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CLINICAL APPLICATIONS

Common Standards of Basal Insulin Titration in T2DM

Sabine Arnolds, M.D.,[1] Tim Heise, M.D.,[1] Frank Flacke, Ph.D.,[2] and Jochen Sieber, M.D.[2]

Abstract

Type 2 diabetes mellitus has become a worldwide major health problem, and the number of people affected is steadily increasing. Thus, not all patients suffering from the disease can be treated by specialized diabetes centers or outpatient clinics, but by primary care physicians. The latter, however, might have time constraints and have to deal with many kinds of diseases or with multimorbid patients, so their focus is not so much on lowering high blood glucose values. Thus, the physicians, as well as the patients themselves, are often reluctant to initiate and adjust insulin therapy, although basal insulin therapy is considered the appropriate strategy after oral antidiabetic drug failure, according to the latest international guidelines. A substantial number of clinical studies have shown that insulin initiation and optimization can be managed successfully by using titration algorithms—even in cases where patients themselves are the drivers of insulin titration. Nevertheless, tools and strategies are needed to facilitate this process in the daily life of both primary health care professionals and patients with diabetes.

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Introduction

There is a worldwide increase in the prevalence and incidence of diabetes, with new figures indicating a rise from 366 million people concerned in 2011 to 552 million by 2030.[1] The majority of these cases relate to type 2 diabetes mellitus (T2DM) and have to be seen in the context of increased obesity rates and a westernized, sedentary lifestyle. Type 2 diabetes patients face a dramatically increased risk of cardiovascular and cerebrovascular morbidity and mortality. It can be anticipated that the predicted rise in the prevalence of T2DM[2] and the trend to develop diabetes earlier in life will lead to a further increase in diabetes complications, including also diabetic visual impairment, renal failure, and amputations.[3]

This review will give an overview on basal insulin therapy for T2DM in daily life, taking into account recommendations by international guidelines, the use of titration algorithms, and future perspectives for patients and primary care physicians. A PubMed search was performed, and clinical studies/scientific articles were considered until June 1, 2012.

Author Affiliations: [1]Profil, Neuss, Germany; and [2]Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany

Abbreviations: (ADA) American Diabetes Association, (EASD) European Association for the Study of Diabetes, (FBG) fasting blood glucose, (FPG) fasting plasma glucose, (HbA1c) hemoglobin A1c, (IDF) International Diabetes Federation, (NICE) National Institute for Health and Clinical Excellence, (NPH) neutral protamine Hagedorn, (OAD) oral antidiabetic, (SIGN) Scottish Intercollegiate Guidelines Network, (T2DM) type 2 diabetes mellitus

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Corresponding Author: Sabine Arnolds, M.D., Profil, Neuss, Germany, Hellersbergstr. 9, D-41460 Neuss, Germany; email address sabine.arnolds@profil.com

Treatment of T2DM: What Do Diabetes Guidelines Recommend?

Quite a number of national[4–7] and international[8–10] guidelines on the treatment of T2DM exist. Apart from those published by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the International Diabetes Federation (IDF), which presumably represent the most influential guidelines within the diabetes community, other guidelines, e.g., those of the World Health Organization, the National Institute for Health and Clinical Excellence (NICE), or the Scottish Intercollegiate Guidelines Network (SIGN), are also well-known and respected.

All guidelines give recommendations on glycemic targets for T2DM [hemoglobin A1c (HbA1c), blood glucose values], on blood glucose self-monitoring by the patients, and on therapeutic options, including specific treatment regimens. The aforementioned guidelines, however, vary considerably—not only in size and scope, but also with regard to time and mode of insulin initiation and with regard to targets (HbA1c). While the EASD, the IDF, and the German Diabetes Association in their evidence-based guidelines refer to a target HbA1c <6.5%, the ADA and the IDF recommend a target HbA1c <7.0%, and the SIGN recommends a cutoff of 7.0%. The NICE sets the highest glycemic target, with an HbA1c <7.5%.

The latest ADA/EASD position statement on the management of hyperglycemia in T2DM[8] emphasizes a flexible patient-centered treatment approach: "Ultimately, it is patients who make the final decisions regarding their lifestyle choices and, to some degree, the pharmaceutical interventions they use; their implementation occurs in the context of the patients' real lives and relies on the consumption of resources (both public and private)." The importance of a partnership between the patient and the physician and the involvement of the patient in medical decisions in order to support adherence to therapy is highlighted in the statement.

After initial drug monotherapy, i.e., usually metformin, the ADA/EASD position statement on its two-drug combinations already mentions insulin, which ideally should be a basal insulin [neutral protamine Hagedorn (NPH) insulin, insulin glargine, insulin detemir], most commonly given in combination with one or two noninsulin agent(s). "Insulin is typically begun at a low dose (e.g. 0.1-0.2 U kg^{-1} day^{-1}), although larger amounts (0.3-0.4 U kg^{-1} day^{-1}) are reasonable in the more severely hyperglycemic."[8] Noteworthy, the authors state that most patients—on the condition that daily self-monitoring of blood glucose occurs during this phase—can be taught to up-titrate their own insulin dose based on several algorithms,[11,12] each essentially involving the addition of a small dose increase, e.g., 1–2 U (for those patients already on higher doses, increments of 5–10 %), to the daily dose once or twice weekly if the fasting blood glucose (FBG) levels are above the pre-agreed target.[13] Dose adjustments should be more modest and less frequent as the target comes close (frequency of self-monitoring of FBG also to be reviewed), and down-titration is recommended in case of occurrence of any hypoglycemia. During self-titration, frequent contact with the physician may be necessary. Remarkably, the position statement points out that practitioners themselves, of course, could also titrate basal insulin but that this would involve more intensive contact with the patient than typically available in routine medical care. Basal insulin should primarily be titrated against the FBG—generally irrespective of the total dose—although the physician should be aware that prandial insulin might be needed if the daily dose exceeds 0.5 U/kg/day or already approaches 1 U/kg/day.[8]

Treatment of T2DM: Who Is Treating Patients with T2DM, and What Are the Challenges?

Given the estimate of an increasing number of people with T2DM on the one hand and the limited availability of health care resources on the other hand, it is easy to conclude that there is an obvious mismatch between supply and demand. It already is and will continue to be unfeasible to treat all patients with T2DM in specialized diabetes clinics or diabetes outpatient centers. The the majority of patients are and continue to be treated in a primary care setting, i.e., by their general practitioner.

These primary care providers, however, are often reluctant and apprehensive about using insulin in patients with T2DM.[14,15] Their concerns/fears are related to the following:

- Lack of confidence in patient's ability to manage insulin therapy,
- Fear of hypoglycemia,
- Presumed unwillingness and/or inability of the patient to inject insulin,
- Complexity of insulin therapy is considered too difficult to be managed in a busy primary care practice,
- Uncertainties regarding initial insulin dosing and titration due to vague prescribing information provided by manufacturers, and
- Difficult logistics of communicating with the patient during/after insulin initiation and titration.

These factors could lead to an undue delay in making the necessary transition from oral agents to insulin.[14] Study data show that mean HbA1c levels are ≥9.0% (one-third >10.0%) and mean diabetes duration is 9.3 years prior to first insulinization with basal insulin in patients with T2DM in a real-world setting in Asia.[16] Data from other countries show similar figures.[17] This frequently observed delay in initiating necessary insulin treatment often leads to prolonged hyperglycemia and increases the risk of diabetes complications.[18]

In another investigation[19] on diabetes knowledge carried out among internal medicine residents, family practice residents, surgery residents, and registered nurses, a 21-question survey revealed similar, but insufficient, levels of knowledge in these groups. Surgery residents had a more pronounced deficit of diabetes knowledge, whereas additional previous diabetes training among nurses was associated with greater diabetes knowledge.

Patients also have several barriers to insulin initiation. These include

- Lack of self-confidence to manage insulin therapy,[20]
- Multifactorial psychological resistance to insulin therapy,[21]
- Fear of hypoglycemia,[22]
- Weight gain,[22]
- Need for frequent blood glucose monitoring,[23]
- Pain associated with needle use,[22] and
- Negative self-perceptions regarding insulin use (insulin, e.g., is regarded as sign of failure[24] or is considered to be responsible for a serious decline in health or for the onset of complications[22] and is sometimes also considered as punishment, and such psychological problems might negatively affect self-care[24]).

Taking the aforementioned issues into account, it is not surprising that insulin initiation occurs only in a minority (approximately 5%) of patients per year from diagnosis or first prescription of oral antidiabetic (OAD) agents, then increases to 10% per year following failure of combination OAD treatment.[25]

Nevertheless, insulin initiation with basal insulin including insulin analog in patients with T2DM can be managed successfully in both primary and secondary care, as shown in a 3-month longitudinal observational study across 761 centers in France;[22] mean HbA1c and FBG values decreased by 1.3% and 56 mg/dl from baseline, and rates of hypoglycemia were low compared with NPH insulin. The first basal insulin evaluation (or FINE) Asia study[16] also demonstrated effective and safe insulin initiation in 2679 patients from 11 Asian countries in a real-world setting.

Basal Insulin Therapy and Basal Insulin Titration Algorithms for T2DM: What Is the Evidence from Clinical Trials?

A number of reviews and meta-analyses or pooled analyses deal with basal insulin therapy, including insulin initiation and titration algorithms for T2DM.[15,25–36] One conclusion is that once-daily basal insulin added to oral medication is an ideal start.[30,36] A pooled analysis of 11 prospective randomized clinical trials involving 2171 adults with uncontrolled T2DM[30] investigated early initiation of insulin glargine—following a specific titration algorithm—added to metformin with or without sulfonylurea. Largest 24-week HbA1c reductions were observed for patients on 0 or 1 OAD or on metformin monotherapy at baseline; 68.1% of patients on metformin monotherapy + insulin glargine achieved an HbA1c ≤7.0%. Weight gain was also lowest when basal insulin was added to metformin, as were hypoglycemic events. Another previous systematic review and meta-analysis[33] found greater HbA1c reductions in insulin-naïve patients treated with biphasic or prandial insulin compared with basal insulin, but at the expense of higher FBG, more hypoglycemic events, and greater weight gain. A later review[25] stresses the urgent need of more simple, clear, consistent, and sustainable treatment regimens and guidelines. The authors also emphasize that enforced intensification of unrealistic complex treatment regimens and glycemic targets may theoretically worsen the psychological wellbeing of some patients.

In addition, numerous studies have been published on basal insulin therapy in patients with T2DM and on basal insulin regimen in combination with OADs or short-acting insulins with specific titration algorithms.[11–13,37–55] **Table 1** provides an overview of these key studies and their intervention details. In the three-year 4-T study,[44] 708 subjects with T2DM and poor glycemic control on metformin and sulfonylurea were randomly assigned to get basal insulin detemir or biphasic insulin aspart or prandial insulin aspart. The basal insulin regimen, which was equivalent to the other treatments after the first year in patients with HbA1c levels of ≤8.5%, was superior to both prandial and biphasic insulin after 3 years with regard to the rate of hypoglycemic events and weight gain. Thus, the three-year 4-T trial also supports the initiation of basal insulin. This is supported by the concept that fasting hyperglycemia has a greater impact on HbA1c levels than has postprandial hyperglycemia, which was demonstrated earlier by Monnier and coauthors;[56] the relative contribution of fasting hyperglycemia to HbA1c levels increased gradually as diabetes proceeded, whereas that of postprandial glucose excursions was prevailing in fairly well-controlled patients. Therefore, this also emphasizes the need to focus on FBG during insulin therapy—especially basal insulin therapy—in T2DM.

The 22 clinical trials cited investigated basal insulin therapy together with the use of different treatment algorithms, either directed by the clinic/physician—with or without central enforcement—or by the patients themselves. All trials have consistently shown substantial improvements in glycemic control as indicated by reductions in HbA1c values and FBG together with a low number of hypoglycemic episodes.

The following important aspects however, should be noted when evaluating basal insulin titration algorithms (see **Appendix 1** for details including studies):

- *Starting insulin dose:*
  The majority of the studies used 10 U per day.
- *Fasting Blood Glucose target:*
  The majority of trials set an FBG target of 100 mg/dl.
- *Insulin titration steps:*
  Most algorithms stated steps of 2 U.
- *Insulin titration frequency:*
  This primarily was twice per week or every 3 days.
- *The driver of the titration (physician- versus patient-driven insulin titration):*
  Patients were found to be as good as physicians in titration.

- *Efficacy of the titration algorithm in terms of HbA1c and FBG:*
  All studies found improvements in HbA1c and FBG.

- *Safety of the titration algorithm in terms of hypoglycemic episodes:*
  Hypoglycemia rates were low in all key studies.

- *Concomitant antidiabetic medication(s):*
  Metformin was continued in all studies.

- *Other factors with potential impact on basal insulin titration:*
  (a) Day-to-day blood glucose variability,
  (b) Insulin dose, and
  (c) Practicability and complexity of titration algorithms.

What Are the Future Perspectives?

Taking all aspects together, there appears to be an apparent gap between international guideline recommendations, the results of clinical trials, and real-life clinical practice[25] as far as basal insulin initiation and treatment optimization in T2DM—including titration algorithms—is concerned. Putting this in the context of exploding diabetes prevalence rates in the near future and the necessity to treat patients at a general practitioner's level, strategies and tools are urgently needed to help both patients and primary care physicians efficiently initiate and continue basal insulin therapy.

One pilot trial investigated the translation of comparative effectiveness into practice by developing and using a decision aid tool, which proved to be acceptable to patients and providers and effective for knowledge translation.[57] Another study evaluated the effectiveness of a computerized order template for basal–bolus insulin among internal medicine resident teams in acute general medical floors. Use of the template was associated with improved mean blood glucose levels without increasing hypoglycemia in patients with T2DM.[58] Safety and efficacy of weekly dose adjustments has been demonstrated in a feasibility study in type 1 and T2DM.[59] Participation of general practitioners in quality assurance programs (repeated audit cycles) led to improved diabetes management in an investigation in Western Australia.[60] As a result of another survey,[19] repeated training provided to general practitioners and diabetes nurses might also lead to improvements in diabetes knowledge and therapy.

Another option could consist of automated insulin dose calculators as supportive tools for both patients with T2DM starting basal insulin therapy and the primary care physician who is treating these patients. Such calculators already exist for bolus insulin (primarily for insulin pumps or intensive care units), and several studies on such devices or programs have been published.[61–70] It is imaginable that the availability of basal insulin dose calculators that incorporate basal insulin titration algorithms—under the condition that the previously mentioned issues are taken into account—assists patients and physicians in real life and leads to substantial improvements of diabetes control. This improvement of diabetes control should be proven in controlled trials.

One major and still unmet need in diabetes therapy is therefore the translation of simple and effective treatment strategies to daily practice and the empowerment of patients who need insulin to self-manage this therapy. The first step to achieve this aim would be to strengthen the self-confidence of patients to master the initiation of insulin treatment, to address their fears, and to provide practical and effective algorithms for initiation and subsequent dose adaptation of insulin administration.

Summary and Conclusion

Type 2 diabetes has become a major health burden with further increasing prevalence rates. The majority of patients already is and will be treated by primary care physicians. The current joint position statement of the ADA and the EASD points out the importance of basal insulin therapy in T2DM. Numerous clinical trials have shown that basal insulin can be initiated successfully using basal insulin titration algorithms. Such algorithms can even be handled

Table 1.
Titration Algorithms Used in Key Clinical Trials[a]

First author	Study/ number of patients	Intervention/OAD continued (yes/no)	Starting dose (U/day) + FBG or FPG target (mg/dl)	Titration algorithm	Titration frequency	Titration managed by	HbA1c (%) start	HbA1c (%) end	Hypoglycemic events: all or <70	Hypoglycemic events: severe
Riddle[12]	24-week treat-to-target trial *n* = 756	Insulin glargine or NPH once daily at bedtime Yes (91% two, rest one)	10 U/day FPG ≤ 100	If mean FPG (mg/dl) over previous three days 100–120 → 0–2 U↑ 120–140 → 4 U↑ 140–180 → 6 U↑ ≥180 → 8 U↑ and no plasma glucose <56 mg/dl	Weekly	Clinic + central enforcement	Insulin glargine 8.6 NPH 8.6	Insulin glargine 7.0 NPH 7.0	Insulin glargine 9.2/patient year NPH 12.9/ patient year	2.5% patients NPH 1.8% patients
Fritsche[41]	4001 Study, 28 weeks *n* = 695	Glimepiride + morning or bedtime insulin glargine or bedtime NPH	According to formula: [FPG (mg/dl) - 50]/10 FBG ≤ 100 mg/dl	If FBG > 100, 120, 140, or 160 mg/dl for at least one of two consecutive days before the visit with no hypoglycemia → 2, 4, 6, or 8 U↑	Every visit (1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 weeks after randomization	Physician	Insulin glargine 9.1 NPH 9.1	Insulin glargine 8.1 NPH 8.3	Insulin glargine 43% patients NPH 58% patients	Insulin glargine 0.04/ patient year NPH 0.12/ patient year
Davies[13]	AT.LANTUS *n* = 4961	Insulin glargine (± OADs/prandial insulin)	10 U/day for insulin-naïve patients for algorithm 1; numerically equivalent to the highest FBG over the previous seven days for algorithm 2 FBG ≤ 100 mg/dl	Clinic-managed titration (algorithm 1): as in Riddle[12] study Patient-managed titration (algorithm 2): mean FBG for the previous three consecutive days: 100–120 mg/dl → 0–2 U↑ (at investigator discretion), 120–139 mg/dl → 2 U↑, 140–179 mg/dl → 4 U↑, ≥180 mg7dl → 6–8 U↑ (at investigator discretion) Only if no plasma glucose <72 mg/dl	Weekly (clinic) versus every three days (patient)	Physician (algorithm 1) versus patient (+ investigator review; algorithm 2)	Physician 8.9 Patient 8.9	Physician 7.9 Patient 7.7	Physician 26% patients Patient 30% patients	Physician 0.9% patients Patient 1.1% patients

Continued→

Table 1. Continued

First author	Study/ number of patients	Intervention/OAD continued (yes/no)	Starting dose (U/day) + FBG or FPG target (mg/dl)	Titration algorithm	Titration frequency	Titration managed by	HbA1c (%) start	HbA1c (%) end	Hypoglycemic events: all or <70	Hypoglycemic events: severe
Raskin[50]	28-week study *n* = 233	Insulin glargine versus biphasic insulin aspart 70/30; yes	10 U/day if FPG < 180 mg/dl, 12 U/d if FPG ≥ 180 mg/dl FPG 80–110 mg/dl	Titration as in Riddle[12] study	Weekly for the first 12 weeks, then every 2 weeks	Investigator	Insulin glargine 9.8 Biphasic insulin aspart 9.7	Insulin glargine 7.4 Biphasic insulin aspart 6.9	Insulin glargine 16% patients (minor hypoglycemia) Biphasic insulin aspart 43% patients (minor hypoglycemia)	Insulin glargine 1 patient Biphasic insulin aspart 0 patient
Gerstein[42]	24-week INSIGHT study *n* = 405	Insulin glargine + OAD versus insulin avoidance	10 U/day FPG ≤ 100 mg/dl	After the start with 10 U/day, increase by 1 U/ day until FPG target is reached		Patient (for insulin glargine)	8.6	7.0	49% patients	
Hermansen[43]	24-week study *n* = 476	Insulin detemir or NPH; yes	10 U/day FPG ≤ 108 mg/dl	Responders (nonresponders): FPG (mg/dl) >180 → 10 (10) U↑, 163–180 → 6 (8) U↑, 145–162 → 4 (6) U↑, 127–144 → 2 (4) U↑, 109–126 → 2 (2) U↑; if one prebreakfast plasma glucose: 56–72 → 2↑, <56 → 4↑	Weekly (first 12 weeks), then every 2 weeks	Clinic or telephone contacts	8.5	6.6	16.0/patient year	0.08/patient year

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Table 1. Continued

First author	Study/ number of patients	Intervention/OAD continued (yes/no)	Starting dose (U/day) + FBG or FPG target (mg/dl)	Titration algorithm	Titration frequency	Titration managed by	HbA1c (%) start	HbA1c (%) end	Hypoglycemic events: all or <70	Hypoglycemic events: severe
Kennedy[46]	24-week GOAL A1C study *n* = 7893	Insulin glargine usual versus active titration; yes (except for thiazolidinediones)	10 U/day FBG ≤ 100 mg/dl	Usual titration = patient instruction at study visits (every 6 weeks) + no contacts between visits; active titration = weekly contacts (telephone, email, fax) + titration reinforcement; if FBG (mg/dl) 100–119 → 0–2 U↑, 120–139 → 2 U↑, 140–159 → 4 U↑, 160–179 → 6 U↑, ≥180 → 8 U↑; if <70 → dose↑ to previous level; if severe hypoglycemia (self-monitoring of blood glucose < 36) → stop of upward titration for 1 week; if HbA1c >8.0% after visit 1, increase of insulin glargine at investigator's discretion of up to 5 U	weekly	Patient versus Central oversight in a predominantly primary care setting	Patient 8.9 Central 8.9	Patient 7.6 Central 7.3	Patient 3.7/patient year Central 6.0/patient year	Patient 0.09/patient year Central 0.14/patient year
Yki-Järvinen[53]	36-week LANMET Trial *n* = 110	Bedtime insulin glargine versus NPH; yes	10 U/day for all patients using only metformin; 20 U/day if on metformin + sulfonylurea + stop of sulfonylurea FPG 72–100 mg/dl	Patient-managed titration: 2 U↑ if FPG >100 mg/dl on three consecutive days and 4 U↑ if > 180 mg/dl; stop titration if ≥1 hypoglycemic event	Every 3 days	Patient (+ clinic assistance)	Insulin glargine 9.1 NPH 9.3	Insulin glargine 7.1 NPH 7.2	Insulin glargine 5.0/patient year NPH 7.7/ patient year	Insulin glargine 0.00/patient year NPH 0.00/ patient year

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Table 1. Continued

First author	Study/ number of patients	Intervention/OAD continued (yes/no)	Starting dose (U/day) + FBG or FPG target (mg/dl)	Titration algorithm	Titration frequency	Titration managed by	HbA1c (%) start	HbA1c (%) end	Hypoglycemic events: all or <70	Hypoglycemic events: severe
Holman[11,44]	One-year 4-T study *n* = 708 Three-year 4-T	Basal versus biphasic versus prandial insulin	According to formula; median dose in basal group: 16 U FPG and premeal plasma glucose 72–99 mg/dl, 2 h postprandial 90–126 mg/dl	Titration suggested by the trial management system based on three self-monitoring of blood glucose profiles (morning and evening for basal group) before the visits at weeks 2, 6, 12, 24, 38, and 52	At visits and between visits, if necessary	Investigator + online trial management system (investigator and patient were encouraged to vary or amend suggested doses, if necessary)	Basal 8.4 Biphasic 8.6 Prandial 8.6	Basal 7.6 Biphasic 7.3 Prandial 7.2	Basal 73.9% patients Biphasic 91.9% patients Prandial 96.2% patients	Basal 1.7% patients Biphasic 4.7% patients Prandial 6.7% patients
Meneghini[48]	26-week PREDICTIVE 303 TRIAL *n* = 5604	Insulin detemir as add-on to OAD or as replacement of prestudy insulin	Mean dose on day 1 was 0.32 U/kg for patient-driven titration and 0.34 U/kg for physician-driven standard-of-care titration FPG 80–110 mg/dl	Patient-managed titration: every three days, mean-adjusted FPG (mg/dl) <80→ 3U↓, 80–110 → no change, > 110 → 3U↑ Physician-managed titration: according to standard of care	Every three days (patients); according to standard-of-care (physician)	Patient versus physician	Patient 8.5 Physician 8.5	Patient 7.9 Physician 8.0	Patient 6.44/patient year Physician 4.95/patient year	Patient 0.26/patient year Physician 0.20/patient year
Yki-Järvinen[54]	24-week INITIATE study *n* = 121	Insulin glargine; yes	10 U/day FPG 72–100 mg/dl	If FPG (mg/dl) for three consecutive days: >99 → 2–4 U↑, 72–100 → no change, <72 and symptomatic hypoglycemia → 2 U↓		Patient (+ individual versus group education)	Patient + individual education 8.7 Patient + group education 8.8	Patient + individual education 6.9 Patient + group education 6.8	Patient + individual education 3.5/patient year Patient + group education 3.1/patient year	Patient + individual education 0.0/patient year Patient + group education 0.0/patient year

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Table 1. Continued

First author	Study/ number of patients	Intervention/OAD continued (yes/no)	Starting dose (U/day) + FBG or FPG target (mg/dl)	Titration algorithm	Titration frequency	Titration managed by	HbA1c (%) start	HbA1c (%) end	Hypoglycemic events: all or <70	Hypoglycemic events: severe
Bergenstal[39]	24-week study *n* = 273	Insulin glargine + insulin glulisine; Yes (metformin)	50% of prerandomization total daily insulin dose FBG < 95 mg/dl	Titration for both insulin glargine and insulin glulisine, based on mean of last three-day self-monitoring of blood glucose; insulin glargine titration: if >180→8 U↑, 140–180→6 U↑, 120–139→4 U↑, 95–119→2 U↑, 70–94→no change, <70→decrease by the same number of units as insulin glulisine increase that titration week or up to 10% of total insulin glargine dose	Weekly	Patient (simple algorithm versus carbohydrate counting)	Patient + simple algorithm 8.1 Patient + carbohydrate count 8.3	Patient + simple algorithm 6.7 Patient + carbohydrate count 6.5		Patients + simple algorithm 0.89/patient year Patients + carbohydrate count 0.67/patient year
Rosenstock[51]	52-week study *n* = 582	Insulin detemir and insulin glargine + OAD	12 U/day FPG ≤ 108 mg/dl	Titration based on the average of 3 FPG (mg/dl); responders (nonresponders): if >180→12 (12) U↑, 164–180→8 (10) U↑, 146–162→6 (8) U↑, 128–144→4 (6) U↑, 110–126→2 (2) U↑, if one self-monitoring of blood glucose 56–72→2 U↓, <56→4 U↓	Weekly	Investigator + titration monitoring committee	Insulin detemir 8.6 Insulin glargine 8.6	Insulin detemir 7.2 Insulin glargine 7.1	Insulin detemir 5.8/patient year Insulin glargine 6.2/patient year	Insulin detemir 0.0/patient year Insulin glargine 0.0/ patient year

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Table 1. Continued

First author	Study/ number of patients	Intervention/OAD continued (yes/no)	Starting dose (U/day) + FBG or FPG target (mg/dl)	Titration algorithm	Titration frequency	Titration managed by	HbA1c (%) start	HbA1c (%) end	Hypoglycemic events: all or <70	Hypoglycemic events: severe
Kawamori[45]	24-week trial *n* = 100 (Japanese)	Insulin glargine + glimepiride	6 U/day, if FPG ≥ 140 mg/dl; (less, if lower FPG) FPG 72–100 mg/dl	Titration according to mean self-monitoring of blood glucose of the previous two days; if FPG (mg/dl): ≥110→2 U↑, 101–109→1–2 U↑, 72–100→no change, 60–71→1 U↓, <60→2 U↓	Every 3 days	Investigator	9.3	7.8	60% patients	0
Blonde[40]	20-week TITRATE Trial *n* = 244	Insulin detemir3 once daily, insulin-naïve patients on OAD; yes (dose reduction or stop of OAD allowed)	0.1–0.2 U/kg or 10 U/day (1) FPG 70–90 mg/dl (2) FPG 80–110 mg/dl	Two FPG (mmol/liter) titration targets: (1) 3.9–5.0, (2) 4.4–6.1. titration as in PREDICTIVE[48]	Every 3 days	Patient	FPG lower target group 7.99 FPG higher target group 7.94	FPG lower target group 6.77 FPG higher target group 7.00	FPG lower target group 7.53/patient year FPG higher target group 5.27/patient year	FPG lower target group 0.02/patient year FPG higher target group 0.00/patient year
Liebl[47]	26-week PREFER study *n* = 719	Insulin detemir + insulin aspart or biphasic insulin aspart 30; no	10 U/day or same dose, if on insulin before FPG 72–126 mg/dl	Insulin detemir titration; if FPG (mg/dl) >200 →10 U↑, 181–200→8 U↑, 163–180→6 U↑, 141–160→4 U↑, 127–140→2 U↑, 57–72→2 U↓, <56→4 U↓	Weekly for the first 6 weeks	Investigator	Insulin detemir + insulin aspart 8.52 Biphasic 8.40	Insulin detemir + insulin aspart 6.96 Biphasic 7.17	Insulin detemir + insulin aspart 31% Biphasic 28% patients	Insulin detemir + insulin aspart 0.9% patients Biphasic 0.0% patients
Arnolds[37]	Four-week proof-of concept study	Insulin glargine + metformin versus insulin glargine + metformin + exenatide versus insulin glargine + metformin + sitagliptin	10 U/day, if new to insulin FBG ≤ 100 mg/dl	Titration based on daily self-monitoring of blood glucose; 20% insulin glargine dose reduction in sitagliptin and exenatide groups two days prior to this medication; titration similar to Riddle[12]	Weekly visits + twice weekly telephone contacts with dose titration	Investigator	Insulin glargine + metformin 7.9 Insulin glargine + metformin + exenatide 8.4 Insulin glargine + metformin + sitagliptin 7.9	Insulin glargine + metformin 6.7 Insulin glargine + metformin + exenatide 6.5 Insulin glargine + metformin + sitagliptin 6.4	Insulin glargine + metformin 1.62/patient year Insulin glargine + metformin + exenatide 1.68/patient year Insulin glargine + metformin + sitagliptin 2.45 (blood glucose < 50mg/dl)	No severe hypoglycemia in all three groups

Continued→

Table 1. Continued

First author	Study/ number of patients	Intervention/OAD continued (yes/no)	Starting dose (U/day) + FBG or FPG target (mg/dl)	Titration algorithm	Titration frequency	Titration managed by	HbA1c (%) start	HbA1c (%) end	Hypoglycemic events: all or <70	Hypoglycemic events: severe
Owens[49]	Six-month study *n* = 106	Insulin glargine alone versus insulin glargine + one dose of insulin glulisine	Transfer from previous insulin to insulin glargine FBG ≤ 100 mg/dl	Insulin glargine titration as in Riddle[12] study; two titration algorithms for insulin glulisine	Weekly	Investigator	Insulin glargine 8.6 Insulin glargine + glulisine 8.5	Insulin glargine 7.8 Insulin glargine + glulisine 7.5	Insulin glargine 11.5/patient year Insulin glargine + glulisine 13.4/patient year	Insulin glargine 0.2/patient year Insulin glargine + glulisine 0.0/patient year
Aschner[38]	24-week study EASIE *n* = 480	Insulin glargine + metformin versus sitagliptin + metformin	0.2 U per kg body weight FPG 72–99 mg/dl	If FPG > 100–139 2U↑, if FPG > 139 4U↑, if FPG < 72 2U↓	Weekly	Patient	Glargine 8.5 Sitagliptin 8.5	Insulin glargine -1.72 Sitagliptin -1.13	Insulin glargine 4.21/patient year Sitagliptin 0.50/patient year	Insulin glargine 0.03/patient year Sitagliptin 0.01/patient year
ATLAS Study Group[52]	Six-month ATLAS study, only rationale published *n* = 554	Insulin naïve, on two OADs	10 U/d (less for India and Japan) FPG 110 mg/dl	If middle value of the last three consecutive FBG (mg/dl), ≤56→dose decrease, ≤70 or symptomatic hypoglycemia→2 U↓, 71–110→ no change, 111–160→2 U↑, >160→4 U↑	Every three days (patient-led group); every visit (physician-led group)	Patient versus physician				
Zinman[55]	16-week study *n* = 245	Insulin-naïve, on metformin; IDeg[b] three times/ week versus once/ day versus insulin glargine once/day	IDeg three times/ week: 20 U (1 U = 9 nmol); IDeg once/day: 10 U (1 U = 6 nmol), group A; IDeg once/day: 10 U (1 U = 9 nmol), group B; insulin glargine: 10 U (1 U = 6 nmol) FPG 4.0–6.0 mmol/liter (72–108 mg/dl)	Lowest value of the last three consecutive self-monitored FBG; <56→4 U↓ (10% reduction for a dose > 45 U); 56–71→2 U↓ (5% reduction for a dose > 45 U); 109–144→2 U↑; 145–162→4 U↑; >162→6 U↑	Once/week	Individual titration by clinic or telephone contact	IDeg three times/week 8.8 IDeg once/ day, group A 8.6 IDeg once/ day, group B 8.8 Insulin glargine 8.7	IDeg three times/week 7.3 IDeg once/ day, group A 7.4 IDeg once/ day, group B 7.5 Insulin glargine 7.2	IDeg three times/week 2.3/patient year IDeg once/day, group A 0.6/patient year IDeg once/day, group B 0.9/patient year Insulin glargine 1.1/patient year	IDeg three times/week 0.1/patient year IDeg once/ day, group A 0.0/patient year IDeg once/ day, group B 0.0/patient year Insulin glargine 0.0/patient year

[a] FPG, fasting plasma glucose.
[b] Insulin degludec.

successfully by the patients themselves, as seen by substantial improvements in metabolic control, i.e., reduced HbA1c levels together with low rates of hypoglycemia. Practical tools, however, are needed to support patients and their physicians and to facilitate everyday life and thereby to prevent undue and harmful delay in initiating necessary insulin treatment. A successful option in this context could be a therapeutic strategy that takes into account patient-relevant aspects of care and facilitates the initiation and dose adaptation of insulin treatment using an automated basal insulin dose calculator that is simple to use and effective in achieving the agreed therapeutic targets. The clinical outcome of this approach should be proven in controlled trials.

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Appendix 1. Important Aspects Concerning Basal Insulin Titration Algorithms

The Starting Insulin Dose

Most studies used a starting insulin dose of 10 U per day,[12,13,37,40,42,43,46,47,50,52,54] others used slightly higher[51,53] (for patients on more than one OAD) or lower[45,52] doses (for some populations) or based their starting insulin dose recommendation on a formula[11,41] or on units per kilogram body weight.[38,40,71]

The Fasting Blood Glucose Target

The FBG or fasting plasma glucose (FPG) target used in the majority of studies was 100 mg/dl.[12,13,37,41,42,46,49] Other trials applied slightly different levels, e.g., 108,[43,51] 110,[52] or 95 mg/dl,[39] or they defined a target range, e.g., 80–110 mg/dl[40] (target range 1),[48,50] 72–100 mg/dl,[11,45,53,54] 70–90 mg/dl[40] (target range 2), 72–99 mg/dl,[38] and 72–126 mg/dl.[47] There is much debate about the adequate FBG target;[35] an increased incidence of severe hypoglycemic events was observed and confirmed at fasting glucose values lower than 100 mg/dl.[35] One study also showed that aggressive titration did not result in better HbA1c values.[55] Data have shown that the absolute morning FPG target has little incremental impact on glycemic results within the 80–120 mg/dl range.[35] The latest ADA/EASD position statement lines out that a FBG level of <130 mg/dl is sufficient to reach the recommended HbA1c target of <7%.[8] This statement could be easily translated in practice in a study with 6000 patients where a mean FBG of 131 mg/dl led to a HbA1c value of 7%.[72] Given these data together, it makes sense to aim at a fasting glucose level of less than 130 mg/dl for the majority of patients.[8]

The Insulin Titration Steps

A common theme as part of most of the algorithms is a titration step of 2 U. Sometimes this is the sole titration instruction. In other studies, this is part of a sequence of titration steps with higher or lower dose increase depending on the blood glucose level. Only one study used bigger steps of 3 U,[48] and another one used smaller steps of 1 to 2 U.[42,45] A broad range from many titration steps to fewer steps (with also different frequency) was used in the studies.

The Insulin Titration Frequency

The burden of work on health care professionals means they need an algorithm that fits with the frequency at which they can contact the patient, typically weekly in studies. It is important to note that, as described by Swinnen and coauthors,[73] the biggest predictor of success in basal insulin titration seems to be contact frequency, enforcing the titration. For patients, little and often is both easier and safer: easier because habits are more easily formed for frequently recurring events and calculation is easier from a few values rather than from many and safer because small increase steps are inherently less risky, even though the more frequent increases mean the overall speed of increase is similar. Patient algorithms in almost all studies are twice per week or every 3 days or every day.[42,71]

The Driver of the Titration (Physician- versus Patient-Driven Insulin Titration)

As can be seen from several randomized controlled trials on basal insulin titration, insulin-naïve patients have been found to be as good as experts at intensifying their own insulin regimens (and primary care physicians are just as competent as endocrinologists).[13,40,42,46,48,53,54] Patients were able to achieve significant improvements in glycemic control—even in a primary care setting: HbA1c values decreased, with a substantial proportion of patients achieving levels below 7.0%, combined with low rates of hypoglycemia.[13,40,42,46,53,54]

The Efficacy of the Titration Algorithm in Terms of Hemoglobin A1c and Fasting Blood Glucose

All studies showed quite pronounced improvements in terms of HbA1c (between 0.5% and 2.8% points), including the achievement of HbA1c values below 7.0% and/or FBG levels, which was also the case for patient-directed insulin titration (**Table 1**).

The Safety of the Titration Algorithm in Terms of Hypoglycemic Episodes

All key studies revealed low rates of hypoglycemic episodes—also with patient-directed titration—when the FBG target was set around 100 mg/dl (**Table 1**).[35] Lowest rates of hypoglycemia were seen for insulin glargine + metformin

monotherapy.[30] A meta-analysis[57] pointed out reductions of approximately 50% of risk for nocturnal hypoglycemia with use of insulin glargine instead of NPH insulin. In contrast to the well-described and standardized titration schedules for the up-dosing of insulin to reach target, insulin dose reduction to counterbalance hypoglycemic events is much less standardized. The definition of hypoglycemia differs between the studies summarized in **Table 1** with regard to blood glucose values and/or symptoms as well as the proposed dose adjustments. Taking into consideration that hypoglycemia is of relevant concern in health care professionals as well as patients, a dose reduction of 2–4 U as proposed in several studies[43,47,51,54] or even 10%[39] may be most useful to avoid recurrence of hypoglycemic events.

Concomitant Antidiabetic Medication(s)

Oral antidiabetic medication consisted mainly of metformin monotherapy, which was continued in all the studies, or metformin + sulfonylureas. Sulfonylureas could be continued, if applicable, with the exception of one study.[39] In the three-year 4-T study, sulfonylureas were also discontinued at the start of the second year.[44] It remains unclear whether sulfonylureas can be safely continued when introducing basal insulin. Another study discontinued thiazolidinediones.[46] One trial allowed dose reduction or discontinuation of OADs.[40] One trial used sitagliptin or exenatide in addition to titrated insulin glargine + metformin (**Table 1**).[37]

Other Factors with Potential Impact on Basal Insulin Titration

Day-to-Day Blood Glucose Variability

A study investigating the day-to-day variability of FPG in 193 newly diagnosed patients with T2DM[74] exhibited FPG variations of ±15% on a daily basis. Subjects with higher FPG were more likely to experience larger changes in FPG values measured from day to day. Another investigation looked at the 8-week mean glucose in 204 subjects with T2DM treated with insulin;[75] the eight-week mean ± standard deviation glucose was 9.9 ± 2.2 mmol/liter, and the average overall coefficient of variation was 35.6% ± 7.7%. A higher variation was seen in older subjects and in those with longer duration of insulin therapy, greater consumption of sugars, and greater confidence in their self-care abilities. Lower variations were observed in obese subjects, subjects who were more compliant, and those receiving larger insulin doses. Multivariate analyses demonstrated that treatment duration, sugar consumption, medication compliance, and insulin doses were independently associated with glucose variation. Fasting variation was more influenced by medication compliance, whereas, before lunch, variation was more strongly influenced by body mass.

Bearing in mind these day-to-day variability factors, it seems appropriate not to titrate the insulin dose too often. Based on clinical experience, dose adjustments every three days as used in several studies could be considered as appropriate in this respect.

Insulin Dose

Longer-term trials have shown that the insulin dose over time keeps increasing, e.g., the insulin detemir dose increased from 0.66 to 0.77 U/kg or 17% from weeks 12 through 24.[35,43] The increase may also be moderate as described by Schreiber and Haak,[72] where patients showed durable control with 20 U daily dose at 9 months and 22 U at 20 months. Therefore, a close eye should be kept on insulin dose development in the long run, and one should not miss the point to think of additional—prandial—insulin as soon as this is deemed to be appropriate, e.g., if the total dose reaches a level between 0.5 and 1.0 U/kg.[8]

Practicability and Complexity of Titration Algorithms

The key clinical studies cited used different kinds of basal insulin titration algorithms, from few to many steps, different step sizes (i.e., amount of insulin units to be increased or decreased), and also different titration frequencies. They also varied as to which person was responsible for the titration: clinic/physician ± central enforcement versus patient.

It is of great importance, however, that insulin titration is manageable for the patients in their daily life. Thus titration algorithms should be as simple as possible to support both primary care physicians and patients in optimizing basal insulin therapy. Increased standardization of titration schemes would benefit health care professionals and patients alike. The algorithms should also be in line with national and international diabetes guidelines that, in addition, need to be consistent in their recommendations.[25]