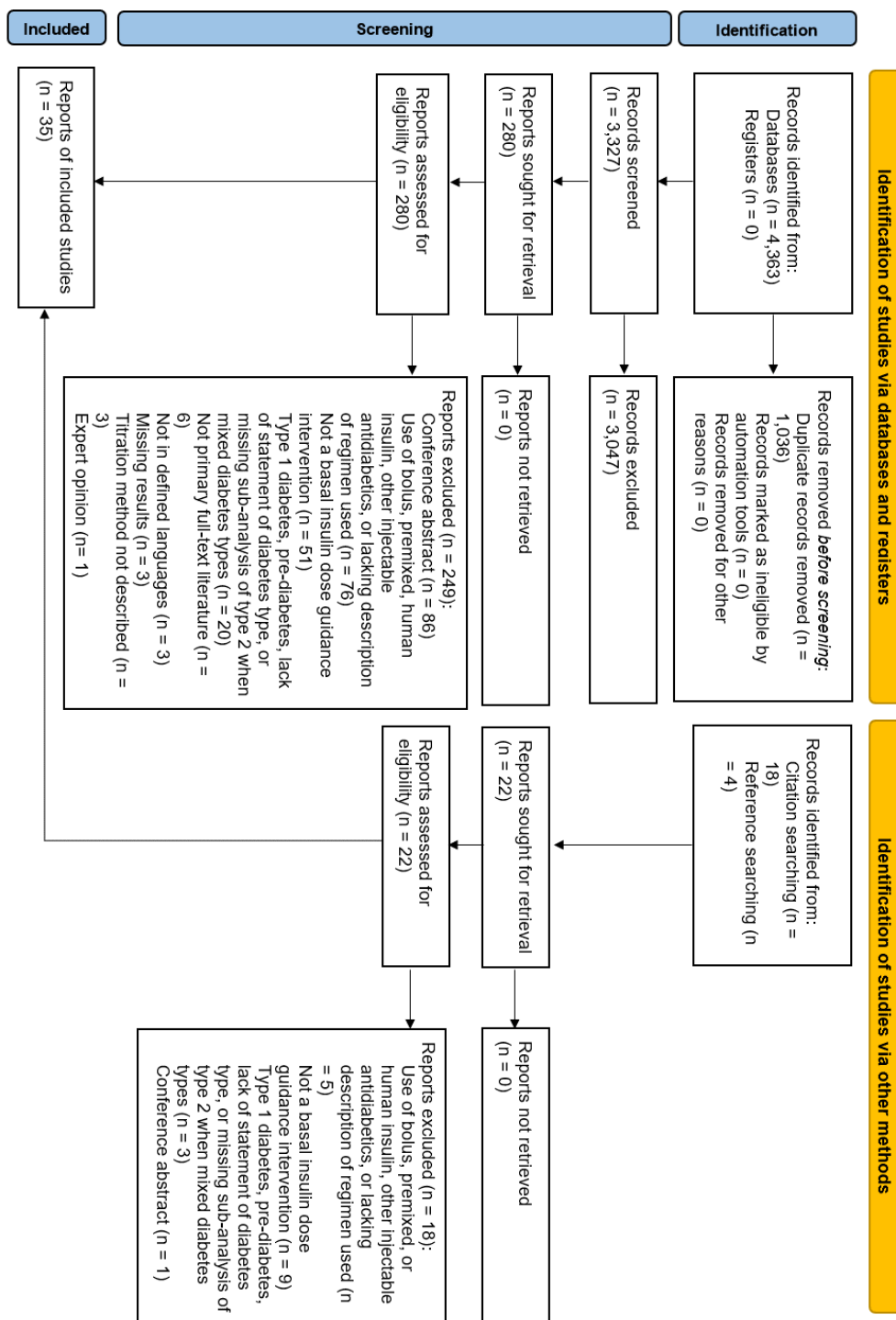
### 120 **3.1 Study selection**

121 A total of 4,363 papers were found. After removing duplicates, 3,327 papers were  
122 included in title and abstract screening. Of those, 280 papers were found eligible for  
123 full-text screening. Thirty-one papers met the inclusion criteria and were included in

124 the review. Four additional papers were identified through reference and citation  
125 searches. Thus, 35 articles were included in this review. The selection process is  
126 presented in Figure 1. Supplementary material contains a tabular overview of data  
127 extracted from the included studies.

128 Some studies seemed eligible but were excluded due to use of human insulin or  
129 basal-bolus regimen in a subgroup of participants without a transparent subgroup  
130 analysis of participants treated only with basal insulin analogs or using bolus insulin  
131 as rescue medication<sup>(13,27–29)</sup>.

132 **Figure 1.** The selection process is illustrated in a PRISMA flowchart<sup>(20)</sup>.



133

134 **3.2 Study characteristics**

135 Seven studies were quasi-experimental design<sup>(30–36)</sup>, 20 studies were randomized  
 136 controlled trials (RCT)<sup>(37–56)</sup>, three studies were mixed method<sup>(57–59)</sup>, one study was  
 137 qualitative design<sup>(60)</sup>, one study was a cohort<sup>(61)</sup>, and three studies were simulation

138 design<sup>(8,10,62)</sup>. Mixed method studies were a mix of quasi-experimental and  
139 qualitative designs. The studies were published from 2006 to 2022 and enrolled  
140 19,432 people with T2D. The length of the studies ranged from 28 days to 12  
141 months.  
142 The studies were conducted in 31 countries across Europa, Asia, North and South  
143 America, the Middle East, and Africa. Seven studies did not specify in which country  
144 it was conducted<sup>(8,10,32,48,55,61,62)</sup>.

### 145 **3.3 Participant characteristics**

146 Characteristics of participants were similar regarding initial BMI, age, and sex  
147 distribution. The most significant difference was whether participants were insulin  
148 naïve at start-of-trial. Study population in 60% of the studies were insulin  
149 naïve<sup>(8,10,31,34,35,37,39–41,45,46,48–51,53,56–58,61,62)</sup>. In 14% of studies, the population  
150 continued basal insulin treatment initiated before the study<sup>(30,32,33,36,43)</sup>, and 26% of  
151 studies included a study population of both insulin naïve and  
152 continuers<sup>(38,42,44,47,52,54,55,59,60)</sup>. Initial HbA1c, duration of diabetes, and whether the  
153 study population was insulin naïve are essential factors to consider when comparing  
154 the impact on glycemic control from dose guidance interventions<sup>(15,63–67)</sup>. All study  
155 populations had initial HbA1c above 7%, and diabetes duration ranged from 2.9-  
156 15.9 years.

### 157 **3.4 Characteristics of the dose guidance methods**

158 Twenty-one of identified dose guidance methods were developed for titration of  
159 glargine<sup>(30,32,34,36–39,41,42,44,45,47,49,51,53–56,58,61,62)</sup>, three for detemir<sup>(40,48,52)</sup>, five for  
160 degludec<sup>(8,10,31,43,46)</sup>, one for icodec<sup>(50)</sup>, and one for glargine and detemir<sup>(59)</sup>. Four  
161 studies did not specify insulin further than it was basal insulin analogs<sup>(33,35,57,60)</sup>.

162 Approximately 70% of the studies were in an outpatient clinic. The remaining  
163 studies were in primary care<sup>(34,35,42,51,52,61)</sup> or did not specify the setting<sup>(8,10,36,50,62)</sup>.

#### 164 **3.4.1. Categorization of the dose guidance methods**

165 Identified dose guidance methods were divided into three categories: paper-based  
166 titration algorithms, telehealth solutions, and mathematical models (Figure 2).

167 Paper-based titration algorithms reflect standard practice at the time of writing.

168 The studies investigated algorithms with varying targets and sizes of dose

169 adjustment carried out during in-person visits. In total, 20 studies investigated

170 paper-based titration algorithms<sup>(32,34,36–38,40–43,46,48–53,56,58,61,62)</sup>.

171 Telehealth solutions covered telemonitoring solutions with titration across a digital

172 platform<sup>(30,45,54,57,59,60)</sup> and combined with home visits<sup>(35)</sup>, or self-titration decision

173 support<sup>(33,39,44,47,55)</sup>. In contrast to studies addressing paper-based algorithms, the

174 organizational setup was altered in these studies. Interactions between participants

175 and healthcare professionals (HCP) were primarily handled over distance via phone.

176 In total, 12 studies investigated telehealth solutions<sup>(30,33,35,39,44,45,47,54,55,57,59,60)</sup>.

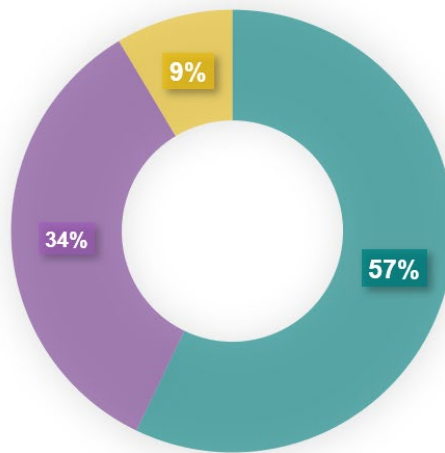
177 Mathematical models were investigated by three studies using used compartment

178 modeling and control theory<sup>(8,10,31)</sup>. Most of these studies did not specify the use

179 case of the method.

180 **Figure 2.** Overview of type of dose guidance methods used in the included studies.

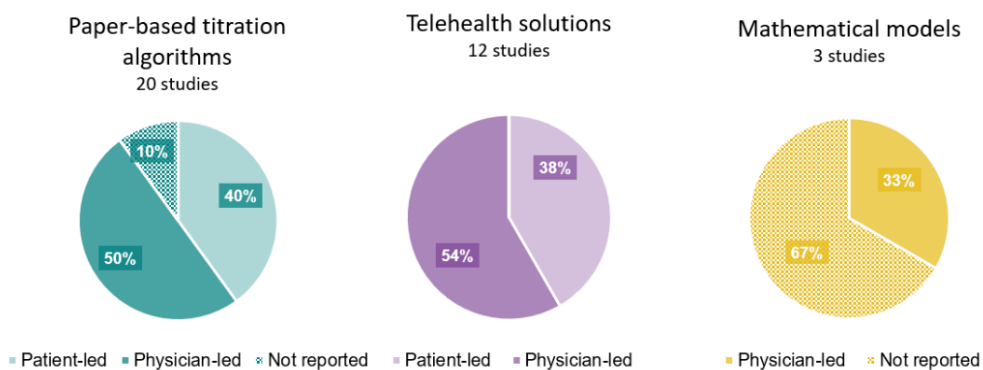
### Categorization of dose guidance methods



■ Paper-based titration algorithms ■ Telehealth solutions ■ Mathematical models

181 Dose guidance methods covered both physician- and patient-led methods. The  
 182 distribution was similar for paper-based titration algorithms and telehealth  
 183 solutions, where most approaches based on mathematical models did not specify  
 184 the intended user (Figure 3).

185 **Figure 3.** Distribution of the intended user of the identified dose guidance methods  
 186 according to the three main categories: paper-based titration algorithms, telehealth  
 187 solutions, and mathematical models.



188

189 Description of the dose guidance method is presented in Table 1.

190 **Table 1.** Overview of how basal insulin was titrated in the included studies grouped  
 191 by the titration algorithm used.

Study	Description of dose guidance method	Category
Yuan et al. 2021 <sup>(37)</sup>	<u>2-0-2 titration algorithm</u> according to three different fasting blood glucose targets; 70<FBG≤100, 100<FBG≤110, or 110<FBG≤126 mg/dL. Titrated based on the lowest of three consecutive fasting SMBG values.	Paper-based titration algorithm
Zhang et al. 2018 <sup>(58)</sup>	Comparison of the use of a titration algorithm to reach different glycemic targets (Group 1: 70 <FBG≤100 mg/dL, Group 2: 100<FBG<110 mg/dL, and Group 3: 110<FBG≤126 mg/dL)  The titration algorithm used was a modification of the 2-0-2 algorithm.	Paper-based titration algorithm
Misra et al. 2019 <sup>(41)</sup>	<u>2-0-2-4 titration algorithm</u> as patient-led compared to physician-led. Insulin doses were titrated every three days.	Paper-based titration algorithm
McGloin et al. 2020 <sup>(57)</sup>	MyMedic hub. Telemonitoring system where people with T2D were titrated	Telehealth solution

	using a <u>2-0-2 titration algorithm</u> twice weekly for three weeks and once weekly after that.	
Ngassa Pioti et al. 2022 <sup>(35)</sup>	Nurse-driven and home-based telehealth intervention where participants were titrated using the <u>2-0-2 titration algorithm</u> to reach the target of 72-126 mg/dL.	Telehealth solution
Seufert et al. 2019 <sup>(61)</sup>	<u>2-0-2 titration algorithm</u> (adjusted every three days) compared to the <u>2-0-2-4-6-8 titration algorithm</u> (adjusted every 3-5 days).	Paper-based titration algorithm
Kadowaki et al. 2017 <sup>(43)</sup>	<u>2-0-2 titration algorithm</u> compared to the <u>2-0-2-4-6-8 titration algorithm</u> at both fixed dosing and flexible dosing. Adjustments to insulin doses were made weekly.	Paper-based titration algorithm
Kennedy et al. 2006 <sup>(49)</sup>	Comparison of usual and active insulin titration using the <u>2-0-2-4-6-8 titration algorithm</u> . If fasting blood glucose was below 70 mg/dL insulin dose was decreased to the previous dose.	Paper-based titration algorithm



Yu et al. 2020 <sup>(40)</sup>	<u>3-0-3 titration algorithm</u> compared to the <u>2-4-6-8 titration algorithm</u> . Titration was performed per three days.	Paper-based titration algorithm
Blonde et al. 2009 <sup>(48)</sup>	<u>3-0-3 titration algorithm</u> to the target of 70-90 mg/dL compared to 79-110 mg/dL. Adjustments to insulin doses were made every three days.	Paper-based titration algorithm
Meneghini et al. 2007 <sup>(52)</sup>	<u>3-0-3 titration algorithm</u> , where adjustments were made every three days, compared to standard-of-care, where adjustments were made at the physician's discretion.	Paper-based titration algorithm
Hsu et al. 2016 <sup>(45)</sup>	Diabetes management program. Telemonitoring system where the <u>3-0-3 titration algorithm</u> was used to reach the target of 79-110 mg/dL.	Telehealth solution
Philis-Tsimikas et al. 2013 <sup>(46)</sup>	<u>4-0-4 titration algorithm</u> compared to the <u>4-2-0-2-4-6-8 titration algorithm</u> . Adjustments of doses were made weekly based on one and the lowest of three	Paper-based titration algorithm

	consecutive days of fasting SMBG measure, respectively.	
Lingvay et al. 2021 <sup>(50)</sup>	<p>Comparison of four titration algorithms: three for icodec and one for glargine.</p> <p>Glargine: <u>4-0-4 titration algorithm</u> to target 79-130 mg/dL</p> <p>Icodec titration A: <u>21-0-21 titration algorithm</u> to target 79-130 mg/dL</p> <p>Icodec titration B: <u>28-0-28 titration algorithm</u> to target 79-130 mg/dL (equivalent to the titration algorithm used for glargine)</p> <p>Icodec titration C: <u>28-0-28 titration algorithm</u> to target 70-108 mg/dL</p>	Paper-based titration algorithm
Garg et al. 2015 <sup>(51)</sup>	<p><u>2-0-2-4 titration algorithm</u> as patient-led compared to physician-led. In the physician-led titration, group doses were adjusted at each visit, whereas doses were adjusted twice weekly in the patient-led titration group.</p>	Paper-based titration algorithm

<p>Sethi et al. 2022<sup>(36)</sup></p>	<p>Using the <u>2-0-2-4 titration algorithm</u> to reach HbA1c&lt;7%.</p> <p>The frequency of dose adjustments was made at least weekly and not more than every 3–4 days unless required for safety.</p>	<p>Paper-based titration algorithm</p>
<p>Ji et al. 2020<sup>(53)</sup></p>	<p><u>2-0-2-4-6 titration algorithm</u> at a standard starting dose (0.2 U/kg) or a higher starting dose (0.3 U/kg).</p>	<p>Paper-based titration algorithm</p>
<p>Bajaj et al. 2016<sup>(44)</sup></p>	<p>LTHome/MyStar WebCoach. Decision support system for self-titration using the <u>4-2-0-2-4 titration algorithm</u> to the target 90-130 mg/dL.</p>	<p>Telehealth solution</p>
<p>Davies et al. 2019<sup>(55)</sup></p>	<p>MyStar DoseCoach. Decision support system for self-titration using the <u>4-2-0-2-4 titration algorithm</u> to reach the 90-130 mg/dL target.</p>	<p>Telehealth solution</p>
<p>Kim et al. 2010<sup>(47)</sup></p>	<p>Decision support system for self-titration using the <u>4-2-0-2-4-6 titration algorithm</u> to the target 79-119 mg/dL.</p>	<p>Telehealth solution</p>

Hu et al. 2021 <sup>(39)</sup>	<p>Self-titration decision support program.</p> <p>One in-person visit was followed by five phone calls where insulin dose adjustments were made if needed, along with empowering coaching from a nurse. Otherwise, the participants self-titrated.</p> <p>Titration algorithm used: <u>6-4-2-0-2-4-6</u> to target 79-110 mg/dL.</p>	Telehealth solution
Levy et al. 2018 <sup>(59)</sup>	<p>Mobile Insulin Titration Intervention (MITI). Telemonitoring system where participants were titrated using the <u>2-1-0-2-3-4-5 titration algorithm</u> through weekly phone calls.</p>	Telehealth solution
Rogers et al. 2019 <sup>(60)</sup>	<p>MITI. Telemonitoring system where participants were titrated using the <u>2-1-0-2-3-4-5 titration algorithm</u> through weekly phone calls to reach the target of 79-130 mg/dL.</p>	Telehealth solution
Levy et al. 2015 <sup>(54)</sup>	<p>MITI. Telemonitoring system where participants were titrated using the <u>2-1-0-</u></p>	Telehealth solution

	<u>2-3-4-5 titration algorithm</u> through weekly phone calls.	
Bae et al. 2022 <sup>(38)</sup>	Comparison of the INSIGHT and EDITION titration algorithm.  INSIGHT: titrate by <u>one unit/day</u> .  EDITION: titrate by <u>three units per three days</u> .	Paper-based titration algorithm
Yale et al. 2017 <sup>(42)</sup>	Comparison of the paper-based titration algorithm INSIGHT and EDITION.  In the INSIGHT group, insulin was titrated by <u>one unit/day</u> .  In the EDITION group, insulin was titration by <u>three units per three days</u> based on median pre-breakfast SMBG values of the last three days.	Paper-based titration algorithm
Hasan et al. 2018 <sup>(34)</sup>	ADA/EASD consensus titration algorithm of 2009. <u>Increased with two units every three days</u> until target (70-130 mg/dL)	Paper-based titration algorithm

	reached. If fasting blood glucose is >180 mg/dL, increase by four units every three days; if fasting blood glucose is <70 mg/dL, reduce by four units or 10% if >60 units.	
Larsen et al. 2010 <sup>(33)</sup>	Electronic diary app to support self-titration by <u>increasing dose by two units every three days</u> if two of the previous three days' fasting SMBG measures >121 mg/dL and no readings were <72 mg/dL.	Telehealth solution
Sieber et al. 2020 <sup>(62)</sup>	Comparison of three paper-based titration algorithms.  Group 1: titrate by <u>two units per three days</u> to target 90-130 mg/dL.  Group 2: titrate by <u>four units per three days</u> and by six units if blood glucose if >180 mg/dL to target 90-130 mg/dL.  Group 3: titrate by <u>two units per three days</u> to target 110-150 mg/dL	Paper-based titration algorithm

<p>Pfützner et al.  2016<sup>(32)</sup></p>	<p>Comparison of four paper-based titration algorithms.</p> <ol style="list-style-type: none"> <li>1) Target: 90-130 mg/dL. Increase dose by <u>two units every three days</u>.</li> <li>2) Target: 90-130 mg/dL. Increase the dose by <u>four units every three days</u> if blood glucose is &gt;180 mg/dL, then increase by two units.</li> <li>3) Target: 110-150 mg/dL. Increase dose by <u>two units every three days</u>.</li> <li>4) Target: 70-100 mg/dL. Increase dose <u>two units every three days</u>.</li> </ol>	<p>Paper-based titration algorithm</p>
<p>Ishii et al.  2021<sup>(56)</sup></p>	<p>Comparison of physician and patient-led titration algorithm.</p> <p>Physician-led: <u>0-1-2-3-4</u> and decrease according to the physician's discretion.</p> <p>Patient-led: <u>1-0-1</u>.</p> <p>The frequency of dose adjustments was not specified.</p>	<p>Paper-based titration algorithm</p>

<p>Tamez-Pérez et al. 2021<sup>(30)</sup></p>	<p>MyDoseCoach. A combination of a mobile app and a web portal suggested basal insulin dose adjustments every three days based on a titration algorithm: 10% increase if SMBG&gt;180 mg/dL, 5% increase if 140&lt;SMBG&lt;180 mg/dL, no change if 79&lt;SMBG&lt;140, 5% decrease if 70&lt;SMBG&lt;79 mg/dL, 10% decrease if SMBG&lt;70 mg/dL.</p>	<p>Telehealth solution</p>
<p>Aradóttir et al. 2021<sup>(31)</sup></p>	<p>Titration was performed using a linear dose-response algorithm.</p> <p>Day 1-4: No insulin.</p> <p>Day 5-9: 10 U insulin.</p> <p>Day 10: Evaluation of whether 10U is sufficient or if the dose should be adjusted with 0.2 U/kg.</p> <p>Day 15: The dose estimation algorithm used CGM data from day 1-14, and 75% of the estimated dose was given to the participant.</p> <p>Day 20-84: titration using stepwise algorithm until target (72-108 mg/dL) reached.</p>	<p>Mathematical model</p>



Krishnamoorthy et al. 2021 <sup>(10)</sup>	Model-free titration approach using recursive least square-based extremum seeking control.	Mathematical model
Aradóttir et al. 2019 <sup>(68)</sup>	A model predictive control-based dose guidance algorithm.	Mathematical model

192

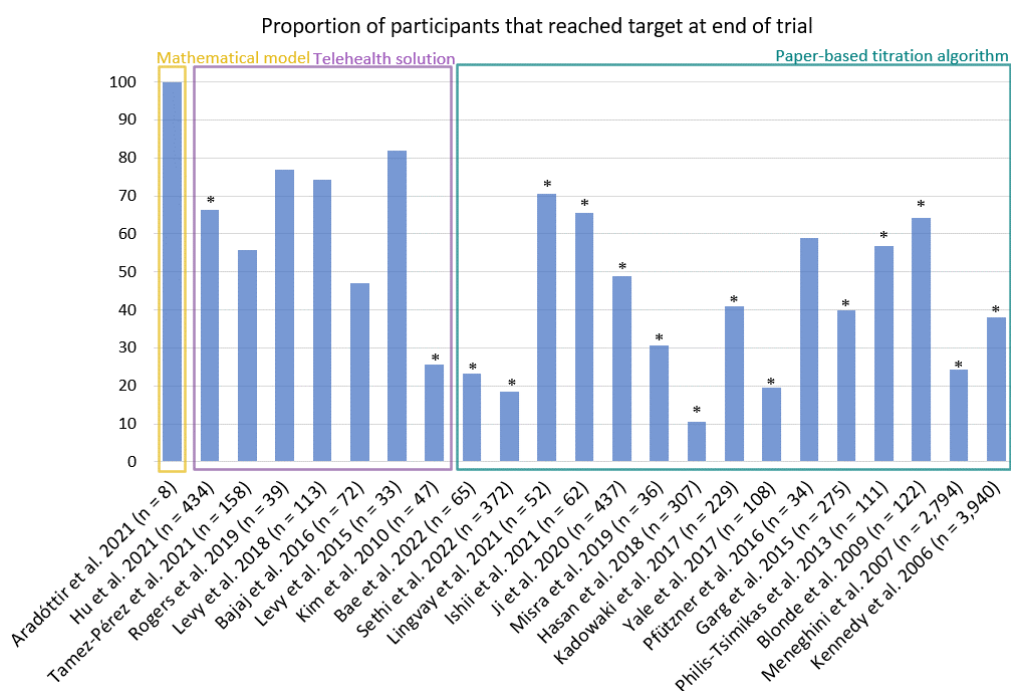
193 Table 1 elucidates that all identified dose guidance methods, except in  
 194 Krishnamoorthy et al., 2021<sup>(10)</sup> and Aradóttir et al., 2019<sup>(8)</sup>, used titration algorithms  
 195 to titrate basal insulin either in a digital tool or in paper-based format. Aradóttir et  
 196 al., 2021<sup>(31)</sup> mixed the use of a mathematical model with use of a paper-based  
 197 titration algorithm. Titration algorithms varied considerably among included  
 198 studies, as approximately 18 algorithms were used. However, similar titration  
 199 algorithms were found in studies investigating paper-based titration algorithms and  
 200 telehealth solutions, e.g., the 2-0-2 titration algorithm.

#### 201 **3.4.2. Effect of the dose guidance methods**

202 Studies reported very heterogeneous glycemic outcomes (Supplementary material).  
 203 The most frequently reported outcome was proportion of participants reaching  
 204 glycemic target. However, this target differed among studies. Some studies used  
 205 HbA1c<7% as target, while others used fasting blood glucose within a specific range.  
 206 The difference in how target was defined made it challenging to compare effect  
 207 across studies. To enable a comparison to some degree to elucidate tendencies in  
 208 effect across different dose guidance methods, an overview of the proportion of  
 209 participants reaching target is presented in Figure 4. Approximately 23% of studies

210 did not report proportion of participants reaching target at end-of-  
 211 trial<sup>(8,10,33,40,45,57,58,62)</sup>.

212 **Figure 4.** Summary of the proportion of participants that reached a predefined  
 213 glycemic target. Only studies that reported target as either fasting blood glucose  
 214 within the target of 79-130 mg/dL, 90-130 mg/dL, or 72-108 mg/dL or HbA1c<7%  
 215 (marked with \*) is included in this figure.



216  
 217 Aradóttir et al., 2021<sup>(31)</sup> reported that all participants reached target with a mean  
 218 time to target of 44 days (n=8).

219 The mean proportion of participants reaching target in studies investigating  
 220 telehealth solutions was 61±20% when considering both targets and 46±29% when  
 221 only considering HbA1c targets. The mean for paper-based titration algorithms was  
 222 41±19% in both cases. This may indicate a tendency for a numerically larger  
 223 proportion of participants titrated using telehealth solutions to reach target  
 224 compared to paper-based titration algorithms.

225 Among these studies, few reported time-to-target. None of the studies about  
226 paper-based titration algorithms reported time-to-target. Three studies about  
227 telehealth solutions reported mean time-to-target, which ranged from 20-66  
228 days<sup>(30,54,59)</sup>. It should be noted that two of these studies investigated the same  
229 telehealth solution<sup>(54,59)</sup>. Since few studies have reported time-to-target, it is  
230 relevant to consider the mean study duration within the three categories to get an  
231 indication of time used to reach target. The mean duration of studies addressing  
232 paper-based titration algorithms was 22±9 weeks, 16±6 weeks for studies  
233 addressing telehealth solutions, and 11±2 weeks for studies addressing  
234 mathematical models, of which most were simulations. On average, study duration  
235 of studies investigating paper-based titration algorithms was twice as long as for  
236 mathematical models and six weeks longer than telehealth studies.

### 237 **3.4.3. User experience of the dose guidance methods**

238 User experience was investigated by 14 studies, of which 11  
239 studies<sup>(36,38,41,42,44,45,51,54-57)</sup> reported outcomes from standardized questionnaires  
240 (e.g., Diabetes Treatment Satisfaction Questionnaire (DTSQ)), three studies<sup>(35,57,60)</sup>  
241 reported outcomes from interviews, and three studies<sup>(35,58,59)</sup> reported outcomes  
242 from non-standardized questionnaires. Studies addressing mathematical models did  
243 not investigate user experience.

244 The studies reporting baseline changes in the DTSQ scores showed varying results  
245 (Supplementary material). For telehealth solutions, the change ranged from 0.8-  
246 10.1 and from 0.1 to 11.7 for paper-based titration algorithms. This revealed no  
247 apparent difference in the change of DTSQ score between the two methods.

248 From non-standardized questionnaires and interviews, HCPs and people with T2D  
249 found telehealth solutions convenient and appropriate for titration of basal

250 insulin<sup>(35,57,59,60)</sup>. Two of these studies investigated the same telehealth  
 251 intervention<sup>(59,60)</sup>. People with T2D found it convenient to have fewer in-person  
 252 interactions while maintaining contact with HCP via phone. In Rogers et al., 2019<sup>(60)</sup>,  
 253 HCPs found telehealth intervention could reduce the burden of titration. McGloin et  
 254 al., 2020<sup>(57)</sup> elucidated an increased workload among HCPs caused by a large  
 255 amount of generated data.

256 Only the study by Zhang et al., 2018<sup>(58)</sup> reported qualitative findings on the use of  
 257 paper-based titration algorithms. The study found a gap between preferences of  
 258 people with T2D and HCPs when choosing a titration algorithm. People with T2D  
 259 preferred simple and easy-to-use algorithms. In contrast, HCPs preferred algorithms  
 260 recommended by guidelines with higher perceived efficacy in lowering blood  
 261 glucose levels and were known to the HCP.

### 262 3.5 Critical appraisal of the studies

263 Table 2-6 shows the results of critical appraisal of the included studies.

264 **Table 2.** Summary of critical appraisal assessed by JBI Critical Appraisal Checklist for  
 265 Randomized Controlled Trials. U = Unclear, + = Yes, and - = No. Question 3: Red  
 266 marks visual inspection of between-group differences in baseline characteristics of  
 267 the population to determine if the groups were similar, and green marks studies  
 268 that performed statistical tests for the difference between groups. Question 9: Red  
 269 marks intention-to-treat analysis was carried out but did not describe how lost-to-  
 270 follow-up was handled. Green indicates that intention-to-treat analysis was carried  
 271 out with an explanation of how lost-to-follow-up was handled.

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	Risk of bias
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Yuan et al., 2021 <sup>(37)</sup>	+	+	+	-	-	-	+	+	+	+	+	+	+	+	Low
Bae et al., 2021 <sup>(38)</sup>	U	+	+	-	-	-	+	+	+	+	+	+	+	+	Moderate
Hu et al., 2021 <sup>(39)</sup>	+	U	+	-	-	-	+	+	-	+	+	+	+	+	Moderate
Lingvay et al., 2021 <sup>(50)</sup>	U	+	+	-	-	-	+	+	+	+	+	+	+	+	Moderate
Ishii et al., 2021 <sup>(56)</sup>	+	U	U	-	-	+	+	+	-	+	+	+	+	+	Moderate
Yu et al., 2020 <sup>(40)</sup>	U	U	+	-	-	-	+	-	-	+	+	-	+	+	High
Ji et al., 2020 <sup>(53)</sup>	U	U	+	-	-	+	+	+	-	+	+	+	+	+	Moderate
Misra et al., 2019 <sup>(41)</sup>	U	+	+	-	-	-	+	+	-	+	+	-	+	+	Moderate
Davies et al., 2019 <sup>(55)</sup>	U	U	+	-	-	-	+	-	+	+	+	-	+	+	High
Yale et al., 2017 <sup>(42)</sup>	U	U	+	-	-	-	+	+	+	+	+	-	+	+	Moderate
Kadowaki et al., 2017 <sup>(43)</sup>	U	U	+	-	-	-	+	-	+	+	+	+	+	+	Moderate
Bajaj et al., 2016 <sup>(44)</sup>	U	U	+	-	-	-	+	-	+	+	+	+	+	+	Moderate
Hsu et al., 2016 <sup>(45)</sup>	U	U	+	-	-	-	+	+	+	+	+	+	+	+	Moderate
Garg et al., 2015 <sup>(51)</sup>	+	+	+	-	-	-	+	-	+	+	+	+	+	+	Moderate
Levy et al., 2015 <sup>(54)</sup>	+	+	+	-	-	-	+	+	+	+	+	+	+	+	Low
Philis-Tsimikas et al., 2013 <sup>(46)</sup>	U	U	+	-	-	-	+	+	+	+	+	+	+	+	Moderate
Kim et al., 2010 <sup>(47)</sup>	+	U	U	-	-	-	+	+	-	+	+	+	+	+	Moderate
Blonde et al., 2009 <sup>(48)</sup>	U	U	+	-	-	-	+	+	+	+	+	+	+	+	Moderate
Meneghini et al. 2007 <sup>(52)</sup>	U	U	+	-	-	-	U	-	-	+	+	+	+	+	High
Kennedy et al., 2006 <sup>(49)</sup>	U	U	+	-	-	-	+	+	-	+	+	+	+	+	Moderate

272

273 **Table 3.** Summary of critical appraisal assessed by JBI Critical Appraisal Checklist for  
 274 Quasi-experimental studies, including assessment of the qualitative part of mixed-  
 275 methods studies. U = Unclear, + = Yes, and - = No. Question 2: red marks visual

276 inspection of between-group differences in baseline characteristics of the  
 277 population to determine if the groups were similar.

Study	1	2	3	4	5	6	7	8	9	Risk of bias
Tamez-Pérez et al., 2021 <sup>(30)</sup>	+	+*	+	-	+	-	+	+	+	Low
Aradóttir et al., 2021 <sup>(31)</sup>	+	+*	+	-	+	+	+	+	-	Low
McGloin et al., 2020 <sup>(57) m</sup>	+	+*	U	U	+	+	U	+	+	Moderate
Zhang et al., 2018 <sup>(58) m</sup>	+	+	+	+	+	-	U	U	+	Moderate
Levy et al., 2018 <sup>(59)</sup>	+	+*	+	-	+	+	+	+	+	Low
Hasan et al., 2018 <sup>(34)</sup>	+	+*	+	-	+	-	+	+	+	Low
Pfützner et al., 2016 <sup>(32)</sup>	+	U	+	U	-	+	+	+	U	Moderate
Larsen et al., 2010 <sup>(33)</sup>	+	+*	+	-	+	+	+	+	+	Low
Ngassa Piotie et al., 2022 <sup>(35)</sup>	+	+*	+	-	+	+	+	+	+	Low
Sethi et al., 2022 <sup>(36)</sup>	+	+*	+	-	+	+	+	+	-	Low

278 <sup>m</sup> Mixed method study.

279 \* Single-arm study.

280 **Table 4.** Summary of critical appraisal assessed by JBI Critical Appraisal Checklist for  
 281 qualitative studies, including assessment of the qualitative part of mixed-methods  
 282 studies. U = Unclear, + = Yes, and - = No.

Study	1	2	3	4	5	6	7	8	9	10	Risk of bias
McGloin et al., 2020 <sup>(57) m</sup>	+	+	+	+	+	-	-	+	+	+	Low
Rogers et al., 2019 <sup>(60)</sup>	-	U	U	U	U	-	-	+	+	+	High
Zhang et al., 2018 <sup>(58) m</sup>	U	U	U	U	U	-	-	U	+	U	High

283 <sup>m</sup> Mixed method study.

284 **Table 5.** Summary of critical appraisal assessed by JBI Critical Appraisal Checklist for  
 285 cohorts. U = Unclear, + = Yes, and - = No.

Study	1	2	3	4	5	6	7	8	9	10	11	Risk of bias
Seufert et al., 2019 <sup>(61)</sup>	+	+	+	-	-	+	+	+	U	U	U	Moderate

286

287 **Table 6.** Summary of critical appraisal assessed by the checklist in Fone et al.

288 2003(26) for simulation studies. Scores that can be given to a question; 0, 1, or 2

289 (poor to good). Overall indicated the overall score; A, B, C, or D (high to low risk of

290 bias).

Study	1	2	3	4	5	6	7	8	9	10	Overall
Krishnamoorthy et al., 2021 <sup>(10)</sup>	2	2	1	2	2	1	1	1	1	1	B
Sieber et al., 2020 <sup>(62)</sup>	2	2	2	1	2	1	1	1	1	2	B
Aradóttir et al., 2019 <sup>(68)</sup>	1	2	1	2	2	1	2	1	2	1	B

291

## 292 **4. Discussion**

### 293 **4.1 Summary of evidence**

294 The review aimed to provide an overview of dose guidance methods supporting

295 basal insulin titration of people with T2D and categorize these according to

296 characteristics, effects, and user experience. Overall results showed three

297 categories of methods: paper-based titration algorithms, telehealth solutions, and

298 mathematical models. Most studies investigated implementations of paper-based

299 titration algorithms. Studies investigating digital solutions for basal insulin titration

300 for people with T2D were limited to simple telehealth solutions and, in one case, a

301 mathematical model embedded into a decision support system. In summary, all

302 studies used titration algorithms either in paper form or digital, except for the  
303 mathematical models.

304 Similar findings are seen in Deerochanawong et al., 2017<sup>(19)</sup>, which highlighted use  
305 of paper-based titration algorithms and telehealth solutions when investigating  
306 titration of insulin glargine 100 U/mL in an Asian population. However, use of  
307 mathematical models was not reported. Furthermore, Kerr et al., 2022<sup>(69)</sup> found  
308 indications for improved glycemic control when using digital solutions to manage  
309 T2D treatment compared to standard of care. This is further supported by Hangaard  
310 et al., 2021<sup>(70)</sup>, which found a significant improvement in HbA1c when using  
311 telemedicine among people with T2D. These studies did not focus on basal insulin  
312 titration but overall treatment of people with T2D. However, it is feasible to assume  
313 that a similar effect may be seen using telemedicine for titrating basal, which aligns  
314 with the tendency observed in this review.

315 User experience was not investigated thoroughly by included studies. Yet, common  
316 characteristics were the wish of people with T2D for simple and easy-to-use  
317 solutions and HCPs' attention to effect on workload. Concerning telehealth  
318 solutions, HCPs, in some cases, uttered concern about increased data being  
319 generated compared to standard practice affecting workload<sup>(57)</sup>. None of the  
320 studies investigating mathematical models looked at user experience. Consideration  
321 of user experience when developing methods for basal insulin dose guidance is  
322 essential to ensure a holistic solution aimed at the intended end-user and thereby  
323 to secure effect in a real-world setting<sup>(71)</sup>. Especially considering solutions aimed at  
324 people with T2D due to known issues of non-adherence to treatment<sup>(72,73)</sup>.

325 **4.2 Strengths and limitations**



326 The broad scope and comprehensive literature strengthen the present systematic  
327 review. However, relevant studies may have been overlooked since the search was  
328 limited to use of basal insulin analogs and English, Danish, Norwegian, and Swedish  
329 language.

330 The heterogeneity of reported glycemic outcomes and differences in study design  
331 complicated comparison of effect.

332 Validity of the review is weakened since mainly one reviewer screened the search  
333 results. To minimize this effect, co-authors were continuously consulted to clarify  
334 doubts about inclusion of studies and during critical appraisal. Furthermore, the  
335 review was strengthened since the structured search was performed with  
336 assistance from a research librarian, ensuring a thorough search.

#### 337 **4.3 Implications for future research**

338 Mathematical models were limited to three studies which were mainly evaluated  
339 through simulation. Expect a study by Aradóttir et al., 2021<sup>(31)</sup> where the solution  
340 was tested on eight participants showing promising results. Limited use of  
341 mathematical models may be due to the complex nature of T2D and heterogeneity  
342 of the population caused by varying insulin sensitivity and production. This  
343 complicates modelling of insulin's effect on blood glucose. The modelling task is  
344 further complicated by the limited available information about people with T2D.  
345 Glucose measures are typically performed using glucometers, and frequency of  
346 these measures varies depending on the individual in question.

347 In contrast, people with type 1 diabetes more often use continuous glucose  
348 monitoring to measure blood glucose, enabling more thorough insight into blood

349 glucose levels throughout the day<sup>(74–76)</sup>. Similar challenges have been recognized by  
350 studies addressing mathematical models<sup>(10,68)</sup>.

351 New technologies enabling improved data collection might ease some challenges in  
352 modeling insulin's effect on blood glucose levels for people with T2D using  
353 mathematical models. Kerr et al., 2022<sup>(69)</sup> highlight that new technology that  
354 supports improved data capturing may facilitate better treatment support when  
355 combined with dose recommendation software. Furthermore, addition of  
356 automated data-driven dose guidance might help rectify the increased workload for  
357 HCP that, in some cases, has been reported when introducing new technology<sup>(77)</sup>.

358 At the time of writing, machine learning methods used for problems related to T2D  
359 have focused on detection or prediction of hypoglycemic events, blood glucose  
360 levels, and optimal bolus insulin dosing<sup>(78)</sup>. In the future, exploring the capability of  
361 machine learning methods for basal insulin dose guidance for people with T2D may  
362 provide insight into the field that could pioneer future research.

## 363 **5. Conclusions**

364 Three basal insulin dose guidance categories aimed at people with T2D were  
365 identified: paper-based titration algorithms, telehealth solutions, and mathematical  
366 models. Compared to paper-based titration algorithms, a numerically larger  
367 proportion of participants reached a predefined target using telehealth solutions.

368 Few studies investigated user experience. Some studies underlined a possible  
369 increase in workload when using telehealth solutions due to increased data.

370 However, it was found that people with T2D preferred simple and easy-to-use  
371 solutions and fewer in-person visits.

372 Future work might benefit from exploring the capabilities of machine learning  
373 methods for basal insulin dose guidance for people with T2D, focusing on a simple  
374 and easy-to-use method that does not increase the workload for HCPs.

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### 378 **Conflict of interest**

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381 Author M.H.J is a former Novo Nordisk employee and holds Novo Nordisk shares.

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