

Less-Stringent HbA_{1c} Goal May Be Appropriate

BY MITCHEL L. ZOLER

NEW YORK — Physicians need to be judicious in choosing a treatment goal for controlling glycemia in patients with type 2 diabetes, three studies have shown.

It may not always be necessary or appropriate to focus on treating a patient to achieve a hemoglobin A_{1c} level of less than 7.0%, Dr. John B. Buse said at a meeting sponsored by the American Diabetes Association.

In some patients, reaching a goal of less than 7.0% may require intensive treatment with multiple oral antidiabetes drugs, regimens that may cause more harm than good. And many patients are not good candidates for inten-

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sive, multidrug regimens because of comorbidities or a limited life expectancy.

The recent study results were "a call to clinical judgment," said Dr. Buse, professor of medicine and director of the diabetes care center at the University of North Carolina at Chapel Hill. "A less stringent A_{1c} goal than less than 7.0% may be appropriate for patients with a history of severe hyperglycemia and a limited life expectancy," he said. "Do the best you can [in lowering a patient's HbA_{1c} level], but don't be a lunatic about it."

Another important message to physicians who treat patients with type 2 diabetes is to "deal with blood pressure and lipids at least as aggressively as you deal with glycemia," he said.

Dr. Buse gave the example of a patient with type 2 diabetes on a regimen of metformin and 60 U/day insulin who has an HbA_{1c} level of 7.2%, with a systolic blood pressure of 127 mm Hg and a serum LDL cholesterol level of 65 mg/dL. The patient maintains a good diet and regular exercise.

"I wouldn't add another oral antidiabetes drug to try to get this patient to an A_{1c} of 6.9%," he said. "I don't believe that for this patient it will make much difference to go from 7.2% to 6.9%." But, he added, he would probably take a different approach to adding more treatment if the patient's HbA_{1c} level was 7.8%, "or especially if it was 8.5%" on the same regimen of metformin and insulin.

"The [percentage] of patients with an A_{1c} of less than 7.0%, a systolic blood pressure of less than 130 mm Hg, and a serum level of [LDL] cholesterol of less than 100 mg/dL who are on daily aspirin and getting an annual flu shot is really small—less than 10%" of all U.S. patients with type 2 diabetes, Dr. Buse said in an interview. "This shows how complicated it is to take care of patients with diabetes."

The three studies he cited, which had their results reported last year or early this

year, were the ACCORD, ADVANCE, and VADT trials. The results of all three showed that setting and reaching a target HbA_{1c} level of less than 7.0% in patients with type 2 diabetes did not uniformly result in improved patient outcomes.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial randomized more than 10,000 patients with an average HbA_{1c} at baseline of 8.1% to a target HbA_{1c} of less than 6.0% or a target

of 7%-8%. The HbA_{1c} level that was achieved during the study was an average of about 6.4% in the intensive-intervention group and an average of about 7.5% in the control group. During an average follow-up of 3.5 years, there was no significant difference in the rate of the primary outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in the two groups, but the intensively treated group did show a statistically

significant increased rate of all-cause mortality (N. Engl. J. Med. 2008;358:2545-59). This finding led to a premature stop to the study. The researchers who ran the study concluded that the findings "identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes."

The ADVANCE (Action in Diabetes and Vascular Disease) trial randomized more than 11,000 patients with an aver-



IMPORTANT TREATMENT CONSIDERATIONS

PRISTIQ 50-mg Extended-Release Tablets are indicated for the treatment of major depressive disorder in adults.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PRISTIQ or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PRISTIQ is not approved for use in pediatric patients.

Contraindications

- PRISTIQ is contraindicated in patients with a known hypersensitivity to PRISTIQ or venlafaxine.
- PRISTIQ must not be used concomitantly with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping PRISTIQ before starting an MAOI.

Warnings and Precautions

- All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients.
- Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including PRISTIQ, particularly with concomitant use of serotonergic drugs, including triptans, and with drugs that impair the metabolism of serotonin (including MAOIs). If concomitant use is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of PRISTIQ with serotonin precursors is not recommended.
- Patients receiving PRISTIQ should have regular monitoring of blood pressure since sustained increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before starting PRISTIQ. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.

age baseline HbA_{1c} of 7.5% to an intensive regimen with a target HbA_{1c} of less than 6.5% or to a standard regimen. The achieved HbA_{1c} level was 6.5% with intensive treatment and 7.3% in the standard-treatment arm. After a median of 5 years, the intensive regimen led to a statistically significant reduction in the combined rate of macrovascular and microvascular events, and a significant cut in the rate of major microvascular events.

Nephropathy was the type of event most frequently prevented with intensive treatment. But the two treatment arms showed no significant differences in the

rates of macrovascular events alone (MI, stroke, or cardiovascular death) or in the rates of cardiovascular death or death from any cause (N. Engl. J. Med. 2008;358:2560-72).

The VADT (Veterans Affairs Diabetes Trial) randomized nearly 1,800 patients with an average baseline HbA_{1c} level of 9.4% to either a standard regimen or an intensive regimen with a target HbA_{1c} level of 1.5% less than what would be achieved in the standard-treatment arm.

After 3 months, this goal was reached, with an average achieved HbA_{1c} level of 6.9% in the intensive-regimen group and

an average level of 8.4% in the standard-treatment patients. After an average of 5.6 years, there was no significant difference in the primary outcome (the rate of major cardiovascular events, including MI, stroke, heart failure, surgery for vascular disease, cardiovascular death, or other cardiovascular events).

The two groups also showed no significant differences in the rate of cardiovascular death or the rate of all-cause death. And there were no significant differences in the rates of microvascular complications between the two groups (N. Engl. J. Med. 2009;360:129-39).

The results from these three studies led to a statement from an expert panel organized by the American Diabetes Association, the American College of Cardiology, and the American Heart Association (Diabetes Care 2009;32:187-92). In part, the statement said: "Less stringent A_{1c} goals than the general goal of less than 7% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions or [for] those with long-standing diabetes in whom the general goal is difficult to attain." ■

For the treatment of adults
with major depressive disorder

The start

is just the beginning

It's not just about starting your adult patients with MDD on therapy; it's about helping them toward their treatment goals. Patients should be periodically reassessed to determine the need for continued treatment.¹

PRISTIQ 50 mg:

- SNRI therapy with efficacy proven in 8-week clinical studies
- One recommended therapeutic dose from the start
- Discontinuation rate due to adverse events comparable to placebo in 8-week clinical studies¹



- SSRIs and SNRIs, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with PRISTIQ; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- PRISTIQ is not approved for use in bipolar depression. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine the risk of bipolar disorder.
- As with all antidepressants, PRISTIQ should be used cautiously in patients with a history or family history of mania or hypomania, or with a history of seizure disorder.
- Caution is advised in administering PRISTIQ to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and small increases in heart rate were observed in clinical studies with PRISTIQ. PRISTIQ has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.
- Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical studies. Measurement of serum lipids should be considered during PRISTIQ treatment.
- On discontinuation, adverse events, some of which may be serious, have been reported with PRISTIQ and other SSRIs and SNRIs. Abrupt discontinuation of PRISTIQ has been associated with the appearance of new symptoms. Patients should be monitored for symptoms when discontinuing treatment. A gradual reduction in dose (by giving 50 mg of PRISTIQ less frequently) rather than abrupt cessation is recommended whenever possible.

- Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or end-stage renal disease (ESRD). The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.
- Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with PRISTIQ.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PRISTIQ. Discontinuation of PRISTIQ should be considered in patients with symptomatic hyponatremia.
- Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of PRISTIQ) therapy have been rarely reported.

Adverse Reactions

- The most commonly observed adverse reactions in patients taking PRISTIQ vs placebo for MDD in short-term fixed-dose premarketing studies (incidence $\geq 5\%$ and twice the rate of placebo in the 50-mg dose group) were nausea (22% vs 10%), dizziness (13% vs 5%), hyperhidrosis (10% vs 4%), constipation (9% vs 4%), and decreased appetite (5% vs 2%).

Reference: 1. Pristiq® (desvenlafaxine) Prescribing Information, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent page.

Pristiq[®]
desvenlafaxine
EXTENDED-RELEASE TABLETS

Wyeth[®]

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