MANUSCRIPT CATEGORY

Narrative review

TITLE

When basal insulin is not enough: successful strategies for insulin intensification in patients with type 2 diabetes mellitus

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STATISTICAL SUMMARY

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| **Abstract Text** | **Manuscript Text**  **(all, including refs and tables)** | **References** | **Figures** | **Tables** |
| N = 178  (Limit = 300) | N = 5,985  (3,997+829+1,159)  (Limit = 6000) | N = 28  (Limit = 60) | N = 0  (Limit = None specified) | N = 2  (Limit = None specified) |

ABSTRACT

Maintaining glycemic control through intensive clinical management of patients with type 2 diabetes mellitus (T2DM) is well recognized to reduce the risk of diabetes-associated complications. Patients in Russia have high rates of microvascular and macrovascular complications as a result of undiagnosed, untreated, or inadequately treated diabetes, emphasizing the need for better clinical management. The introduction of basal insulin therapy is often necessary for patients with T2DM when oral antihyperglycemic drugs and lifestyle management strategies are no longer effective in maintaining glycemic targets. However, after initiation of insulin, patients often remain on basal insulin for long periods despite suboptimal glycemic control, and intensification of insulin therapy is frequently necessary. Here, we report on several different insulin intensification strategies available to clinicians and their patients to improve glycemic control and the advantages and disadvantages of each approach. These strategies include the use of short- and long-acting insulins administered either as bolus doses or as premixed insulins. When selecting the most appropriate intensification strategy, clinicians should consider the lifestyle and treatment goals of their patients to help ensure treatment success.

KEY WORDS

Diabetes mellitus, type 2; Insulin; Insulin mixtures; Insulin intensification; hemoglobin A, glycosylated; Efficacy; Safety.

INTRODUCTION

The number of persons with diabetes mellitus (type 1 [T1DM] and type 2 [T2DM]) is increasing in Russia. By the end of the 2016 there were 4,348 million people with diabetes reported in the official Russian State Register of Patients with Diabetes Mellitus (SRPDM) and approximately 4 million of these patients had T2DM [[1](#Дедов_ИИ)]. In 2015 the International Diabetes Federation (IDF) estimated there were 11,1 million adults in Russia with diabetes and the prevalence of diabetes was 9,2% in persons aged 20 to 79 years [[2](#IDF_Diabetes_Atlas_7th)]. Based on IDF data, over 4,6 million people in Russia had undiagnosed diabetes and 186,123 deaths were related to diabetes [[2](#IDF_Diabetes_Atlas_7th)]. The IDF estimates suggest that there may be 2 to 3 times more people with diabetes in Russia than officially reported by the SRPDM. NATION is a national, epidemiological, observational, cross-sectional study that was published in 2016. According to that study the prevalence of type 2 diabetes mellitus in the adult population of Russia is 5,4% in persons aged 20 to 79 years. It is worth noting that 2,5% of the participants were previously diagnosed and 2,9% were previously undiagnosed. In this way 54% of all subjects had diabetes but they hadn’t known about it [[3]](#NATION).

As a result of undiagnosed, untreated, or inadequately treated diabetes many patients will develop diabetes-related complications (ie, diabetic retinopathy, renal failure, heart attacks and stroke, diabetic foot syndrome). Russia had the high rates of diabetes-related macrovascular (72.4%) and microvascular (89.3%) disease based on the findings of an observational study (A1chieve) of approximately 67,000 patients with T2DM conducted in 2009-2010 across 7 international regions [[4]](#Litwak). Data from detailed national epidemiological monitoring studies of patients in Russia with diabetes (T1DM and T2DM) revealed that rates of diabetic retinopathy (38%) and diabetic nephropathy (41%) were 1.5-fold and 3-fold higher, respectively, than the officially registered levels of these conditions [[5]](#Sountsov). According to the latest data of State Register of Diabetes Mellitus for 2016, basal insulin is leading regimen as a start of insulin therapy and only 52.1% of patients with type 2 diabetes have a level of HbA1c <7% [[1]](#Дедов_ИИ). These findings highlight the need for better diabetes management of patients in Russia.

Rationale for this review

The intensive clinical management of patients with T2DM is well recognized to improve glycemic control and reduce the risk of diabetes-related complications [[6](#Holman),[7]](#UKPDS_33). Generally, treatment with insulin is required when lifestyle interventions such as diet and exercise and use of oral antihyperglycemic drugs (OADs) and/or non-insulin injectable treatments are not effective in maintaining glycemic targets [[8]](#Inzucchi). However, despite initiation of basal insulin therapy, many patients are unable to maintain glycemic control and must progress to insulin intensification to reach glycemic targets and reduce the risk of diabetes-related complications and comorbidities. The aim of this review is to summarize the “real-life” clinical outcomes of patients on basal insulin and some of the key strategies clinicians may consider for intensification of insulin therapy when basal insulin is no longer effective.

Current guidelines for initiating insulin therapy in T2DM

Because of the progressive nature of the disease many patients with type 2 diabetes eventually

require and benefit from insulin therapy [[9]](#ADA_2017). Based on the newest Standards of medical care in diabetes issued by American Diabetes Association (ADA) in 2017 basal insulin therapy is recommended for patients who have not achieved or don’t maintain the A1C target on maximum tolerated dose with metformin +/- other noninsulin agents after 3 months. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if symptoms or any catabolic features (weight loss, ketosis) are present, as well as insulin therapy should be considered in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C ≥ 10% (86 mmol/mol) and/or blood glucose levels ≥ 300 mg/dL (16.7 mmol/L) [[9]](#ADA_2017).

When initiating insulin in patients with T2DM, glycemic targets should be individualized and centred on the patient. Numerous aspects must be considered when setting glycemic targets. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. The ADA proposes optimal target HbA1c <7% to reduce the incidence of microvascular disease , but target must be individualized to the needs of each patient and his or her disease factors. It is noteworthy that the latest recommendations of the ADA Standards of medical care in diabetes experts draw the attention on role of patients and emphasize when possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values [9]. Insulin-treated patients with hypoglycemia unawareness or an episode of clinically significant hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes [[9]](#ADA_2017).

Russian guidelines for initiation of insulin therapy

Russian Diabetes Algorithms also recommends that from the moment of diagnosis all patients should be informed about the progressive nature of type 2 diabetes and possible insulin therapy[[10]](#Standards_2017) Diabetes care guidelines in Russia indicate some groups of patients for whom insulin therapy should be prescribed. These are the first diagnosed T2DM patients if their HbA1c > 9 % (in this case insulin therapy could be temporary); patients who do not achieve the individual goals on optimal doses of non-insulin agents or their combinations; in cases of ketoacidosis. General recommendations for choosing insulin therapy regimens are based on some factors such as lifestyle and specifics of the disease. For patients who have low physical activity and who prefer to use a small number of insulin injections and are not able to do multiple injections, there are two options for insulin therapy – basal or premixed insulin regimens. The choice is based on the glycemic level: If their HbA1c differs from the target level by 1% to 1.5%, and fasting blood glucose needs to be corrected basal insulin should be initiated further, if HbA1c is >1.5% of the target level, fasting and postprandial blood glucose need to be corrected and premixed insulins are recommended. In all other cases for T2DM patients if their HbA1c is >1.5% of the target but they have an active life style and are motivated to self-monitor blood glucose levels and ready to do multiple insulin injections, basal-bolus insulin therapy should be prescribed. Glycemic targets should be individualized based on age, life expectancy, absence or presence of macrovascular complications, and risk of hypoglycemia [[10]](#Standards_2017).

Initiating insulin therapy in T2DM

Based on Russian algorithms management of T2DM there are different options for initiation of insulin therapy[[10]](#Standards_2017). In fact, in real practice basal insulin is the most commonly used regimen to initiate insulin therapy and many patients may remain on this regimen for many years, despite suboptimal glycemic control. Several studies have demonstrated the results of the patients who remained on the initial insulin therapy regimen despite not achieving glycemic goals; these studies are described below.

In a 10-year retrospective study (1995 to 2005) of patients with T2DM in the United Kingdom (UK) who were prescribed OADs and/or insulin, the majority (73.4%) of the 1,513 patients had HbA1c ≥7.5% more than 6 months after initiating insulin therapy (ie, approximately 25% achieved adequate glycemic control). This study found that patients had low levels of faith in the potential efficacy of insulin, and high self-blame for having to take insulin. Professionals may be guilty of clinical inertia leading to suboptimal dosing and lack of treatment intensification; however, it is difficult to determine clinical behaviour with the current data [[11]](#Calvert).

Another retrospective observational study was conducted between 1999 and 2007, using data collected from 2,417 patients with T2DM in a US managed-care health network. In this study patients were followed for up to 7 years after they started insulin. For this period, they were on different insulin regimens, at the beginning of the study the number of patients on basal insulins were 68,7% (66,8% NPH and 1.9% long acting insulin) and at the end 42,5% (36,8% NPH and 5,7% long acting insulin). The study found that only 30% to 37% of patients achieved HbA1c <7%. Analysing the results of the study authors noted that observational data cannot reveal why so many patients did not seek, or were unable to achieve good control. Many patients fear injections, and busy doctors may avoid the complexity of insulin initiation[[12]](#Nichols).

In the randomized, controlled Treat-to-Target trial of 756 patients with T2DM with inadequate glycemic control (HbA1c >7.5%) taking 1 or 2 OADs, patients were randomized to insulin glargine or NPH once daily [[13]](#Riddle) . In this study the number of patients who achieved the target HbA1c ≤7% were higher than in most other studies but not all patients reached treatment goals after 24 weeks of treatment, only 58.0% of those randomized to glargine and 57.3% to NPH achieved the target of HbA1c ≤7%. Analysis of the results of using basal insulin in this study revealed that several factors probably contributed. The titration target was ambitiously low (100 mg/dl [5.6 mmol/l] using a plasma-referenced system; despite significantly fewer patients who experienced hypoglycaemia with glargine group, the risk-benefit balance can be the barrier for the dose titration to reach the target. Also some important questions are not addressed by these findings. For example, which subgroups of patients are most likely to reach the target with a basal insulin regimen, if patients are less strongly encouraged to increase insulin after mild hypoglycaemia? Will they have higher HbA1c and how should patients not reaching or maintaining the HbA1c target with a single basal insulin injection subsequently advance to intensified therapy including mealtime rapid acting insulin? [[13]](#Riddle).

The cross-sectional study including a population of 126 811 T2DM subjects, 9899 of which were treated at least 6 months prior to the beginning of the study with basal insulin, aged 31–90 years registered in the SIDIAPQ primary healthcare electronic database during 2010, demonstrated that one-quarter of T2DM patients treated with basal insulin (23.5% (n = 2322)) have difficulties attaining the recommended HbA1c goal despite adequate FPG levels [[14]](#Mata_Cases). Most patients (51.3%) did not achieve any of the optimal targets. Among the uncontrolled HbA1c patients, those achieving the FPG target (<130 mg/dL) were significantly older, had a longer duration of diabetes, and had lower mean HbA1c, BMI, DBP, and LDL-C values than those who did not achieve the FPG target. In those patients, after intensification of treatment with basal insulin, PPG elevations contributed >60% to hyperglycemia in people with HbA1c >7%. Thus, in individuals in whom basal insulin has been conscientiously titrated, it is the postprandial hyperglycemia that drives the continued elevation of HbA1c levels, regardless of FPG level. The finding the patients treated with basal insulin could not be controlled could be related to the fact that therapeutic changes, such as insulin intensification, are sometimes introduced after several years of inadequate glycemic control. Guidelines propose an early introduction and progression in the combination of drugs to prevent the worsening of glycemic control, but physicians usually adopt a stepwise approach, which often results in patients spending more than 10 years with an HbA1c >7% (53 mmol/mol) and 5 years with an HbA1c >8% (64 mmol/mol) before insulin is started. Patients’ perceptions of physician engagement and attentiveness, the quality of explanation about medical tests and their results and discussion around the prescribed treatment regimen were directly associated with insulin adherence behavior [[14]](#Mata_Cases).

There are some studies that evaluated different approaches for initiating insulin therapy in type 2 diabetic patients who have failed to achieve target glycemic control goals on OAD therapy.

In the INITIATE study, 233 insulin-naive patients with T2DM and poor glycemic control taking metformin alone or in combination with other OADs were randomized to receive either insulin glargine or biphasic premixed insulin containing basal and rapid-acting insulin analogs (biphasic insulin aspart 70/30: 70% insulin aspart protamine/30% insulin aspart) [[15](#_ENREF_16)]. After 28 weeks of treatment, only 66% in the biphasic insulin aspart 70/30 group and 40% in the glargine group reached the HbA1c <7% target after 28 weeks of treatment. Even though minor hypoglycaemia (episodes/year) was greater in the BIAsp 70/30 group than in the glargine group (3.4 ± 6.6 and 0.7 ± 2.0, respectively; P ˂ 0.05) and weight gain and daily insulin dose at study end were greater for BIAsp 70/30 – treated subjects than for glargine-treated subjects (weight gain: 5.4 ± 4.8 vs. 3.5 ± 4.5 kg, P ˂ 0.01; insulin dose: 78.5 ± 39.5 and 51.3 ± 26.7 units/day, respectively), BIAsp 70/30 was significantly more effective than insulin glargine in reducing HbA1c for subjects who entered the present study with HbA1c values ≥ 8.5%. This is consistent with the fact that as b-cell function declines, HbA1c rises, and basal insulin replacement alone is insufficient to control postprandial hyperglycemia [[15](#_ENREF_16)].

A UK-based retrospective 36-month observational study was conducted using data collected from 2002 to 2006 from The Health Improvement Network (THIN) database [[16].](#Gordon) The study included 8,009 patients with T2DM with poor glycemic control (baseline [mean ± standard deviation (SD)] HbA1c: 9.5 ± 1.6%). The patients were prescribed OADs and/or lifestyle management and were initiated on either basal insulin (ie, NPH, detemir, or glargine) or premixed insulin during the data collection period. Although all insulin therapies resulted in a significant decrease (P <0.001) in HbA1c after 12 months of treatment, the mean (± SD) HbA1c (8.4 ± 1.5%) did not meet best-practice recommended targets for HbA1c. Despite not achieving optimal glycemic control, 75% of patients persisted with NPH, 78% with detemir, 83% with glargine, and 92% with premixed insulin over the first 12 months of treatment. At 36 months, patients who were treated with premixed insulin still had the highest level of persistence (83%), followed by glargine (67%) and NPH (57%) (note: 36-month data were not available for detemir as it was licensed in the UK later than the other insulins) [[16].](#Gordon)

In another retrospective observational study of UK patients with T2DM using the THIN database, data were collected from 2004 to 2006 to investigate the treatment patterns of patients with suboptimal glycemic control (mean HbA1c [± SD]: 9.6 ± 2.0%) initiating insulin therapy [[17]](#Blak) . A total of 4,045 patients were included in the study, of which 52.4% initiated basal insulin only, 41.6% initiated premixed insulin only, 4.0% initiated basal-bolus insulin only, and 2.1% initiated prandial insulin only. For those patients with 6 months of follow-up, the mean (± SD) HbA1c was 8.3 ± 1.6% and the mean (± SD) change in HbA1c was -1.27 ± 2.02% (n=2,881); only 17.3% (n=3,024) patients achieved HbA1c <7%. Overall, among those patients with at least 6 months follow-up, 75.1% of patients persisted with the same insulin regimen, 13.7% discontinued insulin, 7.0% switched regimens, and 4.7% received insulin intensification. For those patients initiated on basal insulin, basal-bolus insulin, or premixed insulin only, 5.8%, 0.6%, and 2.3% of patients, respectively, underwent insulin intensification and 8.1%, 4.5%, and 5.2%, respectively, switched their insulin regimens. The authors of this study indicated the two potential problems associated with insulin treatment are weight gain and hypoglycaemia. Clinical studies have shown mean increases in weight gain of up to 3 kg over 6 months when insulin was added to OAD therapy in Type 2 diabetes, although the magnitude of weight gain may differ between different types of insulin.[[17]](#Blak) .

One of the latest studies the Multinational Observational Study Assessing Insulin Use (MOSA1c study), with 4,341 participants from 18 countries assessed the challenges associated with progression of insulin therapy and demonstrated that baseline insulin regimens are different around the world: in Germany basal and mixed insulins are equally used at the start of insulin therapy, these are 44% basal and 44% mixed insulins; in China 16% of patients start with basal insulins and 66% of patients start with mixed insulins; in the US the situation is opposite, 66% of patients start with basal insulins and 17% with mixed insulins; Russia is the leader of using basal insulin to initiate insulin therapy, 82% of patients start insulin therapy with basal insulins and only 8% of patients start with mixed insulins [[18]](#Polinski). All patients who were included in this study took different regimens of insulin therapy except intensive basal-bolus for more than 3 months and differences exist between patient HbA1c and physician’s target at study entry. The MOSA1c study found that patient-physician interactions, as well as diabetes distress, influence insulin adherence. Communication and diabetes distress show a direct relationship with glycaemic control.[[18]](#_ENREF_18).

The treatment patterns and trends for insulin initiation and intensification among US patients with T2DM were assessed in a retrospective observational study using data collected from patients in a private health insurer database [[19](#_ENREF_19)]. A total of 7,932 patients initiating insulin between 2003 and 2008 were included in the analysis. Of these, 61% initiated basal insulin only, 14% mixed insulin, 13% basal plus prandial, 11% prandial only, and 1% initiated combinations of prandial plus mixed, basal plus mixed, or all 3 insulin types. Of the 5,570 with follow-up data 6 months after initiation of insulin, only 38.1% had evidence of insulin intensification. Of those, 22.9% increased the insulin dose or frequency, 5.7% added prandial insulin, and 1.2% added premixed insulin. Overall, 11.8% discontinued all diabetes medications, and 10.0% continued noninsulin medications only. Rates of intensification and discontinuation were similar across patients initiating basal only, mixed, and basal plus prandial insulin regimens. The low rates of treatment intensification and high rates of insulin discontinuation observed in this study suggest that patients remain at risk of inadequate glycemic control following insulin initiation [[19](#_ENREF_19)].

Data from these observational studies assessing “real-life” clinical practices for insulin intensification indicate that approximately 5% to 40% of patients with poor glycemic control had evidence of insulin intensification. This reflects the findings presented earlier that approximately 30% to 70% of patients who initiate basal insulin therapy do not achieve glycemic targets and persist with basal insulin for at least 6 to 12 months, despite poor glycemic control. At the same time, there is another option for initiating insulin therapy such as premixed insulin having some advantages in comparison with basal insulin. In Russia this regimen is not sufficiently used despite the recommendation of Russian algorithms for treatment of patients with T2DM. Together, these data support the view that the majority of patients with T2DM who may require insulin intensification are not receiving optimal therapy.

Why T2DM patients remain on the initial schemes of insulin therapy despite not achieving their individual treatment goals has been a question for many years. One major reason for not achieving targets of therapy is ‘clinical inertia’, defined as ‘failure of healthcare providers to initiate or intensify therapy when indicated’[[20]](#Sachin_Khunti). The reasons for clinical inertia are complex, and include provider-,patient-, and system-level barriers. Provider-level barriers include inertia related to clinicians specialists, time constraints, lack of knowledge, potential risks of hypoglycemia, and variations in guideline recommendations. Patient-level barriers include non-adherence and concerns about hypoglycaemia and weight gain. System-level barriers include inertia due to issues in healthcare, including costs of newer medications. A further study described physicians’ attitudes to the initiation of insulin in patients with type 2 diabetes and demonstrated reluctance in initiating insulin related to attitudes regarding risks and benefits of insulin, patients’ fears about insulin initiation, and patients’ experiences of taking insulin.

These studies highlight the phenomenon of clinical inertia as a continuing and significant problem, despite the availability of clear guidelines proposing specific therapeutic targets. Implementing guideline recommendations would be valuable as an initial step, but the evidence shows that clinical inertia has not improved significantly over the years, despite good evidence of tight glycaemic control[[20]](#Sachin_Khunti).

Strategies for insulin intensification

Clinical care guidelines for the treatment of patients with T2DM recommend insulin intensification with prandial or mealtime insulin if the HbA1c values persist above target levels for -3 months and more on basal insulin or when there are significant postprandial blood glucose (PPBG) excursions (ie, >10 mmol/L) [8,[9,](#ADA_2017)[10]](#Standards_2017) Another possibility provided by the clinical care guidelines is the addition to basal insulin of a GLP-1RA, but this is out of the scope of this review, also considering that, unfortunately, the usage of this class of anti-hyperglycaemic medicines is limited in Russia due to cost, availability and National reimbursement.

Several different strategies may be considered for patients on basal insulin requiring insulin intensification: (1) addition of a single injection of a rapid-acting insulin analog (ie, lispro, aspart, or glulisine), administered just before the largest meal or breakfast (basal+) [[21]](#Owens); (2) stepwise addition of 2 or more daily bolus injections of a rapid-acting insulin analog, administered just before mealtimes (basal-bolus) [[22]](#Rodbard_Visco); and (3) switch to premixed insulin containing a combination of intermediate-acting and rapid-acting insulin analogs (ie, insulin lispro 75/25 [LM25], insulin lispro 50/50 [LM50], biphasic insulin aspart 70/30), generally administered twice daily before morning and evening meals or three times daily before breakfast, lunch and dinner[[23]](#Rosenstock).

When comparing and deciding on insulin intensification strategies, clinicians and their patients should consider the goals of treatment, including target HbA1c values and PPBG excursions, as well as patient-related issues such as age, duration of T2DM, previous hypoglycemic episodes, and other comorbidities. Patient preference, complexity of the intensification regimen, lifestyle, extent of education, patient motivation regarding treatment, and psychosocial factors are also important points to consider when selecting an appropriate intensification regimen [[9,](#ADA_2017)[10]](#Standards_2017) Upon implementing an intensification strategy, it is important to titrate both the basal and prandial insulin doses, based on the patient’s reported blood glucose (BG) values. In most cases, noninsulin agents may be continued, however, sulfonylureas and meglitinides (ie, insulin secretagogues) are generally not continued when insulin is intensified, also GLP-1RAs should be stopped if moving to a basal bolus regimen[[10]](#Standards_2017).

Advantages and disadvantages of insulin intensification strategies

Basal+ and basal-bolus

A basal+ (basal plus 1 prandial injection) insulin intensification strategy provides patients with a transitional approach to the introduction of prandial insulin and improves glycemic control without the need for a full basal-bolus regimen [[21](#_ENREF_21)]. For those patients who are unable to achieve glycemic targets with a basal+ regimen, further prandial doses (ie, basal-bolus approach) may be required. Basal-bolus strategies for insulin intensification most closely mimic physiological insulin fluctuations, and both basal and prandial components may be independently titrated to provide optimal glycemic control of both fasting and postprandial glucose levels.

Basal-bolus regimens provide more flexibility for the timing of prandial insulin and, therefore, greater control of PPBG excursions compared with premixed insulin intensification. However, currently there are no global consensus guidelines that favor basal-bolus regimens over other intensification regimens [[24](#_ENREF_24)]. Basal-bolus regimens are generally more complex than premixed insulin intensification or basal-only regimens and require patient education on 7-point self-monitoring of plasma glucose (SMPG), methods for self-titration of prandial doses, and carbohydrate counting. Three RCTs have examined methods for the introduction of basal+ or basal-bolus regimens in patients previously treated with basal insulin only and are summarized below.

FullSTEP study

The FullSTEP study showed that a basal+ stepwise intensification of basal insulin (detemir) by adding prandial doses of a rapid-acting insulin analog (aspart) was noninferior compared with immediate transition to full basal-bolus treatment with detemir and aspart [[22](#Rodbard_Visco)]. Both treatment strategies were effective in improving glycemic control; however, there was a significantly lower rate of hypoglycemia for patients undergoing basal+ stepwise addition of prandial insulin compared with immediate transition to full basal-bolus treatment. The lower rate of hypoglycemia was postulated to be a result of gradual intensification of prandial doses, allowing patients to familiarize themselves with SMPG measurements and titration of bolus doses of aspart [[22](#Rodbard_Visco)].

In FullSTEP, there was also greater satisfaction with treatment for patients in the basal+ stepwise group; this was possibly related to the need for fewer injections (2 vs 4 injections) and SMPG measurements for those on 1 or 2 prandial doses compared with full basal-bolus treatment. All patients had their basal doses of detemir titrated and optimized before addition of prandial bolus dosing; further, an easy-to-use “1-0-1” titration algorithm was used to help improve patient adherence with the self-titration of the bolus doses [[22](#_ENREF_21), [2](#_ENREF_24)5]. Clinicians may consider implementing a basal+ stepwise approach to bolus dosing as the burden on the patient to titrate doses is less, the risk of hypoglycemia and weight gain is lower, and adherence is improved compared with immediate full basal-bolus dosing [[22](#Rodbard_Visco)]..

AUTONOMY study

The AUTONOMY study showed that prandial rapid-acting insulin lispro could be safely added to basal insulin glargine using 2 different patient self-titrated algorithms (daily dose titration [Q1D] vs dose titration every 3 days [Q3D]) with improved glycemic control. This study also confirmed earlier studies [[[2](#_ENREF_25)6](#Latif)] that basal-bolus insulin intensification also had an acceptable safety profile in the elderly population; patients in the ≥65 years of age subgroup of AUTONOMY could initiate basal-bolus intensification without increased risk of hypoglycemia [[24](#_ENREF_23)]. Patients did gain weight in this study; there was no significant difference in weight gain between the self-titration algorithms Q3D and Q1D, whereas there was a greater weight gain with the Q3D titration algorithm compared with the Q1D algorithm. An important aspect of the AUTONOMY study was that basal glargine doses were titrated before the addition of prandial doses of insulin lispro. For any basal-bolus intensification strategy, the clinician should ensure that the basal insulin dose is optimized before adding the prandial doses of insulin [[24](#_ENREF_23)].

START study

The START study showed that use of a simple patient-led titration (ie, self-titration) algorithm for the addition of bolus doses of prandial insulin to basal insulin therapy was as effective as physician-led titration [[27](#_ENREF_26)]. Patient-led titration was noninferior to physician-led titration of prandial doses of insulin in terms of HbA1c levels at the end of the study [[27](#_ENREF_26)]. There was a significant increase in body weight for both groups compared with baseline, and a significantly greater increase in body weight in the patient-led titration group compared with the physician-led titration group at the end of the study. There were no differences in the rates of hypoglycemia between the 2 groups [[27](#_ENREF_26)].

The START study used a simple, convenient approach of adding the prandial insulin dose before breakfast to maximize patient adherence to the treatment algorithm. Such an approach could improve patient safety by reducing the risk of nocturnal hypoglycemia. This strategy also takes advantage of the common practice of routine self-measurement of fasting blood glucose before breakfast, thus minimizing the need for additional SMPG measures later in the day. This strategy also provides the added convenience of self-injecting at home and allows patients to optimize BG levels earlier in the day with the aim of improving daytime glycemic control [[26](#_ENREF_26)]. As with both the AUTONOMY and FullSTEP studies, the basal insulin dose in the START study had to be optimized before addition of the bolus doses [[27](#_ENREF_26)].

Premixed insulins

The introduction of premixed insulins in patients with poor glycemic control who are using basal insulin, basal+, or basal-bolus strategies offers patients an easy-to-use, simplified alternative to insulin intensification if their current treatments are not suitable or effective. Each premixed dose provides both basal and prandial coverage and is generally administered twice daily, once before breakfast and once before dinner or three times a day before breakfast, lunch and dinner [[10].](#Standards_2017) However, this intensification strategy reduces flexibility with regard to independent titration of the intermediate- and rapid-acting insulins, given the fixed ratio of these components in premixed insulin. Thus, clinicians may wish to consider this intensification strategy for those patients who eat regular meals or who may be unable to adhere to more complex intensification strategies such as the basal-bolus approach [[10].](#Standards_2017).

Currently, best-practice guidelines for T2DM treatments do not provide specific recommendations regarding which patients would be most suitable for premixed insulin intensification. One of the benefits of premixed insulins is the simplicity of use, as patients require fewer injections and less self-monitoring, compared with a basal-bolus strategy [[8](#_ENREF_7),[9](#ADA_2017),[[1](#_ENREF_11)0](#Standards_2017)]. In a systematic review comparing premixed insulin analogs with basal insulin analogs, premixed insulins administered 2 or 3 times daily provided better glycemic control compared with once-daily basal insulin [[28](#_ENREF_27)]. However, there were more episodes of hypoglycemia seen with premixed insulin administered 3 times a day than with once-daily basal insulin glargine. Weight gain was also greater in patients administered premixed insulin 3 times a day compared with a once-daily basal insulin [[28](#_ENREF_27)]. Since that systematic review, 2 different RCTs have been conducted to compare the efficacy and safety of premixed insulins with a basal-bolus regimen; these studies are described below.

The Rosenstock et al. study [[23](#_ENREF_23)] compared the premixed insulin LM50 with basal insulin glargine plus bolus insulin lispro in patients with T2DM who had inadequate glycemic control with previous insulin glargine treatment. The LM50 premixed insulin was administered 3 times a day at mealtime; basal glargine was administered at bedtime and lispro 3 times a day at mealtime (ie, 3 injections per day for the LM50 treatment group vs 4 injections per day for the basal-bolus group). After 24 weeks of treatment, noninferiority of LM50 compared with glargine/lispro intensification was not demonstrated, with significantly more patients achieving a target HbA1c <7% in the basal-bolus group compared with LM50. Both fasting and morning postprandial plasma glucose were also significantly lower in the basal-bolus group compared with the LM50 group. Both therapies were associated with moderate weight gain and the majority of patients in both groups had at least 1 episode of self-reported hypoglycemia; there were no significant differences for these endpoints between the 2 groups [[23](#_ENREF_23)].

The Tinahones et al. study [[29](#_ENREF_29)] compared premixed insulin LM25 with basal insulin glargine plus bolus insulin lispro in patients with T2DM who had inadequate glycemic control with previous insulin glargine and metformin and/or pioglitazone treatment. The LM25 premixed insulin was administered twice daily before breakfast and dinner; basal insulin glargine was administered at bedtime with bolus insulin lispro administered before the largest meal of the day. Therefore, the total number of daily injections was the same (2) for each treatment group. After 24 weeks of treatment, noninferiority of LM25 with glargine/lispro was demonstrated with respect to comparison of the change in HbA1c levels from baseline. There was a significantly greater decrease in HbA1c level for the LM25 group than the glargine/lispro group, but there was no significant difference in the percentage of patients reaching the target HbA1c <7%. Similar to the findings observed in the LM50 vs glargine/lispro head-to-head study, there were no significant differences in rates of hypoglycemia between the LM25 and glargine/lispro groups. However, in this study, there was a significantly greater weight gain in the LM25 group compared with the glargine/lispro group [[29](#_ENREF_29)].

A very recent review including 15 trials comparing basal-bolus (bolus injection ≤ 3 injections/day) and premixed (≤ 3 injections/day) insulin regimens has shown that clinically meaningful differences between regimens in glycemic control was recorded in only four comparisons, all of which favoured basal-bolus therapy. The incidence of hypoglycaemia was significantly different between regimens in only three comparisons, one of which favoured premixed insulin and two basal-bolus therapy. It is recommended that clinicians should adopt an individualized approach to insulin intensification – taking into account the benefits and risks of each treatment approach and the attitude and preferences of each patient – in the knowledge that both basal-bolus and premixed regimens may be successful. [[30](#Giugliano)]

The findings from the basal+, basal-bolus, and premixed insulin intensification studies suggest that these regimens are effective in reducing HbA1c and controlling prandial BG excursions. In addition, the safety profiles are also similar, however, weight gain may be more prevalent in patients treated with premixed insulins compared with basal-bolus regimens or basal-only regimens.

* + Based on the large evidence base using premix insulin in diabetes therapy, the following changes were made in ADA Standards of Medical Care in Diabetes 2017:If a patient is still above the A1C target on premixed insulin twice daily, consider switching to premixed analog insulin three times daily (70/30 aspart mix, 75/25 or 50/50 lispro mix). In general, three times daily premixed analog insulins have been found to be non- inferior to basal-bolus regimens with similar rates of hypoglycemia [[30](#Giugliano)]
  + If a patient is still above the A1C target on basal insulin + 1 single injection of rapid- acting insulin before the largest meal, advance to a basal-bolus regimen with ≥2 injections of rapid-acting insulin before meals.

Consider switching patients from one regimen to another (i.e., premixed analog insulin three times daily to basal- bolus regimen or *vice-versa*) if A1C targets are not being met and/or depending on other patient considerations)Table 1 [[30](#Giugliano),[[3](#Giugliano)1](#Dieuzeide),[32](#Mathieu)] .

At the same time Russian Standards of specialized diabetes care included a new option for the intensification of insulin therapy. If patients are not achieving individual target goals on basal plus regimen of insulin therapy they can switch to the premixed insulins Table 2.[[10](#Standards_2017)]

**conclusions**

Data from observational studies of “real-life” clinical practices in the management of patients with T2DM suggest that one- to two-thirds of patients prescribed basal insulin do not meet the glycemic targets recommended by clinical practice guidelines. These patients may not have their antihyperglycemic therapies modified for many years and, consequently, are at risk of microvascular and macrovascular complications. Recent epidemiological data from Russia highlight the need for better management of patients with T2DM to reduce the incidence of complications associated with suboptimal glycemic control.

Although basal insulin therapies may be initially effective in achieving target HbA1c levels, most patients will eventually require insulin intensification in order to maintain optimal glycemic control. The most commonly used intensification strategies include basal+, basal-bolus intensification, and premixed insulins. These 3 strategies provide effective glycemic control and have favorable safety and tolerability profiles. However, each strategy has advantages and disadvantages in terms of the risk of hypoglycemia, weight gain, and ease of use.

Basal-bolus intensification strategies are more complex and require greater patient education and motivation to achieve treatment goals compared with premixed insulin intensification. Premixed insulin intensification strategies are simpler, require fewer injections and less self-monitoring of BG, and may be more appropriate for certain patients, for example, aged patients or patients with regular mealtimes. Basal-bolus and premixed insulin regimens are associated with a greater overall risk of hypoglycemia compared with a basal-only regimen. Premixed insulin regimens are also associated with greater weight gain compared with basal-bolus and basal-only regimens.

Each regimen type offers different options to allow the clinician to tailor the therapy to suit individual patient treatment goals and needs, including number of injections, need for SMPG, and dose titration. When considering a treatment strategy for their patients with T2DM, clinicians should work together with their patients to select the most suitable approach to help ensure treatment success.

ACKNOWLEDGMENTS

Funding support

Some of the studies described in this review were sponsored by Eli Lilly and Company, the manufacturer/licensee of Humulin® N, Humalog®, Humalog® Mix75/25™, and Humalog® Mix50/50™. Medical writing assistance was provided by Julie A. Ely, PhD, CMPP and Rebecca Lew, PhD, CMPP of ProScribe – Envision Pharma Group, and was funded by Eli Lilly and Company. ProScribe’s services complied with international guidelines for Good Publication Practice (GPP2).

Role of the sponsor

Eli Lilly and Company was involved in the interpretation of data and in the preparation of the manuscript.

Role of contributors

All authors participated in reviewing the literature, and in the drafting, critical revision, and approval of the final version of the manuscript.

Conflicts of interest

SE and AJ are employees of Eli Lilly and Company. AJ owns shares in Eli Lilly and Company. EB has no conflicts of interest to declare.

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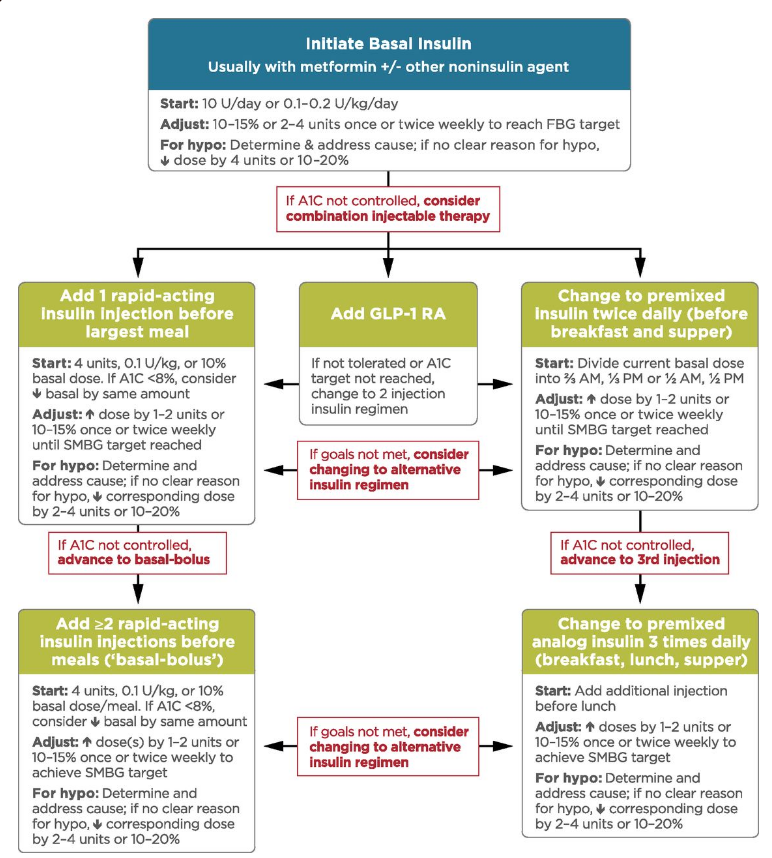
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TABLES

**Table 1.** American Diabetes Association 2017, Insulin Management Algorithm in T2D



**Table 2.** Russian recommendation on start, optimisation and intensification of insulin therapy in management in T2D, 2017

