Diabetes is a significant and growing health concern in the United States with incidence and prevalence rates rising to staggering levels. Recent data indicate that more than 23 million people in the United States have diabetes.\(^1\) Approximately 40% of cases are undiagnosed.\(^2\) Type 2 diabetes mellitus (T2DM) comprises 90% to 95% of diagnosed patients.\(^1\) In addition, approximately 57 million individuals in the United States have increased risk for diabetes based on an impaired fasting glucose (100-125 mg/dL) or an impaired glucose tolerance (2-hour plasma glucose values in the oral glucose tolerance test of 140-199 mg/dL) or an elevated glycated hemoglobin level (HbA\(_1c\)) (5.7%-6.4%).\(^3\)

Evidence supports the benefits of glycemic control in reducing the risk of diabetes-related complications. However, despite the availability of multiple classes of medications and other effective therapies, many patients with T2DM fail to attain or maintain glycemic control over time, which raises their risk of disease progression with attendant loss of control and progression to potentially serious microvascular and macrovascular complications.

The present report includes a comprehensive review of T2DM with an emphasis on achieving and maintaining glycemic control. Strategies are offered to provide practical solutions to the challenges faced by healthcare providers and patients with T2DM. The importance of implementing evidence-based practice guidelines while empowering patients to participate in self-management of their disease is highlighted.

This supplement was developed mainly from a private roundtable discussion held on November 3, 2009, in conjunction with the American Osteopathic Association’s 114th Annual Osteopathic Medical Conference and Exposition in New Orleans, Louisiana. SciMed staff have planned and implemented this educational activity in accordance with the ACCME’s Essential Areas and Elements.

From Healing Our Village, Inc, in Lanham, Maryland, and Emory University School of Medicine in Atlanta, Georgia (Dr Gavin); from Northwestern University Medical School in Chicago, Illinois (Dr Stolar); from Philadelphia College of Osteopathic Medicine in Pennsylvania (Dr Freeman); and from Texas Tech University Health Sciences Center at Permian Basin in Midland-Odessa (Dr Spellman).

Dr Gavin discloses that he is a consultant for Bristol-Myers Squibb Company and a member of the speakers bureaus for Eli Lilly and Company and Novo Nordisk. Dr Stolar discloses that he is a member of the speakers bureaus for Amylin, Novo Nordisk, and Takeda Pharmaceuticals Inc. Dr Freeman discloses that he is a member of the speakers bureaus for GlaxoSmithKline, Merck & Co, Inc, and Novo Nordisk. Dr Spellman reports that he has no financial interests to disclose.

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This supplement is supported by an educational grant from Merck & Co, Inc.
How is Glycemic Control Related to T2DM Morbidity and Mortality?

Legacy Effect in Metabolic Memory

Dr Stolar: The newer concept of legacy effect in metabolic memory—and even cellular mechanisms for metabolic memory—suggests that in early diabetes, glycemic control is important.

Dr Gavin: The point of the legacy effect is to see what happens when patients with diabetes are treated as they should be, with an emphasis on diabetes as a chronic disease...you institute therapy and you do the best you can to maintain the treatment goal for as long as you can. The data suggest, when adjusted for any confounding variables, that instituting early glycemic control makes the difference.

Evidence from clinical studies indicates that poor glycemic control is associated with an increased risk for cardiovascular disease. Additionally, data suggest that glycemic control is most important in early diabetes and support the notion of a legacy effect when patients are treated aggressively early in the course of their diseases. The findings of the United Kingdom Prospective Diabetes Study (UKPDS) found that early intensive therapy aimed at aggressively lowering glucose (median HbA1c: 7.0% using sulfonylureas or insulin; 7.4% using metformin) reduced microvascular complications significantly more than conventional dietary therapy alone (median HbA1c: 7.9%). These UKPDS results confirmed the importance of glycemic control for T2DM the way the Diabetes Control and Complications Trial did for type 1 diabetes mellitus. Both trials showed that lowering HbA1c levels by 1.0% reduces microvascular complications by about 30%. Other trials, including the Steno-2 Study, have shown that early, intensive diabetes management with tight glucose regulation significantly reduces the long-term risk of microvascular events as well as cardiovascular disease and cardiovascular mortality in patients with T2DM.

The earlier glycemic control is achieved in patients with diabetes, the more benefit is potentially derived in terms of slowing the rate of complications or halting the progression of β-cell loss and deterioration of diabetic control. Additionally, because T2DM is a chronic disease, unlike previous treatment approaches that assessed glycemic control and clinical success on a visit-to-visit basis, maintaining achievement of clinical goals over the long-term is critical to optimizing patient outcomes. A 10-year follow-up of the UKPDS data revealed sustained reduction in microvascular risk as well as reduction in the 15- to 20-year risk of myocardial infarction (MI) and death from any cause after 10 years of intensive glucose control in patients with newly diagnosed T2DM (Figure 1).

Interpreting Cardiovascular Trials

Dr Spellman: The reanalysis of ACCORD really gives a better message...most likely it was not hypoglycemia [that caused the excess mortality]...the patients who started with higher HbA1c levels had greater mortality rates...both the intensive and conventional groups had hypoglycemia. In terms of safety, trying to establish the HbA1c goal carefully, slowly, and judiciously would be appropriate.

Dr Stolar: The data will ultimately show that the majority of the mortality was in nonresponders [personal communications with David Kendall]. The patients in the intensive management [group], who had the highest HbA1c levels and were not responding, and therefore were not accruing significant hypoglycemia, had the highest mortality. That makes sense because the most insulin-resistant patients are likely to have more cardiovascular events overall.

Other clinical trials involving patients with established disease demonstrated that intensive treatment interventions affect outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared more than 10,000 patients with T2DM who received either intensive glycemic control (target HbA1c <6.0%) or standard glycemic control (target HbA1c 7.0% - 7.9%). The study was halted after 3.5 years because of an increased rate of mortality in the intensive arm compared with the standard arm.
However, the primary outcome (MI, stroke, or cardiovascular death) was reduced in the intensive glycemic control group, though this finding was not statistically significant when the study was terminated. A previous population-based study in Finland compared the 7-year incidence of MI among subjects with and without diabetes and found that patients with diabetes who had not had a previous MI had as high a risk of MI as patients without diabetes who had a history of a previous MI. Interestingly, the divergence of outcomes between the groups in the Finnish study was most pronounced after 3.5 years, suggesting that the ACCORD trial may have revealed similar results had the trial been continued. Further data analysis from ACCORD revealed that two subgroups of patients—those with lower baseline HbA1c values (<8%) and those with no prior history of cardiovascular disease—had significant reductions in cardiovascular events in response to intensive glycemic control.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial involved more than 11,000 patients and demonstrated a 10% reduction in the combined outcome of microvascular events (nephropathy and retinopathy) and major adverse cardiovascular events (MI, stroke, and cardiovascular death) in patients treated with intensive glycemic control (mean HbA1c: 6.5%) compared to patients who received standard therapy (mean HbA1c: 7.3%).

The Veterans Affairs Diabetes Trial (VADT) was a large prospective randomized study designed to investigate whether intensive glycemic control would reduce the incidence of macrovascular disease events. No significant reduction in events was noted in the full cohort of patients who received intensive glucose lowering therapy for a median duration of 5.6 years, despite an average 1.5% lower median HbA1c throughout the trial. However, the Risk Factors, Atherosclerosis, and Clinical Events in Diabetes (RACED) study, a subanalysis of VADT data, revealed that patients with lower baseline levels of coronary artery calcium who were treated with intensive glucose-lowering therapies had reduced cardiovascular events compared with patients treated with standard therapy. These findings indicate that the effect of intensive glycemic control depends on the initial extent of underlying atherosclerosis and may explain why the full VADT cohort, 40% of whom had extensive atherosclerosis at baseline, did not have significant reductions in cardiovascular disease.

The suggestion that intensive glycemic control may not be effective in patients with advanced vascular disease could also explain why glucose-lowering therapy in the ACCORD and ADVANCE trials did not significantly reduce the incidence of cardiovascular disease. In those studies, the participants were older and had established diabetes, in addition to one or more cardiovascular disease risk factors, which is suggestive of advanced atherosclerosis.

There has been considerable debate regarding the level of HbA1c that represents an optimal therapeutic goal. Review of the ACCORD, ADVANCE, and VADT studies prompted the publication of a recent position statement by the American Diabetes Association (ADA), American College of Cardiology Foundation, and American Heart Association. These organizations concluded that lowering HbA1c to less than 7.0% can reduce the microvascular and neuropathic complications of T2DM. In addition, the authors noted that long-term macrovascular benefits may be achieved in newly diagnosed patients by maintaining an HbA1c less than 7.0% and incremental benefits may be achieved by further reductions in HbA1c in selected patients.

Similarly, a consensus panel on T2DM representing the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommended achieving an HbA1c less than 6.5% but recognized the need for individualization to mini-

### Table

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<th>Study</th>
<th>Nonfatal MI</th>
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* Overall HbA1c was 7.5% for standard treatment and 6.6% for intensive treatment. Event rates were calculated with the total person-years in each study group, which was estimated from the average follow-up in each study.
† Nonfatal strokes only.
‡ Coronary heart disease (CHD) includes cardiac mortality.
§ Calculated by pooling study specific rates with a random-effects model meta-analysis.

mize the risks of hypoglycemia.16 The rationale for this level was based on data from the ACCORD and VADT studies as well as a meta-analysis of five prospective randomized controlled trials that found a significant reduction in coronary events associated with an overall HbA1c of 6.6% compared with an HbA1c of 7.5%.17

Diabetes management requires control of sugars, blood pressure, and lipids; achieving optimal glycemic control without reaching therapeutic goals for the other parameters may not reduce cardiovascular risk. In addition, although an HbA1c of less than 6.5% is clinically acceptable, this level does not represent physiologic glycemia, contrary to physiologic therapeutic goals for cholesterol lowering such as an LDL (low-density lipoprotein cholesterol) of 70 mg/dL, which is physiologic in humans. We have lowered our blood pressure goals to 120/80 mm Hg as aggressive management, because it’s physiologic. An HbA1c of 6.5% is not physiologic glycemia for humans...it’s clinically acceptable on an outcome basis. So in order to truly compare the impact of cholesterol lowering, blood pressure lowering, and glycemic control as valid interventions, you would have to compare an HbA1c of 5.0%. That would be impossible and unnecessary to achieve clinically, but by accepting non-physiologic glycemia in our risk management, we diminish the overall importance of glycemic control.

The importance of tailoring therapies to achieve specific glycemic targets has become increasingly apparent in the management of patients with T2DM. HbA1c levels reflect overall glycemic exposure over the past 2 to 3 months and are determined by both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) exposure.19

The relative contributions of FPG and PPG levels vary and depend on the patient’s overall glycemic control. When HbA1c is at a near-normal level, the contribution of FPG to HbA1c is proportionally greatest. Its contribution diminishes as HbA1c rises above 8.0%, which is when the contribution of FPG predominates.20 This relationship explains the results of a study that demonstrated the contribution of fasting glucose levels to overall glycemia was approximately 70% in patients with HbA1c levels greater than 10.2% and decreased to approximately 30% when HbA1c levels were less than 7.3%. The contributions of FPG and PPG levels were approximately equal when HbA1c levels are between 7.3% and 8.4%.21

These findings support the notion of a glucose triad model of diabetes management, in which all three parameters—HbA1c, PPG, and FPG—are essential targets for intervention when attempting to optimize overall glycemic control (Figure 2). Additionally, these results indicate that in patients who fail to achieve HbA1c goals but who have near-normal FPG levels, the failure to optimize glycemic control is mostly due to a residual and persistent elevation in PPG following the three main meals of the day. Therefore, treatment strategies should initially be aimed at normalizing FPG values and then, if HbA1c remains elevated, should be focused on PPG reduction.

A critical element in the management of patients with T2DM involves monitoring glycemia. What approach should be used

### Key Elements in Diabetes Management: Glycemia, Blood Pressure, Lipids

**Dr. Spellman:** The concept of diabetes requires three things...if you haven’t addressed sugars, blood pressure, and lipids, you haven’t done your job.

**Dr. Stolar:** The reason that we say cholesterol lowering is beneficial is because we target an LDL [low-density lipoprotein cholesterol] of 70 mg/dL, which is physiologic in humans. We have lowered our blood pressure goals to 120/80 mm Hg as aggressive management, because it’s physiologic. An HbA1c of 6.5% is not physiologic glycemia for humans...it’s clinically acceptable on an outcome basis. So in order to truly compare the impact of cholesterol lowering, blood pressure lowering, and glycemic control as valid interventions, you would have to compare an HbA1c of 5.0%. That would be impossible and unnecessary to achieve clinically, but by accepting non-physiologic glycemia in our risk management, we diminish the overall importance of glycemic control.

**Dr. Gavin:** HbA1c is a gold standard right now...even more powerful than the self-monitored glucose. HbA1c is the only number that is associated with outcomes.

**Dr Freeman:** Diabetes control is a trilogy...fasting plasma glucose, postprandial glucose, and HbA1c.

**Dr. Gavin:** You’ve got three legs on a stool—if you fix the fasting glucose and the HbA1c is still bad, you have one more leg of the stool to explore...that’s when you look at postprandial glucose levels.

### Achieving Glycemic Control: What Are Some of the Challenges and Potential Solutions?

**Monitoring Glycemic Control**

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A critical element in the management of patients with T2DM involves monitoring glycemia. What approach should be used

### Self-Monitoring of Blood Glucose

**Dr Freeman:** By empowering patients to check the results of their fingersticks, it actually engages them in therapy...it involves them in what they’re doing and what their targets are.

**Dr. Gavin:** Self-monitored glucose is the snapshot, but the HbA1c is the movie.

A critical element in the management of patients with T2DM involves monitoring glycemia. What approach should be used

### Measures

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<thead>
<tr>
<th>Measures</th>
<th>ADA</th>
<th>AACE</th>
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<tr>
<td>HbA1c, %</td>
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<tr>
<td>Fasting plasma glucose, mg/dL</td>
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<td>2-hour postprandial plasma glucose, mg/dL</td>
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Figure 2. Recommendations for glycemic control from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *The glycated hemoglobin (HbA1c) goal for patients in general is less than 7.0%, while the HbA1c goal for the individual patient is as close to normal (<6.0%) as possible without significant hypoglycemia. Sources: American Diabetes Association. Diabetes Care. 2009;32(suppl 1):S13-S61; ACE/AACE Diabetes Road Map Task Force. Endocr Pract. 2007;13:260-268.
and how often patients should be monitored have been debated. Published guidelines recommend quarterly assessments of HbA1c as well as daily self-monitoring of blood glucose (SMBG) in select patients. Daily SMBG provides snapshot views of an individual’s daily glucose fluctuations, whereas the HbA1c measurement reflects overall glycemic control, which is analogous to a movie. Measuring HbA1c helps guide therapy, reinforces treatment strategies, and provides patients with information regarding the success of their efforts. Daily SMBG engages patients in the day-to-day management of their diseases. It provides immediate assessment of glycemic control, which is analogous to a movie. In addition to antihyperglycemic agents, rapid determination of HbA1c level at the time of the visit facilitates clinical decision-making.

The relationship between HbA1c levels and outcomes in patients with T2DM has been established using population-based data from clinical trials. However, experience with individual patients in clinical practice provides additional information in order to appropriately interpret the population-based data. For example, an HbA1c target for a patient aged 83 years and lean and physically fit might be different than the target for a patient aged 72 years and frail. By assessing HbA1c trends in individual patients, these measurements can serve as tools to advance therapy, can act as benchmarks to assess patient status, and may help determine the cause of worsening glycemic control.

**How Do You Make Medication Decisions?**

Advances in understanding the pathophysiology of T2DM have enabled clinicians to design therapeutic strategies based on the mechanisms of action in various pharmacotherapeutic agents (Figure 3). For example, metformin lowers plasma glucose levels by suppressing hepatic gluconeogenesis and glycogenolysis while increasing peripheral sensitivity to insulin. In addition to antihyperglycemic properties, clinical trial data have demonstrated improvements in lipoprotein profiles, reduced hypercoagulation, and increased fibrinolysis, which suggest that metformin may have other cardiovascular protective actions.

Metformin may also exert a modest protective effect on pancreatic islet cells, which is an important potential benefit in light of the progressive deterioration of β cells in T2DM. Metformin's beneficial effects are not accompanied by weight gain, which is a clear advantage over some other commonly used oral hypoglycemic agents. Metformin is inexpensive and effective and is a rational choice as a platform drug for most newly-diagnosed patients.

In choosing pharmacotherapies for patients with T2DM, the starting HbA1c value is another important consideration—the greater the baseline HbA1c, the greater the therapeutic effect. This observation should also be kept in mind when interpreting the results of clinical trials. Most oral antihyperglycemic agents can reduce HbA1c by 1.5% to 2.0% from baseline levels of 8.5% to 9.5%. Therefore, patients with baseline HbA1c levels greater than 9.0% often will not achieve the therapeutic glycemic goal of less than 7.0%, and these patients will likely require combination therapy.

In patients with very high HbA1c levels at the time of diagnosis, combination therapy should be initiated as initial therapy.

T2DM is characterized by insulin resistance as well as progressive decline in β-cell function and mass (Figure 4). Dysfunction of β cells is present early in the course of the disease and this dysfunction, rather than insulin resistance, is primarily responsible for the progression of disease. Therefore, therapeutic strategies that preserve β-cell function can slow progression of T2DM. Dysfunction of β cells is accelerated by glucose toxicity as well as lipotoxicity, two harmful processes that are interrelated in the sense that lipotoxicity does not exist without chronic hyperglycemia.

Chronic exposure to supraphysiologic glucose concentrations causes potentially irreversible β-cell damage, as well as dyslipidemia, characterized by an increase in circulating free fatty acids, further contributing to progressive β-cell failure in individuals who are genetically predisposed to developing T2DM.29 Thio-
azolidinediones (TZDs) are agonists of peroxisome proliferator-activated receptor γ (PPARγ), a nuclear receptor found in insulin-sensitive tissues, including adipose and pancreas, which regulates the transcription of genes involved in lipid and glucose metabolism. Stimulation of PPARγ increases adipocyte differentiation, thereby enhancing glucose and fatty acid uptake in adipose tissue and reducing levels of circulating free fatty acids. By improving insulin sensitivity, TZDs have the potential to reduce the workload of the pancreas and pancreas, which regulates the transcription of genes involved in lipid and glucose metabolism. Stimulation of PPARγ increases adipocyte differentiation, thereby enhancing glucose and fatty acid uptake in adipose tissue and reducing levels of circulating free fatty acids. 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**Role of Incretin-Based Therapies**

**Dr Stolar:** Incretin-based therapies should be used earlier. If their job really is improving β-cell function and slowing β-cell loss, they have to be used earlier. You can’t salvage what’s not there.

**Dr Gavin:** The data indicate that incretins might have some real surprises with respect to the pleiotropic nonglycemic effects...like cardiovascular protection.

**Dr Spellman:** DPP-4 inhibitors are the 21st century sulfonylureas without the side effects of hypoglycemia.

Incretin-based therapies are secretagogues that take advantage of a more physiologic sequence of mechanisms than older therapies. These agents act through pathways that are receptor-driven. When glucagon-like peptide-1 (GLP-1) binds to specific G-protein receptors on pancreatic β cells, adenylyl cyclase is activated, cyclic adenosine monophosphate (cAMP) is produced, and this, in turn, leads to cAMP-dependent activation of second messenger pathways, most notably cAMP-dependent protein kinase A (PKA) and guanine nucleotide exchange factors.

Protein kinase A mediates many of the phosphorylation reactions required for insulin secretion and the exchange proteins directly associated with cAMP (also known as Epac) are also involved in insulin secretion. Depolarization and deactivation of ATP-sensitive potassium (KATP) channels in pancreatic β cells are entirely responsible for the first phase of insulin secretion. Glucagon-like peptide-1 enhances insulin secretion by facilitating closure of these KATP channels through a PKA-dependent mechanism. Glucagon-like peptide-1 signaling prolongs the activation of calcium channels, which induces greater polarization of the β-cell membrane, thus increasing the number of KATP channels that are closed.

After the depletion of insulin secretory vesicles located close to the β-cell membrane, the second or plateau phase of insulin secretion results from the mobilization of a reserve pool of insulin secretory vesicles located deep in the β-cell cytoplasm; GLP-1 potentially mobilizes these vesicles. Increases in both first phase and plateau phase insulin secretory responses have been demonstrated in patients with T2DM treated with GLP-1 receptor agonists. Glucagon-like peptide-1 also increases insulin synthesis through stabilization of the insulin transcript and cAMP-dependent and -independent upregulation of the insulin gene. In addition to increasing the amount of insulin secreted per cell, GLP-1 also sensitizes more β cells to increases in ambient glucose, which further enhances glucose-induced insulin secretion.

Incretin-based therapies may exert nonglycemic pleiotropic effects, suggesting potential benefits with the use of these agents, although long-term benefits or safety have not been fully established (Figure 5). Although long-term cardiovascular event data are not yet available, other surrogate markers have been analyzed and have demonstrated beneficial effects. Modest improvements in systolic and diastolic blood pressure were noted in patients treated with exenatide for 3.5 years. Clinical trials using sitagliptin monotherapy, 14 liraglutide monotherapy, and liraglutide combination therapy (ie, with metformin and a TZD) showed statistically significant reductions in systolic blood pressure. Beneficial effects on serum lipids, including reductions in high-density lipoprotein cholesterol (HDL-C) and fasting triglyceride levels, have also been demonstrated with incretin-based therapies.

A definitive correlation between
improvements in the lipid profile and decrease in body weight has been seen with the greatest decreases in triglyceride levels and increases in HDL-C levels in those patients who lost the most weight. This finding suggests that the improvements in cardiovascular surrogate markers are related to weight, although the improvements in lipid profiles occurred even in the absence of profound weight loss. Other cardiovascular effects of incretin-based therapies include improvements in myocardial function and suggest a role for these drugs in the clinical setting as adjunctive therapy for postischemic events. In addition, studies have demonstrated that GLP-1 improve endothelial dysfunctions in patients with T2DM and coronary heart disease. Such improvements may have therapeutic implications for GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. In patients who are overweight or obese, incretins provide a therapeutic advantage. Dipeptidyl peptidase-4 inhibitors are weight neutral and can be given orally while GLP-1 agonists have been associated with weight loss and are given by injection.

Why Don’t Patients Take Their Medications and How Can We Improve Adherence?

Concerns About Weight Management

Dr Stolar: Many people are worried about weight gain.

Dr Freeman: It’s weight loss that’s the driver and patients need to have realistic expectations of weight loss.

The value of pharmacotherapy in achieving and maintaining glycemic control in patients with T2DM has been clearly established, and adherence to therapy is essential for optimal outcomes. However, adherence to medications is poor, ranging from 36% to 87% with oral agents and 54% to 81% with insulin-only regimens. Many factors challenge medication adherence in patients with T2DM, and side effects are among the most commonly reported problems.

Although many of the older hypoglycemic agents are associated with weight gain, newer incretin-based therapies are associated with weight loss or weight neutrality. It is important to educate patients about the potential side effects of medications, both beneficial and adverse, in order to optimize adherence. If patients have unrealistic expectations regarding weight loss, for example, they may discontinue therapy if their personal goals are not met. Other factors associated with medication non-adherence include regimen complexity, dosing frequency (ie, greater than twice daily), cost, lack of confidence in the medication’s benefits, lack of education about the use of the product, depression, and fear of hypoglycemia.

Although drug-induced hypoglycemia is less common in T2DM than in type 1 diabetes mellitus, it is a potentially serious complication and a growing concern as recommendations for early, aggressive therapy are aimed at strict glycemic control. Many traditional therapies, including insulin and sulfonylureas, are associated with significant risks for hypoglycemia. Incretin-based therapies enhance insulin secretion and suppress glucagon secretion in a glucose-dependent manner. Consequently, these agents improve glycemic control while maintaining a low risk of hypoglycemia.

Clinicians need to consider that the US Food and Drug Administration (FDA) standards for approval of drugs are often less stringent than those of practitioners in terms of efficacy. Clinical trials demonstrate non-inferiority and, more importantly, safety data. The safety profiles of both GLP-1 agonists and DPP-4 inhibitors have been scrutinized. Recently, submissions to the FDA have included cardiovascular data. Post-marketing cases of pancreatitis raised concerns about this potential complication of incretin-based therapies, but follow-up data have shown no increase in risk above baseline. However, clinicians should be cautious that these data represent a relatively short time frame and continued surveillance is necessary to confirm their safety in this regard.

Practice Management: Guidelines, Treatment Algorithms, and Performance Measures

Limitations of Algorithms

Dr Gavin: The default runs the risk of being too simplistic. Algorithms are basically decision trees—they have been designed to be somewhat reductionist in nature. Algorithms fundamentally focus on what and rarely focus on how...
AACE road map, however noble its intent, had some pitfalls. It was just too much. It was like drinking from an algorithmic water hose.

The size and complexity of the evidence base for diabetes management as well as the complexity of diabetes care itself represent significant challenges faced by clinicians who care for patients with T2DM. Practice guidelines, which try to address some of these challenges, have their own pragmatic issues that may limit utility.

Developers are confronted with the dilemma that comprehensive guidelines may be cumbersome and unusable while abbreviated documents that are functional may lack important information. The stepwise approach to therapy outlined in most treatment algorithms cannot include every possible clinical situation. The overall design of a decision tree with various medications does not allow clinicians’ consideration of disease mechanisms that focus on treatment objectives and may explain a lack of response to therapy. Although the supportive narrative that accompanies treatment algorithms supplies this additional information, clinicians may not have the time or ability to use these lengthy documents.

**Newer Algorithms: How They Differ**

**Dr Gavin:** The new AACE Guidelines attempt to help the clinician make the best decision for patients. The goals included simplification and ease of communication to providers…to use a method of stratification of patient risk that incorporates a measure that is available to everybody—the HbA1c—not duration of disease, not symptoms or lack of symptoms, but the entry level HbA1c, that represents the entry level of risk factors. The algorithm provides a pathway for making a treatment decision based on whether patients are candidates for monotherapy or dual therapy, what combinations would be appropriate, and what generally makes sense for patients who meet certain criteria.

**Dr Freeman:** One thing is that the new AACE guidelines are encompassing, and that’s favorable because drugs are presented within the scope of where they can be used by clinicians treating diabetes. The previous ADA/EASD [European Association for the Study of Diabetes] algorithm was somewhat exclusionary of various drugs for a variety of reasons.

**Dr Gavin:** One of the other differences between this algorithm and the ADA/EASD is the degree to which the DPP-4 inhibitors and the GLP-1 agonists really figure a lot more prominently.

A recently published AACE/ACE consensus statement on T2DM, which
includes an algorithm for glycemic control, helps clinicians to choose therapies for patients with T2DM in various clinical situations. The development of this document was based on evidence from clinical trials and was intended to replace the “road map” algorithm, which was used for several years to guide management of patients with T2DM.

The new AACE/ACE algorithm (Figure 6) has therapeutic approaches that are stratified based on the patient’s current HbA1c level, whether the patient is receiving treatment or is drug naive, and whether the patient is symptomatic or asymptomatic. The algorithm includes all classes of effective drugs in a variety of strategies—monotherapy, dual therapy, and triple therapy—and emphasizes safety as well as the quality of glycemic control. The guidelines attempt to address the disease mechanisms involved in the progression of T2DM and tailor therapies based on the action of various agents. For example, when combination therapy is prescribed, using classes of medications that have complementary mechanisms of action can optimize glycemic control. Specific clinical situations are also considered, including patients with non-alcoholic fatty liver disease where TZDs may be the preferred therapy.

The Challenges of Lifestyle Modification

Dr Gavin: Some patients will be more successful in terms of what they do and what they accomplish with lifestyle modifications. Some people really believe in it, and they’re zealots about it. Some patients become frustrated if they don’t achieve adequate results from attempts at lifestyle modifications, so we move more quickly in adding pharmacotherapies in those cases. Every drug that has ever been approved for the treatment of T2DM is predicated on being an adjunct to lifestyle modifications.

Lifestyle (diet and exercise) modifications are essential for all patients with T2DM, but the authors of the new AACE/ACE algorithm recognized that these interventions alone are usually not adequate. Therefore, the guidelines stress that pharmacotherapy should not be delayed when initiating therapy for patients with T2DM. The effectiveness of therapy must be evaluated frequently and adjustments in medication regimens made as needed to achieve an HbA1c goal of less than 6.5% for most patients. The goal should be customized for individual patients with consideration of many factors including comorbid conditions, duration of diabetes, history of hypoglycemia, awareness of hypoglycemic episodes, patient education, motivation, adherence, age, life expectancy, and concomitant medications.

Newer Algorithms: Role of Incretin-Based Therapies

Dr Stolar: Incretin deficiency is a major physiologic defect. It is a clearly documented deficiency that seems to be present in virtually all patients with T2DM, although the reason for this remains unclear. There is a valid evidence base that the incretin defect can be addressed in virtually all patients with T2DM, with varying degrees of clinical success.

Dr. Stolar: The AACE algorithm does a much better job than the ADA guideline in both achieving and maintaining glycemic control—the AADA algorithm puts agents with documented durability and preservation of β-cell function either below the “recommended” dotted line or not on it at all. Incretin-based therapies remain very valuable in their impact on β-cell function.

The AACE/ACE Consensus Statement recognized that the introduction of several new classes of medication within the past few years—especially incretin-based therapies such as GLP-1 agonists and DPP-4 inhibitors—called for a reevaluation of previously published algorithms (Figure 7).

Incretin hormone deficiency—particularly GLP-1—has been clearly documented as a defective mechanism contributing to the pathogenesis of T2DM. The AACE/ACE algorithm favors the use of incretin-based therapies—GLP-1 agonists and DPP-4 inhibitors—because of their effectiveness and overall safety profiles. Long-term data have demonstrated sustained efficacy for more than 3 years with GLP-1 agonists and for more than 2 years with DPP-4 inhibitors, which is important because metformin and sulfonylureas are less durable therapies.

The benefits of weight loss or at least weight neutrality are additional considerations favoring these medications as alternative therapies. Because these agents have a much lower risk of hypoglycemia compared with sulfonylureas and glinides, they are increasingly preferred over the older antihyperglycemic agents.

Because the progression of T2DM is related to pancreatic β-cell loss, therapies that delay or preserve β-cell function can slow this progression. Evidence from preclinical animal studies has shown that incretin-based therapies are associated with β-cell proliferation and preservation.
treated with these agents.52

...markers of...improvement in...

...addressed the accumulating data and...

...zone and pioglitazone.54 In January 2009,...

...risk of congestive heart failure/fluid...

...and expense of specific agents and com-

...such as incretins.55 The International Diabetes Federation (IDF) also published guidelines for the management of T2DM. The global context of this document presented a unique challenge because the resources of healthcare systems vary widely between countries and even between localities. The approach was based on three levels of care—standard, minimal, and comprehensive. Standard care is evidence-based and cost-effective in most nations with a well-developed service base, as well as with healthcare funding systems consuming a significant part of the national wealth. Although this level of care should be available to all patients with diabetes, the IDF recognized that variations in resources throughout the world prohibit this achievement. Minimal care is the lowest level of care that any patient with diabetes should receive and includes only low cost and/or highly cost-effective interventions. This level of care aims to provide as high a proportion of standard care as possible in areas with limited resources. Comprehensive care includes the most up-to-date and complete range of technologies available and aims to achieve the best possible outcomes. However, the evidence base supporting the use of some of these newer interventions may be weak.56

Figure 8. Treatment algorithm from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus guidelines. *Sulfonylur...
The inability to reach target glycemic goals should not be viewed as anyone’s fault but rather a result of the disease process, economics, or some other intangible issues. It is certainly possible for a patient to be totally adherent with diet and exercise and still not be able to lower their blood sugar or weight. Clinicians too often default to nonadherence rather than considering therapeutic failure. When patients achieve glycemic control, it is important for clinicians to explain the value of the medications, their mechanisms of action, and what patients can expect in the future.

In addition to patient-related barriers to achieving glycemic control, providers are faced with challenges in the implementation of practice guidelines. Time constraints in the office setting are one of the biggest barriers, particularly in the current medical system where diminishing reimbursement rates drive clinicians to see greater numbers of patients with shorter visits. The vast majority of patients truly want to get better, to have normal blood sugars, and to be healthy. If patients are not succeeding in glycemic control, it is the physician’s responsibility to determine the reason and develop strategies to improve patient outcomes.

Improving diabetes control can reduce hospitalizations, improve patient quality of life, increase employment retention and workplace productivity, and reduce healthcare costs. In addition, studies have shown that the provision of preventive care for patients with T2DM improves outcomes. The ADA guidelines include at least semiannual measurement of HbA1c levels, annual retinal examinations to screen for retinopathy, annual comprehensive foot examinations, and annual microalbuminuria testing to screen for nephropathy. Yet despite proven effectiveness, many patients do not receive these recommended services, thereby increasing their risk for diabetes-associated complications. Quality improvement studies have found that interventions targeted at healthcare professionals can improve the process of patient care and clinical outcomes. These strategies include educating patients and health professionals to improve adherence, tracking patients and sending reminders for follow-up care and missed appointments, prompting physicians to deliver recommended services, providing physicians with feedback on their performance, and involving nurses and other members of a multidisciplinary team in patient education and care.

Closing Thoughts

Dr Spellman: The physician’s job is to outline a course of action. It is the patient’s job to implement and the provider’s job to guide them. Be aggressive early on and always emphasize the cornerstones of management—sugars, blood pressure, and lipids.

Dr Freeman: Be sensitive to the patient’s needs. Be flexible. Be aggressive in achieving glycemic control, but be very cautious and careful. Consider whether a medication regimen fits the needs of the patient. Try to give incentives for the patient in some way, at least to inspire them to be part of the team in terms of taking care of diabetes in a very holistic manner.

Dr Gavin: We actually have better tools emerging than we have had before. We are seeing a transition in terms of the tools that are available to manage dia-
betes. Our challenge is going to be to make sure that, at all times, we balance efficacy, safety, and cost in ways in which we can leverage these tools to the best benefit of patients.

Dr. Stolar: The problem is that we have been doing reactive “bottom-up” management rather than treating top-down. Rather than being aggressive early in the disease, with combination therapies to normalize blood sugars and then backing off, as we do for other disease states, we do reactive management as treatment fails. Becoming aggressive only when the disease has progressed cannot work in this disease model as β-cell loss continues its inevitable progression. Earlier treatment is far more durable as you have modified the disease by addressing β-cell function earlier. It is a difficult disease to treat when forced to play catch-up, which epitomizes “bottom-up” management.

References


29. Leiter LA. β-cell preservation: a potential role for thiazolidinediones to improve clinical care in type


