Starting insulin therapy

(AUGUST 2015)

TO THE EDITOR: I would like to add two points to the excellent review on starting insulin in patients with type 2 diabetes by Brateanu et al in the August 2015 issue.[1]

First, in my practice, I review glucose patterns and recommend that mealtime insulin be started early after basal insulin is started and not simply wait for the next hemoglobin A_{1c} result. In my experience, basal insulin is often mindlessly up-titrated, month after month, to fix a high fasting glucose. During the first 2 to 3 weeks of basal insulin titration, I ask patients to test before breakfast, dinner, and bedtime, not just fasting. In so doing, I detect, in most patients, significant bedtime hyperglycemia arising from dinner, usually their largest meal. Then I prescribe dinnertime rapid-acting insulin to correct the bedtime hyperglycemia, and this in turn ameliorates the fasting hyperglycemia. Additional mealtime doses can be added if necessary.[2]

After all, why should we ignore hyperglycemia occurring at other times and focus only on fasting glucose? With blood glucose pattern review, we can detect those glucose elevations that need to be targeted regardless of when they occur. It has been repeatedly shown that up to almost 50% of patients will fail to reach a hemoglobin A_{1c} below 7%, even after months of up-titration of basal insulin.[3,4] Most patients will benefit by starting mealtime rapid-acting insulin early on.

And second, when adjusting mealtime rapid-acting injected insulin, there is no need to measure postprandial glucose in most patients with type 2 diabetes. A rigorous clinical trial[5] showed that testing before the next meal or, in the case of dinner, before bedtime worked as well as or better than postprandial testing. By implementing the above steps, I think we all can provide better, more individualized therapy for our patients.

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IN REPLY: We thank Dr. Weiss for his insightful comments and for the opportunity to clarify a number of points from our article.

We agree that controlling the fasting glucose should not take months. As mentioned in our article, adjusting the basal insulin dose should be done with 2 to 4 units every 2 to 3 days in order to reach the fasting glycemic goal. Applying this approach and systematically titrating the NPH, glargine, or detemir insulin will smoothly decrease the fasting glucose within 12 weeks, as described in the 24-week[1] and 52-week[2] treat-to-target trials in which basal insulin was added to the oral therapy in patients with type 2 diabetes.

When basal insulin is no longer sufficient to reach a target hemoglobin A_{1c}, a glucagon-like peptide-1 receptor agonist or prandial insulin can be used. The basal-bolus or twice-daily premixed insulin analogues can also be considered as the initial therapy, depending on the patient, disease, and drug characteristics.[3] We agree that once a prandial insulin regimen is initiated, the dose titration can be done based on preprandial or postprandial blood glucose measurements, as shown in

Table 2 in our article. However, adding the prandial insulin without first optimizing the basal therapy was considered a limitation of the Orals Plus Apidra and Lantus (OPAL) study,[4] which investigated the addition of one prandial insulin injection to basal glargine insulin.[5] As a consequence, the subsequent studies investigating the effects of initiating and titrating the preprandial rapid-acting insulin (as a single dose or using a stepwise approach) in patients inadequately controlled with once-daily basal insulin and oral antidiabetic drugs had run-in periods of 12 to 14 weeks, in order to optimize the basal insulin dosage and achieve target fasting blood glucose levels of 110 mg/dL or less. This approach had the additional benefit of achieving a target hemoglobin A_{1c} level of less than 7% in a significant number of patients (up to 37%),[6] before starting the preprandial insulin.[6–8]

Regardless of the regimen selected, titration of the insulin doses can only be achieved with understanding the pharmacodynamic characteristics of each type of insulin used.[9]

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Resuming anticoagulation after hemorrhage

(APRIL 2015)

TO THE EDITOR: I read with great interest the article "Resuming anticoagulation after hemorrhage: A practical approach."[1] The article was very well written and thorough, and the authors did a great job discussing such a controversial topic.

For the sake of completeness, I would like to point out another available option when it comes to warfarin-related bleeding. We have two studies so far. Although the results were contradicting in some ways, the Prevention of Recurrent Venous Thromboembolism (PREVENT)[2] and Extended Low-Intensity Anticoagulation for Thromboembolism (ELATE)[3] trials shed light on the possible value of low-intensity anticoagulation (international normalized ratio 1.5–2.0) beyond the conventional treatment period for prevention of recurrent venous thromboembolism. While the PREVENT trial found a lower rate of venous thromboembolism with low-intensity anticoagulation than with placebo without increasing the risk of major bleeding, the ELATE trial

found no difference in bleeding rates between low-intensity and conventional treatment.

To put this in perspective, I believe that low-intensity anticoagulation is still an option for patients with moderate-risk indications and low to moderate bleeding risk.

It will be interesting to see how lower-intensity dosing of the newer anticoagulants will perform in a similar setting.

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IN REPLY: We thank Dr. Jandali for his thoughtful comments on our article. We acknowledge that there may be a small subset of patients in whom low-intensity warfarin may be worth trying—such as patients with a history of idiopathic or recurrent venous thromboembolism in whom problematic (but not life-threatening) bleeding recurs—but only when the international normalized ratio (INR) is at the high end of the therapeutic range or slightly above it. However, when attempting to apply the results from PREVENT[1] and ELATE[2] to clinical practice and the management of anticoagulation after hemorrhage, it is important to note that in ELATE there was a higher incidence of recurrent thromboembolism in patients on lower-intensity anticoagulation than in those on conventional treatment, and no significant difference in major bleeding was noted between the high- and low-intensity groups.

We acknowledge, though, that the rates of major bleeding were surprisingly low in the high-intensity group in this study relative to historical controls and so may not apply to all patients.

It is also important to recognize that several studies have evaluated low-intensity dosing for stroke prophylaxis in atrial fibrillation with generally disappointing results, and at present, expert opinion continues to support a therapeutic INR goal of 2.0 to 3.0.[3]

Therefore, we believe that low-intensity warfarin treatment is only appropriate to try in a very small subset of carefully selected patients with a history of venous thromboembolism who have proven that they cannot tolerate full-dose warfarin and in whom a trial of low-dose warfarin treatment carries acceptable risk.

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