AACE/ACE GLYCEMIC CONTROL ALGORITHM CONSENSUS PANEL

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ABSTRACT

This report presents an algorithm to assist primary care physicians, endocrinologists, and others in the management of adult, nonpregnant patients with type 2 diabetes mellitus. In order to minimize the risk of diabetes-related complications, the goal of therapy is to achieve a hemoglobin A1c (A1C) of 6.5% or less, with recognition of the need for individualization to minimize the risks of hypoglycemia. We provide therapeutic pathways stratified on the basis of current levels of A1C, whether the patient is receiving treatment or is drug naive. We consider monotherapy, dual therapy, and triple therapy, including 8 major classes of medications (biguanides, dipeptidyl-peptidase-4 inhibitors, incretin mimetics, thiazolidinediones, α-glucosidase inhibitors, sulfonylureas, meglitinides, and bile acid sequestrants) and insulin therapy (basal, premixed, and multiple daily injections), with or without orally administered medications. We prioritize choices of medications according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost of medications. We recommend only combinations of medications approved by the US Food and Drug Administration that provide complementary mechanisms of action. It is essential to monitor therapy with A1C and self-monitoring of blood glucose and to adjust or advance therapy frequently (every 2 to 3 months) if the appropriate goal for each patient has not been achieved. We provide a flowchart and table summarizing the major considerations. This algorithm represents a consensus of 14 highly experienced clinicians, clinical researchers, practitioners, and academicians and is based on the American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Guidelines and the recent medical literature. (Endocr Pract. 2009;15:540-559)

Abbreviations:

AACE = American Association of Clinical Endocrinologists;
A1C = hemoglobin Alc;
ACCORD = Action to Control Cardiovascular Risk in Diabetes;
ACE = American College of Endocrinology;
ADA = American Diabetes Association;
ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation;
AGIs = α-glucosidase inhibitors;
DCCTIEDIC = Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications;
DPP-4 = dipeptidyl-peptidase-4;
EASD = European Association for the Study of Diabetes;
FDA = US Food and. Drug Administration;
GLP-1 = glucagonlike peptide-I;
LDL = low-density lipoprotein;
PROACTIVE = Prospective Pioglitazone Clinical Trial in Macrovascular Events;
RCTs = randomized controlled trials;
RECORD = Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes;
SMBG = self-monitoring of blood glucose;
TZDs = thiazolidinediones;
UKPDS = United Kingdom Prospective Diabetes Study;
VADT = Veterans Affairs Diabetes Trial

INTRODUCTION

There are nearly 24 million Americans with diabetes in the United States. Every year, 1.3 million people are diagnosed with type 2 diabetes. The rapid increase in new cases of type 2 diabetes in persons 30 to 39 years of age and in children and adolescents is of special concern. This epidemic of type 2 diabetes is global and closely reflects the epidemic of overweight, obesity, metabolic syndrome, and sedentary lifestyle. An urgent need exists for an authoritative, practical algorithm for management of patients with type 2 diabetes mellitus that considers currently approved classes of medications and emphasizes safety and efficacy, while also considering secondary factors such as the cost of medications or the number of years of clinical experience with use of any specific drug. The introduction of several new classes of medications within the past few years-especially incretin-based therapies such as incretin mimetics and dipeptidyl-peptidase-4 (DPP4) inhibitors-and the results from several recent large-scale clinical trials - Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Veterans Affairs Diabetes Trial (VADT), Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), and Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD)-combined with recently reported longterm follow-up results in patients in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), the United Kingdom Prospective Diabetes Study (UKPDS), and the Steno-2 study, necessitate reevaluation of previously proposed algorithms for selection of therapies. Numerous guidelines for management of patients with diabetes are available - for example, from the American Association of Clinical Endocrinologists (AACE) (1), American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2), Veterans Health Administration/US Department of Defense (VA/DOD) (3), International Diabetes Federation (4), and many others. Several of these need to be updated to reflect the recent literature and clinical experience. A few algorithms are available for that purpose: ADA/European Association for the Study of Diabetes (EASD) 2006 (5,6), ADA/EASD 2009 (7), Canadian Diabetes Association (8,9), and the American College of Endocrinology (ACE)/ AACE Road Maps to Achieve Glycemic Control (10). The cost of medications represents only a very small portion of the total cost of treatment of patients with diabetes. The major cost is related to the treatment of the complications of diabetes. We believe that identification of the safest and most efficacious agents is essential.

METHODS

AACE/ACE convened a panel of experts, including

clinicians and clinical investigators, both academicians and practitioners. An algorithm was developed on the basis of the medical literature, with careful consideration of levels of evidence and evaluation for the consistency of results from multiple studies and sources; greater emphasis was placed on results from randomized controlled trials (RCTs) when available. We also considered meta-analyses, US Food and Drug Administration (FDA)-approved prescribing information, and the extensive experience, collective knowledge, and judgment of the panel members. We envisioned the need for an algorithm that reflected the best practices for expert physicians, recognizing that RCT data are not available to guide every clinical decision. Considerations were based on the AACE Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (1), review of other guidelines (ADA Standards of Medical Care in Diabetes—2009) (2), previous algorithms—ACE/AACE Road Maps to Achieve Glycemic Control (10), ADA/EASD 2006 (5,6), ADAI EASD 2009 (7), Canadian Diabetes Association (8,9), and Inzucchi (11) —the FDA-approved prescribing information for individual agents, pharmacoepidemiologic surveillance studies, and the current literature describing relevant clinical trials: DCCT/EDIC (12), UKPDS (13), Steno-2 (14), ACCORD (15), ADVANCE (16), VADT (17), RECORD (18), PROACTIVE (19), and others.

In the development of this algorithm, we attempted to accomplish the following goals as priorities in the selection of medications:

1. Minimizing risk and severity of hypoglycemia
2. Minimizing risk and magnitude of weight gain
3. Inclusion of major classes of FDA-approved glycemic medication, including incretin-based therapies and thiazolidinediones (TZDs)
4. Selection of therapy stratified by hemoglobin A1c (A1C) and based on documented A1C-lowering potential
5. Consideration of both fasting and postprandial glucose levels as end points
6. Consideration of total cost of therapy to the individual and society at large, including costs related to medications, glucose monitoring requirements, hypoglycemic events, drug-related adverse events, and treatment of diabetes-associated complications

We believe that this algorithm represents the treatment preferences of most clinical endocrinologists, but in the absence of meaningful comparative data, it is not necessarily an official AACE position. Because of the insufficient number or total absence of RCTs for many combinations of therapies, the participating clinical experts used their judgment and experience. Every effort was made to achieve consensus among the panel members. Many details that could not be included in the summarizing algorithm are described in the following text.

RESULTS

Our glycemic control algorithm was developed on the basis of the principles outlined in the subsequent section.

Principles Underlying the AACE/ACE Algorithm

- **Lifestyle** (dietary and exercise) modifications are essential for all patients with diabetes. Reduction of obesity or overweight and adjustment to an active lifestyle can have major beneficial effects. In many cases. delaying pharmacotherapy to allow for lifestyle modifications is inappropriate because these interventions are usually not adequate. Lifestyle modification together with specific diabetes education, dietary consultation, and the introduction of a program of self-monitoring of blood glucose (SMBG) can be initiated concomitantly with medical therapy.
- **Achieving an A1C of 6.5%** is recommended as the primary goal, but this goal must be customized for the individual patient, with consideration of numerous factors such as comorbid conditions, duration of diabetes, history of hypoglycemia, hypoglycemia unawareness, patient education, motivation, adherence, age, limited life expectancy, and use of other medications.
- If a patient has failed to achieve the A1C goal, one can **titrate dosages of medications**, change regimens (add or discontinue medications), or, under some circumstances, reconsider and revise the goal.
- When **combination therapy** is prescribed, it is important to use classes of medications that have complementary mechanisms of action.
- Effectiveness of therapy must be evaluated frequently —for example, **every 2 to 3 months**—with assessment of A1C, logbook data for SMBG records, documented and suspected hypoglycemia, and other potential adverse events (weight gain, fluid retention, and hepatic, renal, or cardiac disease) as well as monitoring of comorbidities, relevant laboratory data, concomitant drug administration, diabetes-related complications, and psychosocial factors affecting patient care.
- Safety and efficacy should be given higher priorities than cost of medications per se, inasmuch as cost of medications is only a small part of the cost of care of diabetes
- The algorithm should be as simple as possible to gain physician acceptance and improve its utility and usability in clinical practice.
- The algorithm should help educate clinicians and help guide therapy at the point of care.
- The algorithm should conform, as nearly as possible, to a consensus for current standards of care by expert endocrinologists who specialize in the management of patients with type 2 diabetes and have the broadest experience in outpatient clinical practice.
- The algorithm should be as specific as possible and provide guidance to physicians with prioritization and a rationale for selection of any particular regimen.
- **Rapid-acting insulin analogues are superior** to "regular human insulin" and provide a better, safer alternative.
- NPH insulin is not recommended. Use of NPH as a basal insulin has been superseded by the synthetic analogues **insulin glargine and insulin detemir**, which provide a relatively peakless profile for approximately 24 hours and yield better reproducibility and consistency, both between patients and within patients, and a corresponding reduction in the risk of hypoglycemia.

The Glycemic Control Algorithm

The AACE/ACE algorithm for glycemic control is presented in Figure 1.

A1C Goal

The rationale for an A1C target of 6.5% is presented in the AACE Diabetes Guidelines (2007) (1). The ACCORD and VADT studies (15,17) have confirmed that progressively lower A1C levels are associated with reduced risk of both microvascular and macrovascular complications. A recent meta-analysis of 5 prospective RCTs demonstrated a significant reduction in coronary events associated with an overall A1C of 6.6% in comparison with 7.5% (20). These studies also indicated that the risk of cardiac events and death is more common in patients with hypoglycemic episodes (and especially severe hypoglycemia) and that the benefit-to-risk ratio decreases progressively with the duration of diabetes, such that the use of intensive therapy may be at least relatively contraindicated in patients with a duration of diabetes longer than 12 years (VADT) (17). The ACCORD study (15) also suggested that excessively rapid or aggressive adjustment of therapy may be associated with increased risk. The A1C levels show an excellent correlation with the mean glucose level, but this relationship is also affected by several other factors, such as hemoglobinopathies, hemolytic anemias, varying rates of individual glycation, genetics, and the variabilities of different laboratory methods.

Frequency of Monitoring of A1C

Many physicians fail to implement the uniformly recommended guidelines to monitor A1C on a quarterly basis. Physicians are often slow in advancing therapy, relative to either dosages of medications or switching to a more efficacious therapeutic regimen in a timely manner. One of the most important aspects of the current algorithm is the strong recommendation to monitor therapy closely (every 2 to 3 months) and to intensify therapy until the goal for A1C has been achieved.

Stratification by Current Al C level

An important element of the current algorithm is the need for stratification of the therapeutic approach on the basis of the current A1C Level.

1. If the patient has an A1C value of 7.5% or lower, it may be possible to achieve a goal A1C of 6.5% with use of monotherapy. If mono therapy fails to achieve that goal, one usually progresses to dual and then to triple therapy; finally, insulin therapy should be initiated, with or without additional agents.
2. If the patient has an Al C level in the range of 7.6% to 9.0%, then one should begin with dual therapy because no single agent is likely to achieve the goal. If dual therapy fails, one can progress to triple therapy and then to insulin therapy, with or without additional orally administered agents.
3. If the patient has an A1C value of >9.0%, then the possibility of achieving a goal A1C of 6.5% is small, even if dual therapy is used. If the patient is asymptomatic, one might begin with triple therapy—for example, based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD. If, however, the patient is symptomatic, or therapy with similar medications has failed, it is appropriate to initiate insulin therapy, either with or without additional orally administered agents.
4. When the algorithm (Fig. 1) indicates insulin therapy, one may use any of the following 4 general approaches:
   - Basal insulin, using a long-acting insulin analogue (glargine, detemir), generally given once daily;
   - Premixed insulins, using a rapid-acting analogue and protamine (NovoLog Mix, Humalog Mix), usually given twice daily with breakfast and dinner but occasionally used only with the largest meal;
   - Basal-bolus insulin or multiple daily injections, using rapid-acting insulin analogues-aspart (NovoLog), lispro (Humalog), or glulisine (Apidra) - together with the long-acting insulin analogue glargine (Lantus) or detemir (Levemir);
   - A "prandial" insulin regimen, involving use of the rapid-acting insulin analogues, but without a basal or long-acting insulin component. This may be possible if the patient is being treated with an insulin sensitizer (metformin) that provides adequate control of fasting plasma glucose.

We do not recommend use of regular human insulin ("R"), nor of NPH insulin ("N") if possible, in view of the fact that these insulin preparations do not have a sufficiently predictable time course that adequately mimics the normal physiologic profile. As a result, the dose required to control hyperglycemia is often associated with an increased risk of hypoglycemia.

We now describe the 3 pathways within the algorithm corresponding to the 3 broad ranges of A1C: 6.5 % to 7.5 %, 7.6% to 9.0%, and >9.0%.

Management of Patients With Al C Levels of 6.5% to 7.5%

Monotherapy

For the patient with an A1C level within the range of 6.5% to 7.5%, it is possible that a single agent might achieve the A1C goal of 6.5%. In this setting, metformin, TZDs, DPP-4 inhibitors, and α-glucosidase inhibitors (AGIs) are recommended. Because of its safety and efficacy, metformin is the cornerstone of monotherapy and is usually the most appropriate initial choice for mono therapy unless there is a contraindication, such as renal disease, hepatic disease, gastrointestinal intolerance, or risk of lactic acidosis.

Some patients with diabetes and A1C levels of <6.5% may also be considered for pharmacotherapy. Use of an insulin secretagogue (sulfonylurea or meglitinide/" glinide") is not recommended in this A1C range. Sulfonylureas may be more potent than metformin, TZDs, DPP-4 inhibitors, or AGIs, although they have a relatively short-lived effectiveness and are associated with a substantial risk of hypoglycemia and weight gain, especially in drug-naive patients.

The 4 agents recommended for the A1C range of 6.5% to 7.5% have a very minimal risk of hypoglycemia, especially when used as monotherapy. The TZDs require several weeks to achieve maximal benefit; likewise, their effects decline slowly after they have been discontinued. In patients with clear evidence of insulin resistance or the clinical "metabolic syndrome" and in patients with nonalcoholic fatty liver disease, TZDs may be preferred. If monotherapy is unsuccessful in achieving the A1C goal even after the dosage has been titrated appropriately, then one should advance to dual therapy.

Dual Therapy

As a result of its safety and efficacy, metformin should be the cornerstone of dual therapy for most patients. When metformin is contraindicated, a TZD may be used as the

foundation for this group of options. Because metformin or a TZD will serve as an insulin sensitizer, the second component of the dual therapy is usually an incretin mimetic, DPP-4 inhibitor, glinide, or sulfonylurea. These agents are recommended in the following order: incretin mimetic, DPP-4 inhibitor, or an insulin secretagogue such as a glinide and sulfonylurea. The glucagon-like peptide-1 (GLP-1) agonist and DPP-4 inhibitors are safer than the glinide or sulfonylurea options with regard to the risk of hypoglycemia. Despite its risk of gastrointestinal side effects (which are usually transitory) and the need for twice-daily injection, the GLP-1 agonist is preferred, in view of its somewhat greater effectiveness in reducing postprandial glucose excursions relative to the DPP-4 inhibitor and the fact that approximately 30% of patients will experience considerable weight loss. The DPP-4 inhibitors are used orally once daily with excellent tolerability and no major effects on weight. Glinides are preferred relative to sulfonylureas because of the greater need for controlling postprandial glucose excursions in patients with an A1C level already below 7.5% and their relative safety. The combination of TZD with metformin has been used extensively and is efficacious, but it carries the risks of the adverse events associated with both agents. We recommend this combination with a higher priority than a glinide or sulfonylurea because of a lower risk of hypoglycemia and greater flexibility in timing of administration. One must consider the potential adverse effects of any of these medications as they apply to an individual patient (see Table 1 and Appendix 1 as well as definitive sources of prescribing information).

Two additional regimens for dual therapy are included in the algorithm: (1) metformin combined with colesevelam and (2) metformin combined with an AGI. These regimens are included because of their safety (minimal risk of hypoglycemia) and the ability of colesevelam to lower the level of low-density lipoprotein (LDL) cholesterol, although these combinations may produce some gastrointestinal side effects.

If dual therapy fails, even after each component has been titrated to its maximally effective dose (commonly. only 50% to 66% of the FDA upper limit for recommended dosage), one can advance to triple therapy or institute insulin therapy.

Triple Therapy

We consider the following 6 options for triple therapy, which are presented in a condensed format in Figure 1:

1. Metformin + GLP-1 agonist + TZD
2. Metformin + GLP-1 agonist + glinide
3. Metformin + GLP-1 agonist + sulfonylurea
4. Metformin + DPP-4 inhibitor + TZD
5. Metformin + DPP-4 inhibitor + glinide
6. Metformin + DPP-4 inhibitor + sulfonylurea

Because of its safety and effectiveness, metformin is selected as the cornerstone for triple therapy, unless specific contraindications are present. The GLP-1 agonist, exenatide, is the second preferred component because of its safety, with nearly complete absence of hypoglycemia attributable to the fact that its stimulation of insulin is dependent on glucose, and because of its potential for inducing weight loss. It also has the ability to inhibit glucagon secretion in a glucose-dependent manner after consumption of meals, to increase satiety, and to delay gastric emptying. Physicians should be aware of the reported possible association of exenatide with pancreatitis and should avoid use of this drug in patients with a history of pancreatitis. A recent analysis of a very large database, however, revealed no greater incidence of pancreatitis in patients with diabetes taking exenatide in comparison with the already substantially increased incidence of this disorder in patients with diabetes. For the third member of the triple-therapy combination, one may select a TZD, glinide, or sulfonylurea. These agents are recommended in order to minimize the risk of hypoglycemia. The combination with metformin, especially when coupled with an incretin mimetic, may partially help to counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.

Insulin Therapy

When triple therapy fails to achieve glycemic control, it is likely that the insulin-secretory capacity of the beta cells has been exceeded; thus, insulin therapy is needed. One can then institute therapy as basal, premixed, prandial, or basal-bolus insulin. At this point, the list of available agents to use as adjuvants to insulin is diminished. Exenatide and DPP-4 inhibitors have not been approved by the FDA for concomitant use with insulin. Agents such as colesevelam and AGIs are not likely to contribute materially to effectiveness. Sulfonylureas and glinides should be discontinued when prandial insulin is introduced, inasmuch as postprandial excursions can usually be managed better with a rapid-acting insulin analogue or a premixed insulin preparation. Use of TZDs jointly with insulin has been associated with a high probability of weight gain, fluid retention, increased risk of congestive heart failure, and significantly increased risk of fractures both in men and in women. Although some studies have been controversial, recent clinical trials—ADVANCE (16), VADT (17), and ACCORD (15)—showed no increased risk of mortality associated with rosiglitazone, and the PROACTIVE trial (19) showed a small beneficial effect of pioglitazone on cardiac events. Overall, metformin is the most commonly used and safest medication to combine with insulin.

Basal Insulin: Long-acting basal insulin is generally the initial choice for initiation of insulin therapy in the United States. Insulin glargine and insulin detemir are strongly preferred over human NPH insulin because they have relatively peakless time-action curves and a more consistent effect from day to day, resulting in a lower risk of hypoglycemia. Basal insulin therapy is generally initiated with a small arbitrary dose (usually 10 U) at bedtime. The dosage is titrated slowly (for example, an increment of 1 to 3 U) every 2 to 3 days if the fasting plasma glucose level reaches the desired target. In contrast, the dosage is reduced if the fasting plasma glucose declines below another specified threshold.

Premixed Insulins: An alternative approach to starting insulin therapy is to use premixed insulin analogues (lispro-protamine or aspart-protamine). One may initiate therapy for the major meal of the day (typically, dinner) and subsequently add another injection at the next largest meal. The insulin dose before breakfast is adjusted by measurement of the glucose level before dinner; the insulin dose before dinner is adjusted primarily by measurement of the fasting glucose concentration on the following day. Use of premixed insulin generally involves 2 injections per day rather than the 4 injections per day required for basal-bolus insulin. In general, however, with use of premixed insulin, the patient must have a fairly constant lifestyle and may have a higher risk of hypoglycemia. If the patient has failed to achieve goals for glycemia with use of a basal insulin regimen, one may institute the premixed insulin regimen with 2 injections per day.

Basal-Bolus Insulin Regimens: In comparison with premixed insulins, a basal-bolus insulin regimen involving 4 injections per day is usually more efficacious and provides greater flexibility for those patients with variable mealtimes and carbohydrate content of meals. In general, before-meal insulin doses for adults can initially be set at about 5 U per meal or about

7% of the daily dose of basal insulin. The before-meal insulin dose can be titrated upward by 2 to 3 U every 2 to 3 days on the basis of monitoring of the 2-hour postprandial glucose level and taking into account the before-meal blood glucose level for the subsequent meal. The dose should be titrated to achieve good control in terms of both the A1C level and the preprandial and postprandial glycemia.

Pramlintide

Pramlintide, an analogue of pancreatic amylin, has been used as an adjunct to prandial insulin therapy in patients with type 1 diabetes and can be helpful in patients with type 2 diabetes for control of postprandial glucose. This involves several additional carefully timed injections immediately before meals.

Insulin Pump

Some patients with type 2 diabetes using basal-bolus insulin therapy benefit from use of an insulin pump (continuous subcutaneous insulin infusion). An insulin pump can provide maximal flexibility with regard to mealtimes, size of meals, exercise, or travel.

Continuous Glucose Monitoring

Some patients with type 2 diabetes clearly benefit from use of continuous glucose monitoring (21). This can educate the patient regarding the glycemic effects of various foods, help the patient titrate insulin, and provide warnings when the patient is experiencing hyperglycemia or hypoglycemia. Continuous glucose monitoring should be considered in patients with type 2 diabetes receiving insulin therapy whose disease is otherwise difficult to control.

Self-Monitoring of Blood Glucose

When a patient begins insulin therapy, SMBG should be increased in frequency. For patients starting basal insulin therapy at bedtime, the morning fasting blood glucose levels should be determined daily. This same approach applies for the patient initiating premixed insulin therapy before dinner. For each additional injection of insulin, SMBG should be increased in frequency to ensure successful titration of each dose.

Reinforcement of Patient Education

Advancement to insulin therapy is an important opportunity to reinforce patient education with regard to lifestyle modification, diet, exercise, weight management (weight loss or weight maintenance), and other aspects of diabetes education, including prevention, identification, and treatment of hypoglycemia. One may also reevaluate and possibly modify goals for therapy, review the needs for treatment of other commonly associated risk factors (such as hypertension, dyslipidemia, smoking, and stress), and consider therapy with low-dose aspirin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins.

Management of Patients with A1C Levels of 7.6% to 9.0%

Management of patients with an A1C value in the range of 7.6% to 9.0% is similar to that just described, except that one can bypass the use of mono therapy and proceed directly to dual therapy because monotherapy is unlikely to be successful in this group. We recommend some changes, however, in the use of dual therapy or triple therapy in this group of patients in comparison with that for patients with A1C ≤.7.5 %, in view of the need for more efficacious therapy.

Dual Therapy

We consider the following 5 options for dual therapy in patients with this A1C range (Fig. 1):

1. Metformin + GLP-1 agonist
2. Metformin + DPP-4 inhibitor
3. Metformin + TZD
4. Metformin + sulfonylurea
5. Metformin + glinide

Metformin is again the foundation of therapy because of its safety, mechanism of action, and insulin sensitization. Usually, a GLP-1 agonist or a DPP-4 inhibitor is the preferred second component, in view of the safety and efficacy of these agents in combination with metformin. A GLP-1 agonist is given a higher priority than a DPP-4 inhibitor, in view of its somewhat greater effect on reducing postprandial glucose excursions and its potential for inducing substantial weight loss. The lower position of TZDs is attributable to their associated risks of weight gain, fluid retention, congestive heart failure, and fractures. Sulfonylureas and glinides are relegated to the lowest position because of their greater risk of inducing hypoglycemia. The relative positions for sulfonylureas and glinides are reversed in comparison with their positions in dual therapy for patients with A1C values ≤ 7.5%. There is a need for the greater glucose-lowering efficacy of sulfonylureas in the A1C range 7.6% to 9.0%.

Triple Therapy

When dual therapy does not achieve the A1C goal, a third agent should be added. The options for triple therapy for patients with an A1C in this range are similar to those recommended for patients with lower A1C values. We consider the following 5 options:

1. Metformin + GLP-1 agonist + TZD
2. Metformin + DPP-4 inhibitor + TZD
3. Metformin + GLP-1 agonist + sulfonylurea
4. Metformin + DPP-4 inhibitor + sulfonylurea
5. Metformin + TZD + sulfonylurea

Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy-either a GLP-1 agonist or a DPP-4 inhibitor. The preference for metformin and the GLP-1 agonist or DPP-4 inhibitor is based on their safety, in view of their minimal associated risks of hypoglycemia. Similarly, TZDs are assigned a priority greater than that for a sulfonylurea because of their low risk of hypoglycemia. A GLP-1 agonist is given a higher priority than a DPP-4 inhibitor owing to its somewhat greater effect on reducing postprandial glucose excursions and the possibility that it might induce considerable weight loss. The combination of metformin, TZD, and sulfonylurea is relegated to the lowest priority because of its increased risk of weight gain for the combination of TZDs and sulfonylureas and the risk of hypoglycemia, particularly for patients at the lower end of this A1C range (~7.5%). Glinides, AGIs, and colesevelam are not considered in this A1C range, in view of their limited A1C-lowering potential.

Insulin Therapy

The considerations for insulin therapy for patients with a

current A1C of 7.6% to 9.0% are similar to those discussed previously for patients with an A1C level of 6.5% to 7.5 %. When transitioning to insulin from a regimen involving triple therapy, it is customary to discontinue one or more of the orally administered agents. Use of TZDs or of sulfonylureas conjointly with insulin is associated with a risk of weight gain and fluid retention. In patients at risk, TZDs may cause or aggravate congestive heart failure, and they increase the risk of bone fractures in both women and men (22,23). Neither GLP-1 agonists nor DPP-4 inhibitors have been approved by the FDA for use with insulin. Thus, metformin is the only medication with a relatively clear indication for use in conjunction with insulin in patients with type 2 diabetes. If it becomes clear that a premixed or a basal-bolus insulin regimen is required to achieve glycemic goals, insulin secretagogues should be discontinued. Use of pramlintide should also be considered in patients with persistent postprandial hyperglycemia.

Management of Patients With Al C Levels of >9.0 %

Combination Therapy

For drug-naive patients with A1C levels of >9%, it is unlikely that use of 1,2, or even 3 agents (other than insulin) will achieve the A1C goal of ≤ 6.5%. If the patient is asymptomatic, particularly with a relatively recent onset of diabetes, a good probability exists for preservation of some endogenous beta-cell function, implying that dual therapy or triple therapy may be sufficient. We consider the following 8 options:

1. Metformin + GLP-1 agonist
2. Metformin + GLP-1 agonist + sulfonylurea
3. Metformin + DPP-4 inhibitor
4. Metformin + DPP-4 inhibitor + sulfonylurea
5. Metformin + TZD
6. Metformin + TZD + sulfonylurea
7. Metformin + GLP-1 + TZD
8. Metformin + DPP-4 inhibitor + TZD

Metformin provides the foundation. One can add an incretin-based therapy (GLP-1 agonist or DPP-4 inhibitor). It may be preferable to use a GLP-1 agonist, in view of its greater effectiveness at controlling postprandial glycemia and its potential for inducing weight loss. The DPP-4 plus metformin combinations have also demonstrated a robust benefit for drug-naive patients in this A1C range. In turn, one can add either a sulfonylurea or a TZD. The sulfonylurea is preferred here because of its somewhat greater efficacy and more rapid onset of action. In contrast, if the patient is symptomatic with polydipsia, polyuria, and weight loss, or if the patient has already been receiving treatment and regimens similar to the aforementioned ones have failed, then it is appropriate to initiate insulin therapy without delay.

Insulin Therapy

Insulin therapy for patients with A1C levels exceeding 9.0% follows the same principles as outlined previously for patients with A1C values of ≤ 9.0%. One can prescribe basal insulin, premixed insulins, or basal-bolus insulin.

Reversal of Glucotoxicity and Lipotoxicity

Insulin therapy, properly instituted, should lower the A1C level to close to the goal of 6.5 %. In the process, it is likely that the effects of glucotoxicity and lipotoxicity on the secretory capacity of the beta cell would have been reduced or nearly eliminated. Hence, after one has achieved a meaningful reduction in A1C to a level below 7.5% with use of insulin therapy, one may then attempt use of dual therapy (as described in the foregoing material) as an adjuvant to insulin therapy, with concomitant reduction of insulin to minimize the risks of hypoglycemic events. If these efforts are successful, one can then attempt to discontinue the use of insulin therapy and consider dual therapy or triple therapy.

The AACE/ACE Glycemic Control Algorithm Consensus Panel has constructed a carefully considered rationale for the choice of each of the regimens in Figure 1 and for their order of presentation. These choices, however, are based on general principles and statistical averages for large groups of patients or based on meta-analyses of large-scale studies. When managing the individual patient, the physician must exercise judgment to weigh the benefits and risks, or the pros and cons of each of these options. A brief useful overview of some of the core considerations for selection of agents or combinations of agents is provided in Table 1. This table is not intended to be a substitute for a comprehensive review of FDA-approved prescribing information.

Hypoglycemia

Perhaps the most important guiding principle of our current algorithm is the recognition of the importance of avoiding hypoglycemia (24-28). Severe hypoglycemia stimulates sympathetic adrenergic discharge, causing arrhythmias or autonomic dysfunction (or both), and has long been recognized to have potential for causing mortality. Hypoglycemia may have a substantial negative clinical effect, in terms of mortality, morbidity, adherence to therapy, and quality of life (24). The recently reported clinical trials of intensive therapy—ACCORD, ADVANCE, and VADT (15-17,20,29)—have shown that intensive glycemic control was associated with a 3- to 4-fold increase in the incidence of hypoglycemia. In the ACCORD study, iatrogenic hypoglycemia was associated with excess mortality in both the intensively treated group and the conventionally treated group (20,29). The risk of hypoglycemia increases with advancing age and duration of diabetes, the duration of insulin therapy (24,28), coexisting severe comorbidities, and the presence of hypoglycemia unawareness.

Insulin and sulfonylurea are the agents that most commonly cause hypoglycemia. The incidence of hypoglycemia in insulin-treated patients with type 2 diabetes is only one-third that in patients with type 1 diabetes (27). The incidence of hypoglycemia necessitating emergency medical treatment in insulin-treated patients with type 2 diabetes approaches that observed for patients with type 1 diabetes. The glinides, repaglinide and nateglinide, are associated with a lower risk of hypoglycemia, presumably because of a more physiologic time course of action combined with somewhat lower efficacy in comparison with sulfonylureas.

For some patients, the risk of hypoglycemia may warrant specific choices of therapy and reevaluation of therapeutic goals. These patients include those who have a duration of diabetes greater than 15 years and advanced macrovascular disease, hypoglycemia unawareness, limited life expectancy, or other serious comorbidities.

DISCUSSION

The current algorithm (Fig. 1) was developed to assist primary care physicians, endocrinologists, and others in the management of patients with type 2 diabetes. In this algorithm, we

consider all classes of effective drugs. We emphasize safety and the quality of glycemic control as our first priorities. Accordingly, we have given sulfonylureas much less priority because use of these agents is associated with hypoglycemia, weight gain, and limited duration of effectiveness after initiation of therapy. Placing greater emphasis on safety and ability to achieve an A1C goal of 6.5% will result in earlier and more frequent use of the incretin-based therapies-the GLP-1 agonists (incretin mimetics) and the DPP-4 inhibitors. At present, only one GLP-1 agonist (exenatide) is available. Two DPP-4 inhibitors (sitagliptin and saxagliptin) are now available. On the basis of the level of ongoing research with these 2 classes of agents, it is likely that several new agents will become available during the next few years. Our algorithm utilizes 4 types of monotherapy, 9 types of dual therapy, and 6 types of triple therapy. We consider 5 types of insulin therapy (basal, premixed, prandial, basal-bolus, and continuous subcutaneous insulin infusion), each of which can be combined with a variety of orally administered agents or with pramlintide.

This algorithm for glycemic control has the following features:

1. It favors the use of GLP-1 agonists and DPP-4 inhibitors with higher priority because of their effectiveness and overall safety profiles. In view of the millions of patients who have benefited from the use of these agents and their excellent performance in a wide range of clinical studies, in combination with the growing literature indicating the serious risks of hypoglycemia, these agents are increasingly preferred for most patients in place of sulfonylureas and glinides.
2. It moves sulfonylureas to a lower priority because of the associated risks of hypoglycemia, weight gain, and the failure of these agents to provide improved glycemic control after use for a relatively short period (1 to 2 years in typical patients).
3. It uses GLP-1 agonists (incretin mimetics) and DPP-4 inhibitors as important components of the therapeutic armamentarium.
4. It includes TZDs as "well-validated" effective agents with demonstrated extended durability of action, but with a lower priority for many patients in light of their potential adverse effects, especially when TZDs are used in combination with sulfonylureas or insulin, and the recent confirmation of previous reports of a significant increase in bone fractures associated with their use in both men and women (22,23).
5. It considers 3 other classes of agents (AGIs, colesevelarn, and glinides) only for relatively narrow, well-defined clinical situations, in view of their limited efficacy. The LDL cholesterol-lowering property of colesevelam is a beneficial factor.

This algorithm is intended to provide guidance. Individual institutions, clinics, and physicians may want to modify it to incorporate their own experience and preferences, the nature of their patient populations, secondary considerations such as the availability of medications in their local formulary, and costs. They may also wish to reconsider the choice of agents for inclusion in their formulary.

CONCLUSION AND RECOMMENDATIONS

The current algorithm is intended for use in conjunction with a more detailed and comprehensive guideline—for example, the AACE Diabetes Guidelines (1) and the ACE/AACE Road Maps to Achieve Glycemic Control (10)—and with comprehensive sets of prescribing information and a compendium of drug-drug interactions. This algorithm represents a significant advance relative to most of the other available "treatment pathways" (3-9) by virtue of its inclusiveness, rationale and justification, emphasis on safety, documentation of supporting evidence, simplicity, and anticipated ease of implementation. This algorithm provides a foundation that can be modified in the future as new medications and classes of medications become available or as new data become available regarding the safety, adverse events, efficacy, and long-term outcomes associated with the medications.

APPENDIX 1

Overview of Therapeutic Agents

Physicians should consult the complete prescribing information and the general literature (for example, 30). The following material is offered as a brief review, a precis. A summary overview of the principal benefits and risks of the therapeutic agents used for management of type 2 diabetes is presented in Table 1 (main text). Further details are provided in the following text.

Metformin

Metformin is a biguanide that improves the effectiveness of insulin in suppressing excess hepatic glucose production, in both the fasting and the postprandial state. Metformin decreases excessive hepatic glucose production in the fasting state primarily by decreasing gluconeogenesis and, to a lesser extent, by decreasing glycogenolysis. Insulin suppression of hepatic glucose production is enhanced in the postprandial state. Thus, metformin is effective in decreasing both fasting and postprandial glucose concentrations. Decreased gastrointestinal glucose absorption, increased insulin sensitivity in peripheral tissues, and enhanced synthesis of GLP-1 may have minor roles. Metformin often has beneficial effects on components of the metabolic syndrome, including mild to moderate weight loss, improvement of the lipid profile, and improved fibrinolysis.

Metformin is effective as monotherapy and in combination with other antidiabetic agents, including sulfonylureas, TZDs, AGIs, DPP-4 inhibitors, GLP-1 agonists, and pramlintide. It can also be used in combination with insulin. Because of its relatively short duration of action, it is usually administered 2 to 3 times daily and is best tolerated if taken with meals. A long-acting, once-daily formulation is also available. The maximal recommended dosage is 2,500 mg daily, although little additional benefit is seen with dosages exceeding 2,000 mg daily.

Side effects include a metallic taste, anorexia, nausea, abdominal pain, and diarrhea. These symptoms are minimized by initiating therapy at a low dosage of 500 mg daily and gradually increasing to the maximal effective dose. Gastrointestinal side effects usually diminish with continued use, although some patients do not tolerate metformin well and discontinue the medication or fail to achieve fully effective doses.

Lactic acidosis is an extremely rare but serious complication of metformin use. Because metformin is primarily excreted by the kidneys, impaired renal function may result in excessive plasma concentrations of metformin and predispose to lactic acidosis. Therefore, impaired renal function is a contraindication for use of metformin. In clinical practice, this is defined as a plasma creatinine concentration of ≥ 1.5 mg/ dL for men and ≥ 1.4 mg/ dL for women or a creatinine clearance of <60

mL/min. Metformin is also contraindicated in patients who are at increased risk for lactic acidosis because of other conditions—for example, patients with congestive heart failure requiring pharmacologic management, elderly patients with decreased creatinine clearance, active liver disease, chronic alcohol abuse, or sepsis, or patients who have other acute illnesses with an associated risk of decreased tissue perfusion or hypoxemia. Metformin is also contraindicated during intravenous administration of radiographic contrast material, which may impair renal function.

When used as mono therapy, metformin has a very low risk of hypoglycemia. When metformin is used in combination with an insulin secretagogue or insulin, however, hypoglycemia may occur. Another rare adverse effect of metformin is megaloblastic anemia due to impaired absorption of vitamin B12. This can be prevented by administration of vitamin B12.

Insulin Secretagogues

Insulin secretagogues include the sulfonylureas, repaglinide, and nateglinide. Sulfonylureas stimulate the delayed, second phase of insulin secretion after meal ingestion and have little effect on first-phase insulin secretion. These characteristics may result in fasting or late postprandial hypoglycemia, which is the most severe adverse side effect of the sulfonylureas.

Repaglinide has a more rapid onset of action and a shorter duration of action in comparison with the sulfonylureas. These features result in earlier insulin secretion and a somewhat decreased risk of late postprandial hypoglycemia. For achievement of maximal benefits, however, administration before each meal is necessary. Nateglinide also has a rapid onset of action and a short duration, increases both the first and second phases of insulin secretion, and is primarily glucose dependent in its action. Like repaglinide, its major effect is to reduce postprandial hyperglycemia, and it should be administered before each meal. Most of the beneficial effects of insulin secretagogues are achieved at submaximal doses, and if adequate glucose control is not achieved, adding a second agent of a different class is generally more effective than increasing the insulin secretagogues to their maximal dosage level. The durability of effectiveness of sulfonylureas is less than with TZDs or AGIs.

The major side effect of sulfonylureas is hypoglycemia. This occurs more commonly with the long-acting sulfonylureas, chlorpropamide and glyburide, than with shorter-acting compounds. Mild to moderate weight gain is frequently observed. When sulfonylureas are used in combination with insulin or TZDs, risks of weight gain, fluid retention, and congestive heart failure are increased.

Thiazolidinediones

The TZDs first became available for treatment of patients with type 2 diabetes in the mid-1990s. The first approved TZD, troglitazone, was associated with rare cases of liver damage, leading to liver failure and death; therefore, its use was discontinued approximately 10 years ago. The currently available TZDs, pioglitazone and rosiglitazone, are effective insulin-sensitizing agents. These agents increase the insulin sensitivity of skeletal muscle, adipose tissue, and, to a lesser extent, the liver, resulting in increased insulin-stimulated glucose uptake and metabolism and improved insulin-mediated suppression of hepatic glucose production. They also stimulate the formation of pre-adipocytes in peripheral adipose tissue, accompanied by decreases in ectopic fat deposition, plasma free fatty acid concentration, and insulin resistance.

When used as monotherapy or in combination with other antidiabetic agents (including insulin), TZDs are effective in decreasing both fasting and postprandial glucose concentrations. When used as monotherapy, they do not cause hypoglycemia. When TZDs are used with insulin secretagogues or insulin, however, hypoglycemia can occur. The major side effect of the TZDs is weight gain, due to both increased adipose tissue mass and fluid retention. Peripheral edema occurs in some patients and typically responds poorly to loop diuretics and angiotensinconverting enzyme inhibitors. Mild anemia may occur.

The TZDs not only are effective in the management of hyperglycemia but also have beneficial effects on the lipid profile, with lowering of plasma triglycerides, increasing the level of high-density lipoprotein cholesterol, and decreasing small, dense LDL cholesterol. The associated weight gain and fluid retention, however, may precipitate congestive heart failure (19). In patients with New York Heart Association class III or class IV congestive heart failure, TZDs are contraindicated. Weight gain can be a major problem for patients who are overweight or obese. An extensive but highly controversial meta-analysis suggested the possibility of increased ischemic heart disease associated with use of rosiglitazone. Subsequent, more definitive analyses, however, have indicated that rosiglitazone has no effect, positive or negative, on the occurrence of cardiovascular disease. A 1.5- to 2.5-fold increased risk of bone fractures has been documented in both men and women using TZDs (22,23).

α-Glucosidase Inhibitors

The AGIs, acarbose and miglitol, inhibit the conversion of oligosaccharides into monosaccharides at the intestinal brush border and thereby decrease the rise in plasma glucose concentrations after ingestion of complex carbohydrates. Although the main effect of AGIs is to decrease postprandial hyperglycemia in patients with type 2 diabetes, their use is also associated with a slight decrease in fasting glucose concentrations. This change is probably attributable to an overall improvement in glycemic control and reduction of glucose toxicity. They are effective as monotherapy or in combination with other antidiabetic agents, particularly if the diet contains at least 50% carbohydrate.

The major side effects of AGIs are gastrointestinal and include abdominal discomfort, increased formation of intestinal gas, and diarrhea. These adverse gastrointestinal effects are due to excessive amounts of carbohydrate reaching the large intestine and undergoing bacterial fermentation. Acarbose is not substantially absorbed from the gastrointestinal tract, whereas miglitol is absorbed rapidly and excreted by the kidneys. Acarbose, however, is metabolized by bacterial action in the colon, and its metabolites are absorbed, conjugated, and excreted in bile. Rare cases of cholestatic jaundice have been reported. Effectiveness is moderate in people consuming a typical Western diet, and AGIs are most effective when the diet contains large amounts of complex carbohydrates, as is typical of many Asian diets. The risk of hypoglycemia is minimal when AGIs are used as monotherapy. Hypoglycemia may occur when AGIs are used in combination with insulin secretagogues or insulin therapy. When hypoglycemia does occur, it must be treated with glucose, inasmuch as digestion and absorption of sucrose and complex carbohydrates are inhibited by these drugs.

Dipeptidyl-Peptidase-4 Inhibitors

The DPP-4 inhibitors decrease the metabolism of the incretin hormones, GLP-1 and gastric inhibitory polypeptide, by inhibition of the DPP-4 enzyme, which removes the 2 end-terminal amino acids and causes rapid inactivation of these gastrointestinal hormones. Active GLP-1 and gastric inhibitory polypeptide plasma

levels are increased approximately 2-fold after meal ingestion. This results in increased first-phase insulin secretion, suppression of glucagon secretion in the postprandial state, and improved suppression of hepatic glucose production and peripheral glucose uptake and metabolism. Hepatic glucose production is also decreased in the fasting state; the result is lower fasting plasma glucose concentrations. Thus, the DPP-4 inhibitors decrease both fasting and postprandial glucose levels. In clinical trials, they have effectiveness similar to that of metformin and sulfonylureas. Because the effects of GLP-1 on insulin and glucagon secretion are glucose dependent, there is insignificant risk of hypoglycemia when it is used as monotherapy or in combination with metformin or a TZD. The currently available DPP-4 inhibitors, sitagliptin and saxagliptin, are conveniently administered once daily. Sitagliptin is eliminated almost entirely by the kidneys; its dosage must be reduced for patients with moderate or severe renal insufficiency. Saxagliptin is likewise primarily excreted by the kidneys but is also subject to hepatic metabolism; its dosage must be reduced only in subjects with severe renal insufficiency. No major long-term toxicities have been reported. Rare allergic reactions have been described.

Long-Acting GLP-1 Analogues

Currently, one long-term GLP-1 analogue is available for clinical use, although several others are in various stages of development and may become available in the near future. The currently available compound, exenatide, is a biosynthetic version of a salivary peptide from a lizard, the Gila monster. Exenatide has approximately 50% homology to human GLP-1 but is highly resistant to inactivation by the DPP-4 enzyme. The binding of exenatide to the human GLP-1 receptor results in glucose-dependent stimulation of insulin secretion and glucose-dependent suppression of glucagon secretion. Exenatide is administered by injection twice daily and is effective in decreasing both fasting and postprandial plasma glucose concentrations. Exenatide has central nervous system effects to reduce appetite and increase the sense of satiety; the outcome is decreased food intake and weight loss. The major side effects are gastrointestinal, with nausea and vomiting in some patients. These effects are dose related and usually wane over time. Exenatide is administered at a low dosage (5 ug twice daily) for the first 4 weeks of treatment and then increased to a higher dosage (10 ug twice daily) after the gastrointestinal side effects have abated. Overall effectiveness is generally very good when exenatide is added to single- or dual-agent regimens involving metformin, sulfonylureas, or TZDs. Currently, exenatide is not approved for use as monotherapy or in combination with insulin.

Additional effects that have been observed with long-acting GLP-1 agonists are substantial reductions in plasma triglyceride levels, diminished liver fat content, and decreased systolic and diastolic blood pressures. To what extent these are direct effects of the drugs or are attributable to weight loss is not yet clear.

Bile Acid Sequestrants

Colesevelam is a bile acid sequestrant used primarily to treat hypercholesterolemia, either as mono therapy or in combination with hydroxymethylglutaryl-coenzyme A reductase inhibitors {HMG-CoA}. Colesevelam also reduces the blood glucose level in patients with type 2 diabetes mellitus, particularly in persons inadequately controlled with metformin, a sulfonylurea, or insulin. The major side effect of colesevelam is constipation; thus, it should not be used in patients with gastroparesis or other gastrointestinal motility disorders, in patients after major gastrointestinal surgical procedures, and in others at risk for bowel obstruction. Other side effects include an increase in the level of serum triglycerides and possible malabsorption of fat-soluble vitamins.

Pramlintide

Pramlintide is a synthetic analogue that exhibits many of the properties of the natural beta-cell hormone, amylin. When injected preprandially, pramlintide lowers plasma glucagon, delays gastric emptying, and promotes satiety. The major effects are to decrease postprandial hyperglycemia and facilitate weight loss. Pramlintide can be used effectively in the treatment of obese patients with type 2 diabetes who use before-meal insulin injections, with or without orally administered antidiabetic agents. The recommended starting dose is 60 ug (10 U) injected immediately before the main meal; some patients tolerate the medication better with an initial starting dose of 30 ug (5 U) before meals. The dose should then be titrated gradually to 120 ug (20 U), as tolerated. The major side effect is nausea, which generally wanes with continued administration. Pramlintide decreases postprandial glycemic excursions and increases satiety. The dosage of the preprandial rapid-acting insulin may need to be reduced and the time of its administration may need to be delayed to compensate for the expected reduced food intake and delayed gastric emptying associated with pramlintide therapy. Hypoglycemia may also occur if pramlintide is used in combination with a sulfonylurea, and dosages may need to be adjusted appropriately.

Insulin

We consider nine types of insulin (Table A1). These can be administered in any of several regimens (Table A2). Exogenous insulin provides replacement for the deficiency of the natural hormone.

Physiology

Normally, insulin is delivered to the portal vein and thus reaches the liver within seconds. When insulin is administered subcutaneously, a very lengthy delay ensues before it dissociates from hexamer to monomer and is then absorbed into the circulation. Accordingly, regular human insulin administered subcutaneously does not mimic the normal kinetics and dynamics of endogenous insulin. As a result, regular human insulin does not provide adequate effect for control of postprandial glycemic excursions and has a propensity to cause delayed hypoglycemia.

Rapid-Acting Insulin Analogues

The rapidly acting insulin analogues lispro, aspart, and glulisine have a time course of action that closely mimics the normal physiologic features.

Premixed Insulins

Both insulin lispro and insulin aspart are available in mixtures with protamine. These premixed insulins provide a time course that is suitable for coverage for breakfast and lunch or for dinner and the overnight period. These mixtures or "biphasic insulins" do not result in 2 discrete peaks. Instead, there is a single maximum at approximately 1.5 hours, followed by a slow decline. Accordingly, they do not mimic the normal physiologic processes and are not as effective as a fully optimized basal-bolus regimen with use of rapidly acting insulin analogues and a long-acting

insulin analogue. Use of mixtures of regular human insulin and NPH insulin is not recommended because the maximal activity does not occur until approximately 2 to 2.5 hours after injection.

Basal Insulin

NPH insulin shows wide variability in its absorption rate from day to day, even within individuals, and does not have a sufficiently long time course to provide a basal insulinization for a 24-hour period. It has a pronounced peak at approximately 9 hours. Accordingly, the long-acting insulin analogues glargine and detemir are strongly preferred.

The various types of insulin regimens as shown m Table A2 are discussed in the main body of the text.

Drug-Drug Interactions

Thiazide diuretics, niacin, and β-adrenergic blocking agents are well known to impair glucose homeostasis (31). Systemic administration of glucocorticoids can severely impair glucose tolerance. One should be cautious when initiating therapy with these agents in patients with diabetes and should anticipate an increased risk of hypoglycemia when one of these agents is discontinued. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have demonstrated beneficial metabolic effects.

Combined use of any 2 agents that are independently capable of producing hypoglycemia is likely to increase the risk of hypoglycemia. Accordingly, it is customary to reduce the dosage of one or both agents when a second agent is added and to proceed cautiously. The most important interactions of antidiabetic agents are those among sulfonylureas, TZDs, and insulin; combined use of any 2 or all 3 of these agents may result in increased risk of weight gain, retention of fluid, and hypoglycemia.

The combination drug trimethoprim-sulfamethoxazole has been associated with a 6.6-fold increased risk of hypoglycemia (32), and case reports of extreme hypoglycemia have been reported. The "floxacin" antibiotics have been associated with a small risk of hyperglycemia and an even smaller risk of hypoglycemia (33).

There is a strong interaction of gemfibrozil with repaglinide and TZDs, resulting in considerable elevation of plasma levels of repaglinide (34) or TZDs. Fortunately, gemfibrozil is now less commonly used than in the past for management of dyslipidemia. Sulfonylureas are metabolized by CYP2C9. Thus, agents that induce or inhibit CYP2C9 can potentially affect the metabolism of sulfonylureas. Major drug-drug interactions have not been reported for nateglinide.

Metformin is eliminated by tubular secretion and glomerular filtration. Metformin may potentially compete with other cationic drugs, such as cimetidine, for renal secretion (35). In principle, rosiglitazone and pioglitazone metabolism could be affected by inhibitors or inducers of CYP2C8, but substantial drug-drug interactions have not been reported (36,37).

Acarbose and miglitol do not appear to have appreciable metabolic interactions. These drugs are associated with a small decrease in the absorption of digoxin and an increase in absorption of warfarin (38,39). Exenatide may slow absorption of some medications, such as acetaminophen and digoxin. There do not appear to be any important metabolic interactions for sitagliptin.

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