Management of Type 2 Diabetes: What Is the Next Step After Metformin?

Sharon W. Lahiri, MD

PRESENTATION

O.B. is a 67-year-old African-American man who has had type 2 diabetes for 11 years. He was diagnosed incidentally through laboratory testing. Metformin was initiated at diagnosis and eventually titrated to his current dose of 1,000 mg twice daily. Because of his A1C of 7.5%, his primary care provider started him on sitagliptin, 100 mg daily, 4 years ago. Despite dual oral therapy, his blood glucose levels are still not at goal.

He is self-referred to the clinic for help with blood glucose management. He checks his blood glucose once daily fasting. His results, by memory, are 175–190 mg/dl in the morning before breakfast.

He has seen a dietitian in the past and is trying to maintain a diet that includes carbohydrates in the amounts of 60 g for breakfast, 45 g for lunch, 15 g for a snack, and 60 g for dinner. However, he has restaurant carryout food for dinner about five times per month, consisting of pizza or barbecue items with French fries. His exercise is limited by right-knee osteoarthritis.

His medical and surgical history includes hypertension treated with lisinopril, hyperlipidemia treated with pravastatin, right-knee osteoarthritis, a right hip replacement at the age of 61 years, pneumothorax at the age of 35 years, and benign prostatic hypertrophy. He has no complications from his diabetes.

On physical exam, his height is 5′9″, weight is 210 lb, and BMI is 31 kg/m^2. His blood pressure is 146/77 mmHg, and his heart rate is 83 bpm. He has no acanthosis nigricans or skin tags on the neck. Physical exam is remarkable for limited range of motion in the right knee and a scar on the right lower extremity from previous hip surgery. He has no peripheral neuropathy.

In the clinic, his random blood glucose is 254 mg/dl. On laboratory testing, his A1C is 8.1%. His liver and kidney functions are normal, and urine microalbumin is negative. His total cholesterol is 129 mg/dl, triglyceride level is 81 mg/dl, HDL cholesterol is 40 mg/dl, and LDL cholesterol is 73 mg/dl.

We discussed options for further treatment, including the addition of basal insulin to lower his fasting plasma glucose (FPG) levels, changing sitagliptin to a glucagon-like peptide-1 (GLP-1) receptor agonist, or adding glipizide twice daily. O.B. did not want to start any injectable medications but was willing to start an additional oral agent. With the addition of glipizide, 5 mg twice daily, to his regimen, his A1C decreased to 7.1% 3 months later. He is also working on reducing his carbohydrate intake to 45 g with meals and increasing his duration of exercise.

QUESTIONS

1. Why is metformin used as initial therapy? What are the benefits and contraindications to metformin use?
2. What are the options for additional agents after metformin? What are the advantages and disadvantages of the different classes of agents?
3. What is recommended by consensus guidelines?
4. When should insulin be considered?

COMMENTARY

Metformin should be used as initial therapy in type 2 diabetes unless contraindications exist. The benefits of metformin include its ability to lower A1C by 1–2% and FPG by 60–70 mg/dl. Other advantages of metformin over other oral agents include no hypoglycemia when used as monotherapy, no weight gain, possible modest weight loss, and availability as a generic agent, providing a cost advantage.

Metformin has also been found to decrease diabetes-related endpoints in overweight individuals with type 2 diabetes.[1,2] The 10-year follow-up of the U.K. Prospective Diabetes Study showed persistent and significant risk reductions for diabetes-related endpoints, myocardial infarction, and death from any cause.[3] Metformin also was found to be at least as efficacious in nonobese type 2 diabetic patients.[4]

The main adverse effect of metformin use is gastrointestinal symptoms, which may include abdominal cramping, nausea, bloating, and diarrhea. These symptoms are dose related and result in

discontinuation of metformin in 5–10% of patients.[5] Lactic acidosis may also occur with metformin use in conditions that predispose to tissue hypoxemia.[5] These conditions include hypotension, decompensated congestive heart failure, chronic obstructive pulmonary disease requiring oxygen, surgery, renal insufficiency (creatinine > 1.4 mg/dl in females or > 1.5 mg/dl in males), intravenous contrast for radiology studies, liver dysfunction, and alcohol use. Being > 80 years of age is also a relative contraindication because of a higher incidence of renal insufficiency.

If patients still are not at a goal A1C of < 7% after maximal metformin and lifestyle changes for 3 months, further therapy is indicated. Several options for further oral therapy exist. Agents that can be added to metformin include sulfonylureas, meglitinides, thiazolidinediones (TZDs), or acarbose. Newer medications such as the incretin agents are also an option. These include GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Sulfonylureas have been in existence since the 1950s. They are usually considered as second-line therapy after metformin because they are effective, can lower A1C by 1–2%, and are available in inexpensive generic forms. They work by binding to the adenosine triphosphate (ATP)-dependent potassium channels in the β-cells of the pancreas, resulting in insulin secretion.

Sulfonylureas have several disadvantages, however. They cause hypoglycemia, especially in patients who are elderly or have renal insufficiency. They also result in weight gain of 3 kg on average over 3–4 years, and their efficacy decreases over time. Furthermore, there is a question of cardiovascular toxicity with sulfonylurea use. A study published in 1970 by the University Group Diabetes Program[6] found that cardiovascular disease risk mortality was higher in those treated with tolbutamide than in those given insulin (12.7 vs. 6.2%, respectively).

Glipizide is the sulfonylurea of choice because it has a shorter duration of action and inactive metabolites, making hypoglycemia less likely, especially in the setting of renal insufficiency. Of note, when using sulfonylureas, there is minimal benefit in increasing the dose to > 50% of the maximum dose, which is 10 mg daily for glipizide and glyburide. American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus guidelines recommended sulfonylureas as second-line agents after metformin.

If hypoglycemia is a concern, however, especially in elderly patients or those who have renal insufficiency, meglitinides are an option. Meglitinides are nonsulfonylurea insulin secretagogues that bind to a different site on the ATP-sensitive potassium channels. The two drugs in this class are repaglinide and nateglinide.

The advantages of meglitinides are that they are shorter acting, with a half-life of about 1 hour, thus lowering the risk of hypoglycemia. These medications are taken from 0 to 30 minutes before meals and act mainly to reduce first-phase insulin secretion and postprandial glucose (PPG) levels. They are also safe in patients with a sulfa allergy, whereas sulfonylureas are not.

Both repaglinide and nateglinide are metabolized in the liver. Nateglinide is renally excreted and has active metabolites. However, < 10% of repaglinide is renally excreted, making it safe in renal insufficiency.

The disadvantages of these medications are their frequent dosing (three times daily), their expense because they are not available as generic agents, and their limited efficacy. These drugs mainly lower only PPG and lower A1C by only 0.5–1% compared to A1C-lowering of 1–2% with metformin or the sulfonylureas. Therefore, these drugs may play a role in the treatment of type 2 diabetes in patients who are at high risk for hypoglycemia, have renal insufficiency, and have only mildly elevated A1C.

TZDs are a third class of agents that could be used in conjunction with metformin or other oral therapies to achieve a goal A1C of < 7%. The two drugs available in this class are rosiglitazone and pioglitazone. These drugs are selective agonists for peroxisome proliferator–activated receptor-γ, a superfamily of nuclear receptors that function as ligand-activated transcription factors.[7] They activate gene transcription involved in lipid and carbohydrate metabolism. Because they act on gene expression at the nuclear level, onset of action may not occur for 4–12 weeks.

TZDs decrease insulin resistance, FPG, insulin, and free fatty acids. TZDs can lower A1C by 1–1.5% and do not result in any hypoglycemia when used as monotherapy. Pioglitazone has an added benefit on HDL cholesterol and triglyceride levels.

Despite these beneficial effects, TZDs have fallen out of favor recently for several reasons. Aside from the known side effects of weight gain of 2–20 lb, edema, and potential elevation of transaminases, concerns regarding increased cardiovascular risk and cancer have surfaced.

A 2007 meta-analysis by Nissen et al.[8] showed that rosiglitazone was associated with a significant increase in the risk of myocardial infarction (odds ratio [OR] 1.43, $P = 0.03$) and a borderline significant increase in

death from cardiovascular causes (OR 1.64, $P = 0.06$).

Home et al.[9] then published an unplanned interim analysis of a randomized multicenter open-label trial with 4,447 patients with type 2 diabetes inadequately controlled on metformin or a sulfonylurea. A total of 2,220 patients were assigned to receive add-on rosiglitazone, and 2,227 patients were assigned to receive a placebo add-on to metformin plus sulfonylurea. The study duration was 3.375 years. There were no statistically significant differences between the rosiglitazone and control groups regarding myocardial infarction and death from cardiovascular causes or any cause, but there were more patients with heart failure in the rosiglitazone group than in the control group (hazard ratio 2.15).

As a result of these trials, rosiglitazone has been removed from the market in Europe. In the United States, its use is restricted to type 2 diabetic patients who cannot achieve adequate control with other medications.

As for pioglitazone, in June 2011, the U.S. Food and Drug Administration (FDA) informed the public that use of pioglitazone for > 1 year may be associated with an increased risk of bladder cancer. French and German agencies suspended further use of pioglitazone based on these data, but the United States is still reviewing the data.

Other concerns with the use of TZDs include studies showing a lowering of bone density and increased fracture risk with their use in women with type 2 diabetes. This was first described in a footnote in ADOPT (A Diabetes Outcome Progression Trial).[10]

Alternative medications include the incretin mimetics and DPP-4 inhibitors. In type 2 diabetes, levels of active GLP-1 are decreased, and GLP-1 response to increased fasting and postprandial glucose levels is impaired. GLP-1 mimetics lower PPG excursions by stimulating glucose-dependent insulin secretion, slowing gastric emptying, suppressing postmeal glucagon secretion, and increasing satiety.[11] The GLP-1 mimetics include liraglutide, which is administered once daily independent of meals, and exenatide, which is given twice daily 30 minutes before a meal.

GLP-1 mimetics are approved for use as add-on therapy in type 2 diabetes when optimal glycemic control has not been achieved on one or two oral hypoglycemic agents. It can be considered as monotherapy in patients with contraindications or adverse effects with oral agents. Furthermore, in October 2011, exenatide was approved by the FDA as add-on therapy to glargine insulin.

GLP-1 mimetics significantly improve PPG levels, lower A1C by 1–2%, have a low incidence of hypoglycemia, and can result in significant weight loss over time (~ 2–5 kg).[11] Drawbacks of GLP-1 mimetics include nausea, which wanes over time and is minimized through slow dose titration. Post-marketing reports of pancreatitis and acute renal failure or renal insufficiency are also a concern. Based on animal data, C-cell proliferation and medullary thyroid carcinoma are a potential concern with liraglutide use. These medications tend to be costly because a generic version does not yet exist.

The GLP-1 mimetics should be considered for use for patients with poor PPG control, a high risk of hypoglycemia, and obesity with a high risk of further weight gain.

DPP-4 inhibitors block the enzyme that is responsible for inactivation of GLP-1, therefore prolonging the effects of GLP-1, as listed above. The FDA-approved medications in this class include sitagliptin, saxagliptin, and linagliptin.

The benefits of these medications are their safety in patients with chronic kidney disease, that they cause no hypoglycemia, and that they are weight neutral. The drawbacks are lower efficacy with A1C lowering of only 0.6–0.8%, expense, limited clinical experience, and lack of established long-term safety.

These medications are a good second-line agent after metformin in patients who are close to their A1C goal and have concerns about hypoglycemia and weight gain.

Finally, α-glucosidase inhibitors, a rarely prescribed class of medications including acarbose and miglitol, are also an option. These medications inhibit enzymes needed to digest carbohydrates. They are not used commonly because of their low efficacy and side effects of flatulence and diarrhea.

In 2006, ADA and EASD published a consensus statement with an algorithm for the management of hyperglycemia in type 2 diabetes,[12] which was revised in 2009.[13] The algorithm recommends metformin and lifestyle changes as initial therapy. If A1C is still > 7% despite metformin and lifestyle changes, sulfonylureas or basal insulin are recommended as top-tier choices. New in the 2009 algorithm is the recommendation of a GLP-1 receptor agonist or pioglitazone as a second-tier choice if sulfonylureas or insulin are not ideal or if hypoglycemia is a significant concern. DPP-4 inhibitors are not included in the algorithm. This revision also does not take into consideration the risk of bladder cancer recently linked to pioglitazone use.

In 2009, the American Association of Clinical Endocrinologists and American College of Endocrinology developed an alternative algorithm for

glycemic control.[14] Their A1C goal is 6.5%. The therapeutic approach is stratified based on patients' A1C. Monotherapy is recommended if A1C is < 7.5%; dual therapy is recommended for patients with an A1C between 7.6 and 9%; and triple therapy is recommended for those with an A1C > 9%. If patients are symptomatic or failing to achieve goal with triple therapy, insulin is indicated.

This algorithm differs from the ADA/EASD guidelines in that GLP-1 receptor agonists and DPP-4 inhibitors are recommended over sulfonylureas or meglitinides as initial add-on therapy after metformin or a TZD. The reasons given for this are the low risk of hypoglycemia with GLP-1 agonists and DPP-4 inhibitors and potential for weight loss with GLP-1 agonists.

Although algorithms are helpful in providing guidance in the choice of medications after metformin, the decision should be individualized depending on the degree of hyperglycemia present, the patient's risk for hypoglycemia, the patient's BMI, and the risk for further weight gain. Agents to be considered after metformin should be DPP-4 inhibitors or GLP-1 agonists if hypoglycemia and weight gain are a concern, or alternatively, sulfonylureas if fasting and postprandial glucose levels are elevated and a greater degree of A1C lowering is needed. Insulin should be considered if the patient has very high FPG, is symptomatic, or if blood glucose is poorly controlled on dual or triple therapy.

In this case, patient O.B. was treated with a DPP-4 inhibitor as a second-line agent after metformin. This was a reasonable choice because his degree of A1C elevation was mild (7.5%) at the time. His BMI is also 31 kg/m^2 (class 1 obesity), so avoidance of further weight gain with sulfonylureas was preferable.

However, once his A1C reached 8.1% and his FPG was poorly controlled, a more potent agent was indicated. Basal insulin or a sulfonylurea could have been added. Another option would have been to switch the DPP-4 inhibitor to a GLP-1 agonist to avoid the hypoglycemia and weight gain associated with insulin and sulfonylureas. O.B. opted for trying a third oral agent, and this has worked reasonably well so far. Future treatment would likely include addition of basal insulin if his FPG is persistently above goal.

CLINICAL PEARLS

- Metformin should be used as initial therapy for type 2 diabetes unless contraindications exist. Second-line agents include sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, meglitinides, and α-glucosidase inhibitors. TZDs are no longer recommended because of potential increases in cardiovascular risk and fracture risk.
- The incretin agents are a reasonable second choice if the main problem is PPG elevation and if hypoglycemia and weight gain are concerns. If FPG and postprandial glucose are elevated and if cost is a concern, sulfonylureas are a reasonable second-line agent.
- If a patient has symptomatic hyperglycemia, poor control despite two to three oral agents, or an A1C > 8.5%, insulin should be considered.

REFERENCES

[1]U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998

[2]U.K. Prospective Diabetes Study 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* 352:837–853, 1998

[3]Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW: 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359:1577–1589, 2008

[4]Ong CR, Molyneaux LM, Constantino MI, Twigg SM, Yue DK: Long-term efficacy of metformin therapy in nonobese individuals with type 2 diabetes. *Diabetes Care* 29:2361–2364, 2006

[5]Bailey CJ, Turner RC: Metformin. *N Engl J Med* 334:574–579, 1996

[6]Meinert CL, Knatterud GL, Prout TE, Klimt CR: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. *Diabetes* 19 (Suppl. 2):789–830, 1970

[7]Yki-Järvinen H: Thiazolidinediones. *N Engl J Med* 351:1106–1118, 2004

[8]Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356:2457–2471, 2007

[9]Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ: Rosiglitazone evaluated for cardiovascular outcomes: an interim analysis. *N Engl J Med* 357:28–38, 2007

[10]Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group: Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355:2427–2443, 2006

[11]Chia CW, Egan JM: Incretin-based therapies in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 93:3703–3716, 2008

[12]Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29:1963–1972, 2006

[13]Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B: 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* 32:193–203, 2009

[14]Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, Handelsan Y, Horton ES, Lebovitz H, Levy P, Moghissi ES, Schwartz SS: Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An algorithm for glycemic control. *Endocr Pract* 15:540–559, 2009

Sharon W. Lahiri, MD, is a senior staff physician in the Department of Endocrinology at the Henry Ford Health System in Detroit, Mich.