Treating type 2 diabetes: Targeting the causative factors

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Glycemic control in diabetes begins with a patient’s adherence to several non-pharmacologic measures. Without such a commitment, success in controlling the disease will be difficult to achieve, and otherwise appropriate drug therapy will be hindered.

Most antidiabetic agents comparably reduce glycosylated hemoglobin (A1c) levels. However, a particular agent may be preferred depending on a patient’s characteristics. And some circumstances call for combination therapy. This article reviews the advantages and disadvantages of the many pharmacologic treatments for glucose control and hyperglycemia in type 2 diabetes.

**Practice recommendations**

- Self-monitoring of blood glucose is an integral component of diabetes therapy and should always be included in the management plan (SOR: C).
- Medical nutrition therapy should be individualized, preferably by a registered dietitian familiar with diabetes (SOR: B).
- A regular physical activity program is recommended for all patients with diabetes who are capable of participating (SOR: B).
- When a monotherapy fails, combine drugs with different mechanisms of action to achieve an additive effect (SOR: A).
- The combination of sulfonylurea and metformin has proven effective in many studies. One showed that initial treatment with glyburide/metformin improved glycemic control better than either glyburide or metformin monotherapy (SOR: A).

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**Benefits of diabetes control**

The benefits of diabetes control are detailed in this issue of The Journal of Family Practice (“Strategies to reduce complications in type 2 diabetes,” pages 366–374). For every percentage-point reduction in hemoglobin A1c, it is possible to achieve a 22% to 35% reduction in microvascular complications.1,2 Cardiovascular disease can be reduced in patients with diabetes by treating hypertension3,4 and hyperlipidemia, prescribing aspirin therapy, using angiotensin-converting enzyme (ACE) inhibitors, and with smoking cessation.5,6
TARGETS FOR GLYCEMIC CONTROL
The American Diabetes Association’s (ADA) recommended targets for glycemic control are a preprandial blood glucose level of 80–120 mg/dL, a bedtime blood glucose level of 100–140 mg/dL, and a hemoglobin A1c level of <7% (with a level of >8% requiring additional measures). Hemoglobin A1c is the best determinant of glycemic exposure, and its mean value is a nationally recognized indicator of how well diabetes is being managed.7 The American College of Endocrinology has adopted a more aggressive approach by designating an A1c level of 6.5% as both a target and action level.8

Self-monitoring of blood glucose
Self-monitoring of blood glucose (SMBG) is an integral component of diabetes therapy (strength of recommendation [SOR]: C) and should always be included in the management plan (SOR: C). The optimal frequency and timing of SMBG for type 2 diabetes is not known, but they should be sufficient to facilitate reaching glucose goals. The A1c test should be performed at least semi-annually for patients with stable glycemic control, and quarterly for patients not meeting glycemic goals or those who are changing therapy. A1c levels and mean plasma glucose levels can be approximately correlated (Table 1).7

NONPHARMACOLOGIC THERAPY
Nonpharmacologic measures remain the cornerstone of managing type 2 diabetes. Hyperglycemia adversely and reversibly affects both insulin resistance and insulin secretion. Improvement in glycemic control can occur through dietary modification and regular exercise.

A recent meta-analysis of randomized controlled trials of diabetes patient education observed a net decrease in HbA1c of 0.32% in intervention groups vs control.9 Interventions that included a face-to-face delivery, cognitive reframing teaching method, and exercise content were more likely to improve glycemic control.

TABLE 1
Correlation between hemoglobin A1c levels and mean plasma glucose levels

<table>
<thead>
<tr>
<th>Hemoglobin A1c (%)</th>
<th>Mean plasma glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>135</td>
</tr>
<tr>
<td>7</td>
<td>170</td>
</tr>
<tr>
<td>8</td>
<td>205</td>
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<td>9</td>
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<td>10</td>
<td>275</td>
</tr>
<tr>
<td>11</td>
<td>310</td>
</tr>
<tr>
<td>12</td>
<td>345</td>
</tr>
</tbody>
</table>

Education
Lifestyle changes involving diet, exercise, and usually weight loss are key to effective management of diabetes. If patients are to change their behavior, they must be given detailed training.6 Self-management also necessitates that patients engage in problem solving. This requires that each aspect of the management plan is understood and agreed upon by the patient and providers, and that the goals and treatment plan are individualized and reasonable.

Diet: recommend soluble fiber, reduce calories
Medical nutrition therapy should be individualized and preferably provided by a registered dietitian familiar with diabetes (SOR: B). The goals of nutrition therapy, according to the ADA, are to attain recommended body weight and prevent or reverse obesity. The means of achieving these goals are nutrition assessment and modification of nutrient intake and lifestyle through healthy food choices and physical activity.7

A high intake of dietary fiber (particularly the soluble type) above the level recommended by the ADA improves glycemic control, decreases hyperinsulinemia, and lowers plasma lipid concentrations.10
Physical activity: a little goes a long way
A regular physical activity program is recommended for all patients with diabetes who are capable of participating (SOR: B). It improves blood glucose control, reduces cardiovascular risk factors, aids weight loss, and enhances well being. A recently published prospective cohort study showed that walking at least 2 hours a week was associated with a 39% lower all-cause mortality (hazard rate ratio [HRR], 0.61; 95% CI, 0.48–0.78) and a 34% lower cardiovascular mortality (HRR, 0.66; 95% CI, 0.45–0.96) across a diverse spectrum of adults with diabetes. The NNT (to prevent 1 death per year) is 61 for patients who walk at least 2 hours/week.

In prescribing a physical activity plan for a
### Pharmacologic treatments for type 2 diabetes: monotherapies

<table>
<thead>
<tr>
<th>Target population</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Dosing</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent type 2 DM diagnosis</td>
<td>Rapid FPG reduction</td>
<td>Weight gain</td>
<td>Glyburide: 1.25–20 mg once or twice daily (micronized, 0.75–12 mg once or twice daily)</td>
<td>$22.80 (5 mg, #120)</td>
</tr>
<tr>
<td>Type 2 DM &lt;5 years duration</td>
<td>Low cost</td>
<td>Increased risk of hypoglycemia</td>
<td>Glipizide: 2.5–40 mg once or twice daily (extended-release, 2.5–20 mg once daily)</td>
<td>$14.66 (10 mg, #120)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glimepiride: 1–8 mg once daily</td>
<td>$51.98 (10 mg, #60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$57.98 (4 mg, #60)</td>
</tr>
<tr>
<td><strong>Non-sulfonylurea secretagogues (meglitinides)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent type 2 DM diagnosis</td>
<td>Reduced risk of hypoglycemia</td>
<td>Higher cost</td>
<td>Nateglinide: 60–120 mg 3 times daily</td>
<td>$85.99 (120mg, #90)</td>
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<tr>
<td>Elevated PPG</td>
<td>Short-acting Meal-adjusted dosing</td>
<td>Frequent dosing</td>
<td>Repaglinide: 0.5–4 mg 3 or 4 times daily</td>
<td>$216.06 (2 mg, #240)</td>
</tr>
<tr>
<td><strong>Biguanides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>No weight gain</td>
<td>GI side effects</td>
<td>Metformin: 500–1000 mg 2 or 3 times daily</td>
<td>$77.99 (850 mg, #90)</td>
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<tr>
<td>Insulin resistant</td>
<td>Reduced risk of hypoglycemia</td>
<td>High cost Rare lactic acidosis</td>
<td>Metformin XR: 1000–2000 mg once or twice daily</td>
<td>$89.98 (500 mg, #120)</td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td><strong>TZDs</strong></td>
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<td></td>
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<tr>
<td>Insulin resistant</td>
<td>Reduced amount of insulin</td>
<td>High cost</td>
<td>Rosiglitazone: 4–8 mg once or twice daily</td>
<td>$135.99 (8 mg, #30)</td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>Reduced risk of hypoglycemia</td>
<td>Slow onset of action Liver toxicity</td>
<td>Pioglitazone: 15–45 mg once daily</td>
<td>$153.99 (45 mg, #30)</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td><strong>AGIs</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Elevated PPG</td>
<td>Reduced risk of hypoglycemia</td>
<td>High cost</td>
<td>Acarbose: 50–100 mg 3 times daily</td>
<td>$67.99 (100 mg, #90)</td>
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<tr>
<td>Contraindications to other agents</td>
<td>Non-systemic action</td>
<td>GI side effects</td>
<td>Miglitol: 50–100 mg 3 times daily</td>
<td>$66.99 (100 mg, #90)</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; TZD, thiazolidinediones; AGT, a-glucosidase inhibitors; FPG, fasting plasma glucose; PPG, postprandial glucose; GI, gastrointestinal

Patient, consider cardiovascular disease risk factors or complications to minimize the risk of untoward events. Micro- and macrovascular disease are of course prevalent among persons with diabetes, often resulting in functional limitations that make exercise more difficult.
Other priorities
Other recommended components of care include daily aspirin use, foot care exams, tobacco cessation, pneumococcal and influenza vaccinations, and an annual dilated retinal exam.

Pharmacologic therapy
The coexisting defects in type 2 diabetes mellitus are as follows:

- resistance to insulin action in muscle
- defective pancreatic insulin secretion
- unrestrained hepatic glucose production, aggravated by increased lipolysis in adipose tissue.

Drug therapy is aimed at each of these defects, and also at reducing carbohydrate absorption in the small intestine (Figure 1). As far as antihyperglycemic effect is concerned, no one category of antidiabetic agent is favored over another.15 Except for nateglinide and α-glucosidase inhibitors (AGIs), each of the drug categories leads to a similar reduction in A1c.16 However, patient characteristics may lead to selection of a particular agent. Table 2 summarizes oral treatment options, their relative advantages and costs.

Sulfonylureas
Sulfonylureas directly increase insulin secretion by binding to the sulfonylurea receptor on pancreatic beta cells; they provide a relatively quick onset of action. First-generation sulfonylureas (eg, tolbutamide, chlorpropamide) and second-generation sulfonylureas (eg, glyburide, glipizide, glimepiride) are equivalent in their maximum hypoglycemic effect.17 Second-generation agents are probably safer than first-generation drugs, being less likely to cause hyponatremia, disulfiram-like reactions, or prolonged hypoglycemia.18 At maximal doses, sulfonylureas lower A1c levels by 1–2 percentage points and fasting plasma glucose concentrations by 60–70 mg/dL.15

TABLE 3
Pharmacological treatments for type 2 diabetes: combination therapies

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylureas</th>
<th>Meglitinides</th>
<th>Biguanides</th>
<th>TZDs</th>
<th>AGIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double combination therapy option*</td>
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<tr>
<td>Double combination therapy option</td>
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<td>Double combination therapy option</td>
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<tr>
<td>Double combination therapy option</td>
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<tr>
<td>Triple combination therapy option</td>
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<tr>
<td>Triple combination therapy option</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If therapeutic goals are not met using the above combinations; switch to insulin with or without oral agent.

*Available as Glucovance (metformin/glyburide) or as Metaglip (metformin/glipizide)
† Available as Avandamet (rosiglitazone/metformin)
however, the glucose lowering effect typically plateaus after half the maximal recommended dose is reached. Sulfonylureas have no consistent effect on dyslipidemia. In UK Prospective Diabetes Study (UKPDS) 33, though improved glycemic control with sulfonylureas (or insulin) led to a 25% reduction in microvascular endpoints (mostly less retinal photoagulation) \( P<.01 \), sulfonylureas (or insulin) did not significantly reduce death or all-cause mortality compared with diet treatment.\(^5\)

**Adverse effects.** The primary adverse effects of sulfonylureas are weight gain and hypoglycemia. In UKPDS 33, weight gain at 10 years was 2.6 kg (99% confidence interval [CI], 1.6–3.6) with chlorpropamide and 1.7 kg (99% CI, 0.7–2.7) with glyburide, compared with patients receiving diet therapy (each \( P<.001 \)).\(^5\) In the same study, the rate of major hypoglycemic episodes (third-party help or medical intervention necessary) while on therapy was 0.4%/year for chlorpropamide and 0.6%/year for glyburide, compared with 0.1%/year for diet.

Glyburide and chlorpropamide have active metabolites with renal elimination, and they should therefore be used with caution in patients with renal insufficiency. In 1971, the University Group Diabetes Project (UGDP) observed a twofold increase in the rate of cardiovascular death among patients receiving tolbutamide compared with those receiving insulin or placebo.\(^18\) This led to a decades long debate on the validity of this conclusion.\(^19\) More recently, UKPDS 33 did not demonstrate any increased cardiovascular mortality among patients receiving glyburide or chlorpropamide, and has largely negated this earlier concern.\(^5\)

**Cost.** Sulfonylureas are the least expensive oral agents used to treat type 2 diabetes.

### Non-sulfonylurea secretagogues

Like sulfonylureas, the non-sulfonylurea secretagogues (non-SU), repaglinide and nateglinide, stimulate beta cells to increase insulin secretion. However, the non-SU agents mediate their action through a different, adjacent site on the “sulfonylurea receptor.” Comparatively, the non-SU agents have a faster onset of action (20 minutes), shorter half-life (about 1.0–1.5 hours), and greater effects on postprandial glucose excursions than do sulfonylureas.\(^5\) In contrast to the sulfonylureas, the extent of insulin release with non-SU agents is glucose dependent, and therefore they may have less risk of hypoglycemia several hours after meals.\(^5\)

Repaglinide lowers the \( A_{1c} \) level by 1.7–1.9 percentage points, similar in efficacy to sulfonylureas. Nateglinide appears somewhat less efficacious and lowers \( A_{1c} \) by 0.6–1.0 percentage points.\(^5\) Nateglinide was significantly less
effective than glyburide at lowering A1c levels and the fasting plasma glucose in one 24-week study. Non-SUs added to sulfonylureas produce no additional benefit in glycemic control. The effect of non-SUs on microvascular or macrovascular endpoints is unknown.

**Adverse effects.** Hypoglycemia is the primary adverse effect of non-SUs. Confirmed hypoglycemia (plasma glucose <60 mg/dL) was observed in 2.4% of patients taking nateglinide compared with 0.4% of those receiving placebo. Mild or moderate hypoglycemia occurred in 16% of repaglinide patients, 20% of glyburide patients, and 19% of glipizide patients in one-year comparative studies. Further comparative studies are needed to determine if non-SUs produce significantly less hypoglycemia and weight gain than sulfonylureas.

**Cost.** Non-SUs must be dosed 3 times daily at the start of meals. One relative disadvantage is their increased cost compared with sulfonylureas.

**Biguanides**

The only biguanide marketed in the US is metformin. Its primary action is to inhibit hepatic glucose production and, to a much lesser extent, enhance insulin sensitivity in peripheral tissues. Metformin does not stimulate insulin secretion and does not cause hypoglycemia when used as monotherapy, but it can potentiate hypoglycemia in combination with insulin or insulin secretagogues.

Metformin is similar in efficacy to the sulfonylureas. It lowers A1c by 1.5–2.0 percentage points and fasting plasma glucose by 60–80 mg/dL. Its antihyperglycemic efficacy is independent of patient age, duration of diabetes, or BMI.

In the UKPDS 34 study, a subgroup of obese patients was randomized to receive intensive control (group 1, metformin; group 2, a sulfonylurea or insulin) or conventional diet therapy (group 3). Despite a similar reduction in the A1c level between the 2 intensive-treatment groups, patients treated with metformin had a 32% reduction in all cause mortality, compared with the diet therapy group (95% CI, 9–47; \(P=.002\)).

Metformin also showed significant benefit when compared with patients receiving sulfonylurea or insulin (group 2). The absolute risk of any diabetes endpoint was 29.8 vs. 40.1 (events per 1000 patient-years; \(P=.0034\)), all-cause mortality (13.5 vs 18.9; \(P=.021\)), and stroke (3.3 vs 6.2; \(P=.032\)), respectively, for metformin vs sulfonylurea or insulin (group 2). Thus, metformin is the only oral hypoglycemic agent proven to reduce macrovascular risk in overweight patients with type 2 diabetes. For perspective, in overweight patients, metformin significantly reduced all-cause mortality (NNT per year=141; 95% CI, 115–183; \(P=.011\)), and any diabetes-related outcome (NNT per year=74; 95% CI, 63–90; \(P=.0023\)), compared with diet alone.

Metformin induces weight loss (2–3 kg), preferentially involving adipose tissue in obese patients with type 2 diabetes over 4 to 6 months. In UKPDS 34, weight gain was similar among those treated with metformin and diet (approximately 2 kg); weight gain over 10 years was less with metformin, however, than with sulfonylurea (approximately 4 kg) or insulin (approximately 6 kg). Metformin also significantly improved levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides when compared with glyburide or placebo.

**Risk of lactic acidosis.** Lactic acidosis associated with metformin is a rare but serious adverse event, with an estimated prevalence of 3 cases per 100,000. The product labeling notes most of these cases have occurred among patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion. Absolute contraindications include renal disease (serum creatinine \(\geq 1.5\) mg/dL [males] and \(\geq 1.4\) mg/dL [females]), congestive heart failure requiring pharmacological treatment, and acute or chronic metabolic acidosis. It should also be discontinued at the time of radiologic studies using intravascular iodinated contrast materials.

Additional “precautionary conditions” include
ADA recommendations for the treatment of type 2 diabetes

Initiate nonpharmacologic measures, such as meal planning and physical activity

Are any of the following true of the patient?
- Severe symptoms
- Severe hyperglycemia
- Ketosis
- Possible type 1 disease
- Pregnancy

YES

Combine oral therapies.
Are glycemic goals achieved?

NO

Initiate monotherapy with one of the following: α-glucose inhibitor, biguanide, insulin, meglitinide, sulfonylurea, thiazolidinedione

Are glycemic goals achieved?

NO

Combine oral agents and insulin

NO

Prescribe insulin as appropriate:
- Intermediate 2x daily
- Intermediate + short-acting before meals, 2x daily
- Multiple (3 or more) injections
- Intermediate or long-acting + short-acting before meals
- Continuous insulin infusion pump

Are glycemic goals achieved?

YES

Continue with therapy: monitor appropriately

YES

Are any of the following true of the patient?
- Severe symptoms
- Severe hyperglycemia
- Ketosis
- Possible type 1 disease
- Pregnancy

NO

Are glycemic goals achieved with nonpharmacologic measures only?

YES

Initiate nonpharmacologic measures, such as meal planning and physical activity

NO

Age ≥80 years (unless measurement of creatinine clearance demonstrates that renal function is not reduced), hepatic disease, cationic drug use, conditions associated with hypoxia (eg, chronic obstructive pulmonary disease [COPD], acute myocardial infarction, dehydration, sepsis), excessive alcohol intake, and surgery, until patient’s oral intake is resumed.

Is the risk overstated? Despite these extensive precautions, published studies show that metformin is commonly prescribed to patients with absolute contraindications. One recent study observed that 11.2% of Medicare beneficiaries hospitalized with congestive heart failure and concomitant diabetes were treated with metformin. In the absence of advanced renal dysfunction, metformin rarely accumulates in the body, and accumulation of metformin is rarely reported as a cause of lactic acidosis. Rather, tissue hypoxia acts as a trigger in most cases. Metformin should therefore be discontinued whenever tissue hypoxia is suspected.

A recent systematic review and meta analysis found no evidence that metformin was associated with an increased risk of lactic acidosis if the drug was prescribed under study conditions, taking into account contraindications. Refinement and clarification of the risk for lactic acidosis in these various populations is needed, to ensure optimal patient safety and to further assess this highly effective medication.

Common adverse effects associated with metformin are diarrhea and nausea, which can be minimized by administering the drug with meals.
and slowly titrating the dose, or perhaps by using the extended-release formulation.

**Thiazolidinediones**

Thiazolidinediones (TZDs) include rosiglitazone and pioglitazone. These agents, like metformin, do not increase insulin secretion but depend on the presence of insulin for their activity. TZDs are agonists at peroxisome-proliferator-activated receptor gamma (PPAR-γ) receptors in peripheral tissues such as skeletal muscle, where they increase glucose uptake. Thus, their predominant effect is to decrease insulin resistance.

TZDs have similar antihyperglycemic efficacy as sulfonylureas or metformin. They decrease A1c levels by 0.6–1.9 percentage points and lower fasting plasma glucose levels by 50–80 mg/dL. They have a slower onset of action compared with other hypoglycemic drugs, and intervals of 3 to 4 weeks should be allowed between doses before increasing the dosage. TZDs also have favorable effects on lipid levels: HDL concentrations increase and triglyceride concentrations decrease with their use. It is not known whether they decrease macrovascular or microvascular complications, although such studies are underway.

**Adverse effects.** TZDs are typically well tolerated, though weight gain of 1–3 kg, edema (4%–5%) and anemia (1%–2%) can occur. Weight gain and edema are more pronounced when TZDs are used in combination with insulin. Anemia is likely due to increased plasma volume rather than any significant hematological effect.

Due to adverse events related to volume expansion, TZDs are not recommended for patients with New York Heart Association class III or IV heart failure. A recent consensus statement from the American Heart Association and the ADA stresses that before administering TZD treatment, the physician should explore the possible presence of cardiac disease, use of other drugs that cause fluid retention, and the pathogenesis of any existing edema or dyspnea. Although troglitazone was removed from the market due to its association with hepatocellular injury, pioglitazone and rosiglitazone are not as convincingly associated with liver injury. In preapproval clinical studies, less than 0.5% of patients treated with rosiglitazone and pioglitazone had elevations in alanine transaminase (ALT) >3 times the upper limit of normal.

The incidence of hepatitis or acute liver failure from troglitazone was compared with rosiglitazone, pioglitazone, metformin, and glyburide, by analysis of spontaneously reported adverse events to the Food and Drug Administration (FDA) MEDWATCH database during the first 15 months of marketing of each drug. The incidence of hepatitis per million prescriptions was 21.5, 14.7, 9.4, 2.9, and 4.1, respectively, while the incidence of acute liver failure per 100,000 prescriptions was 4.6, 0.9, 0.8, 0.2, and 0. It appears that postmarketing data support preclinical studies, in that the incidence of acute liver failure is an order of magnitude higher for troglitazone vs. other TZDs. However, the FDA recommends avoiding their use in patients with baseline ALT levels >2.5 times the upper limit of normal. The FDA recently reduced the recommended frequency for ALT monitoring for pioglitazone (and is currently considering the same for rosiglitazone). Serum ALT is recommended prior to initiation and then periodically thereafter.

**Cost.** TZDs are expensive relative to other hypoglycemic agents.

**α-glucosidase inhibitors**

The α-glucosidase inhibitors (AGIs), acarbose...
and miglitol, act through competitive, reversible inhibition of membrane-bound intestinal \( \alpha \)-glucosidase, which hydrolyzes complex carbohydrates to glucose and other monosaccharides. This inhibition delays glucose absorption and decreases postprandial hyperglycemia.\(^{37}\) Thus, they have a nonsystemic mechanism of action.

These agents cause a modest reduction in the \( \text{A}_{1c} \) level (0.5–1.0 percentage points) and are thus less effective than sulfonylureas, metformin, or TZDs. They do not reduce fasting plasma glucose levels, but reduce postprandial hyperglycemia by 50 mg/dL.\(^{38}\) No long-term studies have evaluated whether AGIs reduce diabetes-related macrovascular or microvascular outcomes.

**Adverse effects.** While AGIs are virtually free of serious toxicities, patient tolerability can be a problem due to adverse gastrointestinal effects. In indirect comparisons from placebo-controlled trials, patients treated with miglitol and acarbose commonly reported abdominal pain (11.7%, 19%), diarrhea (28.7%, 31%), and flatulence (41.5%, 74%), respectively. Systemic accumulation of AGIs has been shown to increase in proportion to the degree of renal insufficiency, and their use is not recommended for patients with serum creatinine >2.0 mg/dL. However, whether such patients are at greater risk of any toxicity is unknown. Acarbose at doses above 100 mg 3 times daily has been associated with elevated serum transaminase levels; however, this risk appears negligible at standard doses.

**Insulin**

Insulin is the oldest therapy for diabetes, and it has no upper dose limit.\(^{39}\) It increases insulin levels and can reduce \( \text{A}_{1c} \) levels by 1.5 to 2.5 percentage points. Though half of diabetes patients need insulin eventually for optimal control, historically it has been introduced late in the disease process unless patients have severe hyperglycemia (fasting blood sugar >350 mg/dL) or ketonuria.\(^{38}\) However, it is effective in gaining initial control, decreasing gluconeogenesis and increasing glucose uptake. Disadvantages are weight gain, hypoglycemia, and patient reluctance to give injections.

**When insulin is indicated.** Patients who exhibit persistent hyperglycemia despite oral hypoglycemic therapy may stop the oral drug(s) and begin insulin. By combining insulin with oral therapy, lower insulin doses may be used to achieve desired control vs using insulin alone.\(^{40}\) For some patients a basal supplement of insulin may be sufficient and can be given as a single dose at bedtime, without an oral hypoglycemic drug.\(^{41}\)

**Insulin regimens.** Various insulin regimens are available: very rapid acting (lispro and aspart), rapid acting (regular), intermediate acting (isophane insulin [NPH] and lente) and very long acting (ultralente and glargine). Glargine insulin (Lantus) has more predictable absorption than NPH, lente, and ultralente. Lantus, compared with NPH, has been associated with less nocturnal and postprandial hypoglycemia.\(^{38,42,43}\) This is consistent with the peakless and longer duration of glargine compared with NPH.\(^{44}\) A recent randomized controlled trial demonstrated that morning insulin glargine lowered \( \text{A}_{1c} \) levels more than a bedtime dose of NPH (−1.24 vs −0.84; 95% CI, 0.23%–0.58%) or a bedtime dose of glargine (−1.24 vs −0.96%; 95% CI, 0.11%–0.46%).\(^{45}\) Glargine’s only relative disadvantage is increased cost.

**Combination products.** Combination insulin options are 70 NPH/30 regular, 50 NPH/50 regular, and 75 lispro protamine/25 lispro. Many combinations of insulin regimens have been used successfully. The typical range of insulin needed for monotherapy is 0.4–1 U/kg/d. Once-daily injection of intermediate acting or long acting insulins at bedtime or before breakfast, once-daily or twice-daily combinations of intermediate and rapid acting insulins, and more complex regimens have been used to good effect.

Using prandial insulin at each meal with separate basal insulin adds flexibility to meal times and doses administered.\(^{43}\) With multiple-dose intensive insulin therapy, a basal dose suppresses hepatic glucose output and the bolus doses...
enhance postprandial glucose uptake. This intensive insulin treatment reduces mortality among critically ill patients in surgical intensive care units and for those with acute myocardial infarction.\textsuperscript{46,47} An algorithm for using progressive therapy in diabetes mellitus is shown in Figure 2.\textsuperscript{48}

\section*{COMBINATION THERAPY}

Over time glycemic control becomes more difficult, even with maximum monotherapy for patients with healthy lifestyles. It was shown in UKPDS 49 that monotherapy with sulfonylurea, metformin, or insulin eventually fails in most cases—by 3 years after diagnosis, about 50\% of patients need more than monotherapy; 75\% by 9 years.\textsuperscript{49} In UKPDS 33, the median A1c level increased steadily over 10 years with both conventional therapy and intensive therapy (Figure 3).\textsuperscript{2}

Several options are available when monotherapy fails. Based on expert opinion, the principle is to combine drugs with different mechanisms of action to achieve an additive effect for glycemic control. Combination products may simplify the treatment regimen and improve adherence. In many instances, they may also cost less.\textsuperscript{50} Successful combinations. The combination of sulfonylurea and metformin has proven effective in many studies.\textsuperscript{22,51,52} One study showed that initial treatment with glyburide/metformin improved glycemic control better than either glyburide or metformin monotherapy (SOR: A).\textsuperscript{53,54} The addition of the non-SU secretagogues repaglinide and nateglinide to metformin significantly improved glycemic control, with repaglinide showing superiority over nateglinide.\textsuperscript{55} A TZD added to a sulfonylurea has also significantly improved A1c and fasting blood sugar results.\textsuperscript{56} Patients whose diabetes was inadequately controlled with diet alone or diet plus a sulfonylurea showed improvement with the addition of the AGI miglitol, compared with addition of placebo.\textsuperscript{57} The AGI acarbose has shown to be an effective addition to diet, metformin, sulfonylurea, and insulin.\textsuperscript{58} A TZD added to metformin has also been shown to improve glycemic control.\textsuperscript{59} A non-SU added to patients inadequately controlled with a TZD has also been effective.\textsuperscript{60}

The early addition of insulin when maximal sulfonylurea therapy is inadequate has been effective.\textsuperscript{61–63} When introducing insulin, a nighttime regimen of NPH or glargine, 10 units at bedtime, is an appropriate dose (SOR: C). This is easier and less costly than often assumed, and helps improve glycemic control.\textsuperscript{64} Most patients require combination therapy as their disease progresses.\textsuperscript{65}

\section*{IMPROVING OUTCOMES}

Cumulative survey data reveal a wide gap between guideline recommendations and the care patients receive.\textsuperscript{66} One study showed that physicians initiated treatment changes only after the A1c level had reached 9.0\% or higher instead of the 8.0\% level recommended by ADA.\textsuperscript{66} How can the quality of management be improved?

In private practices and institutions, many interventions have been shown to improve outcomes in diabetes mellitus. Education measures work, and they include chart audits, reminder cards, pharmacist collaboration, flow sheets, and nursing initiatives.\textsuperscript{67,68} Effective disease-management programs have also used clinical guidelines, outcomes reporting, coverage of glucose meters and strips, and the support of clinical leadership.\textsuperscript{69} Computerized systems that track patients and recommended laboratory tests have improved screening rates and glycemic and blood pressure control.\textsuperscript{70} Monitoring patients’ readiness to change has allowed targeted education to improve A1c levels.\textsuperscript{71} Continuity of care has also improved the quality of disease control by increasing adherence to recommended tests and exams.\textsuperscript{72}

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