



### eDiabetes Review VOLUME 1, ISSUE 1

#### STRATEGIES FOR INTENSIFYING THERAPY FOR GLYCEMIC CONTROL



**Program Directors' Note:** *It is with great pleasure that we welcome you to this first issue of the Johns Hopkins School of Medicine eDiabetes Review. Over the next year, our authors will be sharing their knowledge and experience on topics critical to improving the management of patients with Type 2 diabetes mellitus. Next month's Podcast interview discusses how the information presented in this Newsletter can be effectively translated into clinical practice.*

#### In this Issue...

One of the key challenges in managing type 2 diabetes is preventing hyperglycemia in patients undergoing treatment with antidiabetic drugs. Clinical inertia — specifically, the delay in intensifying therapy when current medications no longer achieve acceptable glycemic control — is common among primary care clinicians (as well as many specialists). While the number of pharmacologic agents continues to increase, the lack of clear consensus recommendations challenges clinicians to find the most appropriate and effective intensification regimen for each patient.

In this issue, we review recent publications describing:

- The incidence of clinical inertia in intensifying therapy
- Quantifying metformin dosing
- Add-on therapies to metformin
- Weekly versus daily GLP-1 agonists
- Sequential intensification with metformin, GLP-1s, and basal insulin
- Basal-bolus vs premixed insulin regimens

### LEARNING OBJECTIVES

**After participating in this activity, the participant will demonstrate the ability to:**

- Recognize the barrier of clinical inertia in intensifying the care of patients with uncontrolled type 2 diabetes.
- Evaluate therapy in type 2 diabetes based on glycemic lowering effect, side effect profiles, and cost of pharmacologic options.
- Describe when to initiate and how to intensify insulin therapy in a safe and effective manner.

**The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.**

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#### Length of Activity

- 1.0 hour Physicians
- 1.0 contact hour Nurses

#### Launch Date

April 3, 2014

#### Expiration Date

April 2, 2016

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### Guest Faculty Disclosures

**Nestoras Mathioudakis, MD** has indicated that he has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of his presentation.

### Unlabeled/Unapproved Uses

Dr. Mathioudakis has indicated that there will be no references to

## COMMENTARY

Clinical inertia is unfortunately all too common in diabetes management, at both the primary care and specialist levels.<sup>1</sup> As a diabetes specialist, I am constantly astonished by how long patients referred to me have been exposed to chronic hyperglycemia without some escalation in their therapy. As Khunti et al point out in this issue, there is a sobering six-year lag time between maximal doses of three oral antidiabetic drugs and initiation of insulin therapy. Given the increasing number of antidiabetic agents currently available and the lack of clear consensus recommendations among professional societies, it can be challenging for the clinician to decide how best to sequentially intensify pharmacotherapy in patients with uncontrolled type 2 diabetes. Several principles, many of which have been outlined in this issue, can help guide the clinician to intensify therapy in a timely manner.

First of all, metformin should be the cornerstone of any diabetes regimen (unless contraindicated), given the fact that it is really the only medication in the diabetes armamentarium shown to have a beneficial effect on cardiovascular disease outcomes.<sup>2</sup> As Hirst et al (reviewed in this issue) demonstrated, the clinically meaningful effect of metformin is not fully realized until a dose of 1,500 mg or higher is used. Therefore, barring any contraindications or side effects, metformin should be maximized (2,000 to 2,500 mg daily), with consideration of the ER formulation in those patients with GI intolerance. Metformin should be adjusted based on the eGFR, not serum creatinine, and it should be continued whenever possible in patients receiving insulin to improve insulin sensitivity.

If patients are still not at goal A1C after maximal metformin doses for three months, a second agent should be started. Several factors play into the decision to add a second glucose-lowering agent, including the glucose-lowering effect, convenience, side effects, effect on weight, hypoglycemia risk, cost, and availability of long-term outcome data. Currently 11 classes of commercially available noninsulin glucose-lowering medications are available in the United States, and it can be increasingly challenging for clinicians to understand the rationale behind choosing a particular medication. The fact that professional society recommendations differ with respect to choice of second-line agents illustrates the complexities of diabetes management and calls for greater research to clarify effective intensification strategies. Currently, the American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) place priority on incretin-based therapies, with GLP-1 receptor agonists being the first-line medication after metformin.<sup>3</sup> On the other hand, The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guidelines provide less specific advice on the choice of a second agent, recommending five treatment options after metformin.<sup>4</sup>

To help guide the clinician in selecting a second or third line medication to intensify glycemic control, several key articles published in this field over the last two years are reviewed in this issue. The meta-analysis of 39 random control trials (RCTs) by Liu et al compares the glycemic efficacy and risk of hypoglycemia and weight gain of commonly used medications as add-on therapy to diabetes. This study showed that the GLP-1 agonists are the most effective agents as add-on therapy to metformin.

Given their clinical efficacy and increasing use in clinical practice, clinicians need a greater understanding of the effectiveness and side effects of the individual GLP-1 agonists when used in combination with oral glucose lowering medications or insulin. As Buse et al (reviewed in this issue) show, liraglutide is slightly more effective than once-weekly extended-release exenatide, while the latter is better tolerated from a gastrointestinal standpoint. Both of these GLP-1 agonists are effective when added to oral anti-hyperglycemic medications. The prandial effect of GLP-1 agonists can be augmented by the addition of a basal insulin, as shown by DeVries et al (reviewed in this issue). In their study, the addition of basal insulin to metformin and liraglutide provided meaningful glycemic lowering effect.



As an endocrinologist, I am frequently referred patients who have failed maximal doses of three glucose-lowering medications and who have clearly reached a state of insulin deficiency. Many of these patients have gone years without transitioning to insulin, with various untoward consequences on their health. The reasons for this delay have been the subject of several studies. Limitations to starting insulin by primary care physicians or specialists include, among other things, lack of time required to train patients, lack of clear guidelines and definitions, lack of support (certified diabetes educators), and lack of motivation by the patient.<sup>5</sup> While many primary care physicians understand how to start basal insulin, in my experience, there appears to be a knowledge gap in understanding how and when to initiate insulin or how to adjust insulin doses in patients on intensive basal-bolus insulin regimens. As the reviewed article by Testa et al demonstrates, a basal-bolus insulin regimen, while more burdensome for the patient, may be associated with greater glycemic efficacy and, consequently, greater patient satisfaction compared to premixed insulins, especially in patients with long duration of diabetes. Physicians need a good understanding of insulin actions to guide therapeutic adjustments in insulin doses. Empowering patients to make small dose changes based on their self-monitored blood glucose readings will lead to more timely attainment of glycemic targets and conceivably greater patient satisfaction.

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## CLINICAL INERTIA

Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care*. 2013 Nov;36(11):3411-3417.



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Khunti and colleagues retrospectively studied the timeliness of intensification of therapy in a large cohort of 80,000 people with uncontrolled type 2 diabetes. This study, which took place between 2004 and 2011 in the United Kingdom, used the Clinical Practice Research Database (CRPD), the world's largest computerized database containing longitudinal primary care data of > 13 million patients in the UK.

The study assessed the time to intensification of treatment in patients who did not meet glycemic control on one, two, or three oral antidiabetic drugs (OADs). Treatment intensification was defined as either the addition of another OAD or initiation of insulin irrespective of changes in OAD doses. The researchers could not account for increases in dose of an OAD because that information was not available in the clinical database.

The main findings of the study were: 1) in people with HbA1C  $\geq$  7.0%, 7.5%, or 8.0% taking one OAD, the median time to intensification with an additional OAD was 2.9, 1.9,



and 1.6 years respectively; 2) in people with HbA1C  $\geq$  7.0%, 7.5%, or 8.0% taking two OADs, the median time to intensification with an additional OAD was >7.2, >7.2, and >6.9 years; 3) among patients taking three OADs, the median time to intensification with insulin was > 6.0 years; 4) among patients with poor glycemic control taking OADs, only 20%-40% had intensification of therapy with an additional OAD and only 5%-12% with insulin therapy.

This is one of the largest studies to date to quantify "clinical inertia" in diabetes management in a real-world primary care setting. The most notable and sobering finding of the study was the > 6 year delay in starting insulin in patients on three OADs. Despite the clear lack of glycemic control on three OADs, only 5-12% of patients were started on insulin therapy by seven-year follow-up. Although this study took place in the UK., similar findings have been observed in the US<sup>1-2</sup> and abroad.<sup>3-5</sup> Along the therapy continuum, the greatest hurdle for primary care physicians appears to be starting insulin. Better glycemic control by specialists compared to primary care physicians has been attributed primarily to more aggressive or earlier initiation of insulin, rather than titration of oral or noninsulin antidiabetic agents.<sup>1,6</sup>

Since clinical practice guidelines recommend titrating therapy at three-month intervals based on glycemic response,<sup>7</sup> it is untenable to imagine that a six-year lag time in insulin initiation would result from time required to titrate medications to maximal doses. Rather, the delay in starting insulin is most likely related to PCPs' perceptions of patient resistance to insulin injections or poor self-management skills.<sup>8</sup> Evidence suggests that primary care physicians may not be completely accurate in their assessment of patients' attitudes about insulin or their self-management capacity.<sup>8</sup> If resources are not available for diabetes education and support, early referral to specialty clinics that have certified diabetes educators is likely to be the most effective strategy in motivating a patient to start insulin therapy when indicated.

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## QUANTIFYING THE CLINICALLY EFFECTIVE DOSE OF METFORMIN

Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the effect of metformin treatment and dose on glycemic control. *Diabetes Care*. 2012 Feb;35(2):446-454.



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Metformin is the first-line drug in diabetes management and is one of the few currently available glucose-lowering agents that has been associated with cardiovascular benefits.<sup>1</sup> In this study, Hirst and colleagues performed a meta-analysis of 35 double-blinded randomized controlled trials (RCTs) in which metformin was used as either monotherapy or as add-on therapy to determine the glycemic lowering potential of metformin, and more specifically, the dose of metformin associated with maximal glycemic benefit.

As monotherapy, metformin was shown to lower HbA1C by 1.12% (95% CI 0.92-1.32) compared to placebo. As combination therapy, metformin lowered A1C an additional 0.95% (95% CI 0.77-1.13). When added to insulin, metformin lowered HbA1C 0.60% (95% CI 0.30-0.91). The dose of metformin used in the RCTs ranged from 500 mg to 3000 mg daily. There was a clinically significant difference in A1C lowering with high-dose metformin (at least 2,000 mg daily) compared to low dose metformin (1,000 or 1,500 mg daily). Higher doses of metformin resulted in an additional 0.26% A1C lowering (95% CI -0.38 to -0.14). The study found no incremental benefit of increasing metformin beyond 2,500 mg daily (ie, 3,000 mg daily). A dose of 1,500 mg appears to be most clinically meaningful, with A1C lowering generally > 1.0% with this dose, compared to generally < 1.0% at lower doses.

This study is the first meta-analysis to compare dose effectiveness of metformin, and it provides some salient clinical take-away messages. First, metformin should be maximized as tolerated until glycemic targets are achieved, with a dose of at least 1,500 mg appearing to be most clinically meaningful. Metformin is available as both an immediate release (IR) tablet of 500, 850, or 1000 mg; or as 24 hour extended release (ER) formulation of 500, 750, or 1000 mg daily. The maximum recommended IR dose is 2550 mg, and at doses above 2000 mg, the drug may be better tolerated in three daily divided doses. The maximum dose of the ER formulation is 2000 mg, and if glycemic control is not achieved at the maximum dose, the ER formulation may be divided and administered twice daily.

The second important clinical point is that metformin should always be continued in patients taking insulin unless there is a contraindication. As this study shows, metformin can provide additional glucose-lowering effect on top of insulin therapy. Given metformin's role as an insulin sensitizing agent, its addition to insulin therapy results in lower insulin requirements and therefore less weight gain and hypoglycemia.<sup>2</sup>

The main limiting factors to metformin use are gastrointestinal (GI) side effects and concerns about lactic acidosis in the setting of renal or liver disease. To improve GI tolerability, switching from the IR to ER formulation can be an effective strategy. A previous study found that the incidence of diarrhea was reduced from 58% to 14% and the incidence of nausea was reduced from 18% to 6% after switching from the IR to ER formulation.<sup>3</sup> With respect to renal function, it has recently been shown that the likelihood of lactic acidosis is exceedingly low, even in patients with renal insufficiency.<sup>4</sup>

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## EFFICACY OF ADD-ON THERAPY TO METFORMIN

Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. *Diabetes Obes Metab*. 2012 Sep;14(9):810-820.



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In this meta-analysis, Liu and colleagues studied the risk/benefit profile of glucose-lowering medications as add-on therapy to metformin. Thirty-nine RCTs involving 17,860 individuals were included. The primary variables of interest were HbA1C lowering, weight change, and hypoglycemia risk. Network meta-analysis was used to incorporate evidence from both direct and indirect comparisons of these drugs. Second-line medications for diabetes included in the study were sulfonylureas (SUs), glinides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide (GLP-1) analogues, basal insulin, and biphasic (premixed) insulins.

From a glycemic control standpoint, GLP-1 agonists were more effective than SUs, glinides, TZDs, AGIs, and DPP-4 inhibitors, providing an additional 0.20% to 0.36% A1C lowering compared to these agents. Their effect was comparable to basal insulin and biphasic insulin. SUs lowered A1C more than DPP-4 inhibitors (- 0.12%; 95% CI - 0.23 to - 0.03%) and biphasic insulin lowered A1C more than glinides (- 0.36%; 95% CI - 0.82 to - 0.11%). The risk of hypoglycemia was greatest for SUs, glinides, basal insulin, and biphasic insulin. Weight increase of ~ 2 kg was seen with SUs, glinides, TZDs, while GLP-1 agonists and AGIs were associated with weight loss of ~ 1.80 kg. DPP-4 inhibitors had no effect on weight.

The findings of this meta-analysis can help guide the clinician in selecting a second-line agent in patients with type 2 diabetes uncontrolled on metformin. These results largely align with the glycemic control algorithm outlined by the American Association of Clinical Endocrinologists (AACE) in 2013<sup>1</sup>. In these practice guidelines, second-line agents are listed according a suggested hierarchy of usage. The first choice is a GLP-1 agonist because of glycemic efficacy, weight benefit, and low hypoglycemic potential. The second choice is a DPP-4 inhibitor because of weight neutrality and low hypoglycemic potential. The third choice is a TZD (pioglitazone); however this is to be used with caution given concerns about bone loss, fluid retention, and bladder cancer. The fourth choice is the newest drug class, SGLT-2 inhibitors (sodium glucose transport 2 inhibitors), based on the results of Phase 3 clinical trial data. The fifth choice is basal insulin; however, it carries the risk of weight gain and hypoglycemia. The sixth choice is colesevelam, a bile acid resin that has modest glucoselowering effects. The seventh choice is bromocriptine, a dopamine agonist that also has modest glucose-lowering effects. The eighth choice is an AGI, which although clinically effective, is often poorly tolerated. The last choice on the AACE algorithm is a SU or glinide, both of which have a higher likelihood of hypoglycemia and weight gain. It should be noted that there is limited long-term data with respect to micro- and macrovascular risk reduction with colesevelam, bromocriptine, and the SGLT-2 inhibitors, so these are not widely used in clinical practice.

It is also worth noting that the 2013 AACE algorithm differs from the 2012 ADA/EASD<sup>2</sup> position statement in several respects<sup>3</sup>. The ADA/EASD lists SUs first and TZDs second as combination therapy, followed by DPP-4 inhibitors and GLP-1 agonists. The new SGLT-2 inhibitors are not listed. The ADA/EASD recommendations reflect concern about the higher cost of newer treatment modalities (ie, GLP-1 agonists) compared to the AACE algorithm.

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# EFFECTIVENESS OF WEEKLY EXENATIDE VERSUS DAILY LIRAGLUTIDE INJECTIONS

Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013 Jan 12;381(9861):117-1124.



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Two GLP-1 agonists are commercially available in the United States: exenatide, which can be given as a twice-daily or once-weekly extended-release injection, and liraglutide, which is given as a once-daily injection. In this randomized, open-label study, Buse and colleagues compared the efficacy and safety of once-weekly exenatide with once daily-liraglutide injections in patients with type 2 diabetes. The study involved 105 sites in 19 countries and enrolled patients with type 2 diabetes treated with lifestyle and oral antihyperglycemic drugs. They were randomized 1:1 to receive once daily injections of the maximum dose of liraglutide 1.8 mg daily or exenatide 2 mg once weekly. The primary endpoint was HbA1C change from baseline at 26 weeks.

The study found that both once daily liraglutide and once weekly exenatide were effective in improving glycemic control, with HbA1C change of - 1.48% and - 1.28%, respectively. Contrary to their hypothesis, daily liraglutide was found to be more effective, with a treatment difference of 0.21% in A1C. With respect to tolerability, the weekly exenatide group reported less nausea (21% vs 9%), diarrhea (13% vs 6%) and vomiting (11% vs 4%), compared to the liraglutide group. The incidence of side effects decreased in both groups over time. A greater proportion of patients allocated to liraglutide dropped out of the study because of side effects compared to exenatide (5% vs 3%). Weight loss was more pronounced in patients taking liraglutide (~ - 3.5 kg), with 95% CI of treatment difference of 0.39-1.40 kg at 26 weeks. These results were in line with a previous study by the same author showing greater A1C lowering and weight loss with liraglutide compared to twice daily injections of exenatide.<sup>1</sup>

It is important to note that the study was not designed to test the superiority of liraglutide, and the A1C difference of 0.21% was not tested for significance.<sup>2</sup> Furthermore, the study design may have biased the interpretation of tolerability, since patients not tolerating the 1.8 mg dose of liraglutide after four weeks were excluded from the trial. In clinical practice, many patients tolerate the 1.2 mg daily dose of liraglutide and are able to achieve glycemic goal, so a more meaningful comparison might have been to examine the glycemic control and side effects of the maximum tolerated doses of each drug.<sup>2</sup> Furthermore, as the study was not blinded or placebo-controlled, the patients' perception of side effects may have been biased by their preference for a weekly versus daily injection.

Despite some limitations of this study, this is an important publication that helps to inform choices of drugs within this class. Given the modest superiority and increased convenience of once daily liraglutide compared to once weekly exenatide both with respect to weight loss and glycemic control, the former may be a more attractive option. On the other hand, in light of the more favorable side effect profile and fairly comparable glycemic efficacy, extended-release exenatide may enhance patient compliance.

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## SEQUENTIAL INTENSIFICATION OF THERAPY WITH METFORMIN, GLP-1 AGONIST, AND BASAL INSULIN



DeVries JH, Bain SC, Rodbard HW, et al; Liraglutide-Detemir Study Group. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care*. 2012 Jul;35(7):1446-454.



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In this study, DeVries and colleagues tested a simple diabetes treatment intensification sequence of metformin (MET), liraglutide (LIR), and insulin detemir (DET). It involved 988 participants from North America and Europe with insulin-naïve type 2 diabetes who had been treated for at least three months with MET at a dose  $\geq 1,500$  mg with A1C values between 7%-10% or treatment with MET and a sulfonylurea (SU) (at  $\leq$  half the maximum approved dose) with A1C values of 7.0%-8.5%. This was a 38 week, open-label trial comprised of a 12-week run-in of MET + LIR followed by a 26-week randomized, two-armed, parallel group period for patients not achieving A1C  $< 7.0\%$ . At run-in, if SU was being taken it was discontinued and LIR was initiated in 0.6 mg/day weekly increments to final dose of 1.8 mg/day. The MET dose remained the same. After the 12-week run-in period of MET + LIR, participants were randomized 1:1 to MET + LIR + DET or continued on MET + LIR. Participants whose A1C was  $< 7.0\%$  after the 12-week run-in period were included in an observational group (ie, not randomized).

Among the 988 participants, 821 completed the run-in phase, and 61% of them achieved A1C  $< 7\%$  (mean change 1.3%). At week 26, those randomized to MET + LIR + DET achieved an additional 0.5% A1C reduction, whereas the MET + LIR group experienced a 0.02% A1C increase ( $P < 0.0001$ ). Forty-three percent of participants treated with DET achieved A1C  $< 7.0\%$ , compared to only 17% who did not receive basal insulin. There was a 3.5 kg weight loss during the run-in phase of MET + LIR, with no significant weight increase when DET was added. There were no major hypoglycemia events and minor hypoglycemic rates were 9.2 vs 1.3% in those with and without DET.

This was the first prospective RCT to study the addition of basal insulin to a GLP-1 agonist in type 2 diabetes. Previous studies have tested the reverse sequence in which a GLP-1 agonist is added to insulin and showed favorable results.<sup>1-3</sup> Several interesting clinical take-home points emerged from this study. First, in patients failing treatment on the combination of MET + SU, 17% achieved therapeutic target when the SU was switched to a GLP-1 agonist. While this finding may seem unimpressive, it is actually significant when the pharmacologic action of these drugs is considered. SUs work to control both fasting and prandial hyperglycemia by stimulating insulin secretion, whereas GLP-1 agonists mainly target prandial hyperglycemia through the incretin effect. Secondly, it is notable that only the 43% taking the combination of MET, LIR, and DET achieved glycemic targets. The authors acknowledge that this could have been due to failure to aggressively titrate insulin. However, an alternative explanation is that these individuals have less residual beta cell function and actually require a more intensive insulin regimen to provide prandial coverage. Third, this combination of therapy was well-tolerated with no significant weight gain despite initiation of insulin therapy, suggesting that the weight loss effects of GLP-1 agonist therapy can offset insulin-induced weight gain.

### References

1. Buse JB, Bergenstal RM, Glass LC, et al. [Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial.](#) *Ann Intern Med*. 2011;154:103-112.
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## EFFECTIVENESS AND TOLERABILITY OF BASAL-BOLUS VERSUS PRE-MIXED INSULIN ANALOGUE REGIMENS

Testa MA, Gill J, Su M, Turner RR, Blonde L, Simonson DC. Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. *J Clin Endocrinol Metab.* 2012 Oct;97(10):3504-3514.



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In this multicenter, randomized crossover trial, Testa and colleagues evaluated the effect of two insulin intensification approaches in 82 patients with type 1 diabetes and 306 patients with type 2 diabetes who were treated with insulin. These included a basal-bolus regimen (glargine plus glulisine) versus premixed insulin regimen (Humalog® Mix 75/25 or Novolog® Mix 70/30) twice daily. Participants underwent the intervention for 12 weeks and crossed to the alternate intervention for 12 weeks. The baseline A1C was 7.87% for both groups at randomization. The mean duration of diabetes was 15-17 years.

Study participants were asked to perform self-monitoring of blood glucose (SMBG) four times per day and were contacted weekly to review hypoglycemia and adverse events and to adjust insulin doses.

Insulin glargine was adjusted (based on fasting glucose readings) according to the following schedule:

- < 70 mg/dl, decrease by 10%
- 70-94 mg/dl, no change
- 95-119 mg/dl, increase by 2 units
- 120-139 mg/dl, increase by 4 units
- 140-179 mg/dl, increase by 6 units
- ≥ 180 mg/dl, increase by 8 units

Insulin glulisine was adjusted based on the premeal dose and the preprandial blood glucose patterns by ~ 10% changes. The premixed insulin doses were adjusted according to the mean fasting blood glucose (FBG) and predinner SMBG readings, according to the same titration schedule used for insulin glargine.

The main findings of the study were: 1) Basal-bolus insulin was more effective than premixed insulin, with mean A1C change of - 0.397% vs - 0.05%, respectively ( $P < 0.0001$ ); 2) patient acceptance was comparable for both regimens; 3) patient satisfaction was greater on basal-bolus insulin, related to reduced glucose variability, better glycemic control, improved general health perceptions, and reduced symptom distress, which outweighed the negative burden of additional injections in basal-bolus insulin.

This study provides an important contribution to the field in that it challenges the assumption that more frequent injections necessarily equate to lower patient satisfaction. Basal-bolus insulin regimens provide the most physiologic method of insulin delivery and address both fasting and prandial insulin requirements. Interestingly, in this study, better glycemic control and reduced glycemic variability resulted in improved patient satisfaction.

Many titration schedules have been developed to guide initiation and titration of basal and prandial insulin. The simplest approach is to titrate the basal insulin according to the fasting glucose levels. However, in cases where basal insulin doses have been titrated to high doses (ie, beyond 50 units) and the A1C remains elevated, it is likely that the patient has little remaining beta cell function and that prandial insulin is required. Further increases in basal insulin doses at this point may result in "overbasalization," in which the patient develops hypoglycemia during the fasting state but continues to have postprandial hyperglycemia due to lack of mealtime insulin.<sup>1</sup> In this case, switching to a basal-bolus



regimen is the best strategy. While premixed insulin regimens provide prandial and basal coverage, they are not ideal since hypoglycemia is more likely to result from mismatch between nutritional intake and fixed doses of premixed insulins, while hyperglycemia can result from gaps in prandial coverage with a twice-a-day regimen.

## Reference

1. LaSalle JR, Berria R. [Insulin therapy in type 2 diabetes mellitus: a practical approach for primary care physicians and other health care professionals](#). *J Am Osteopath Assoc*. 2013;113:152-162.

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- Clinicians do not appropriately intensify therapy as necessary to maintain glycemic control.
- Conflicting data about the safety of incretin agents may unduly deprive patients of treatment benefits.
- Clinicians are not aware of and/or are not implementing strategies to maximize the value of SMBG readings to improve patient outcomes.
- Clinicians do not adequately understand or treat to control CVD risk factors in their patients with T2D.
- Clinicians do not have a sufficiently current knowledge base to effectively consult patients about potential T2D therapeutic advances.
- Clinicians do not adequately counsel and treat their overweight/obese patients with T2D.

### INTENDED AUDIENCE

The target audience for this initiative includes: endocrinologists, primary care clinicians, nurse practitioners, physician assistants, Certified Diabetes Educators, and other health care practitioners whose work/practice includes treating patients with T2D.

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