



Ask the Expert: Issues in Selecting Antidiabetic Drug Therapy for Patients with Type 2 Diabetes

A continuing education (CE) activity entitled *Practical Strategies for Glycemic Control in Type 2 Diabetes: Exploring Benefits versus Risks* was presented as one of three CE in the Mornings topics at the 45th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 (which are available at www.ashpadvantage.com/cemornings). The program was presented by Stuart T. Haines, Pharm.D., FASHP, BCPS, BC-ADM. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Haines in a live webinar conducted on February 17, 2011. The highlights of this webinar pertaining to issues in the selection of antidiabetic drug therapy for patients with type 2 diabetes are described in this e-newsletter. Webinar highlights pertaining to safety concerns in the use of antidiabetic drug therapies will be addressed in another e-Newsletter to be released in May 2011.

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Question: Guidelines for the management of type 2 diabetes from the American Diabetes Association do not seem helpful and do not reflect the availability of the newest antidiabetic drug therapies. What other evidence-based guidelines could be used to select drug therapy for these patients?

The treatment approach in guidelines from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), which were released in January 2009, is based on outcomes studies, and some therapies discussed in these guidelines are less well-validated than others.¹ Tier 1 strategies are well-validated based on substantial amounts of robust data. Lifestyle modification and metformin are called for as the initial step in treating newly-diagnosed type 2 diabetes, with the addition of a sulfonylurea or insulin as step 2 if glycemic goals are not achieved with metformin. Less well-validated tier 2 therapies based on fewer, less robust data include thiazolidinediones and the injectable glucagon-like peptide-1 (GLP-1) analog exenatide (another injectable GLP-1 analog, liraglutide, was approved in January 2010, after the ADA/EASD guidelines were released). These tier 2 drugs may be used in certain



situations (e.g., for patients who cannot tolerate hypoglycemia). Other therapies addressed in the ADA/EASD guidelines are not supported by outcomes data and include α -glucosidase inhibitors (e.g. acarbose), glinides (e.g., repaglinide), pramlintide (an amylin agonist), and dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin). The DPP-4 inhibitor saxagliptin was approved by the Food and Drug Administration (FDA) in July 2009.

The treatment approach used in an algorithm for glycemic control released by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) in December 2009 is based on the patient's A1C as well as outcomes data (Table 1).² In practice, a combination of the treatment approaches advocated by ADA/EASD and AACE/ACE may be most appropriate.

Table 1. American Association of Clinical Endocrinologists and American College of Endocrinology Diabetes Algorithm for Glycemic Control Based on A1C^{2,a}

Treatment	A1C		
	6.5%-7.5%	7.6%-9.0%	>9.0%
	Lifestyle Modification ^b		
First line	MET, DPP-4, GLP-1, TZD, or AGI (i.e., drugs with a low risk of hypoglycemia) monotherapy	Dual therapy (MET plus GLP-1/DDP4/TZD or SU/glinide)	<i>If symptomatic,</i> insulin with or without other agents <i>If asymptomatic,</i> dual or triple therapy (oral agents/GLP-1)
Second line	Dual therapy (oral agents/GLP-1)	Triple therapy (oral agents/GLP-1)	
Third line	Triple therapy (oral agents/GLP-1)	Insulin with or without other agents	
Fourth line	Insulin with or without other agents		

AGI = α -glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 analog; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione

^aThe A1C goal is 6.5% or less, although it may not be appropriate for all patients.

^bLifestyle modification with dietary changes and increased physical activity is recommended in conjunction with drug therapy for all patients.



The choice of drug therapy may hinge on whether blood glucose values are elevated while fasting, after meals, or both. Metformin, and thiazolidinediones primarily lower fasting plasma glucose concentrations. DPP-4 inhibitors, GLP-1 analogs, glinides and α -glucosidase inhibitors are particularly useful for lowering elevated postprandial plasma glucose concentrations. Sulfonylureas lower both elevated fasting and post-prandial plasma glucose concentrations.

Question: Which sulfonylurea should be chosen when therapy using this drug class is warranted? Does long-term use of glyburide increase morbidity and mortality in patients with type 2 diabetes? How do first-generation and second-generation sulfonylureas differ?

Sulfonylureas can cause weight gain and hypoglycemia. Second-generation sulfonylureas (glimepiride, glipizide, and glyburide) are more potent than first-generation sulfonylureas (acetohexamide, chlorpropamide, tolazamide, and tolbutamide), but the risk for adverse effects is not necessarily lower with second-generation agents than first-generation ones. The risk of hypoglycemia is lower with some sulfonylureas (e.g., glipizide and glimepiride) than others because of glucose-dependent insulin release. The risk for hypoglycemia is substantially higher with glyburide and its use should be avoided in elderly patients and those with renal impairment.¹

In the University Group Diabetes Program (UGDP) study, a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs for preventing or delaying vascular complications in patients with type 2 diabetes, an increased risk of cardiovascular mortality was associated with the use of tolbutamide compared with diet alone or diet plus insulin.³ Although tolbutamide was the only sulfonylurea evaluated in the UGDP, a special warning about the increased risk of cardiovascular mortality was added to the product labeling of all sulfonylureas because of the similarities in mechanism of action and chemical structure of these drugs.

In the landmark United Kingdom Prospective Diabetes Study (UKPDS), intensive glycemic control using sulfonylureas (chlorpropamide or glyburide) or insulin decreased the risk of diabetes-related complications, but, unlike the UGDP study, the use of sulfonylureas did not have an adverse effect on cardiovascular outcomes.⁴ Indeed, in a 10-year follow-up study to the UKPDS, those patient who receive intensive therapy (sulfonylurea, insulin or, if overweight, metformin) or conventional therapy (dietary restriction) during the initial clinical trial were followed for a total of 17 years.⁵ There was no difference in glycemic control between the intensive and conventional treatment groups 1 year after the UKPDS study had concluded in 1997. Compared with conventional therapy, intensive therapy using a sulfonylurea or insulin was associated with significant reductions in any diabetes-related end point (relative risk reduction [RRR] = 9%), myocardial infarction (RRR = 15%), and death from any cause (RRR = 13%) at the end of the 17 year follow-up period.

In the randomized Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation study (known as ADVANCE) of 11,140 patients with type 2 diabetes and cardiovascular risk factors, intensive glycemic control using gliclazide (a sulfonylurea not available in the United States) in combination with other drugs as



needed to achieve an A1C of 6.5% or less was compared with standard glycemic control using a target A1C in accordance with local guidelines.⁶ After a median follow-up time of 5 years, the median A1C was lower in the intensive-control group (6.4%) than in the standard-control group (7.0%). Compared with standard glycemic control, intensive glycemic control significantly reduced the incidence of combined major macrovascular and microvascular events (RRR = 10%) and major microvascular events (RRR = 14%). The incidence of major macrovascular events was slightly lower (RRR = 6%) with intensive control than with standard control, but the difference was not statistically significant. The incidence of severe hypoglycemia was significantly higher in the intensive-control group (2.7%) than in the standard-control group (1.5%), although it was low in both groups. These findings and those from the 10-year follow-up study to the UKPDS appear to refute the UGDP findings of an increased risk for cardiovascular mortality observed with sulfonylurea use and suggest that the special warning about the increased risk of cardiovascular mortality in the product labeling for all sulfonylureas might not be necessary. If a sulfonylurea is indicated, glyburide should be avoided because of the risk of hypoglycemia. Glimepiride or glipizide is preferred.

Question: What data are available to support the use of fixed-dose combination oral antidiabetic agents as first-line therapy at the time of diagnosis of type 2 diabetes?

Numerous fixed-dose combination antidiabetic products are available, all of which reduce blood glucose concentrations and A1C values to a greater extent than either component alone. Potential advantages of use of these products include a reduced pill burden, improved patient adherence, and reduced out-of-pocket cost (e.g., from the use of a single product with one copayment instead of two products with two copayments), although the use of some combination products (especially brand name products with no generic equivalents) increases costs.

The best initial approach to treating newly diagnosed patients with type 2 diabetes (i.e., whether to use step-wise therapy beginning with monotherapy before trying combination therapy versus initial combination therapy) remains to be determined. How early to initiate insulin therapy after the diagnosis of type 2 diabetes and whether the early use of insulin instead of delayed insulin use improves outcomes also is unclear. Long-term outcomes in patients receiving GLP-1 analogs or DPP-4 inhibitors are unknown because data are not yet available. The safety of thiazolidinediones currently is a concern (this topic will be addressed in the e-newsletter to be released in April). Whether preservation of β -cell function should be an explicit treatment goal and how best to achieve this goal have been the subject of debate and remain unanswered questions.

Selection of antidiabetic therapy for patients with type 2 diabetes should be based on A1C and blood glucose monitoring data, including fasting and postprandial plasma glucose. Combination therapies that address both fasting and postprandial plasma glucose often are helpful. The risk of hypoglycemia, patient's body weight (i.e., need to lose weight or avoid weight gain), duration of diabetes, renal function, and comorbid conditions (especially cardiovascular disease) should be taken into consideration when choosing drug therapy. Patients with newly-diagnosed type 2 diabetes or a relatively short duration of the disease stand to benefit from intensive glucose-lowering therapy.⁷



“ Patient-specific factors should guide the selection of drug therapy for patients with type 2 diabetes. These factors include A1C and fasting and postprandial plasma glucose values, body weight, duration of diabetes, renal function, and comorbid conditions. ”

—Stuart T. Haines, Pharm.D., FASHP, BCPS, BC-ADM

Question: The use of metformin has been banned at my institution because of concerns about lactic acidosis. Are these concerns valid given the recent lack of evidence of an increased risk of lactic acidosis in metformin users?

Metformin is the drug of choice for patients with elevated fasting plasma glucose concentrations who are overweight or obese because it does not cause weight gain and it is a well-validated therapy based on outcomes trials. Metformin is rarely associated with hypoglycemia. In the 10-year UKPDS follow-up study, significant reductions in any diabetes-related end point (RRR = 21%), myocardial infarction (RRR = 33%), and death from any cause (RRR = 27%) were observed in the metformin group.⁵

Metformin is excreted renally, and the drug is contraindicated in patients with renal disease or dysfunction (e.g., serum creatinine ≥ 1.5 mg/dL in men or ≥ 1.4 mg/dL in women, abnormal creatinine clearance).⁸ A warning appears on the FDA-approved labeling for metformin-containing products about lactic acidosis, a rare but serious and potentially fatal metabolic complication that can occur due to metformin accumulation in patients with renal insufficiency. The risk of lactic acidosis has been largely based on data collected several decades ago from the use of phenformin, a previously available biguanide similar to metformin. Newer data have raised questions about the need for the warning.

In a pooled analysis of 347 studies with 70,490 patient-years of metformin use and 55,451 patient-years of no metformin use, there was no significant difference between groups in serum lactate levels and no change from baseline in serum lactate levels in the metformin group.⁹ In a nested, case-controlled study of 50,048 patients with type 2 diabetes, the incidence of lactic acidosis was lower in patients receiving metformin (3.3 cases per 100,000 person-years) than in patients receiving sulfonylureas (4.8 cases per 100,000 person-years).¹⁰ Most patients with lactic acidosis had experienced acute worsening of comorbid conditions known to cause lactic acidosis (e.g., acute heart failure, urosepsis, hypovolemia, seizure, acute renal failure).

In a prospective study, 393 patients with type 2 diabetes and mild renal dysfunction (serum creatinine 1.5-2.5 mg/dL) were randomly assigned to stop or continue metformin for 2 years.¹¹ Plasma lactate concentrations did not differ between the two groups at baseline or the end of the study. No cases of lactic acidosis occurred.

Diabetes is a risk factor for lactic acidosis.¹² Patients with metformin-associated lactic acidosis typically present



with gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), which can lead to dehydration.¹³ Dehydration may be a precipitating factor in lactic acidosis because it leads to acute reductions in renal perfusion. Metformin-associated lactic acidosis is characterized by acute renal dysfunction and severe acidosis. While the prognosis in cases of metformin-associated lactic acidosis is somewhat better than other causes (a 50% mortality rate versus 74%, respectively), the risk of mortality is still quite high.¹⁴

Whether to initiate or continue metformin in patients with renal impairment requires the use of clinical judgment after evaluating the risks and potential benefits, taking into consideration the presence of comorbid conditions and the response to therapy. Patients should be involved in therapeutic decision making, and this involvement should be documented by the health care provider.

Metformin therapy should be interrupted if acute changes in renal function occur or are anticipated due to an acute major illness (e.g., heart failure exacerbation or other illness requiring hospitalization). The drug should be stopped before procedures involving the administration of iodinated contrast media, which can acutely alter renal function and may lead to lactic acidosis. Renal function should be reevaluated after the procedure before resuming metformin therapy.

“ The approach to using metformin in patients with renal impairment requires caution. I recommend initiating the drug only in patients with a creatinine clearance above 60 mL/min. When I encounter a patient who already is receiving metformin, I estimate the creatinine clearance and would stop metformin therapy only if the creatinine clearance is less than 45 mL/min. In patients with a creatinine clearance less than 50 mL/min, I repeat renal function tests 1-2 weeks later to ensure that renal function has not deteriorated. ”

—Stuart T. Haines, Pharm.D., FASHP, BCPS, BC-ADM

On-Demand CPE Activity

If you were unable to attend the live symposium, *Practical Strategies for Glycemic Control in Type 2 Diabetes: Exploring Benefits versus Risks* in Anaheim, a web-based CPE activity is available on-demand at <http://www.ashpmedia.org/symposia/cemornings/overview.html>.



References

1. Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009; 32:193-203.
2. American Association of Clinical Endocrinologists and American College of Endocrinology. AACE/ACE diabetes algorithm for glycemic control. December 2009. <http://www.aace.com/pub/pdf/GlycemicControlAlgorithmPPT.pdf> (accessed 2011 Feb 9).
3. Meinert CL, Knatterud GL, Prout TE et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes*. 1970; 19(suppl 2):789-830.
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998; 352:837-53.
5. Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008; 359:1577-89.
6. ADVANCE Collaborative Group, Patel A, MacMahon S et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008; 358:2560-72.
7. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care*. 2011; 34 (suppl 1):S11-61.
8. Glucophage package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2009 Jan.
9. Salpeter S, Greyber E, Pasternak G et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2006; (1):CD002967.
10. Bodmer M, Meier C, Krähenbühl S et al. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care*. 2008; 31:2086-91.
11. Rachmani R, Slavachevski I, Levi Z et al. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. *Eur J Intern Med*. 2002; 13:428-33.
12. Scale T, Harvey JN. Diabetes, metformin and lactic acidosis. *Clin Endocrinol (Oxf)*. 2011; 74:191-6.
13. Biradar V, Moran JL, Peake SL et al. Metformin-associated lactic acidosis (MALA): clinical profile and outcomes in patients admitted to the intensive care unit. *Crit Care Resusc*. 2010; 12:191-5.
14. Friesecke S, Abel P, Roser M et al. Outcome of severe lactic acidosis associated with metformin accumulation. *Crit Care*. 2010; 14:R226.