Intensification of Insulin Therapy for Type 2 Diabetic Patients in Primary Care: Basal-Bolus Regimen Versus Premix Insulin Analogs

When and for whom?

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In April 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a joint position statement regarding treatment of hyperglycemia in type 2 diabetes, "Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach" (1). As most diabetic patients (>366 million worldwide) (2) are treated by their primary family physician and not by an endocrinologist or diabetologist, the guidelines were intended to help physicians choose the best treatment for their patients. Some of the advantages of this position statement, over previous guidelines (3–8), are as follows: emphasizing the importance of individualization of treatment, widening treatment options, and stating the pros and cons of the different treatment option. However, as the statement was written by a group of world-known diabetologists, without the input of nurses, dietitians, family physicians, or the patients themselves, questions have been raised as to how "patient-centered" it actually is and how useful and relevant it is to the primary care setting. Choosing the best insulin regimen for initiation and intensification of insulin therapy in type 2 diabetic patients is still debatable both in the specialist clinic and in the primary care setting. The intention of this article is to review the data available and offer reasonable guidance regarding the selection of the preferred insulin regimen for initiation and intensification of insulin treatment, especially in a primary care setting.

The ADA/EASD statement includes recommendations for the initiation and titration of insulin therapy (1). The recommendations point out three important aspects that need to be addressed when choosing or adjusting insulin regimens: the number of injections needed and the complexity and the flexibility of the regimens. The insulin regimens under consideration include basal insulin, premixed, basal insulin with one premeal short-acting insulin injection (referred to as basal plus regimen), and basal insulin with two or more short-acting insulin injections (basal bolus). In this article, we will attempt to better define the place of premix insulin analogs in comparison with other possible insulin regimens. We will focus on premix insulin analog use in the primary care setting, the benefits and drawbacks of this kind of treatment, its target patient population, and its appropriate use in the various stages of the disease.

Definition and nomenclature of premixed human insulin and premix insulin analogs

Primary care physicians are often puzzled by the many options available regarding insulin selection. A better understanding of the pharmacology of the different insulin preparations is necessary in order to insure proper insulin selection. Human soluble insulin exists in a hexameric form in pharmaceutical preparations, which delays its absorption into the bloodstream after subcutaneous injection. The dissociation into the dimer and monomer forms, which are more readily absorbed into the bloodstream, requires the molar concentration of insulin to decrease to $<10^{-7}$ mol/L and the absence of zinc ions (9). In order to control their postprandial glucose, patients need to inject human insulin at least one-half hour before the meal. Rapid insulin analogs were developed to address this issue, and this was demonstrated in pharmacokinetic and euglycemic clamp studies (10,11). Premix human insulin contains a mixture of two components: human insulin (Humulin R or Actrapid) and the same insulin attached to protamine, which prolongs its absorption so that it becomes intermediate-acting insulin (Humulin N and Insultard, respectively). Premix insulin analogs are also a mixture of two components: rapid-acting insulin analog (insulin aspart or insulin lispro) and the same rapid-acting insulin analog attached to protamine, which prolongs its absorption so that it transforms into an intermediate-acting insulin with NPH-like pharmacokinetic (10,11). The rapid-acting component of the premix insulin analog is the one that appears in its name, e.g., biphasic insulin aspart 30 includes 30% insulin aspart and 70% intermediate-acting insulin, while biphasic insulin lispro 25 includes 25% lispro and 75% intermediate-acting insulin. Unlike premix human insulin, premix insulin analog can be injected immediately before (12) or right after (13) a meal. Aside from the convenience for the patient, studies that compared the clinical effect gained by uses of premix insulin analog compared with premix human insulin have somewhat conflicting results. While some

studies demonstrated improvement in postprandial glucose (14–20) or HbA$_{1c}$ (18,21), others demonstrated reduction in mild hypoglycemia, severe hypoglycemia, or nocturnal hypoglycemia (15,22,23). Several meta-analyses combined the results of some of these studies (24–27), Qayyum et al. (24) concluded that premix insulin analogs provided better postprandial glucose than premixed human insulin, while Davidson et al. (27) concluded that premix insulin analogs provided significant reduction in major hypoglycemic events compared with premix human insulin (0.45 [95% CI 0.22–0.93], $P < 0.05$). The markets in developed countries have switched over the past few years from premix human insulin to premix insulin analogs as well as to other insulin analogs (28,29).

Initiation of insulin therapy with basal versus premix insulin analogs

During the course of type 2 diabetes, because of the progressive nature of β-cell destruction many patients at some point require insulin therapy (1,30). Most patients and physicians delay starting insulin therapy for several reasons: fear of increased risk of hypoglycemia and weight gain, the "bad reputation" that insulin therapy is a sign of disease progression, fear of dependency on the medication, and other beliefs and myths (31). The primary physician may be even more hesitant to begin insulin therapy than the endocrinologist/diabetologist as a result of lack of knowledge and/or experience with initiation of insulin therapy, lack of a supporting team (nurses, dietitians, diabetes educators, etc.), and lack of time and incentives. The UK Prospective Diabetes Study (UKPDS) 10-year follow-up (32) demonstrated the importance of early diabetes control in order to avoid the accumulation of "bad metabolic memory." The Outcome Reduction With Initial Glargine Intervention (ORIGIN) Trial (33) was carried out in order to determine whether insulin therapy, using insulin glargine to target fasting normoglycemia (fasting plasma glucose ≤95 mg/dL [5.3 mmol/L]), compared with standard care can reduce cardiovascular morbidity or mortality in people at high cardiovascular risk with early type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance. The ORIGIN failed to prove its primary end point; however, it did demonstrate the durability, safety, and tolerability of insulin therapy in patients with relatively short diabetes duration (average duration of diabetes 5.5 ± 6.1 and 5.3 ± 5.9 years in the intervention and control groups, respectively)

and even in the prediabetic state ($n =$ 1,449, 11.6%). The ORIGIN study also demonstrated that in these relatively new-onset diabetic patients, excellent glucose control can be achieved. Most of the patients with short disease duration are treated by primary care physicians, and therefore it is of great importance to support these physicians with all the necessary tools to be able to treat these patients with the best therapy available, including insulin, when necessary. The importance of early glucose control and its influence on patient prognosis cannot be overemphasized; unfortunately, there is often a major delay in the initiation of insulin therapy. Brown et al. (34) have shown in their prospective, population-based study using retrospective observational data that the average patient accumulated nearly 5 years of HbA$_{1c}$ > 8.0% and ~10 years of HbA$_{1c}$ >7.0% from diagnosis until initiation of insulin therapy. Insulin therapy is an ongoing process that may be divided into the following steps: *1)* setting HbA$_{1c}$ goal for a particular patient, *2)* initiating insulin therapy, *3)* titration of insulin doses to target, and *4)* intensification of the insulin regimens if target is not achieved. The role of the primary care health professional team (family physician, nurse, dietitian, etc.) in all of these steps is crucial. Their frequent and easier contact with the patient makes them ideal partners for the difficult mission of ensuring proper insulin use to improve glucose control. Currently, the most common approaches to initiating insulin therapy are with basal insulin analogs, usually at bedtime, or with premix insulin analogs, usually with breakfast and dinner (35). However, as the use of basal insulin analogs (glargine and detemir) as a replacement for NPH insulin became widespread, there is now a greater tendency to use this once-daily and more convenient approach as the first step in insulin therapy.

The first question to address is whether basal insulin therapy is the best way to initiate insulin therapy for all diabetic patients requiring insulin or whether we can identify a group of patients for whom it is better to start insulin therapy with premix insulin analogs.

The results of randomized control studies comparing initial treatment with basal insulin analogs to premix insulin analogs demonstrated mixed results. Most studies demonstrated a higher reduction of HbA$_{1c}$ with premix insulin analogs (36–42). However, some studies did not demonstrate statistically significant differences between the two groups (43–46). Increased risk of weight gain (36,40–42) and minor

hypoglycemic events (36,42–44), however, were reported more frequently using premix insulin analogs.

There are many limitations to the above-mentioned group of studies. Most of these studies are small, unblinded, and sponsored by industry.

The 4-T study (40) randomized insulin-naïve patients in an open-labeled, multicenter study to receive either basal insulin (detemir) ($n = 234$) once or, if required, twice daily; prandial short-acting insulin (aspart) ($n = 239$) three times daily; or premix insulin analog (biphasic premix insulin aspart 30) ($n = 235$) twice daily. After a year of treatment, both the prandial and the premix treated groups reached better glucose control (HbA$_{1c}$ 7.2 ± 0.9 and 7.3 ± 0.9%, respectively, $P = 0.08$) compared with the basal insulin-treated group (HbA$_{1c}$ 7.6 ± 1.0%, $P < 0.001$). However, patients in whom HbA$_{1c}$ at the beginning of the study was <8.5% achieved similar reduction in HbA$_{1c}$ regardless of the insulin regimen. The hypoglycemic events rates and mean weight gained were higher among the prandial group, intermediate in the premix-treated group, and lowest in the basal insulin–treated group (12.0, 5.7, and 2.3 events/patient/year and 5.7, 4.7, and 1.9 kg, respectively, $P < 0.001$).

How meaningful is comparison of one injection a day (often with much lower dose) to two injections? Unfortunately, studies comparing initiation of insulin therapy by basal insulin analogs versus premix insulin analogs did not help to define which patients are better suited to each treatment arm.

A community-based 18-month retrospective observational study collected data from the USA National Medical Records to compare reduction of HbA$_{1c}$ in patients who were initiated on basal insulin regimen (glargine, $n = 3,624$) with patients who were initiated with premix insulin ($n = 4,542$) and specifically with premix insulin lispro 25 ($n = 895$) (47). This observational study has shown that both insulin regimens demonstrated a reduction in HbA$_{1c}$. The reduction in HbA$_{1c}$ was, however, greater with the combined premix therapy (that included both premix human insulin and premix insulin analogs) (0.04–0.14%; $P < 0.05$) and greatest in the premix lispro 25 group (0.26–0.65%; $P < 0.05$) compared with the basal insulin group. This study was limited, however, since it was supported by industry and was based on a retrospective, nonrandomized cohort analysis with a large and unequal patient

drop-out rate. Its strengths, on the other hand, are the relatively large patient sampling and "real-life" setting. The results of this observational study are supported by a meta-analysis that compared the efficacy of basal versus premix insulin analogs in achieving glucose control in randomized control trials (RCTs) (48). The meta-analysis included RCTs that lasted ≥12 weeks, had >30 patients in each arm, and reported the percentage of patients who reached the goal of HbA_{1c} <7%. Eight of the 10 studies that fit these criteria enrolled insulin treatment-naïve patients. A greater percentage of patients treated with premix insulin analogs achieved HbA_{1c} <7% (46.5%) compared with patients treated with basal insulin (36.1%) (odds ratio 1.88 ([95% CI 1.38–2.55], $P = 0.0012$). However, treatment with premix insulin analogs, compared with basal analogs, used two instead of one injection per day. Compared with basal analogs, premix insulin analogs use was associated with an increased incidence of minor hypoglycemia (mean difference 0.34 events/patient/30 days [range 0–0.69], $P = 0.05$, and after the use of mixed-effects model, with estimates adjusted for the correlation within studies and heterogeneity between studies, mean difference 0.28 events/patient/30 days [0.10–0.45], $P = 0.006$). Weight gain averaged 2.42 kg in the premix group compared with 1.44 kg in the basal group (between-groups difference of 1.0 kg [range 0.28–1.73], $P = 0.01$). Major hypoglycemia events were very low and similar between groups. The previously mentioned studies had surrogate markers of HbA_{1c} as their primary end point; more information is required regarding the clinical outcome of controlled fasting versus postprandial glucose levels. Only one long-term study, the Hyperglycemia and its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (HEART 2D), compared cardiovascular outcomes in post–myocardial infarction patients treated with basal versus prandial or premix insulin (49). The goal of the study was to examine the effect on cardiovascular outcomes of decreasing fasting versus postprandial glucose while maintaining similar HbA_{1c} levels. The study did not demonstrate any difference in cardiovascular outcomes between the treatment strategies. The HEART 2D trial ended prematurely for futility; however, classification and regression tree was used to identify baseline subgroups with potential treatment differences (50). Classification and regression tree estimated the age of >65.7 years

to best predict the difference in time to first event. In the subgroup aged >65.7 years (prandial, $n = 189$; basal, $n = 210$), patients treated with prandial regimen had a significantly longer time to first event, and a lower proportion experienced a first event ($n = 56$ [29.6%] vs. $n = 85$ [40.5%]; hazard ratio 0.69 [95% CI 0.49–0.96]; $P = 0.029$) despite similar HbA_{1c} levels (50). The results of the previously mentioned meta-analysis, as well as other trials (35,51), suggest that most type 2 diabetic patients in whom insulin treatment is initiated will benefit most from basal insulin because of the relative ease of treatment and the reduced risk of hypoglycemia and weight gain compared with other insulin treatment regimens (3). The results of the previously quoted studies (35–51) were not conclusive in demonstrating that one insulin regimen is better than the other. Owing to their design and size, most studies are not able to define which subgroups of patient will benefit more from the premix or basal insulin regimen. However, since most studies demonstrated higher efficacy of premix insulin in the entire population (36–42), it can be assumed that in the subgroup of patients where despite high HbA_{1c} the fasting plasma glucose is relatively low, postprandial glucose is relatively high, and therefore, premix insulin regimen in this subgroup might demonstrate even better efficacy and safety than in the entire population. The 4-T study (40) demonstrated the superior efficacy of premix insulin analogs over basal insulin in achieving glucose control in the entire study population but not in the group with HbA_{1c} <8.5%; therefore, it can be assumed that in patients with HbA_{1c} >8.5% the stronger effect of premix insulin over basal insulin in HbA_{1c} reduction is even more dominant.

To the best of our medical judgment, there may be three important exceptions to initiating insulin therapy with basal insulin. The first involves patients with high HbA_{1c} (>8.5%) who may not be able to reach their HbA_{1c} goal solely with basal insulin, since they also need insulin "cover" for their postprandial glucose. Most RCTs and meta-analyses have demonstrated the superiority of premix insulin analogs over basal insulin in reducing HbA_{1c} (36–42), including in patients with HbA_{1c} >10% (36). In this high-risk patient population an increase in weight gain and mild hypoglycemia with premix insulin analogs might be justified. Ideally, patients who are very far from proper glucose control should be considered for basal-bolus treatment.

However some of these patients cannot adhere to a complex insulin regimen such as basal-bolus regimen (due to advanced age, need for assistance with injection, lack of support, etc.). Insulin nonadherence, including injection omission, is common among adults with type 2 diabetes (52–55) and correlates with poorer glucose control; however, a direct comparison of compliance among premix insulin analogs versus basal-bolus–treated patients is lacking.

The second exception is patients with lower compliance, who are often more hesitant to titer their insulin doses and therefore may benefit more from initiation of premix insulin analogs usually initiated with larger doses of insulin, requiring less titration in order to reach goals.

The third exception includes patients with relatively low (<150 mg/dL) fasting or preprandial plasma glucose and a relatively high HbA_{1c}, suggesting high postprandial hyperglycemia. The family physician's long-term and multifaceted acquaintance with the patient may be an advantage for recognizing/identifying these three specific groups of patients. This approach to initiating insulin therapy is summarized in Fig. 1.

When basal insulin is not enough: premix insulin analogs versus basal plus and basal-bolus regimens

Glucose control can be referred to as a three-part challenge: control of fasting glucose, postprandial glucose, and
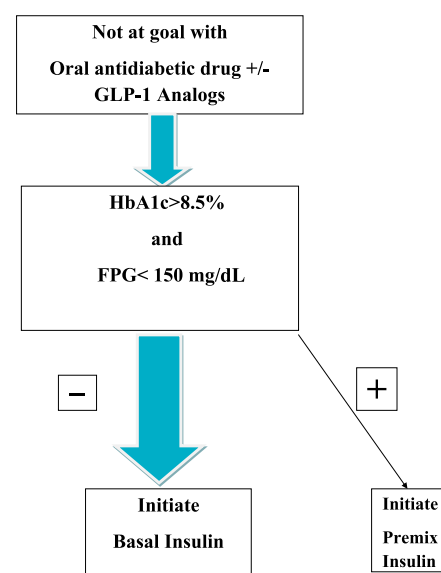

Figure 1—*Rationale for initiating basal versus premix insulin analogs. GLP-1, glucagon-like peptide 1; FPG, fasting plasma glucose.*

Table 1—*Which patient should be offered a premix versus basal-bolus/basal plus regimen?*

Premix insulin analogs	Basal plus/basal bolus
Patient preference	Type 1 diabetes (any age)
Older age	Younger age
Need assistance with injections	Highly motivated and compliant
Organized lifestyle	Active lifestyle
Two meals a day or evening main meal	High variability in eating habits

HbA_{1c}. While basal insulin analog doses can usually be titered until they control fasting plasma glucose levels, a large proportion of patients will immediately or eventually need a more complete replacement of insulin that also includes prandial insulin (56,57). Postprandial insulin deficiency can be addressed in some patients using glucagon-like peptide 1 analogs; for others, however, this treatment might be insufficient, intolerable, or simply unaffordable. According to the ADA/EASD position statement (1), "glucose-lowering effects should be balanced with the convenience of the regimen, in the context of an individual's specific therapy goals." The addition of prandial/mealtime insulin to basal insulin should be considered when fasting glucose is at target, or cannot be achieved, while HbA_{1c} is above target for 3–6 months after basal insulin titration (1). When basal insulin therapy is not enough, ideally, the family physician should either intensify insulin therapy by him/herself or, if lacking time or a support team, consider referring the patient to an endocrinologist/diabetologist for further evaluation and consideration of the different possible treatment strategies. It is important to note that availability of such a consultation differs greatly among regions, countries, and health insurance systems. The frequency of such consultations might also be sparse; therefore, the active involvement of the family physician and his/her team in the treatment of diabetic patients should not be underestimated at any stage.

The three main options available for patients who need further intensification of their insulin regimen are the addition of rapid-acting insulin with one of the daily meals (basal plus regimen); the addition of rapid insulin with two–three daily meals (basal bolus); or a switch to premix insulin before two–three daily meals (57,58). Is there a preferred way to intensify insulin therapy?

The meta-analysis of Giugliano et al. (48) included only three RCTs comparing premix insulin analogs with basal-bolus regimens that met the above-mentioned quality measurements (study duration >12 weeks, sample size >30 in each arm, and report of the proportion of patients reaching HbA_{1c} <7%). They compared premix insulin analogs to basal-bolus regimens in non–insulin-naïve patients. The meta-analysis concluded that patients treated with premix insulin analog compared with basal-bolus regimen had a lower chance of reaching the HbA_{1c} goal: 50.8 vs. 63.5% (odds ratio 0.57 [95% CI 0.36–0.9], $P = 0.034$), while there was no evidence of difference in incidence of hypoglycemia and weight gain between the two regimens. It is reassuring to note the low overall incidence of hypoglycemic events, almost all of which were entirely mild hypoglycemia, in the entire meta-analysis—0.4 events/patient/30 days (range 0–4.71 [interquartile range 0.3–1.0])—and the limited weight gain (1.0 and 1.9 kg in the premix and prandial groups, respectively). It is not surprising that treatment with four to five daily insulin injections was more effective in achieving HbA_{1c} <7% than two to three injections per day; however, when considering basal-bolus versus premix insulin regimens we must keep in mind the important difference between clinical trials and real-world patients and protocols. Patients in clinical studies are preselected for better compliance and are more closely followed up than is feasible in a real-world scenario. The question is whether similar results could be achieved in a real-world setting and especially in the primary care setting, where resources are often limited; this question has not yet been resolved. It is important to remember that insulin intensification is not always a single step or in one-way direction. As stated in the section of the ADA/EASD position statement (1) regarding insulin intensification, if treatment with premix insulin analogs is unsuccessful in achieving glucose control goals after proper titration of this regimen was done, a progression to basal-bolus regimen is possible. On the other hand, if patient compliance with lifestyle modification improves, simplification of insulin regimen is sometimes possible.

An important issue in real-world insulin treatment is the adherence to regimen. Nonadherence to insulin therapy is associated with both worse glycemic control (52,59) and increased risk of diabetes-related microvascular complications (53). Omitting insulin dose is common among type 2 diabetic patients (52–55,59) and might be even more common than among type 1 diabetic patients (52). Nonadherence to insulin therapy was found to be significantly and independently associated with two aspects of injection burden: having to plan daily activities around insulin injections and injections interfering with activities of daily life (54). In a recent telephone survey (55) that included 1,530 insulin-treated adults (110 type 1 diabetic and 1,420 type 2 diabetic) from eight countries, 35% of patients reported ≥1 day of insulin omission/nonadherence (average 3 days) in the past month. Insulin nonadherence varied widely across countries (20–44%) (55).

One option tested to ease the intensification of insulin treatment for patients in whom basal insulin therapy did not achieved glucose control target are the addition of one shot of rapid-acting insulin per day with one of the meals (basal plus) instead of adding two or more injections of rapid-acting insulin per day (basal bolus). However, even in the well-controlled setting of a treat-to-target clinical trial (60) over 1 year, >70% of the patients who were initiated on basal plus were shifted to basal-bolus regimen. Therefore, switching from basal insulin to basal plus instead of basal bolus may ease the change for the patient, but both the clinician and the patient should be aware of the possibility that the treatment will need to be further intensified within a short time to basal plus regimen in order to achieve glycemic goals. When deciding whether to put a patient on a basal plus regimen, the clinician should ensure that the patient is able to manage his/her diabetes with all the complexity of basal-bolus treatment: multiple daily injections and multiple daily glucose monitoring. Deciding which patient will benefit from the more complex basal-bolus regimen and will be able to comply with its demands involves complex and important clinical judgment. The family physician, who is more familiar with the patient, is in a good position to evaluate which regimen will be the best for the patient. Some points to help decision making are summarized in Table 1.

In conclusion, intensification of basal insulin to premix insulin analogs instead
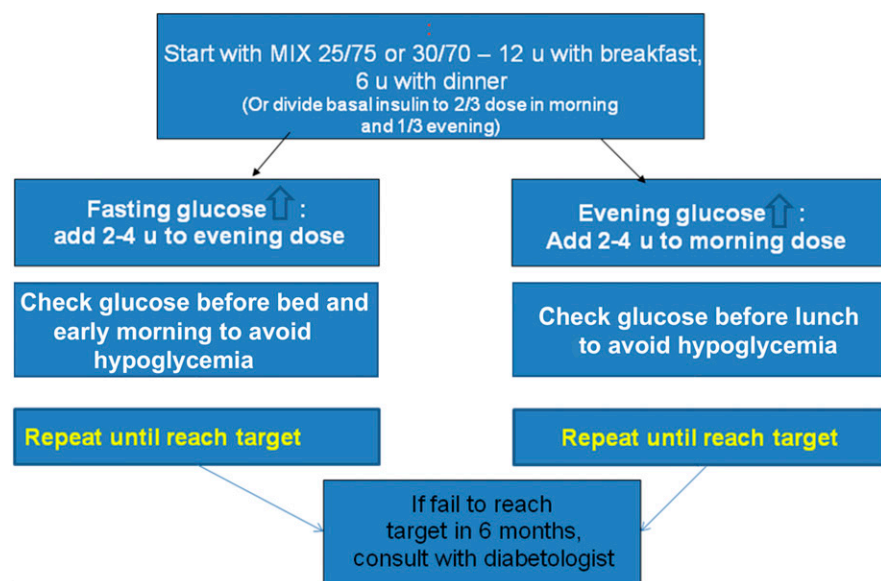
Figure 2—*Initiation and intensification of premix insulin analogs.*

of basal bolus is suitable for *1*) patients in whom we are satisfied with less strict diabetes control, *2*) patients who cannot comply with basal-bolus treatment, and *3*) patients with a well-organized daily life. In these patients, treatment with premix insulin analogs can help achieve acceptable and safe glucose control while allowing them an easier way to manage their disease. Figure 2 presents guidance for physicians on changing from basal insulin to a premix insulin analog including titration to goal.

Conclusions

The family physician should initiate insulin treatment, when required, in a timely manner. The primary care health team should be involved in all the steps of insulin treatment: setting glucose control goal, initiating insulin therapy, titration of insulin dose, and intensification of treatment regimen if necessary. The endocrinologist/diabetologist should be available for advice and guidance as needed. Basal insulin is preferable when adding insulin therapy to antidiabetes drugs. Three exceptions that can often be identified by the family physician are patients with relatively low fasting or preprandial glucose (<150 mg/dL) despite high HbA$_{1c}$, patients with difficulty in compliance with the high demands of basal-bolus treatment, and patients in whom self-titration might not be feasible (Fig. 1). When basal insulin fails to achieve the target in spite of titration, the family physician should proceed to insulin

intensification and consider consulting with an endocrinologist/diabetologist. The three common regimens used to intensify insulin therapy are premix, basal plus, and basal bolus. Most patients who begin a basal plus regimen will eventually need a basal-bolus regimen; therefore, basal plus regimen should be initiated if the treating physician decides that the patient will be able to adhere to a basal-bolus regimen. Basal bolus most closely resembles physiological insulin secretion; however premix insulin analogs can be a good option with less complicated and demanding glucose monitoring and injection schedule. Often, family physicians have a long-standing and more personal understanding of their patients and are in a good position to select the appropriate patients for basal plus/basal-bolus versus premix treatment. In order to properly treat their patients with insulin, the family physician should be knowledgeable and have enough time, support (nurse, dietitian, etc.), and incentive to accomplish this task. The rule should be tailoring insulin treatment to suit the patient and not the other way around.

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