AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS' COMPREHENSIVE DIABETES MANAGEMENT ALGORITHM 2013 CONSENSUS STATEMENT

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Abbreviations:
A1C = hemoglobin A1C; **AACE** = American Association of Clinical Endocrinologists; **ACCORD** = Action to Control Cardiovascular Risk in Diabetes; **ACCORD BP** = Action to Control Cardiovascular Risk in Diabetes Blood Pressure; **ACEI** = angiotensin-converting enzyme inhibitor; **ACS** = acute coronary syndrome; **AGI** = alpha-glucosidase inhibitor; **ALLHAT** = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; **apo** = apolipoprotein; **ARB** = angiotensin II receptor blocker; **ATP** = adenosine triphosphate; **BAS** = bile acid sequestrant; **BMI** = body mass index; **CAD** = coronary artery disease; **CCB** = calcium channel blocker; **CDP** = Coronary Drug Project; **CHD** = coronary heart disease; **CKD** = chronic kidney disease; **CrCl** = creatinine clearance; **CVD** = cardiovascular disease; **DASH** = Dietary Approaches to Stop Hypertension; **DHA** = docosahexaenoic acid; **DPP** = dipeptidyl-peptidase-4; **eGFR** = estimated glomerular filtration rate; **EPA** = eicosapentaenoic acid; **ER** = extended-release; **ESRD** = end-stage renal disease; **FDA** = Food and Drug Administration; **GLP-1** = glucagon-like peptide 1; **HDL-C** = high-density lipoprotein cholesterol; **IDL** = intermediate-density lipoprotein; **ILI** = intensive lifestyle; **JNC** = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; **LDL-C** = low-density lipoprotein cholesterol; **LDL-P** = low-density lipoprotein particle; **MI** = myocardial infarction; **NHLBI** = National Heart, Lung, and Blood Institute; **NMR** = nuclear magnetic resonance; **NPH** = neutral protamine Hagedorn; **OAD** = oral antidiabetic drug; **RAS** = renin-angiotensin system; **RR** = relative risk; **SAE** = serious adverse events; **SFU** = sulfonylurea; **SGLT2** = sodium-glucose cotransporter 2; **SMBG** = self-monitoring of blood glucose; **T2DM** = type 2 diabetes mellitus; **TLC** = therapeutic lifestyle changes; **TZD** = thiazolidinedione; **VLDL** = very low-density lipoprotein

EXECUTIVE SUMMARY

This new algorithm for the comprehensive management of persons with type 2 diabetes mellitus (T2DM) has been developed to provide clinicians with a practical guide that considers the whole patient, the spectrum of risks and complications for the patient, and evidence-based approaches to treatment. In addition to advocating for glycemic control so as to reduce microvascular complications, this document focuses on obesity and prediabetes as the underlying risk factors for diabetes and associated macrovascular complications. It is now clear that the progressive beta-cell defect that drives the deterioration of metabolic control over time begins early and may be present before the diagnosis of diabetes (1).

This document is organized into discrete sections that address the following topics: obesity, prediabetes, management of hyperglycemia through lifestyle modifications, pharmacotherapy and insulin, management of hypertension, management of hyperlipidemia, and other risk-reduction strategies.

Obesity

Obesity is a disease with genetic, environmental, and behavioral determinants that confers increased morbidity and mortality (2). An evidence-based approach to the treatment of obesity incorporates lifestyle, medical, and surgical options, balances risks and benefits, and emphasizes medical outcomes that address the complications of obesity rather than cosmetic goals. Weight loss should be considered in all overweight and obese patients with prediabetes or T2DM, given the known therapeutic effects of weight loss to lower glycemia, improve the lipid profile, and reduce blood pressure.

The American Association of Clinical Endocrinologists (AACE) Obesity Treatment Algorithm emphasizes a complications-centric model as opposed to a body mass index (BMI)-centric approach for the treatment of overweight or obese patients. (See Comprehensive Diabetes Management Algorithm-Complications-Centric Model for Care of the Overweight/Obese Patient). The patients who will benefit the most from medical and surgical intervention have obesity-related comorbidities that can be classified into two general categories: insulin resistance/cardiometabolic disease and mechanical consequences of excess body weight (3). Clinicians should evaluate and stage patients for each category. The presence and severity of complications, regardless of patient BMI, should guide treatment planning and evaluation (4,5). Once these factors are assessed, clinicians can set therapeutic goals and select appropriate types and intensities of treatment that will help patients achieve their weight-loss goals. Patients should be periodically reassessed to determine if targets for improvement have been reached; if not, weight loss therapy should be changed or intensified. Therapeutic lifestyle changes (TLC) can be recommended for all overweight/obese patients, and more intensive options can be prescribed for patients with comorbidities. For example, weight-loss medications can be used in combination with lifestyle modification for all patients with a BMI ≥27 kg/m^2 and comorbidities. In 2012, the U.S. Food and Drug Administration approved 2 drugs, lorcaserin and phentermine/topiramate extended-release (ER), as adjuncts to lifestyle modification in overweight/obese patients. In clinical trials, both drugs were associated with placebo-subtracted weight loss (lorcaserin, 3.6%; phentermine/topiramate ER, 9.7%) after 1 year of treatment. Both drugs improved blood pressure, triglycerides,

and insulin sensitivity, prevented progression to diabetes during the trial period, and improved glycemic control and lipids in patients with T2DM (6-11). Bariatric surgery should be considered for patients with a BMI ≥35 kg/m^2 and comorbidities, especially if therapeutic goals have not been reached using other modalities.

Prediabetes

Prediabetes reflects failing pancreatic compensation to an underlying state of insulin resistance, most commonly caused by excess body weight or obesity. Current criteria for the diagnosis of prediabetes include impaired glucose tolerance, impaired fasting glucose, or metabolic syndrome. (See Comprehensive Diabetes Management Algorithm-Prediabetes Algorithm). Any one of these factors is associated with a 5-fold increase in future T2DM risk (12).

The primary goal of prediabetes management is weight loss. Whether achieved through TLC, pharmacotherapy, surgery, or some combination thereof, weight loss reduces insulin resistance and can effectively prevent progression to diabetes as well as improve lipids and blood pressure. However, weight loss may not directly address the pathogenesis of declining beta-cell function. When indicated, bariatric surgery can also be highly effective in preventing progression to diabetes (12).

Antihyperglycemic medications such as metformin and acarbose reduce the risk of future diabetes in prediabetic patients by 25 to 30%. Both medications are relatively well-tolerated and safe, and they confer a cardiovascular risk benefit (13,14). In clinical trials, thiazolidinediones (TZDs) prevented future development of diabetes in 60 to 75% of subjects with prediabetes, but this class of drugs has been associated with a number of adverse outcomes (15,16). Glucagon-like peptide 1 (GLP-1) receptor agonists may be equally effective, but data on these drugs are inadequate, particularly regarding safety (17). Therefore, TZDs and GLP-1 receptor agonists are reserved for patients at the greatest risk of developing future diabetes and those failing more conventional therapies.

As with diabetes, prediabetes increases the risk for cardiovascular disease (CVD). Patients with prediabetes should be offered TLC and pharmacotherapy to achieve lipid and blood pressure targets that will reduce CVD risk.

Pharmacotherapy

In patients with T2DM, achieving the glucose target and hemoglobin A1C (A1C) goal requires a nuanced approach that balances age, comorbidities, and hypoglycemia risk (18). The AACE supports an A1C goal of ≤6.5% for most patients and a goal of >6.5% if the lower target cannot be achieved without adverse outcomes. (See Comprehensive Diabetes Management Algorithm-Goals for Glycemic Control). In one large clinical trial, intensive glucose-lowering therapy (A1C target of <6.0% in patients with baseline A1C >8.5%) was associated with increased mortality in older and middle-aged patients with longstanding diabetes who were at high risk for or had established CVD. In contrast, a clinical trial with a higher A1C target for intensively treated patients (1.5% lower than the standard treatment group) showed no between-group differences in CVD endpoints, cardiovascular death, or overall death (19,20). Therefore, selection of glucose-lowering agents should consider a patient's therapeutic goal, age or other factors that impose limitations on treatment, and the attributes and adverse effects of each regimen. Regardless of the treatment selected, patients must be followed regularly and closely to ensure that glycemic goals are met and maintained.

For patients with recent-onset T2DM or mild hyperglycemia (A1C <7.5%), TLC with monotherapy is recommended. (See Comprehensive Diabetes Management Algorithm-Glycemic Control Algorithm). Metformin has a low risk of hypoglycemia, can promote modest weight loss, produces durable antihyperglycemic effects, and has robust cardiovascular safety; however, it cannot be used in patients with advanced renal impairment (21-23). Metformin should be continued as background therapy and used in combination with other agents, including insulin, in patients who do not reach their glycemic target on monotherapy. Acceptable alternatives to metformin include GLP-1 agonists, dipeptidyl-peptidase-4 (DPP-4) inhibitors, and alpha-glucosidase inhibitors (AGIs). TZDs, sulfonylureas (SFUs), and glinides may also be used, but these agents should be used with caution owing to the potential for weight gain, hypoglycemia, or other risks.

Patients who present with an A1C >7.5% or who do not reach their target A1C with metformin should be started on a second agent (24). (See Comprehensive Diabetes Management Algorithm-Glycemic Control Algorithm). In metformin-intolerant patients, 2 drugs with complementary mechanisms of action from other classes should be considered.

- GLP-1 agonists have robust A1C-lowering properties, promote weight loss (25), and are available in several formulations. (See Comprehensive Diabetes Management Algorithm-Profiles of Antidiabetic Medications). The risk of hypoglycemia with GLP-1 agonists is low (26), and they reduce fluctuations in both fasting and postprandial glucose levels.
- DPP-4 inhibitors have modest A1C-lowering properties, are weight-neutral, and they are available in combination tablets with metformin. The risk of hypoglycemia with DPP-4 inhibitors is low (26-28). Most of the DPP-4 inhibitors are excreted by the kidneys except for linagliptin; therefore, dose restrictions may be advisable for some patients.
- AGIs have modest A1C-lowering effects and low risk for hypoglycemia (29). Clinical trials have

shown CVD benefit in patients with impaired glucose tolerance and diabetes (14,30). Side effects (e.g., bloating, flatulence, diarrhea) have limited their use in the United States.

- The TZD pioglitazone has relatively potent A1C-lowering properties, a low risk of hypoglycemia, possible CVD benefit (31), and durable glycemic effects (22). Side effects that have limited its use include increased bone fracture risk, elevated risk for chronic edema or heart failure, and a possible association with bladder cancer (32).
- The insulin-secretagogue SFUs have relatively potent A1C-lowering effects but lack durability and are associated with modest weight gain and hypoglycemia. SFUs have the highest risk of serious hypoglycemia of any noninsulin therapy (22,24). By comparison, the secretagogue glinides have reduced A1C-lowering effects and hypoglycemia risk (33).
- Colesevelam, which is a bile acid sequestrant (BAS), lowers glucose modestly, does not cause hypoglycemia, and decreases low-density lipoprotein cholesterol (LDL-C). Gastrointestinal intolerance limits its use, and it can increase triglyceride levels (34).
- The dopamine receptor agonist bromocriptine mesylate has slight glucose-lowering properties (35) and does not cause hypoglycemia. It can cause nausea and orthostasis and should not be used in patients taking antipsychotic drugs. Bromocriptine mesylate may be associated with reduced cardiovascular event rates (36).
- The sodium-glucose cotransporter-2 inhibitor canagliflozin has been tested as a monotherapy and in combination with metformin and other agents. In clinical trials, canagliflozin had a modest A1C-lowering effect and promoted weight loss and reduction of systolic blood pressure, but it also slightly increased LDL-C levels. This medication was only recently approved, so there is little experience (as of this writing) with its use (37).

The addition of a third agent may safely enhance treatment efficacy to a modest degree, possibly benefitting patients with A1C <8.0%. (See Comprehensive Diabetes Management Algorithm-Glycemic Control Algorithm). Patients with A1C >9.0% would derive greater benefit from the addition of insulin. Progression of therapy should be accompanied by intensified TLC and anti-obesity treatment.

Certain patient populations are at higher risk for adverse treatment-related outcomes, underscoring the need for individualized therapy. Many antihyperglycemic agents (e.g., metformin, GLP-1 agonists, DPP-4 inhibitors, AGIs, SFUs) have limitations in patients with impaired renal function and may require dose adjustments or special precautions. In general, diabetes therapy does not require modification for mild to moderate liver disease, but the risk of hypoglycemia increases in severe cases.

Insulin

Many factors come into play when deciding at what point to start insulin therapy and what type of insulin to use. (See Comprehensive Diabetes Management Algorithm-Algorithm for Adding/Intensifying Insulin). These decisions, made in collaboration with the patient, depend greatly on each patient's motivation, cardiovascular and end-organ complications, age and general well-being, risk of hypoglycemia, and overall health status. Patients with A1C >8.0%, patients on two or more oral antidiabetic drugs (OADs) or on GLP-1 therapy, and patients with long-standing T2DM are unlikely to reach their target A1C with additional OADs. In such cases, a single daily dose of basal insulin should be added to the OAD regimen. The dosage should be adjusted at regular and fairly short intervals to achieve the glucose target while avoiding hypoglycemia. Recent studies (38,39) have shown that titration is equally effective, whether it is guided by the healthcare provider or a patient who has been instructed in self-monitoring of blood glucose (SMBG).

Basal insulin analogues are preferred over neutral protamine Hagedorn (NPH) insulin because a single basal dose provides a relatively flat serum insulin concentration for up to 24 hours. Although insulin analogs and NPH have been shown equally effective in reducing A1C in clinical trials, insulin analogs caused significantly less hypoglycemia (40-44).

Premixed insulins are popular with patients, but they provide less dosing flexibility and have been associated with a higher frequency of hypoglycemic events compared to basal and basal-bolus regimens (45-47). Nevertheless, there are some patients for whom a simpler regimen is a reasonable compromise.

Patients who fail to achieve glucose control with basal or premixed insulin and those with symptomatic hyperglycemia and A1C levels >10% often achieve better glycemic control with combined basal and mealtime bolus insulin. A full basal-bolus program is most effective and provides greater flexibility for patients with variable mealtimes and meal carbohydrate content (48). A simpler approach is to cover the larger meal with a prandial injection and then add additional mealtime injections later, if needed. Several randomized controlled trials have shown that the stepwise addition of prandial insulin to basal insulin is safe and effective in achieving target A1C with a low rate of hypoglycemia (38,39,48).

It is important to avoid hypoglycemia. Approximately 7 to 15% of insulin-treated patients experience at least one annual episode of hypoglycemia (49), and 1 to 2% have severe hypoglycemia (50,51). Several large randomized

trials found that T2DM patients with a history of one or more severe hypoglycemic events have an approximately 2- to 4-fold higher death rate (52,53). It has been proposed that hypoglycemia may be a marker for persons at higher risk of death, rather than the proximate cause of death (51). Patients receiving insulin also gain about 1 to 3 kg more weight than those receiving other agents.

Pramlintide is indicated for use with basal-bolus insulin regimens; the incretin therapies have been studied with basal insulin. Pioglitazone is indicated for use with insulin at doses of 15 and 30 mg, but this approach may aggravate weight gain. There are no specific approvals for the use of SFUs with insulin, but when they are used together the risks of both weight gain and hypoglycemia increase (54,55). Incretins also increase endogenous insulin secretion, decrease basal and postprandial glucose and, when added to basal insulin therapy, may minimize weight gain and hypoglycemia associated with basal-bolus insulin (8,56-60).

Blood Pressure

Elevated blood pressure in patients with T2DM is associated with an increased risk of cardiovascular events. (See Comprehensive Diabetes Management Algorithm-CVD Risk Factor Modifications Algorithm). AACE recommend a blood pressure target of approximately 130/80 mm Hg based on results of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial (61). The ACCORD BP trial demonstrated no significant differences in primary cardiovascular outcomes or all-cause mortality between standard therapy (which achieved a mean blood pressure of 133/71 mm Hg) and intensive therapy (mean blood pressure of 119/64 mm Hg). Intensive therapy did produce a comparatively significant reduction in stroke and microalbuminuria, but these reductions came at the cost of requiring more antihypertensive medications and produced a significantly higher number of serious adverse events (SAEs) (61). A meta-analysis of antihypertensive therapy in patients with T2DM or impaired fasting glucose demonstrated similar findings. Systolic blood pressure ≤135 mm Hg was associated with decreased nephropathy and a significant reduction in all-cause mortality compared with systolic blood pressure ≤140 mm Hg. Below 130 mm Hg, stroke and nephropathy, but not cardiac events, declined further, but SAEs increased by 40% (62). Given these findings, the mean blood pressure achieved by standard therapy in the ACCORD BP trial (approximately 130/80 mm Hg) appears to be a prudent goal for most patients; those at high risk for stroke may benefit from a lower target, however (62-64).

Therapeutic lifestyle modification can help T2DM patients reach their blood pressure goal:

- Weight loss can improve blood pressure in patients with T2DM. Compared with standard intervention, the results of the Action for HEAlth in Diabetes (Look AHEAD) trial found that significant weight loss is associated with significant reduction in blood pressure, without the need for increased use of antihypertensive medications (65).
- Sodium restriction is recommended for all patients with hypertension. Clinical trials indicate that potassium chloride supplementation is associated with blood pressure reduction in people without diabetes (66). The Dietary Approaches to Stop Hypertension (DASH) diet, which is low in sodium and high in dietary potassium, can be recommended for all patients with T2DM (67-72).
- Numerous studies have shown that moderate alcohol intake is associated with a lower incidence of heart disease and cardiovascular mortality (73,74).
- The effect of exercise in lowering blood pressure in people without diabetes has been well-established. In hypertensive patients with T2DM however, exercise appears to have a more modest effect (75,76); still, it is reasonable to recommend a regimen of moderately intense physical activity in this population.

Most patients with T2DM and hypertension will require medications to achieve their blood pressure goal. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers (CCBs), and diuretics are favored choices for first-line treatment. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (77) recommends starting with a thiazide diuretic, based on the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ALLHAT found no differences between chlorthalidone and amlodipine or lisinopril with respect to coronary heart disease (CHD) mortality, nonfatal myocardial infarction (MI), all-cause mortality, or end-stage renal disease, but chlorthalidone was superior in preventing heart failure (78). However, many other trials support the recommendation that ACEIs/ARBs be considered as first-line treatment (79-82).

Selection of an antihypertensive regimen for patients with T2DM must also consider special circumstances. Patients with heart failure could benefit from beta blockers, those with proteinuria from ACEIs or ARBs, those with prostatism from alpha blockers, and those with coronary artery disease (CAD) from beta blockers or CCBs. In patients with blood pressure >150/100 mm Hg, 2 agents should be given initially because it is unlikely any single agent would be sufficient to achieve the blood pressure target. An ARB/ACEI combination more than doubles the risk of renal failure and hyperkalemia and is therefore not recommended.

Table 1
AACE Lipid Targets for Patients With Type 2 Diabetes

	Moderate-Risk Patients	High-Risk Patients
LDL-C (mg/dL)	<100	<70
Non–HDL-C (mg/dL)	<130	<100
Triglycerides (mg/dL)	<150	<150
TC/HDL-C	<3.5	<3.0
Apo B (mg/dL)	<90	<80
LDL-P (nmol/L)	<1,200	<1,000

Abbreviations: AACE = American Association of Clinical Endocrinologists; Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; TC = total cholesterol.

Lipids

Compared to nondiabetics, patients with T2DM have a significantly increased risk of CVD (83). To reduce the significant risk of CHD in T2DM patients, early, intensive management of dyslipidemia is warranted. (See Comprehensive Diabetes Management Algorithm-CVD Risk Factor Modifications Algorithm).

The classic major risk factors that modify the LDL-C goal for all individuals include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medications), high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, family history of CHD, and age ≥45 years for men or ≥55 years for women (84). Recognizing that T2DM carries a high lifetime risk for developing CHD, risk should be stratified as "moderate" (patients <40 years of age; no major risk factors) or "high" (one or more major risk factors). A potential third category of "very high" risk (patients with T2DM and established CVD) could also be considered. Risk stratification in this manner can guide management strategies.

In addition to hyperglycemia, the majority of T2DM patients have a syndrome of "insulin resistance," which is characterized by a number of CVD risk factors, including hypertension, hypertriglyceridemia, low HDL-C, elevated apolipoprotein (apo) B and small, dense LDL, and a procoagulant and proinflammatory milieu. All of these additional factors justify classifying these patients as being at high risk (85,86). The lipid targets recommended by the AACE for patients with T2DM are shown in Table 1.

Many patients with T2DM can achieve lipid profile improvements using TLC (smoking cessation, physical activity, weight management, and healthy eating) (84). However, most patients will require pharmacotherapy to reach their target lipid levels and reduce their cardiovascular risk.

Numerous studies have demonstrated that statins significantly reduce the risk of cardiovascular events and death in patients with T2DM, making these drugs the first-line therapy (87,88). However, considerable residual risk persists even after aggressive statin monotherapy, especially in patients with clinical atherosclerotic disease or CVD risk factors (88-90). Intensification of statin therapy (e.g., through use of higher dose or higher potency agents) can further reduce LDL-C and the risk of cardiovascular events (91), although residual risk will remain (92). Data from several studies have shown that even when LDL-C reaches an optimal level (20th percentile), non–HDL-C, apo B, and low-density lipoprotein particle (LDL-P) number can remain suboptimal (93). Furthermore, side effects (e.g., myositis/myopathy) can limit the use of intensive statin therapy in some patients (94).

- Other lipid-modifying agents must often be utilized in combination with statins when therapeutic levels of LDL-C, non–HDL-C, apo B, or LDL-P have not been reached. Drugs such as ezetimibe, BASs, fibrates, niacin, and fish oil-derived prescription-grade omega-3 fatty acids have lower efficacy for lipid modification and CVD risk reduction compared with statins, but they may have potential additive effects.
- Ezetimibe decreases hepatic cholesterol stores, upregulates LDL receptors, and lowers apo B, non–HDL-C, LDL-C, and triglycerides (95).
- The BAS colesevelam reduces LDL-C and LDL-P and improves glycemic status, but it can increase triglycerides when statins are not utilized (95-98).
- Fibrates are best known for lowering triglycerides, but they also have been shown to have inconsistent primary outcome cardiovascular benefits that may be explained by differences in the targeted

trial populations (99-102). The use of fibrates together with statins in the ACCORD study (103) showed no benefit.

- Niacin lowers apo B, LDL-C, and triglycerides, and raises HDL-C. Niacin is the most powerful lipid-modifying agent available for raising HDL-C (104), but it may reduce cardiovascular events through a mechanism other than an increase in HDL-C (105). Although niacin may increase blood glucose, its beneficial effects appear to be greatest among patients with the highest baseline glucose levels and those with metabolic syndrome (106).
- Dietary intake of fish and omega-3 fish oil is associated with reductions in the risks of total mortality, sudden death, and CAD through various mechanisms of action other than lowering of LDL-C. In a large clinical trial, highly purified eicosapentaenoic acid (EPA) added to a statin regimen was associated with a 22% reduction in the risk of CHD in patients with impaired fasting glucose or T2DM (107-109).

PRINCIPLES OF THE AACE ALGORITHM FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

1. Lifestyle optimization is essential for all patients with diabetes. Lifestyle optimization is multifaceted, ongoing, and should engage the entire diabetes team. However, such efforts should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it.
2. The hemoglobin A1C (A1C) target should be individualized based on numerous factors, such as age, comorbid conditions, duration of diabetes, risk of hypoglycemia, patient motivation, adherence, and life expectancy. An A1C level of ≤6.5% is still considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
3. Glycemic control targets include fasting and postprandial glucose as determined by self-monitoring of blood glucose (SMBG).
4. The choice of diabetes therapies must be individualized based on attributes specific to patients and the medications themselves. Medication attributes that affect their choice include: risk of inducing hypoglycemia, risk of weight gain, ease of use, cost, and safety impact for heart, kidney, or liver disease. This algorithm includes every U.S. Food and Drug Administration (FDA)-approved class of medications for diabetes. This algorithm also stratifies choice of therapies based on initial A1C level.
5. Minimizing risk of hypoglycemia is a priority. It is a matter of safety, adherence, and cost.
6. Minimizing risk of weight gain is also a priority. It too is a matter of safety, adherence, and cost.
7. The algorithm provides guidance as to what therapies to initiate and add, but respects individual circumstances that could lead to different choices.
8. For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination.
9. Therapeutic effectiveness must be evaluated frequently until stable (e.g., every 3 months) using multiple criteria, including A1C, SMBG records (fasting and postprandial), documented and suspected hypoglycemia events, adverse events (weight gain, fluid retention, and hepatic, renal, or cardiac disease), comorbidities, other relevant laboratory data, concomitant drug administration, diabetic complications, and psychosocial factors affecting patient care.
10. Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain.
11. Rapid-acting insulin analogs are superior to regular insulin because they are more predictable.
12. Long-acting insulin analogs are superior to neutral protamine Hagedorn (NPH) insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk.
13. This algorithm conforms, as nearly as possible, to a consensus for the current standard of practice of care by expert endocrinologists who specialize in the management of patients with type 2 diabetes mellitus (T2DM) and have the broadest experience in outpatient clinical practice.
14. This algorithm is as specific as possible and provides guidance to physicians, with prioritization and a rationale for the selection of any particular regimen.
15. This algorithm has been made as simple as possible in order to gain physician acceptance and to improve its utility and usability in clinical practice.
16. This algorithm should serve to help educate clinicians as well as guide therapy at the point of care.

THERAPY OPTIONS

Obesity is a disease with genetic, environmental, and behavioral determinants that confer increased morbidity and mortality risk in patients with T2DM (2). Recent therapies for obesity included lifestyle modification, several pharmacologic options with modest efficacy, and bariatric surgery (reserved for more intractable cases) (3,110). Weight-loss medications included the intestinal lipase inhibitor orlistat and several sympathomimetic drugs, such as phentermine, that are approved for short-term treatment (i.e., <3 months). In the summer of 2012, the U.S. FDA approved 2 medications, lorcaserin and phentermine/topiramate ER, for use as adjuncts to a lifestyle modification program for the treatment of overweight patients (body mass index [BMI] ≥27 kg/m^2 but <30 kg/m^2) with comorbidities such as T2DM, hypertension, and dyslipidemia, and for obese patients (BMI ≥30 kg/m^2) regardless of whether comorbidities are present (111,112).

In a key phase 3 clinical trial, patients on lorcaserin (a selective 5-hydroxytryptamine [serotonin]-2C receptor agonist) experienced an average 5.8% weight loss after 1 year, compared with an average 2.2% weight loss in the placebo group (3.6% placebo-subtracted), with some weight regain in lorcaserin-treated patients in the second year of the study (11). In the EQUIP study, phentermine/topiramate ER, a combination of drugs that enhance sympathomimetic and gamma-aminobutyrate activity, respectively, produced a 10.9% weight loss at 1 year, compared with 1.2% weight loss in the placebo group (9.7% placebo-subtracted) (6). Both drugs improved cardiometabolic disease manifestations such as blood pressure, triglycerides, and insulin sensitivity, prevented progression to diabetes over the course of the study, and improved glycemic control, blood pressure, and lipids when used in patients with T2DM (6-11).

The availability of effective pharmacotherapy has enhanced the ability of clinicians to treat obesity according to an evidence-based medical model that incorporates lifestyle, medical, and surgical options, as illustrated in the *AACE Obesity Treatment Algorithm*. Any intervention entails risk, and treatment must be targeted to patients who will derive the greatest benefit based on benefit-risk considerations. In patients receiving medications or surgical interventions, medical rather than cosmetic outcomes should be emphasized. While an average weight loss of approximately 10% will not suffice cosmetically, or even bring many patients below the BMI obesity threshold (i.e., <30 kg/m^2), it is sufficient to impart substantial benefits with respect to obesity complications (3,110). Furthermore, considering safety and cost issues and that almost 70% of adults in the U.S. are overweight or obese (113), it is neither desirable nor feasible to treat all overweight and obese patients with medical or surgical therapy.

TREATMENT BASED ON COMPLICATIONS

The AACE Obesity Treatment Algorithm emphasizes a complications-centric model for the treatment of the overweight or obese patient, as opposed to a BMI-centric approach (113). Patients who will benefit the most from medical and surgical intervention have obesity-related comorbidities that can be classified into two general categories: those that relate to insulin resistance and cardiometabolic disease and those that relate to the mechanical consequences of excess body weight (3). Therefore, step 1 in the algorithm is to evaluate and stage the patient for cardiometabolic and mechanical complications and the severity or impact of these complications. The clinician should evaluate the patient for cardiometabolic disease (e.g., waist circumference, fasting and 2-hour oral glucose tolerance test, lipids, blood pressure, nonalcoholic steatohepatitis, polycystic ovary syndrome, and certain cancers) and mechanical complications (e.g., obstructive sleep apnea, problematic degenerative joint disease, stress incontinence, or chronic pulmonary diseases such as asthma). This will certainly include the identification of metabolic syndrome and prediabetes, since doing so effectively identifies individuals at high risk of future T2DM and cardiovascular disease (CVD), albeit with high specificity and low sensitivity for predicting future T2DM (114,115).

It is important to note, however, that not all patients who are overweight or obese have cardiometabolic disease or mechanical complications. The observation that up to 30% of obese individuals may be insulin sensitive without cardiometabolic disease and may not progress to T2DM or CVD gave rise to the term "healthy obese" to characterize these patients (115,116). For this reason, it will be the presence or absence of complications—regardless of patient BMI—that will predominate in formulation of the treatment plan.

Step 2 for the medical treatment of obesity involves: (*1*) setting therapeutic targets for improvements in cardiometabolic and/or mechanical complications to be achieved via weight loss, (*2*) selecting the treatment modality, and (*3*) setting the appropriate treatment intensity to achieve targets for the improvement of complications. It is important to consider that all three treatment approaches for obesity (lifestyle modification, pharmacotherapy, and bariatric surgery) are characterized by a wide range of intensities that can be employed to achieve a greater or lesser degree of weight loss.

Many cardiometabolic disease complications exist to a large degree independent of baseline BMI. From this perspective, baseline BMI is less important than the existence and severity of presenting complications and the degree of improvement in these complications obtained with weight loss (4,5). Lifestyle modification can be recommended for all overweight and obese patients, and more intensified

treatment options involving lifestyle, medical, and surgical options can be prescribed for patients with comorbidities. Weight-loss medications can be considered as an adjunct to lifestyle modification for all patients with a BMI ≥27 kg/m^2 who have comorbidities, and bariatric surgery can be considered for patients with a BMI ≥35 kg/m^2 and comorbidities (especially if therapeutic goals are not achieved in these patients via lifestyle modification and weight-loss medications).

Step 3 is initiated once equilibrium weight loss is achieved with the initial treatment plan and involves reassessing the patient for the impact of weight loss on complications. If the targets for improvement in complications are not reached, then the weight-loss therapy should be intensified, for example, by proceeding to a more highly structured, intensive lifestyle therapy program or increasing daily medication dose(s). Thus, the AACE medical model employs weight loss as a tool to treat cardiometabolic disease and the mechanical complications of obesity.

MANAGEMENT AND PREVENTION OF DIABETES

The Obesity Treatment Algorithm should be incorporated into the algorithms for the treatment of prediabetes and metabolic syndrome as well as diabetes. An important benefit of weight loss, whether achieved by lifestyle changes, medications, or surgery, is diabetes prevention, and this has profound implications regarding the burden of individual patient suffering, public health, and healthcare cost containment (114,117,118). The complications-centric approach will identify patients at highest risk of future T2DM who will derive the greatest benefits from more aggressive therapy. Furthermore, weight loss should be considered in all overweight and obese patients with T2DM, given the known therapeutic effects of weight loss in lowering glycemia, improving lipid profiles, and reducing blood pressure. Therefore, the AACE Obesity Treatment Algorithm is incorporated into the diabetes treatment algorithm as a critical component of lifestyle intervention, which constitutes the cornerstone of diabetes management. Thus, weight loss, including medication-assisted weight loss, should be considered in all overweight and obese diabetes patients, including patients with new-onset disease, or in combination with other glucose-lowering medications, regardless of baseline A1C. In this way, both lifestyle modification-produced weight loss and weight-loss medications are integral components of the T2DM management strategy.

AACE 2013 PREDIABETES ALGORITHM

Prediabetes is recognized as an abnormal metabolic state sufficient to predict an excess risk of future diabetes. Under the current criteria, a prediabetes diagnosis is made when any of the following conditions exists: (*1*) impaired glucose tolerance (2-hour postglucose challenge of 140 to 200 mg/dL), (*2*) impaired fasting glucose (fasting plasma glucose of 99 to 126 mg/dL), or (*3*) the "insulin resistance" syndrome or metabolic syndrome (12). Any one of these diagnoses is associated with a 3- to 10-fold increase in the future risk of T2DM. However, the combination of two or more of these diagnostic criteria is associated with up to a 20-fold increase in future diabetes risk (12).

Prediabetes reflects failing pancreatic beta-cell compensation, which results from an underlying state of insulin resistance. The most common cause of insulin resistance is being either overweight or obese (84). The beta-cell inadequacy characteristic of prediabetes may be caused by genetic predisposition. Other causes may include the adverse metabolic environment resulting from excessive blood sugar concentrations (glucotoxicity) and perhaps excessive lipids (lipotoxicity).

Management of Prediabetes

Management of prediabetes should focus first on weight reduction. The reduction of insulin resistance that typically accompanies weight loss is most important; reducing food intake is also beneficial (12,84). Weight loss may be achieved in several ways in addition to lifestyle modification. Bariatric surgery has good-to-excellent short-to-intermediate–term benefits for the prevention of T2DM. Weight-loss medications also ameliorate prediabetes in the short term. Large cohort clinical trials have shown that the greater the weight loss, the greater the reduction in prediabetes, especially in studies using bariatric surgery (12).

Management of obesity in prediabetes differs little from management in patients without diabetes, except that there is much greater urgency in the case of patients with diabetes. Reducing the burden on pancreatic beta-cell function through weight loss appears to be one method of addressing the inherent beta-cell loss in diabetes.

Treatment of prediabetes patients with antihyperglycemic medications reduces dysglycemia and may prevent or delay the appearance of diabetes. It is unclear whether subsequent treatment for prediabetes patients failing an initial lifestyle modification program should focus on aggressive weight reduction with pharmacological assistance and/or bariatric surgery, antihyperglycemic medications, or some combination of strategies. Weight loss, whether surgically or medically assisted, clearly addresses the insulin resistance that burdens pancreatic insulin secretion in prediabetes. Weight loss does not, however, deal directly with the pathogenesis of declining beta-cell function that underpins the evolution of dysglycemia into frank diabetes (12). Therefore, as body mass declines, the residual insulin secretory function becomes sufficient to maintain euglycemia, and diabetes or prediabetes seem to disappear. However, as time goes by, the ongoing, progressive loss of beta-cell function may continue; beta-cell function may

reach such a low level as to become insufficient for the new reduced body weight, resulting in the reemergence of dysglycemia. As surgery produces greater weight loss than most available medications, it may be more efficacious than medication at reversing diabetes or preventing the disease. However, this efficacy comes at the price of increased morbidity and mortality from the surgical procedure.

Antihyperglycemic Medications

Medications such as metformin and acarbose reduce future diabetes incidence in patients with prediabetes by 25 to 30% (12,14,119). Both drugs are relatively well-tolerated, with a good record of safety. Both medications have indications of cardiovascular risk benefit, although the precise mechanism is unclear. Other medications are effective at delaying or preventing diabetes in patients with prediabetes, including thiazolidinediones (TZDs), which have been shown to prevent 60 to 75% of future diabetes in patients with prediabetes (15,16,84). Unfortunately, TZDs are also associated with increased risks of bone fracture and fluid retention and may worsen underlying heart failure (12). Glucagon-like peptide 1 (GLP-1) receptor agonists may be equally effective, but there are less data regarding both the safety and efficacy of GLP-1 receptor agonists compared with TZDs (17). For these reasons, either class should be reserved for failures of treatment, progressive worsening of dysglycemia despite the use of other therapies or options, or for those patients at greatest risk of future diabetes (12).

CVD Risk

Because prediabetes confers the same 2- to 3-fold excess risk of CVD as in patients with overt diabetes (84,120), the AACE recommends that the management of CVD risk factors be as vigorous in patients with prediabetes as is now the case in patients with overt diabetes. This recommendation applies specifically to lipid targets (especially atherogenic lipoprotein markers, low-density lipoprotein cholesterol [LDL-C], non–high-density lipoprotein cholesterol [HDL]-C, and apolipoprotein [apo] B or low-density lipoprotein particle [LDL-P]) and blood pressure targets (84). Consult the "Dyslipidemia" and "Blood Pressure" sections of the algorithm for details.

If or when prediabetes progresses to overt diabetes, management should focus on attainment of the glycemic goal using oral antihyperglycemic agents. Glycemic management is outlined in detail in the "AACE 2013 Algorithm for Glycemic Control in Patients with Type 2 Diabetes Mellitus."

AACE 2013 PHARMACOTHERAPY ALGORITHM

INTRODUCTION

This algorithm for the comprehensive management of persons with T2DM has been developed to provide clinicians with a practical guide that considers the whole patient, the spectrum of risks and complications for patients, and that incorporates evidence-based approaches to treatment. In addition to advocating reduction of the risk of microvascular disease through glycemic control, the algorithm includes a focus on macrovascular disease and addresses the underlying problems of obesity and prediabetes. A comprehensive care plan for persons with diabetes must consider obesity management as an integral part of overall treatment in order to effectively reduce morbidity and mortality and prevent disability in patients with T2DM, the majority of whom are obese. Management of diabetes and related comorbidities should begin in the prediabetic phase of the disease, because it is now clear that the progressive beta-cell defect that drives the deterioration of metabolic control over time begins early and may be present before diabetes diagnosis (1).

The rise in obesity across all age groups and ethnicities in the U.S. has increased the number of people at risk for diabetes and the incidence and prevalence of T2DM (2). A comprehensive approach that addresses both reducing the development of T2DM and the management of glycemic parameters (including overall hyperglycemia as measured by A1C, fasting glucose, postprandial glucose, and treatment-associated hypoglycemia, in addition to CVD risk reduction) should consider obesity management as part of the treatment paradigm. Individualization is a key component in the development of a comprehensive care plan, as T2DM now affects individuals of all ages, with both diabetes-related and non-diabetes-related comorbidities. The current algorithm incorporates evidence-based medicine to improve the outcomes of persons with T2DM.

ANTIHYPERGLYCEMIC PHARMACOTHERAPY

The goals of lifestyle modification and antihyperglycemic pharmacotherapy for persons with T2DM are: (*1*) to achieve clinical and biochemical glucose targets, (*2*) to avoid hypoglycemia, (*3*) to avoid weight gain in persons who are obese and to assist with weight loss, and (*4*) to reduce or avoid increasing CVD risk. Determining the precise glucose target and A1C goal for each patient requires a nuanced approach that balances patient age, comorbidities, and the ease of achieving a glucose level that is as close to normal as possible while avoiding hypoglycemia (18). The AACE continues to support an A1C goal of <6.5% in the majority of patients with T2DM, recognizing that this target may be too aggressive for some patients and should be modified to >6.5% if the lower target cannot be achieved without hypoglycemia or other adverse outcomes (121). A lower target should be the goal of treatment in younger patients and those in whom a lower target can be achieved in order to avoid later complications (122). Lifestyle modification, including instruction in medical nutrition therapy, plays a role at every stage of diabetes management (123). All patients should be instructed in SMBG. Frequent

monitoring is crucial for patients who are at risk for hypoglycemia and those who use SMBG results to adjust therapy (124).

The selection of glucose-lowering agents for the treatment of individuals with diabetes should consider the goals of therapy for each patient, the limitations imposed by age or other factors, and the specific attributes, side effects, and potential adverse effects of each antidiabetes drug. Because many patients will require a combination of agents, the benefits and risks of drug combinations should also be considered when designing or modifying treatment regimens. The role of anti-obesity therapies and the implications of adding insulin to antidiabetes therapies will be discussed in other sections. A schematic of recommended antidiabetes therapies that consider the goals listed above and the relative safety and efficacy of each class of agents is presented in the "Glycemic Control Algorithm" of the "AACE 2013 Comprehensive Diabetes Management Algorithm." A major tenet in the treatment of diabetes is close follow-up, with changes or additions to a patient's therapy at intervals no greater than every 3 months until the patient has reached his or her glycemic goal.

Monotherapy

For patients with recent-onset T2DM and those with mild hyperglycemia (defined as an A1C <7.5%), initial monotherapy is generally satisfactory. The majority of these patients will achieve their glycemic goal with lifestyle modification and metformin (generally at doses of 1,500 to 2,000 mg/day). Metformin is recommended as either initial or monotherapy because of its low risk of hypoglycemia, the likelihood of modest weight loss, the reasonable durability of its antihyperglycemic effects, and its long-term general and cardiovascular safety record (21-23). Metformin's mechanism of action is activation of intracellular adenosine monophosphate-kinase, which reduces hepatic glucose output and secondarily may improve beta-cell function and insulin resistance (125). Due to its short half-life, metformin should be taken 2 to 3 times per day in divided doses unless an ER preparation is utilized. The major side effects of metformin are nausea and diarrhea, which are dose-related and can be sufficiently severe to preclude its use in 10 to 15% of patients. In some metformin-intolerant patients, a lower dose, slow dose titration, use of a long-acting formulation, or some combination of thereof may improve tolerance (21). The ER formulations reduce gastrointestinal (GI) side effects to tolerable levels in some, but not all, metformin-intolerant patients. Metformin lowers A1C by 1 to 1.5% at maximum or near-maximum doses (dose range, 500 to 2,550 mg/day), which compares favorably to other antidiabetes therapies (21). Hypoglycemia is uncommon to rare in patients on metformin monotherapy, even when A1C is normalized. Metformin should be continued as background therapy and used in combination with other agents, including insulin, in patients who do not reach their glycemic target on monotherapy.

Due to the risk of lactic acidosis, metformin use is contraindicated in patients with impaired renal function, generally defined as a creatinine level >1.5 mg/dL in males and >1.4 mg/dL in females or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. This limitation has been challenged, however, and lower doses have been proposed for patients with moderate renal insufficiency (126). The AACE agrees with the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease recommendations, which state that metformin should be continued in patients with an eGFR ≥45 mL/min/1.73 m^2 (GFR categories G1-G3a), that its use should be reviewed in those with an eGFR of 30 to 44 mL/min/1.73 m^2 (GFR category G3b), and that it should be discontinued in patients with an eGFR <30 mL/min/1.73 m^2 (GFR categories G4-G5) (127).

Metformin should be prescribed with caution in patients with alcoholism or extremes of age, where existing creatinine cutoffs may not be applicable. Vitamin B12 deficiency has been described with metformin, and the risk of clinically significant vitamin B12 deficiency is higher in patients taking metformin than those on other therapies. In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives, such as GLP-1 receptor agonists, dipeptidyl-peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors (AGIs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors provide glucose lowering with varying degrees of potency but without weight gain or hypoglycemia risk. TZDs and the insulin secretagogue sulfonylurea (SFU) drugs and glinides may also be used, but they should be used with caution owing to their propensity for weight gain (all) and hypoglycemia (SFUs and glinides).

Combination Therapy

Patients who present with an A1C >7.5% or who do not reach their target A1C with metformin should be started on a second agent to be used in combination with metformin (24). In metformin-intolerant patients, 2 drugs from other classes with complimentary mechanisms of action should be used. There are many oral combination tablets or capsules containing metformin plus a DPP-4 inhibitor, the TZD pioglitazone, or an SFU. Some employ a longer-acting metformin formulation, which may be useful for patients with tolerance problems or who prefer once-daily dosing. Compared with 2 agents prescribed separately, combination tablets also reduce pill burden, which is associated with better persistence and adherence in patients with chronic conditions (128).

GLP-1 Receptor Agonists

GLP-1 receptor agonists are peptides with significant homology to the native incretin hormone, GLP-1. GLP-1 receptor agonists stimulate insulin secretion from the beta-cells of the pancreas through a G-protein receptor-mediated process that is regulated by the intracellular glucose level (i.e., it is glucose-dependent). GLP-1 receptor agonists also reduce glucagon secretion from the alpha-cells and slow gastric emptying (129). These combined mechanisms contribute to a robust A1C lowering of 0.8 to 2.0% and to weight loss that ranges from 1 to 4 kg across studies (25). Short-acting exenatide is available in two fixed-dose formulations (5 μg and 10 μg), while long-acting exenatide is injected once weekly at a fixed dose of 2 mg. Liraglutide, with a half-life of 8 to 14 hours, is administered once-daily in doses ranging from 0.6 to 1.8 mg and can be titrated to tolerance to achieve the desired glucose-lowering effect. The risk of hypoglycemia is low when a GLP-1 receptor agonist is used as monotherapy, with metformin, or with other low-risk medications but increases when used with SFUs (26). GLP-1 receptor agonists reduce both fasting glucose and postprandial glucose excursions, which may be beneficial if they are used in combination with oral agents that target insulin resistance or with basal insulin (130). Side effects of GLP-1 receptor agonists include nausea and vomiting, and a feeling that is sometimes described as a sense of fullness. In general, the side effects are more pronounced with the shorter-acting GLP-1 receptor agonists and may be managed by dose titration. Safety signals were observed for C-cell hyperplasia and malignancy in rodents (liraglutide) and pancreatitis (all) in registries and postmarketing reports, but confirmatory population studies are lacking (131). Clinical trials report lower blood pressure, slight tachycardia, modest lipid reductions, and no signal for adverse CVD outcomes with GLP-1 receptor agonists. CVD outcome trials are underway at the time of this writing. Although the GLP-1 receptor agonists are injectable and require more instruction than oral antidiabetic drugs (OADs), the combination of robust efficacy and weight loss, along with low hypoglycemia risk, makes them preferred agents after metformin for patients that would benefit from weight loss.

DPP-4 Inhibitors

DPP-4 inhibitors increase endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) by inhibiting the enzyme that breaks down the incretin hormones (130). The elevated level of GLP-1 increases insulin secretion in a glucose-dependent manner from beta-cells and reduces glucagon secretion from alpha-cells in the pancreas (132,133). The contribution of GIP to the overall efficacy of DPP-4 inhibitors is unclear. Four DPP-4 inhibitors are approved for use in the U.S., including sitagliptin (available daily doses, 25, 50, and 100 mg), saxagliptin (2.5 and 5 mg), linagliptin (5 mg), and alogliptin (6.25, 12.5, and 25 mg). Vildagliptin (50 and 100 mg) is approved for use in Europe and Asia. Most of the DPP-4 inhibitors are available in combination tablets with short-acting metformin, with the exception of saxagliptin-metformin and ER sitagliptin-metformin, which utilize longer-acting metformin formulations and can be dosed once daily. The DPP-4 inhibitors have modest glucose-lowering effects, with A1C decrements of 0.5 to 0.9%, are weight-neutral, and have a low hypoglycemia risk when used as monotherapy or in conjunction with metformin (27,28). The otherwise low risk of hypoglycemia increases when DPP-4 inhibitors are prescribed along with SFUs (26). Concerns regarding the increased risk of pancreatitis and pancreatic cancer remain unresolved (134). A meta-analysis of CVD endpoints suggests that DPP-4 inhibitors may be cardioprotective, but as of this writing cardiovascular endpoint trials have not been completed (135).

Alpha-glucosidase Inhibitors

AGIs lower postprandial glucose by inhibiting the gut enzyme that breaks down complex carbohydrates, thus delaying polysaccharide absorption. The A1C-lowering effect of AGIs is modest, on the order of 0.4 to 0.7%, but there is no independent risk of hypoglycemia (29). Clinical trials have shown CVD benefit in patients with impaired glucose tolerance and diabetes (14,30). Adverse events are rare, but include elevated transaminases and intestinal infections (29). Side effects such as bloating, flatulence, and diarrhea have limited the use of AGIs in the U.S. The AGIs acarbose (available daily doses, 50 and 100 mg), miglitol (25 and 50 mg), and vogliobose (0.2 and 0.3 mg) must be given before each meal, further limiting their acceptability.

Thiazolidinediones

The TZDs reduce insulin resistance in skeletal muscle and other tissues through the downstream effects of peroxisome proliferator activator receptor-gamma (PPARγ) activation (136). Pioglitazone (available daily doses, 15, 30, and 45 mg) has many positive attributes, including A1C lowering of 0.7 to 1.2%, low hypoglycemia risk, and possible CVD benefit (31). The TZDs have been shown to have durable glycemic effects (22). Side effects such as weight gain and fluid retention, which may contribute to chronic edema or heart failure, and adverse metabolic effects on bone causing an increased risk of fracture have limited the use of TZDs. The reported association of pioglitazone and bladder cancer is an unresolved issue (32). The benefits and risks of pioglitazone should be weighed when considering it for long-term management of diabetes.

SFUs and Glinides

SFUs are the oldest class of noninsulin antihyperglycemic agents. One or more SFUs have been in continuous use since 1957, and newer compounds continue to

be developed. The mechanisms of action of SFUs and glinides are similar, so they will be considered together. Due to covalent bonding to the adenosine triphosphate (ATP)-sensitive potassium channel, now known as the SFU receptor-1, both the immediate release of insulin and the delayed release of stored insulin continue as long as the drug is systemically present (137). SFUs have relatively potent antihyperglycemic effects, with A1C reductions of 0.4 to 1.2%, but they lack durability and are associated with modest weight gain and hypoglycemia (22,24,138). The second-generation SFUs, which are the most widely utilized, include glipizide (daily dose range, 5 to 40 mg), glyburide (1.25 to 20 mg), glimepiride (1 to 8 mg), and gliclazide (40 to 160 mg for short-acting, 30 to 120 mg for the modified-release; not available in the U.S.). The efficacy of SFUs may plateau at doses lower than the maximum approved dose (139). SFUs and glinides have the highest hypoglycemia risk of any noninsulin therapy, and due to the long half-life of many agents, hypoglycemia can be recurrent or prolonged and may require hospitalization (140). Concerns about CVD safety are reemerging following analyses of large data sets, reaffirming that the risk is higher with SFUs than with metformin (23,141-143). The secretagogue glinides (repaglinide, 0.5, 1, and 2 mg; nateglinide, 60 and 120 mg) have a shorter half-life than most SFUs and consequently have both reduced A1C-lowering effects and hypoglycemia risk. They are administered with meals and exert their main glycemic effect in the postprandial period (33).

Colesevelam

The bile acid sequestrant (BAS) colesevelam lowers glucose modestly through an unknown mechanism. The A1C drop is generally 0.4 to 0.6%, but it is coupled with a decrease in LDL-C that may be beneficial (34). The major side effect is GI intolerance, which limits its use. Increased triglyceride levels can be problematic for some patients. Colesevelam does not cause hypoglycemia or increase hypoglycemia risk when used with other agents and thus may be of value as an adjunctive therapy.

Bromocriptine Mesylate

The dopamine receptor agonist bromocriptine mesylate (0.8 mg tablets; daily dose, 1.6 to 4.8 mg) has glucose-lowering properties and reduces A1C by about 0.5%, although the mechanisms are unclear (35). While neither hypoglycemia nor other metabolic changes occur with this drug, nausea and orthostasis can be limiting. Because bromocriptine mesylate inhibits the release of glutamate in addition to acting as an agonist at both dopamine D2 and serotonin receptors, it should not be used in patients who are taking antipsychotic drugs. Bromocriptine mesylate needs to be given shortly after waking, and may be useful in some patients to help reestablish circadian rhythms, though the relationship between this effect and the antidiabetes treatment effects is not known. Preliminary data suggest that bromocriptine mesylate may be associated with reduced cardiovascular event rates (36).

SGLT2 Inhibitors

The recent addition of the SGLT2 inhibitor class of antihyperglycemic drugs has broadened therapeutic choices for patients with T2DM (144). Dapagliflozin is approved in Europe, and canagliflozin (100 mg, 300 mg) has been approved by the U.S. FDA (13). Both agents have been tested in combination with metformin and as add-on therapy to other diabetes drugs. Across clinical trials, canagliflozin has been shown to lower A1C by 0.45 to 0.92%; this is accompanied by a weight loss of 0.7 to 3.5 kg. The primary side effects are increased urinary tract and genital infections; however, an unexplained adverse effect is increased LDL-C (37). Cardiovascular safety studies are planned. Clinicians have little experience with these agents, so the utility of the SGLT2 inhibitors and their place in the diabetes armamentarium remains undefined. The SGLT2 drugs will likely be used as add-on therapy to two or three other agents, including insulin, in patients who would benefit from weight loss.

The "Glycemic Control Algorithm" of the "AACE Comprehensive Diabetes Management Algorithm 2013" shows the progression of antihyperglycemic therapy schematically, but cannot capture the many decisions that a physician must make to treat individual patients. For example, if one of the goals of therapy is hypoglycemia avoidance, then an SFU or SFU/insulin combination would be undesirable. Using an SFU with either a GLP-1 receptor agonist or DPP-4 inhibitor increases an otherwise low risk of hypoglycemia observable with both drug classes. If weight loss is a therapeutic goal, then metformin plus a GLP-1 receptor agonist or an SGLT2 inhibitor along with intensive lifestyle management would be preferable to other therapies that are weight-promoting. The addition of basal insulin may be necessary for patients who do not reach targets on noninsulin therapies or who present with significant hyperglycemia. Metformin-intolerant patients have many other choices for monotherapy and combination therapy. Drug classes that should not be used in combination, either because of lack of efficacy or increased risk of adverse effects, include SFUs with meglitinides and GLP-1 receptor agonists with DPP-4 inhibitors.

Three-Drug Combination Therapy

Many of the newer antidiabetes drugs have been tested in combination with metformin and an SFU or TZD and show additive efficacy and acceptable safety. For example, drugs in both the DPP-4 inhibitor and GLP receptor agonist classes have been tested in patients taking metformin and an SFU or metformin and a TZD (28,131,132). In general, the efficacy of the third antidiabetes agent when added to dual therapy is reduced compared with the efficacy of the

same drug used as monotherapy or combination therapy with one other agent. Consequently, a patient who is not at target on 2 antidiabetes drugs with an A1C <8.0% has a high likelihood of getting to target with a third agent, but a patient with an A1C >9.0% while taking 2 drugs is less likely to get to target with a third or fourth antidiabetes drug, so insulin should be considered. Progression of therapy should be undertaken in conjunction with intensified lifestyle management and renewed consideration of anti-obesity treatment. The effects of new therapies should be evaluated in 3 months so that insulin initiation is not delayed in patients with beta-cell failure or intolerance or nonadherence to other therapies. Continuation of noninsulin antidiabetes therapies while starting basal insulin is common and does not raise CVD risk, but the risk of hypoglycemia is increased when SFUs are taken in conjunction with insulin (145).

Special Populations

Patients with chronic kidney disease (CKD) face more treatment challenges than those with normal kidney function. Many antihyperglycemic drugs are excreted in part or totally by the kidney and require dose reductions or special precautions. Not all of the drugs used to treat T2DM have been tested in patients with CKD, so data are limited for some classes. Furthermore, dose reductions may be recommended based on serum creatinine or creatinine clearance (CrCl) or eGFR. While the prescribing information for metformin recommends using it with a serum creatinine level of >1.4 mg/dL in women and >1.5 mg/dL in men, Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest reducing the dose at CKD stage 3b and discontinuing the drug at stage 4 (127,146).

Both short- and long-acting exenatide should be used with caution in patients with stage 3 CKD and avoided in cases of CrCl <30 mL/min. Liraglutide is not excreted via the kidney, so there are no restrictions in CKD, but it has not been tested in patients with end-stage renal disease (ESRD) or in kidney transplant recipients. Most of the DPP-4 inhibitors are excreted by the kidneys, so dose reductions are advised for sitagliptin (use 50 mg daily for CrCl <50 mL/min and 25 mg daily for CrCl <30 mL/min), saxagliptin (use 2.5 mg daily for CrCl <50 mL/min), and alogliptin (use 12.5 mg for CrCl <60 and ≥30 mL/min, and 6.25 mg for CrCl <30 mL/min and ESRD). Linagliptin has a predominantly nonrenal route of elimination, so dose adjustment is not needed for any stage of CKD. The AGIs are not recommended in CKD, specifically if the serum creatinine is >2 mg/dL. Canagliflozin, which is now approved for use in the U.S., should not be used if the eGFR is <45 mL/min/1.73 m^2 (147). All SFUs are excreted by the kidney, so lower starting doses are recommended. Due to the prolonged half-life and higher blood levels of SFUs or metabolites in patients with CKD, the risk of hypoglycemia may be higher, and these agents should be used with caution. Pioglitazone is not excreted renally, so dose adjustment is not needed; however, caution is advised regarding fluid accumulation and heart failure. Likewise, no dose adjustment is needed for colesevelam or bromocriptine, but these agents may have limited utility in this population for other reasons.

The most common cause of liver disease in patients with obesity and T2DM is nonalcoholic fatty liver disease (NAFLD), but patients with T2DM are also at higher risk of hepatitis B and C compared with nondiabetic cohorts (148). In general, diabetes therapy does not need to be modified for mild to moderate liver disease, but the risk of hypoglycemia increases in severe liver disease due to impaired gluconeogenesis. Weight loss is recommended for patients with NAFLD, and both liraglutide and pioglitazone have been used with positive effects (149).

Patients with T2DM are at increased risk of CVD events and mortality, equivalent in epidemiologic studies to nondiabetic persons with established CVD (150,151). The United Kingdom Prospective Diabetes Study (UKPDS) found that intensive glucose therapy in patients with newly diagnosed diabetes is associated with reduced myocardial infarction (MI) (risk reduction, 16%; $P = .052$) (141). This finding was subsequently substantiated with an observed risk reduction for MI and death from any cause at 6 to 10 years of follow-up (122). Recent intervention studies have tested whether intensified glucose reduction strategies would reduce cardiovascular events and death in patients with established T2DM (19,152,153). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, patients showed increased mortality when randomized to intensified treatment regimens that targeted normal A1C levels (<6.0%) with one or more of the following drugs taken alone or in combination: metformin, SFUs, TZDs, and insulin (20). In contrast, the Veterans Affairs Diabetes Trial (VADT) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) clinical trials had higher A1C targets for intensively treated patients (1.5% lower than the standard treatment group in the VADT and <6.5% in the ADVANCE trials) and showed no between-group differences in CVD endpoints, cardiovascular death, or overall death (154,155). It is not known whether other medication combinations or individualized treatment targets would have had the same or different effects. The Outcome Reduction with Initial Glargine Intervention study, which compared basal insulin therapy to placebo in patients with impaired glucose tolerance or recent-onset T2DM, achieved low glycemic targets and was also completely neutral with regard to CVD morbidity and mortality (152). A meta-analysis of CVD outcome trials in diabetes concluded that intensive glucose control, with a between-group A1C difference of 0.9%, reduced cardiovascular events and mortality by 17%, but the analysis could not exclude a higher risk for certain patient

subgroups (e.g., those with established CVD or diabetes of long duration) (156).

Limitations of antidiabetes treatments may involve patient factors that are not well understood. Financial constraints need to be considered to avoid the pitfalls of nonadherence and poor follow-up. Imposing glucose targets that are not achievable in high-risk patients may have detrimental outcomes. Likewise, the inadequate treatment of recent-onset diabetes may promote further beta-cell failure and place the patient at risk for both microvascular and macrovascular complications. Finally, the incorporation of obesity management—whether lifestyle, medical, or surgical—may provide long-term benefits not achievable by antidiabetes therapies alone.

AACE 2013 INSULIN THERAPY ALGORITHM

INSULIN THERAPY

Many factors come into play when deciding at what point to start insulin therapy and what type of insulin to use. The decision to start insulin can be easy if a patient has marked hyperglycemia despite treatment with several OADs and is symptomatic with polyuria and weight loss. In most patients with T2DM, however, the decision to start insulin is less clear-cut and follows the inability to achieve a target A1C despite the use of ≥2 OADs or GLP-1 therapy. The insulin regimen to be prescribed and the exact treatment goals should be discussed with the patient. These decisions depend on the patient's motivation, presence of cardiovascular and end-organ complications, age, general well-being, hypoglycemia risk, and overall health status. For younger patients with no complications, a stringent A1C goal should be set to prevent the development and progression of chronic complications. In older, frail individuals with high hypoglycemia risk or patients with known cardiovascular disease, ambitious A1C goals may not be appropriate.

Initiating insulin therapy takes time and can be difficult in a busy practice. If needed, patients should be asked to return for instruction at a quieter time when a longer appointment can be scheduled, or they should be referred to a certified diabetes educator for the instruction phase of insulin initiation. A recent publication reported a high degree of patient acceptance of insulin use when prior discussions took place with their healthcare providers related to disease progression and patient anxieties (157).

Patients with an A1C level >8.0% while receiving ≥2 OADs or GLP-1 therapy, particularly individuals with long duration of diabetes, have significant impairment of beta-cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further OADs. Some of these patients may have slowly progressive beta-cell deficiency from autoimmune destruction and can often be diagnosed with one of several diabetes autoantibodies (158-160). At this point, insulin treatment should be added to the current OAD regimen.

Basal Insulin

Patients whose A1C level is not at goal while receiving ≥2 OADs or GLP-1 therapy can be started on a single daily dose of basal insulin as an add-on to the patient's existing regimen. A starting dose of 0.1 to 0.2 units/kg is reasonable in patients with an A1C of ≤8.0%, and a dose of 0.2 to 0.3 units/kg is reasonable if the A1C level is between 8 and 10%. This starting insulin dose is seldom sufficient to achieve metabolic control, so insulin dosage should be adjusted at regular and fairly short intervals to the achieve glucose target. Recent studies have shown that titration is equally effective if it is guided by a healthcare provider or if patients are instructed in self-titration. Popular approaches are to ask patients to increase their daily dose by 2-unit steps (38,39,161). In the event of hypoglycemic events, insulin dosages should be reduced by about 10 to 20% for glucose levels <70 mg/dL and by 20 to 40% for severe hypoglycemia.

Insulin-treated patients should be instructed in SMBG. SMBG allows patients to evaluate and assess their individual response to therapy, adjust insulin dosage, and prevent hypoglycemia and severe hyperglycemia. The frequency and timing of SMBG should be dictated by the particular needs and goals of the patient and by their hypoglycemia risk. For most insulin-treated patients with T2DM, SMBG is recommended at least twice daily.

The use of basal insulin at bedtime as an add-on therapy to OADs goes back several decades to the bedtime insulin and daytime SFU regimen, which added NPH insulin to oral therapy (136,162). Although effective in reducing A1C by 1 to 2%, NPH insulin is associated with a higher frequency of hypoglycemia than basal insulin analogs (glargine and detemir) due to a pronounced peak effect between 4 and 8 hours after injection, substantial variability of action between patients, and the requirement for repeated daily injections (44,163,164). A popular insulin regimen is to use a premixed insulin formulation in which rapid- and long-acting components are included in the same vial or pen. Premixed insulins address the endogenous deficits in prandial as well as basal insulin secretion; however, these preparations provide less flexibility and have been associated with a higher frequency of hypoglycemic events compared with basal and basal-bolus insulin regimens (136,165,166). Nevertheless, despite these clear deficiencies with premixed insulins, there are some patients who may not be sophisticated enough to excel with basal-bolus therapy, and for whom a simpler regimen is a reasonable compromise.

Basal insulin analogues are preferred over NPH insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. The efficacy of once-daily basal

analogues versus NPH insulin was first demonstrated in the Treat-to-Target Trial (40). In that study, individuals with T2DM failing on OADs were randomized to receive either evening insulin glargine or NPH. The patients were given an algorithm using weekly insulin increments of 0 to 8 units and were asked to up-titrate the dose until their fasting glucose was 100 mg/dL. At the end of the 26-week trial, approximately 58% of patients in both groups achieved A1C levels <7.0%, with a reduction of approximately 1.6% in both groups. Insulin glargine showed a clear, statistically significant reduction in hypoglycemia (22%), primarily owing to a reduction in nocturnal events. Similar results were reported in a Treat-to-Target study comparing detemir and NPH insulin (163). Several other studies and meta-analyses have confirmed the efficacy and safety of basal insulin in improving glycemic control, reducing A1C levels by approximately 1.5 to 1.8% from baseline, with most showing a reduced risk for hypoglycemia compared with NPH. Both basal analogues have a predictable duration of action that is a function of the injected dose. At a dose of 0.8 units/kg, the duration of action of both insulins is extended to 24 hours. A recent head-to-head comparison study of glargine and detemir in patients failing with one or two oral agents showed an equivalent decrease of A1C levels and similar hypoglycemia rates (42). In that trial, patients treated with detemir experienced slightly less weight gain, but required a higher total daily insulin dose (about one-half of the patients required twice-daily injections).

Basal-Bolus Insulin Regimens

Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and A1C levels >10% often respond better to combined basal and mealtime bolus insulin. However, clinicians should also consider basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia (56,57,60). However, a full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides greater flexibility for patients with variable mealtimes and meal carbohydrate content (48). A simpler approach than advancing directly from a basal to a full basal-bolus insulin replacement regimen is to cover the largest meal with a prandial injection, and then add additional mealtime injections later, if needed. In general, initial before-meal insulin doses for adults can be set at about 5 units per meal or about 10% of the daily basal insulin dose. Consider recommending that premeal insulin be taken 10 to 15 minutes before eating (to compensate for the lag time between administration and peak insulin levels seen with rapidly absorbed analog preparations). Several randomized controlled trials have shown that the stepwise addition of prandial insulin to basal insulin is safe and effective in achieving target A1C levels with a low rate of hypoglycemia (38,39,48) and confirm that a single prandial injection is adequate for many patients failing basal insulin therapy. The prandial dose can be titrated upward by 2 to 3 units every 2 to 3 days on the basis of 2-hour postprandial glucose monitoring and taking into account the before-meal blood glucose level when dosing for a subsequent meal (48).

Major Adverse Effects of Insulin

Hypoglycemia and weight gain are the most common adverse effects of insulin therapy (167). The rate and clinical impact of hypoglycemia are frequently underestimated (51), but about 7 to 15% of insulin-treated patients with T2DM experience at least one hypoglycemic episode per year (49) and 1 to 2% have severe hypoglycemia (51,167). The frequency of hypoglycemia increases with intensive insulin targets, SFU use, decreased caloric intake, delayed meals, exercise, alcohol consumption, renal dysfunction, diabetes duration, and cognitive impairment. Large randomized trials conducted in patients with established T2DM indicate that persons with a history of one or more severe hypoglycemic events have a 2- to 4-fold higher mortality rate, though the reasons are unknown (168,169). It has been proposed that hypoglycemia may be a marker for persons at higher risk of death, rather than being its proximate cause (51). Given this consideration, avoidance of hypoglycemia by appropriately reducing insulin dosages seems prudent. Patients receiving insulin also gain about 1 to 3 kg more weight than with other treatment agents. In addition, the rapid improvement in diabetes control with insulin may result in progressive worsening of retinopathy in approximately 5% of patients (170,171). Patients with proliferative retinopathy and an A1C >10% are at highest risk (172).

Basal and Incretin Therapy Regimens

Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with T2DM (54,55). The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement. Pharmacokinetic and pharmacodynamic studies of combination GLP-1 receptor agonists and basal insulin analogs have shown an additive effect for decreased blood glucose levels (57,58,173). Less information is available on the combined use of DPP-4 inhibitors with insulin, but increasing evidence indicates that this combination is also effective in improving glycemic control with a low risk of hypoglycemia (56,60).

AACE 2013 BLOOD PRESSURE MANAGEMENT ALGORITHM

BLOOD PRESSURE GOALS

Elevated blood pressure in patients with T2DM is associated with an increased risk of cardiovascular events. In epidemiologic analyses, the increased risk has been noted to begin with blood pressure >115/75 mm Hg (174). However, there have been only a few interventional studies in T2DM populations that attempted to demonstrate that lowering blood pressure below 115/75 mm Hg would significantly impact cardiovascular risk. Thus, the optimal blood pressure goal remains elusive, and most recommendations have settled on the conservative target of <140/80 mm Hg (175,176).

A blood pressure goal of <140/80 mm Hg has been defended based upon the results of several randomized trials that showed lowering blood pressure had benefits associated with coronary events, stroke, and nephropathy. Much has been made of the "failure" of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial to show improved outcomes in terms of MI, heart failure, or mortality in patients randomized into the intensive study arm, which achieved a mean blood pressure of 119/64 mm Hg (61). What is often overlooked is that patients in the conventional arm achieved a mean blood pressure of 133/71 mm Hg, significantly below the target (<140/80 mm Hg) recommended by several groups (118). Furthermore, while the results of blood pressure-lowering interventions in patients participating in the UKPDS have been used to justify "tight" blood pressure control, patients randomized to this study's "tight" group achieved a mean blood pressure of 144/82 mm Hg, far above that seen in patients in the "conventional" ACCORD BP group (175,177). Thus, a prudent blood pressure goal might be that achieved in ACCORD BP trial. On the other hand, patients in the "intensive" arm of the ACCORD BP trial recorded a significant 41% reduction in stroke, as well as benefit regarding albuminuria progression (61). These benefits carried a cost in terms of more medications needed (3.4 vs. 2.1 per patient) to achieve the target systolic blood pressure of <120 mm Hg, and patients accrued more adverse events (hypotension, syncope, bradycardia, hypokalemia, and hyperkalemia). However, there might be specific patient groups for whom lower blood pressure would be warranted (i.e., younger patients or those with nephropathy) (63,64).

The optimal approach to identifying blood pressure targets is to perform a meta-analysis of randomized controlled trials. Such an analysis of 13 randomized clinical trials, including 37,736 participants randomized to systolic blood pressure groups of ≤140 mm Hg versus ≤135 mm Hg, with a difference of 3 mm Hg or more, has been reported (62). That study found a significant 13% mortality reduction in trials comparing systolic blood pressure ≤135 mm Hg versus ≤140 mm Hg and a significant 10% reduction in mortality in trials comparing systolic blood pressure ≤130 mm Hg versus ≤140 mm Hg. Diabetic nephropathy, as ascertained by albuminuria measurement, was reduced by 17 and 37% at systolic blood pressures ≤135 mm Hg and ≤130 mm Hg, respectively. There was no evidence of cardiac or retinal benefit with the interventions, and there was a 20% increase in adverse events. Stroke incidence decreased by 3% with every 1-mm Hg reduction in systolic blood pressure to levels <120 mm Hg. There was, however, no evidence of trends toward reductions in mortality or MI at lower blood pressure levels, but at systolic blood pressure <130 mm Hg there was a 40% increase in adverse events. The authors concluded:

A treatment goal of 130 to 135 mm Hg, similar to the achieved BP [blood pressure] of 133.5 mm Hg in the standard therapy group of the ACCORD trial, is therefore acceptable, and more aggressive goals to 120 mm Hg can be considered in patients at higher risk of stroke. However, at a systolic BP <130 mm Hg, there may be target organ heterogeneity, and these cerebrovascular benefits have to be balanced against an increased risk of SAEs [serious adverse events] and a lack of benefit for cardiac, renal, and retinal outcomes.

Therapeutic Lifestyle Changes to Achieve Goals

Weight Loss

The association between obesity and hypertension suggests that lifestyle attempts at weight loss are likely to be beneficial in improving blood pressure in patients with T2DM. In the diabetic population, weight loss has had inconsistent effects on blood pressure, but benefit was shown in the Action for HEAlth in Diabetes (Look AHEAD) trial (65). After 1 year, patients in the intensive lifestyle (ILI) group (dietary, exercise, and behavior modification) lost an average of 8.6% (±6.9%) of their initial body weight. Blood pressure decreased in the ILI group by 6.8 ± 0.4 mm Hg systolic and 3.0 ± 0.2 mm Hg diastolic. The standard group also experienced reduced blood pressure, albeit to a lesser degree (–2.8 ± 0.3 mm Hg systolic and –1.8 ± 0.2 mm Hg diastolic). This reduction in blood pressure occurred despite an increased use of antihypertensive medications in the standard group and no change in use in the ILI group.

Nutritional Factors

Sodium

Given the association between excessive sodium intake and blood pressure, sodium limitation might be an effective strategy for the treatment of diabetic hypertension (178). The efficacy of dietary sodium reduction on

lowering blood pressure in patients with T2DM has not been extensively characterized. One randomized study showed a blood pressure-lowering effect of sodium restriction in T2DM among patients with severe hypertension (blood pressure >160/90 mm Hg). In a more recent study (179) of diabetic patients with modest high blood pressure (blood pressure of 130/85 to 165/100 mm Hg), the addition of a low-sodium diet was evaluated against a baseline of losartan therapy. The experimental group restricted their sodium intake during a 2-week period to a target of <1,750 mg daily (70 mmol/day; control intake 2,300 mg [100 mmol]/day). Sodium restriction resulted in a decreased average 24-hour arterial blood pressure of 9.7 mm Hg (range, 2.2 to 17.2 mm Hg; $P = .002$), reflecting a mean blood pressure reduction of 5.5/7.3 mm Hg ($P = .003$).

The AACE recommendation for hypertensive patients in general is a sodium restriction of <2,300 mg/day. Furthermore, adoption of the Dietary Approaches to Stop Hypertension (DASH) diet would seem to provide additional overall benefits and can be recommended (67-72). Originally developed to prevent or treat high blood pressure, the DASH diet is now recommended as an ideal eating pattern for all adults. The beneficial effects seen in small studies with patients with metabolic syndrome and diabetes, as well as other populations, can be generalized to all individuals with diabetes. Physicians should advise patients to choose foods low in salt, minimize the use of salt during cooking, and reduce their intake of table salt.

Potassium

Population studies have shown an inverse relationship between potassium intake and blood pressure and the prevalence of hypertension (180,181). In people without diabetes, a meta-analysis of randomized controlled trials showed that potassium chloride supplementation of 60 to 100 mmol/day decreased systolic blood pressure by 4.4 mm Hg and diastolic blood pressure by 2.5 mm Hg (66). There are no such studies in patients with T2DM. It has been suggested that one of the most important features of the study by Whelton et al (66) was the relatively high dietary intake of potassium via large amounts of fruits and vegetables (67). The Institute of Medicine has advised that people with normal renal function should have a daily potassium intake of approximately 4.7 g, preferably from fresh fruits and vegetables (182,183).

Other Micronutrients and Macronutrients

Epidemiologic studies suggest an inverse relationship between calcium and magnesium (and potassium) intake and blood pressure (183-185), but there are little data indicating that these micronutrients are significant, independent determinants of hypertension risk. The Cochrane collaboration reviewed 13 trials of calcium supplementation, ranging from 8 to 15 weeks. They reported a small, statistically significant reduction in systolic blood pressure (mean difference, –2.5 mm Hg, 95% confidence interval: –4.5 to –0.6 mm Hg), with little effect on diastolic pressure. None of these trials reported data from patients with diabetes (186). Dietary macronutrient components (e.g., fat, fatty acids, carbohydrate, fiber, and protein) have no independent effect on blood pressure.

Alcohol

Despite the observation that alcohol intake increases blood pressure, numerous cross-sectional studies have shown that moderate alcohol intake is associated with lower incidence of heart disease or total cardiovascular mortality (73,74). This is true even in men with preexisting hypertension or diabetes (187,188). Adults should limit the consumption of alcohol to ≤2 drinks per day (24 ounces of beer, 10 ounces of wine, or 3 ounces of 80-proof liquor), and consumption should not exceed 14 drinks weekly for men or 9 drinks per week for women (189).

Physical Activity

The efficacy of exercise training to lower blood pressure is well-established in patients who do not have diabetes (76). The data regarding blood pressure reductions with exercise in hypertensive patients with diabetes are not as clear, with a recent trial of a general exercise intervention failing to lower blood pressure among 120 patients with diabetes (75,190). A published meta-analysis of resistance training (9 studies), however, reported a 6-mm Hg reduction in systolic blood pressure, with no change in diastolic blood pressure (191).

Moderately intense physical activity, such as 30 to 45 minutes of brisk walking most days of the week, has been shown to lower blood pressure in the general population and is recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (77). It is reasonable to recommend this level of exercise in hypertensive diabetic patients as well, although more intensive exercise may be associated with decreased cardiovascular risk in these individuals (120). Patients with diabetes, especially those treated with insulin, should be aware of the risk of hypoglycemia with exercise and should have readily absorbed glucose handy for use if necessary.

Medications to Achieve Blood Pressure Goals

In most patients with T2DM, medications will be required to achieve blood pressure goals. The choice of the initial drug and order of addition of various agents has been the subject of many consensus statements and recommendations. This debate might not be settled in the near future. Most clinicians, however, agree that achievement of a patient's therapeutic target is more important than the sequential addition of individual medications, especially given the reality that most patients will require two to five different agents before their blood pressure goal

is achieved. Medications from the "ABCD" group (i.e., angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin II receptor blockers [ARBs], beta blockers, calcium channel blockers [CCBs], and diuretics) have been favored as initial choices. The traditional approach has included an agent from the renin-angiotensin system (RAS) inhibitor class, given its putative advantage based on evidence of improved cardiovascular event outcomes in several studies (79,192-196). No apparent advantage has been demonstrated with more aggressive RAS blockage by combining an ACEI and ARB. Indeed, this combination more than doubles the risk of both renal failure and hyperkalemia compared with receiving only one of the agents (197).

Several studies have questioned the automatic choice of an ACEI or ARB as the initial drug for hypertensive patients with T2DM. First, ACEIs and ARBs are not as effective for lowering microalbuminuria as previously believed. Second, RAS blockade was shown to be ineffective in preventing the development of microalbuminuria in people with diabetes with no albuminuria at baseline (197). Third, microalbuminuria might not be a definitive marker of a process that inexorably leads to renal failure (198,199). Fourth, not all studies of high-risk individuals with hypertension (with or without diabetes) found RAS blockade protective against CVD. Fifth, ACEI drugs are less effective in lowering blood pressure than other antihypertensive medications in patients with diabetes; this is especially the case for African Americans (78).

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (78) was a large study comparing the effects of several drug classes. It included over 33,000 participants, of whom 36% had T2DM. All participants had hypertension and at least one other CVD risk factor. Participants were randomly assigned to chlorthalidone (12.5 to 25 mg/day), amlodipine (2.5 to 10 mg/day), or lisinopril (10 to 40 mg/day). A fourth arm, using doxazosin, was stopped prematurely because of an increased incidence of heart failure. Each of these drugs was associated with a similar incidence of the primary outcome of coronary heart disease (CHD) mortality or nonfatal MI. There were no differences in most secondary end points such as all-cause mortality and ESRD, but chlorthalidone was superior for the prevention of heart failure. Based on the ALLHAT findings, the JNC 7 recommended thiazide diuretics as first-line agents for the treatment of hypertension, both in people with and without diabetes (77). However, many other trials have led to the recommendation that ACEIs/ARBs be considered as first-line treatment (79-82).

Drug Therapy in Special Circumstances

In choosing a regimen for blood pressure therapy in people with diabetes, consideration should be given to special circumstances. Patients with heart failure would benefit from beta blockers, those with proteinuria would benefit from ACEIs or ARBs, those with prostatism would benefit from alpha blockers, and those with coronary artery disease (CAD) would benefit from beta blockers or CCBs. Given the degree of blood pressure-lowering that is feasible with any one agent and the general target of approximately 130/80 mm Hg, it is advisable to start treatment with a combination of 2 agents in individuals with blood pressure >150/100 mm Hg.

AACE 2013 DYSLIPIDEMIA MANAGEMENT ALGORITHM

RATIONALE, RISK STRATIFICATION, TREATMENT GOALS, AND MANAGEMENT

The purpose of the 2013 AACE Algorithm for the Management of Dyslipidemia in Patients with T2DM is to suggest to clinicians a stepwise, practical approach to lipid management. Because the application of lipid research observations is rapidly evolving, it requires frequent reassessment. Additionally, the National Heart, Lung, and Blood Institute (NHLBI) is expected to soon release clinical practice guidelines for cholesterol, hypertension, and obesity management, as well as integrated CVD prevention guidelines utilizing systematic reviews of the scientific evidence (200).

The approaches utilized in this algorithm are based on our understanding of the typical lipid abnormalities and metabolic disturbances known to be present in this population. It incorporates suggested guidelines and expert opinions from several lipid expert panels and organizations over the last decade. Many of the expert opinions and guidelines noted herein remain untested in large randomized, controlled trials.

Impact of Diabetes on Cardiovascular Disease

Heart disease and stroke represent approximately 65% to 85% of diabetes-related mortality. Therefore, patients with T2DM have a significantly increased risk of CVD in the form of CHD, cerebrovascular disease (stroke), or peripheral arterial disease, compared to those without T2DM (200).

According to data from the National Diabetes Information Clearinghouse (NDIC), the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institutes of Health, at least 68% of people over 65 years of age with diabetes die of some form of CHD; 16% die of stroke, and CHD death rates among adults with diabetes are two to four times higher than rates for adults without diabetes. Similar data from the Framingham Heart Study and the NHLBI show that having diabetes significantly increases the risk of developing CVD (hazard ratios [HRs] 2.5 for women and 2.4 for men) and of dying when CVD is present (HRs 2.2 for women and 1.7 for men). Men

and women with diabetes at age 50 lived an average of 7.5 and 8.2 years less than their equivalents without diabetes (201).

T2DM as a CHD Risk Equivalent

Some, but not all, long- and short-term epidemiological studies have demonstrated that people with diabetes and no history of MI have similar CVD risk as those with a history of CHD but without diabetes. For example, this CHD risk equivalence was noted in a 2-year mortality follow-up of a 6-country postacute coronary syndrome (ACS) study population (n = 8,100); a 7-year follow-up of a Finnish population (n = 2,400) for cardiovascular events (non fatal MI, stroke, or cardiovascular mortality); and a relatively large 25-year longitudinal Scottish study (n = 15,400) of CHD mortality, other vascular mortality, and nonvascular mortality (150,151,202) These study findings point out the need to manage patients with T2DM as aggressively as patients with CHD but without diabetes. The National Cholesterol Education Program Adult Treatment Panel III guidelines established T2DM as a CHD risk equivalent (84).

Diabetes is not a CHD risk equivalent in all studies. For example, a dramatic difference was observed between patients with prior CHD and new onset T2DM in one Scottish study (n = 2,509). The study compared a group of nondiabetic patients who had experienced MI in the preceding 8 years (between January 1980 and December 1987) with a group of patients with no prior MI but with T2DM newly diagnosed between January 1988 and December 1995. Over the 8-year follow-up, 438 (32.5%) of the patients in the MI group died, and 274 (20.3%) were hospitalized for a further MI. In the T2DM group, 284 (24.6%) died, and 113 (9.8%) were hospitalized for an MI. Kaplan-Meier survival curves showed that patients with long-term established CHD had a higher relative risk (RR) of death from all causes (RR 1.35), cardiovascular causes (RR 2.93), and of hospital admission for MI (RR 3.10) compared to patients with newly diagnosed T2DM (203).

A meta-analysis of 13 studies evaluated 45,108 patients (age range, 25 to 84 years), with follow-up duration ranging from 5 to 25 years (mean, 13.4 years) (204). Patients with diabetes without prior MI had a 43% lower risk of developing CHD events compared to patients without diabetes with previous MI. This meta-analysis did not support the hypothesis that diabetes is a CHD equivalent. The authors concluded that the decision to initiate cardioprotective drugs in patients with T2DM for primary CHD prevention should therefore be based on an individual's CHD risk estimate rather than a blanket approach to treatment. Demonstrating CHD risk equivalence depends on the stratification of risk, which includes: the number of classical major risks, additional risks, and nontraditional risks (see below), as well as the duration of diabetes and the proximity of CHD events in the comparator patient group without diabetes (203).

Toward Establishing Desirable Lipid Levels

The classic major risk factors that modify LDL-C goals include cigarette smoking, hypertension (defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medications), low HDL-C (<40 mg/dL), family history of premature CHD, CHD in male first-degree relative at <55 years, CHD in female first-degree relative at <65 years, and age (men, ≥45 years; women, ≥55 years). HDL-C >60 mg/dL counts as a "negative" risk factor; its presence removes 1 risk factor from the total count (84).

Recognizing that T2DM represents a high lifetime risk for CHD, shorter-term differences in stratification among patients with T2DM could include a "moderate risk" category including patients <40 years and possessing no single major risk. A "high risk" category then represents patients with T2DM possessing ≥1 major risks. This risk stratification would potentially guide management strategies.

In the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry study, the 2-year postACS mortality for patients with diabetes alone or prior CVD alone was 13.0% and 12.8%, respectively, while for the group with diabetes with a prior CVD event it was 20.3% (151). For the 7-year Finnish study, CVD mortality was 15.4% for the diabetes-alone group and 15.9% for the prior MI group alone, but 42% for the diabetes plus prior MI group (150). In the 25-year Scottish study, CHD mortality for men was 23.4% with diabetes alone and 21.3% with CHD alone, but 56.9% for men with both diabetes and prior CHD (202). For women, the Scottish study demonstrated CHD mortality at 16.9% for diabetes alone and 9.8% for prior CHD, but 43% for diabetes plus prior CHD. Furthermore, in all epidemiological studies where the comparison was made, patients with diabetes plus a prior cardiovascular event had subsequently higher event rates than high-risk nondiabetic patients with a prior event or those patients with diabetes without a prior event (205). Patients with T2DM are at particular risk for sudden cardiac death after MI compared with nondiabetic patients. The incidence of sudden cardiac death in post MI T2DM patients with left ventricular ejection fraction >35% is equal to that of nondiabetic patients with left ventricular ejection fraction <35% (206). Therefore, a third potential risk category, "very-high risk," would include those patients with T2DM and established prior CVD events. To date, however, no dedicated large randomized controlled trial has been designed or has demonstrated that more aggressive management of this highest-risk group could achieve additional risk reduction for the secondary prevention of cardiovascular events.

In addition to hyperglycemia, a majority of individuals with T2DM have a syndrome of "insulin resistance" or metabolic syndrome, characterized by a number of other CVD

risk factors, including hypertension and dyslipidemia, in a procoagulant and proinflammatory milieu. The classical "dyslipidemia of insulin resistance" noted in T2DM and also in prediabetes is typified by varying degrees of hypertriglyceridemia; increased levels of small, dense LDL-C and apo B; and low levels of HDL-C and apo A-1.

Furthermore, AACE recognizes multiple risk factors contributing to CAD in patients without and with T2DM and categorizes them as major, additional, and nontraditional. The major risk factors include advancing age, high total cholesterol level, high non-HDL-C, high LDL-C, low HDL-C, hypertension, cigarette smoking, family history of CAD, and CKD. Additional risk factors include abdominal ("central") obesity; family history of hyperlipidemia; small, dense LDL-C; elevated apo B; elevated LDL-P number; fasting or postprandial hypertriglyceridemia; polycystic ovary syndrome (PCOS); and the dyslipidemic triad. Nontraditional risk factors include elevated lipoprotein (a); elevated clotting factors; elevated markers of inflammation (i.e., high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, myeloperoxidase); hyperhomocysteinemia; the presence of the apo E4 isoform; elevated uric acid; decreased apo A-1; elevated apo B/apo A-1 ratio; and decreased HDL particle (HDL-P) numbers (86,207,208).

Greater atherogenicity of small, dense LDL relative to large LDL has been suggested. Observations that support this include increased susceptibility to oxidation, binding, and penetration of the arterial wall; endothelial cell toxicity; promotion of plasminogen activator inhibitor type 1 (PAI-1) and thromboxane production by endothelial cells; accumulation of calcium in vascular smooth muscle cells; and binding to LDL scavenger receptors. Furthermore, small, dense LDL is associated with a greater number of apo B-containing particles (209). There is considerable controversy over whether LDL size predicts disease or whether the association with increased risk merely reflects the relationship to increased LDL-P numbers or concentrations (210).

Because LDL particles vary in both their cholesterol and triglyceride contents, LDL-C does not always provide a precise and/or accurate measure of the circulating concentration of heterogeneous LDL particles. This is particularly true in patients with the metabolic syndrome or T2DM, and in a hypertriglyceridemic environment (where LDL particles are particularly cholesterol-depleted, small in size, and large in number). LDL-C is the concentration of cholesterol (mg/dL) in all of the LDL particles and is calculated using the Friedewald equation (LDL-C = total cholesterol minus very low-density lipoprotein [VLDL]-C – HDL-C). Non-HDL-C is the concentration of total cholesterol in all of the atherogenic particles. It is calculated as the total cholesterol minus the cholesterol in HDL particles. As a gradient-driven diffusion process, the more atherogenic particles that are present in the circulation, whether by overproduction or by reduced clearance, the more atherogenic particles infiltrate arterial walls to initiate atherosclerosis. Apo B is the number of or concentration of all atherogenic particles (mg/dL), while LDL-P is the number of or concentration of LDL particles. Apo B and LDL-P are both measures of particle number.

LDL particle numbers or concentrations can be estimated from apo B measurements or by nuclear magnetic resonance (NMR) spectroscopy. NMR, which measures lipoprotein particle concentrations directly, has been utilized to study the clinical significance of elevated LDL-P. Split-sample comparisons of Friedewald-calculated LDL-C and NMR-measured LDL-P numbers were reported for 2,355 patients with T2DM and "optimal" LDL-C <100 mg/dL (211). Patients were categorized according to their LDL-P values; 61% had suboptimal LDL-P levels (>1,000 nmol/L), and 24% had LDL-P >1,300 nmol/L despite "optimal" LDL-C levels. Even among patients with "ideal" LDL-C levels (<70 mg/dL), 40% were at high risk based on having LDL-P >1,000 nmol/L, and about 10% had LDL-P >1,300 nmol/L. Therefore, LDL-C might fall short in predicting disease.

An analysis of the Framingham Offspring Study compared the ability of LDL-C versus LDL-P to predict a first CVD event in 3,066 middle-aged participants (210). After 14.8 years of follow-up, 265 men and 266 women experienced a CVD event, and LDL-P was more strongly related than LDL-C to future CVD in both genders. Patients with a low LDL-P level (<25th percentile) had a lower CVD event rate (59 events per 1,000 person-years) than those with an equivalently low level of LDL-C (81 events per 1,000 person-years, respectively). Thus, low LDL-P, regardless of LDL-C, predicted event-free survival, while high LDL-P numbers, regardless of LDL-C level, predicted poor survival. Non-HDL-C was intermediate between LDL-C and LDL-P.

Recognizing that measurements of apo B or LDL-P number by NMR may more closely quantitate the total atherogenic lipoprotein particle burden, a July 2007 American Diabetes Association and the American College of Cardiology Foundation consensus conference was convened. Their 2008 published consensus statement recommended that for patients on statin therapy with cardiometabolic risk typical of patients with T2DM or prediabetes, therapeutic adequacy should be guided with measurements of apo B (212). Furthermore, these patients should be treated to the population-equivalent apo B goals, in addition to LDL-C and non-HDL-C. The consensus statement recommended that the highest-risk individuals with CVD or diabetes (possessing ≥1 major CVD risk factors) be treated to an LDL-C goal <70 mg/dL, non-HDL-C <100 mg/dL, and apo B <80 mg/dL. High-risk individuals without CVD but with diabetes (and with no major risks) should be treated to an LDL-C goal <100 mg/dL, non-HDL-C <130 mg/dL, and apo B <90 mg/dL. The authors concluded that

while the NMR measurement of LDL-P number was more accurate than LDL-C or non-HDL-C in assessing risk, its clinical use was limited as it was not widely available, was relatively expensive, and was in need of more independent data confirming its accuracy and consistency in CVD prediction across various ethnicities, ages, and conditions that affect lipid metabolism. In 2011, a 16-member expert panel of lipid specialists convened by the National Lipid Association advised for the equivalent utility of apo B or LDL-P in initial clinical assessment and on-treatment management decisions (213).

In patients with T2DM, AACE recommends an LDL-C goal <100 mg/dL if no additional CVD risk exists or in patients <40 years of age ("moderate" risk). In patients with T2DM at higher risk (≥1 additional risk factors), an LDL-C goal <70 mg/dL is warranted. Because risk factors commonly occur in patients with T2DM, most patients with diabetes will qualify for the more aggressive LDL-C goal. Some advocate an even more aggressive goal (perhaps ≤50 mg/dL) for those at the very highest risk (i.e., T2DM and established CVD) (209,214-216). An optimal apo B level for patients at risk for CVD is <90 mg/dL and <80 mg/dL in patients with diabetes and additional CVD risk factors. When triglyceride levels are >150 mg/dL and/or HDL-C levels are <40 mg/dL, the apo B or the apo B/apo A ratio may be particularly useful in assessing residual risk in patients at risk for CVD, even when LDL-C levels are at goal. Apo B testing is therefore recommended in such patients.

Elevated triglycerides may be an independent risk factor for CVD, although no therapeutic goal has been specified. As a characteristic of insulin resistance syndrome, triglyceride levels that are even mildly elevated (>150 mg/dL) identify individuals at risk for CVD. Although low HDL-C is an independent risk factor for CVD, no specific treatment goals are as yet defined; values <40 mg/dL in men or <50 mg/dL in women are considered high risk. Population and individual studies show that a low HDL-C is associated with an elevated LDL-P concentration. As with progressively low HDL-C, progressive hypertriglyceridemia is associated with elevated LDL-P concentrations. AACE recommends that fasting triglycerides should be <150 mg/dL. Results of several cross-sectional studies show that CVD risk is higher in hypertriglyceridemic subjects with an increased apo B level than in hypertriglyceridemic subjects with a normal apo B level (217). Results from 3 prospective studies showed that risk is related to apo B independently of triglycerides (218-220).

AACE recommends a non-HDL-C goal (total cholesterol – HDL-C) that is 30 mg/dL higher than the patient-specific LDL-C goal. Calculated non-HDL-C incorporates a series of atherogenic particles, making this measurement very useful, particularly in patients with triglycerides >200 mg/dL where LDL-C alone cannot adequately assess CVD risk.

In 2009, the American Association of Clinical Chemistry's Lipoproteins and Vascular Diseases Division Working Group issued a position statement on best practices regarding apo B and CVD risk (221). They reported that apo B is a better measure of circulating LDL-P concentration and is a more reliable indicator of risk than LDL-C. Therefore, there is growing support for the addition of apo B measurement to the routine lipid panel (209,221,222). Importantly, non-HDL-C concentrations in treated patients may not reflect residual risk associated with increased LDL- numbers or concentrations. Therefore, many experts believe that apo B and LDL-P must be recognized and included in treatment recommendations, rather than focusing on just LDL-C and non-HDL-C (213). Furthermore, the medical decision cut-points, in terms of population percentiles, should be set so that apo B and LDL-P targets are equivalent to those for LDL-C and non-HDL-C.

Several alternatives to advanced lipid testing (i.e., LDL-P or apo B determinations) have been evaluated using the area-under-the curve data from LDL-P receiver operating characteristic (ROC) curves. Two approaches were suggested to "most effectively" identify subjects meeting the ATP III very high-risk secondary prevention target levels (LDL-P <1,000 nmol/L or apo B <70 mg/dL or an apo B/apo A1 ratio <0.50). One alternative is a simple composite of lipid panel-based treatment targets (triglycerides ≤99 mg/dL, LDL-C ≤65 mg/dL, non-HDL-C ≤90 mg/dL, and HDL-C ≥54 mg/dL). A second alternative was the simple TC/HDL-C ratio <3, which demonstrated the best performance (223).

TLC

One goal of the AACE algorithm is to increase the number of patients with T2DM who are adequately managed with TLC and lipid-modifying agents to achieve the lowest possible risk for CVD progression and events.

TLC includes smoking cessation and avoidance of tobacco smoke exposure, increased physical activity, weight management and weight loss when necessary, and healthy eating approaches. Dietary modifications for enhancement of lipid modification with the goal of lowering LDL-C include reduction of saturated fat to <7% of calories (full-fat dairy products, bacon, sausage, ribs, fatty meats, and pastries), reduction of cholesterol intake to <200 mg/day (organ meats, egg yolks, excessive meat and dairy products), increase in viscous (water-soluble) fiber (10-25 g/day) to reduce bile acid reabsorption, and increase in plant stanols/sterols (2 g/day) to competitively inhibit intestinal cholesterol uptake (84).

Dietary recommendations for lowering triglycerides include calorie restriction if overweight or obese, weight loss (5-10% loss might lead to a 20% triglyceride reduction), reduction in simple carbohydrates/sugars (sucrose, fructose, starch), reduction in high-fat foods (especially for very high triglycerides), increased intake of unsaturated

fat, elimination of trans fats, restriction of saturated fats, increased intake of marine-based omega-3 ethyl esters, and alcohol restriction (<20-30 g/day). Physical activity is recommended 5 days per week for >30 minutes to achieve a >60% age-related heart rate (84).

Dyslipidemia may occur in patients with T2DM secondary to other medical conditions. Evaluation and optimization of comorbidities that contribute to dyslipidemia is recommended (84,200). These comorbidities include poor glycemic control, obesity, chronic kidney disease/nephropathy, hypothyroidism, chronic inflammatory disorders, pregnancy, Cushing's syndrome, and human immunodeficiency virus.

Also recommended is evaluation of co-administered pharmacologic agents that could contribute to elevated LDL-C, such as glucocorticoids, beta blockers, amiodarone, cyclosporine, high-dose thiazide diuretics, retinoids, paroxetine, and digoxin. Triglyceride-lowering therapies, in particular insulin sensitizers (i.e., thiazolidinediones), fibrates, and prescription-grade docosahexaenoic acid [DHA]-containing omega-3 ethyl ester preparations, can increase LDL-C levels, and this effect is most obvious in the absence of statin therapy. While considered problematic, most lipid experts are not clinically concerned as the mechanism of action of these agents, at least in part, involves the normalization of atherogenic apo B-containing triglyceride-rich lipoprotein (chylomicrons and VLDL) clearance and conversion to intermediate-density lipoprotein (IDL)-C and LDL-C, with variable but not significant changes in apo B levels. Therefore, these agents have little or no effect on total cholesterol or LDL-C but do result in an overall increase in LDL-C particle size, with a reduction in small LDL-C particles. This may ultimately contribute to reduced atherogenicity in hypertriglyceridemic patients (84). Several classes of pharmacologic agents can lead to hypertriglyceridemia: high-dose thiazides, high-dose beta blockers (with the exception of carvedilol), BAS, exogenous glucocorticoids, oral estrogens (as birth control or postmenopausal hormone replacement), tamoxifen, immunosuppressants (cyclosporine and/or sirolimus), selected antipsychotics, retinoic acid derivatives (selected anticancer drugs, acne products, isotretinoin), and protease inhibitors (highly active antiretroviral agents).

Statin Therapy

The Heart Protection Study (HPS) demonstrated that treatment with simvastatin 40 mg/day reduced the risk of CHD and stroke in people with and without diabetes with no prior MI or angina pectoris; this effect was independent of baseline cholesterol (224).

The Collaborative Atorvastatin Diabetes Study (CARDS), a primary prevention study that performed randomized controlled trial in T2DM (n = 2,838), demonstrated that atorvastatin 10 mg/day decreased the risks of first-event CHD and stroke by 37% and 48%, respectively (225). The mean baseline LDL-C of 118 mg/dL in the atorvastatin group was reduced by 46 mg/dL, and there was a 21% average reduction (by 35 mg/dL) in triglycerides. Compared with placebo, atorvastatin treatment lowered LDL-C by a mean of 40.9%, non-HDL-C concentrations by 38.1%, and apo B concentrations by 24.3% (all $P<.0001$). The Cholesterol Treatment Trialists' (CTT) Collaboration's meta-analyses of heterogeneous patient populations in 26 placebo-controlled randomized trials where statin therapies were utilized and meta-analyses of 14 randomized trials of statin use in patients with diabetes demonstrated significant reductions in major adverse cardiovascular events, nonfatal MIs, nonfatal strokes, and deaths in both primary and secondary prevention settings (87,88).

Therefore, statin therapy is established as the drug of choice in CVD prevention for patients without and with diabetes. However, considerable residual risk persists after statin therapy. CVD events in statin-treated groups are about two-thirds those in placebo groups, and patients with diabetes have particularly high residual risk. The challenge has been to identify the means by which clinicians can reduce this considerable residual risk in those already prescribed statin therapy. Utilizing intensified (highest-dose) statin versus the previously utilized moderate statin doses has demonstrated additional CVD event risk reduction in several trials (89,90,226).

Utilizing calculated LDL-C, statin trials have consistently shown that the lowering of LDL-C was associated with a substantial lowering of relative CHD risk. While statins reduce RR, the absolute risk reduction for CHD is far less dramatic. Individuals with atherosclerotic disease or combinations of associated risk factors remain at risk of adverse CVD events despite aggressive statin monotherapy. Even in the best-case scenario of statin treatment, the incidence of CVD events in secondary prevention cohorts was 20% to 30% after 4 to 5 years of therapy. Thus, considerable residual risk exists with statin monotherapy; 70% to 80% of events still occur despite statin therapy. That is, CVD events in statin-treated groups are about two-thirds those in placebo groups in patients with or without diabetes, and patients with diabetes have particularly high residual risk (227).

Approaches to Lowering Residual CVD Risk

One approach to reducing residual risk is to intensify statin therapy (i.e., increase statin dosage or use statins of higher potency than utilized in earlier statin trials). Utilizing intensified (highest dose) statin versus previously utilized moderate statin doses has led to additional CVD event risk reductions in several trials (89,90,226). In the Treating to New Targets (TNT) Study (n = 10,000), intensive statin therapy (atorvastatin, 80 mg/day) was compared with standard statin therapy (atorvastatin, 10 mg/day) (228). After

4.9 years of follow-up, patients randomized to atorvastatin 10 mg/day had an LDL-C of 101 mg/dL, whereas those randomized to the more intensive dose of atorvastatin 80 mg/day had an LDL-C of 77 mg/dL. The absolute reduction in the rate of major cardiovascular events was 2.2%, with a 22% reduction in RR seen in the intensively treated patients ($P<.001$). In the subgroup analysis of 1,501 T2DM patients, a 25% reduction in risk of primary events was documented, including cerebrovascular events and all cardiovascular events (91).

The National Cholesterol Education Program Adult Treatment Panel III guidelines were revised in 2004 to include an optional therapeutic goal of LDL <70 mg/dL in high-risk patients. When LDL-C-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that therapy intensity be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels (229). In the 2006 NHLBI-endorsed American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease, the recommended reasonable LDL-C target in patients at very high CVD risk was <70 mg/dL or a ≥50% LDL-C reduction when the target level cannot be reached (230).

Choosing a statin and dose depends on several factors, including cost and formulary availability, potential drug-drug interactions, potency, dosage, and tolerability. Some clinicians choose a high dose from the start, with the expectation of its ability to reduce LDL-C to the desirable goal. Other clinicians start with a low dose and test tolerability before titration to the high dose. A useful guideline was published as a table by the European Society of Cardiology and the European Atherosclerosis Society; it estimates distance from the target LDL-C and the average response to existing statins toward reaching that identified target (231). However, even after the intensification of statin therapies, residual risk persists (92). Furthermore, the ability to utilize high-dose statins (or other lipid-modifying agents) may be limited by dose-dependent myositis/myopathy in many patients (94).

Addressing the residual risk noted at the end of statin trials, Sniderman evaluated data from 11 published studies that included 17,035 subjects (93). All commonly used statins and doses were included. In order to compare the different trials, outcomes were expressed as population percentiles based on the Framingham Offspring Study. Thus, the absolute value for a particular atherogenic marker was described according to the corresponding percentile of the Framingham Offspring reference population, with the assumption that lower percentiles would have a lower CVD risk. It was assumed that targeting the 20th percentile as a desirable or optimum value would be associated with reduced CVD risk. While LDL-C reached the 21st percentile with aggressive statin therapy, non-HDL-C only reached the 29th percentile, providing a clear rationale for non-HDL-C as a secondary target. Furthermore, while apo B was lowered substantially by statin therapy, it only declined to the 55th percentile, a substantially lower drop than in LDL-C or non-HDL-C, indicating a larger treatment gap. In 8 studies (n = 889) in which LDL-P was measured by NMR, average decreases in LDL-C and LDL-P levels were 35.9% and 30.6%, respectively. This brought the average achieved LDL-C to the 27th percentile; in contrast, the average on-treatment LDL-P was only reduced to the 51st percentile ($P<.007$). Thus, the reduction in LDL-P was significantly less than that for LDL-C, and further therapy would be needed to reduce LDL-P (or apo B) to an equivalent percentile. These types of analyses clearly illustrate that an inadequate reduction of LDL-P numbers despite apparently adequate LDL-C reductions is a potentially major source of residual risk.

Other monotherapies (ezetimibe, fibrate, niacin, or BAS are capable of reducing LDL-P concentrations but less potently than statins. While statin monotherapies have been proven to reduce cardiovascular events in multiple large clinical trials, the evidence supporting the use of fibrates, niacin, and ezetimibe as monotherapy or in combination with statins, is limited. Furthermore, no large clinical trials have been designed to demonstrate the additive utility of these agents in patients expected to respond based on the drug's mechanism of action or in patients who have not yet reached atherogenic particle concentration goals.

Having both elevated triglycerides and low HDL-C is common in patients with established CVD, T2DM, or metabolic syndrome; contributes to macrovascular and possibly microvascular risk; and is associated with higher LDL-P concentrations. Therapeutic interventions to reduce residual vascular risk should focus on all lipid targets. Combination therapies for patients with low HDL-C and/or high triglycerides or elevated non-HDL-C, apo B, or LDL-P can be utilized to achieve lipid targets. In several shorter, small placebo-controlled or usual care-controlled settings, antilipid therapies, alone or in combination, have slowed or stopped progression or led to regression or quiescent progression, which is characteristic of stabilized plaque and reduced cardiovascular events (232,233).

Statin Intolerance

Because statins are the mainstay first-line therapy, every effort should be made to ensure adherence with their use. Some individuals, however, will complain of associated onset of myalgia or develop myopathies. Patients with complaints of muscle symptoms require evaluation (234). In a study of 7,924 French patients, muscle symptoms were reported by 5.1% of patients on fluvastatin (80 mg/day), 14.9% on atorvastatin (40-80 mg), 10.9% on pravastatin (40 mg), and 18.2% on simvastatin (40-80 mg) (94). A variety of pre-existing conditions may masquerade as statin-induced muscle complaints, including peripheral neuropathy, spinal stenosis, peripheral arterial

disease, alcohol myopathy, fibromyalgia, rheumatologic and inflammatory conditions, or vitamin D deficiency (235). Statin discontinuation may be required to determine if symptoms resolve within a few weeks. Rechallenging with the statin to determine if symptoms return can confirm cause and effect. Evaluation for statin-myopathy risk factors should be done; these include drug-drug interactions (statin use in combination with drugs metabolized by cytochrome P450 3A4, such as antifungals, some antibiotics, cyclosporine, and antiretrovirals). Some drugs, such as gemfibrozil, should be used with extreme caution in combination with statins. Grapefruit juice consumption should be limited to <1 quart per day. Prescribing information should be inspected with patients utilizing multidrug regimens. Occasionally, changing the statin to another statin (e.g., to 1 with less or no CYP3A4 interaction) or reducing the dose and/or frequency of use might be successful in eliminating symptoms.

When the tolerated statin does not lower LDL-C to the desirable level, adding nonstatin agent(s) in combination (e.g., ezetimibe, colesevelam, and niacin) may be necessary. When no statin can be tolerated, some patients tolerate red yeast rice, which contains a natural statin (236). Combinations of nonstatin LDL-C-lowering agents may help some patients reach their LDL-C target. Any associated medical problems, such as vitamin D deficiency or hypothyroidism, must be addressed.

Combinations of Lipid-Modifying Agents

Other lipid-modifying agents must often be utilized in combination with statins when therapeutic levels for critical atherogenic markers (LDL-C, non-HDL-C, and apo B or LDL-P) have not been reached. Nonstatin lipid-modifying agents have lower efficacy for lipid modification and CVD risk reduction. In theory, combinations of these agents with statins should reduce atherogenic dyslipidemia. However, recent trials attempting to demonstrate the potential additive CVD benefit of these nonstatin lipid-modifying agents against the background of statins have not succeeded. It has been argued that these studies may have been hampered by suboptimal trial designs. For example, fenofibrate was utilized in patients with a mean triglyceride level of 162 mg/dL in the ACCORD Lipid Trial, despite previous evidence indicating that fibrate CVD benefits are limited to patients with moderate hypertriglyceridemia (>200 mg/dL) (154,237,238).

In patients who are either tolerant only of suboptimal statin doses or completely statin-intolerant, combinations of ≥2 nonstatin lipid-modifying agents are typically required to approach or reach desirable levels for atherogenic markers. For example, in comparison with baseline, colesevelam and HCl-ezetimibe combination therapy was associated with significant reductions in mean levels of total cholesterol (by 27.5%), LDL-C (by 42.2%), and non-HDL-C (by 37.1%) (155).

Ezetimibe

Ezetimibe is an inhibitor of the Niemann-Pick C-like 1 (NPC1L1) protein that mediates cellular cholesterol uptake through vesicular endocytosis by intestinal enterocytes. Ezetimibe also promotes biliary excretion of cholesterol by preventing biliary cholesterol from returning to the liver via NPC1L (239). In patients with T2DM and/or type IIb hyperlipidemia, ezetimibe decreases hepatic cholesterol stores; upregulates LDL receptors; and lowers apo B, non-HDL-C, LDL-C, and triglycerides. Consistent with decreases in the numbers of fasting VLDL and LDL particles, ezetimibe significantly decreases total cholesterol, LDL-C, apo B-48 and -100, triglycerides, remnant lipoprotein cholesterol levels, and cholesterol and triglyceride levels in VLDL and LDL (95).

The ongoing IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is the only large, randomized clinical trial evaluating additional lowering of LDL-C levels using ezetimibe in patients with recent ACS being treated with a statin to a LDL-C level <70 mg/dL (240). A limitation of IMPROVE-IT is the possibility that no further benefit will be attained in patients with baseline LDL-C <70 mg/dL, as suggested by results of the 3-year Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study and 4-year HPS2-THRIVE study (see niacin section, below) (154,237).

Bile Acid Sequestrants (BAS)

BAS are nonabsorbable, water-insoluble, hydrophilic, large polymers that bind negatively charged bile salts or acids in the small intestine and facilitate fecal excretion. This effect ultimately reduces the enterohepatic reabsorption pathway that would otherwise be initiated at the distal portion of the small intestine (terminal ileum) via an ileal bile acid transporter (IBAT). Consequently, lower hepatic bile acid pools stimulate hepatic bile acid synthesis, leading to lower intrahepatic cholesterol pools. As a result, two major pathways for hepatic cholesterol pool repletion are turned on: hepatic HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) synthesis of cholesterol (and subsequently VLDL) and upregulation of LDL receptors to sequester LDL-C particles from circulation. BAS can lower total cholesterol, LDL-C, apo B, and LDL-P and raise HDL-C and HDL-P. Relative to first-generation BAS (cholestyramine and colestipol), the second-generation BAS colesevelam has enhanced affinity and specificity for binding bile acid and less affinity for fat-soluble vitamins, other nutrients, or drugs such as warfarin. It tends to be better tolerated with fewer gastrointestinal side effects (principally constipation, bloating, and abdominal pain). In T2DM, colesevelam reduces the concentrations of LDL-C and LDL-P, primarily small LDL-P relative to large LDL-P, with little change in IDL-P or VLDL-P concentrations,

and it also improves glycemic status (98). Due to increased VLDL production and secretion, BAS treatment can result in increased triglyceride levels, which limits the use of these compounds in patients with hypertriglyceridemia unless they are also on a statin to reduce VLDL-C synthesis (96). Due to its glucose-lowering efficacy, colesevelam was approved in the U.S. in 2008 as an adjunct for T2DM therapy (97).

Approach to Hypertriglyceridemia

For patients with triglycerides >500 mg/dL, the primary treatment objective is to lower triglyceride levels to avoid pancreatitis (84). While no large clinical trials have been designed to test this objective, long-term dietary and lipid management of hypertriglyceridemia in patients with acute pancreatitis associated with hypertriglyceridemia is recommended by AACE because small observational studies have demonstrated that this approach is effective in preventing or reducing relapses. Treating high triglyceride levels may also reduce atherosclerosis risk, but no large clinical trials have been designed to test this hypothesis. However, in randomized controlled trials utilizing fibrates, CVD benefits were demonstrable in patients with moderate hypertriglyceridemia (>200 mg/dL) when subgroup analyses and meta-analyses of these subgroups were performed (99,100).

Fibrates

Fibrates are peroxisome proliferator-activated receptor (PPAR-α) selective ligand agonists that mediate the transcriptional regulation and expression of at least 14 genes involved in lipid metabolism (241,242). Fibrates promote β-oxidation of fatty acids, thus reducing the availability of free fatty acids for triglyceride synthesis, and de novo fatty acid synthesis is inhibited through reductions in acetyl-CoA carboxylase and fatty acid synthase activity. Lipolysis and plasma clearance of atherogenic triglyceride-rich lipoproteins is enhanced via expression and increased activity of endothelial lipases (e.g., lipoprotein lipase, LPL) and reduced production of apo CIII, further enhancing or potentiating LPL activity. Fibrates are effective at raising HDL-C and reducing VLDL, triglycerides, and chylomicrons. Their effects on LDL-C are variable. Fibrates increase expression of HDL proteins (apo A-I, apo A-II), reverse cholesterol transport proteins ATP-binding cassette transporter ABCA1 (ABCA1) and scavenger receptor class B member 1 (SR-BI), and can reduce inflammation.

Over the last 25 years, the effects of fibrates on CVD risk reduction have been tested in several randomized controlled trials that have shown inconsistent primary cardiovascular outcomes benefits, potentially due to the targeted trial populations. The Helsinki Heart Study, for example, demonstrated that gemfibrozil reduced the incidence of CHD in asymptomatic, middle-aged subjects with non-HDL-C >200 mg/dL (relative risk reduction 34%; *P*<.02) (99). The reduced risk was especially notable in patients with high triglycerides and a high LDL-C/HDL-C ratio (100). The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), which was confined to men with CHD and low HDL-C (32 mg/dL) and LDL-C (111 mg/dL), excluded those with LDL-C >140 mg/dL and triglycerides >300 mg/dL, and utilized gemfibrozil, demonstrated an association between raising HDL-C and a significant reduction in the incidence of major coronary events.[101] The use of fibrates together with statins in the ACCORD-Lipid (103) study showed no cardiovascular benefit.

Studies examining possible benefits of lipid-lowering with fibrates in T2DM have shown inconsistent results. Combination fibrate-statin therapy favorably modifies the atherogenic, triglyceride-rich lipoprotein environment common to insulin resistance, T2DM, and elevated CVD risk. The results of 5 large randomized controlled trials demonstrated several consistent features. The highest CVD event rates occurred in the placebo subgroups with atherogenic dyslipidemia (triglycerides >200 mg/dL and HDL-C <35-40 mg/dL). This subgroup demonstrated the greatest "hypothesis-generating" fibrate benefit (27% to 65% RR reduction, with variable significance [*P*-values ranging from .005 to .057]). Those subgroups with lesser degrees of dyslipidemia had relatively lower CVD event rates and little or no benefit from fibrates. In addition, independent meta-analyses combined 5 randomized controlled trials, which provided a large sample of "moderate" dyslipidemia participants (102,238,243). As an example, one meta-analysis evaluated 5 trials covering 25,015 patients taking either fibrates or placebo and demonstrated a fibrate benefit in all lipid subgroups (102). Among patients with low HDL-C only (<40 mg/dL), CVD events were reduced by 17% (*P*<.001). Among patients with hypertriglyceridemia (triglycerides >200 mg/dL), fibrates reduced CVD events by 28% (*P*<.001). The greatest fibrate benefit was observed in patients with atherogenic dyslipidemia (low HDL-C and high triglycerides), who achieved a 30% reduction in CVD events (*P*<.0001), compared with a nonsignificant 6% reduction (*P* = .13) in nonatherogenic dyslipidemia patients. Thus, the 5 major trials consistently support the concept that fibrate use to attain cardiovascular benefit be limited to patients with moderate dyslipidemia (triglycerides >200 mg/dL and HDL-C <40 mg/dL). A dedicated trial in this population is needed.

Niacin

Niacin has multiple beneficial effects on the lipid panel. It inhibits hormone-sensitive triglyceride adipocyte lipase, thereby reducing the mobilization of free fatty acids (which are otherwise substrate for hepatic triglyceride synthesis). Niacin also inhibits diacylglycerol acyltransferase-2 and the hepatic assembly of apo B, cholesterol, and triglycerides into VLDL particles, thereby suppressing

the hepatic release of VLDL. It reduces circulating atherogenic markers, including apo B, VLDL-C, and VLDL-triglyceride, as well as remnants and byproducts including IDL-C and LDL-C; small, dense LDL-C; and LDL-P. Niacin is the only classical lipid-modifying agent that lowers lipoprotein(a) [Lp(a)]. Although niacin can raise apo A-1 somewhat, it is the most powerful lipid-modifying agent available to raise HDL-C (104), and it does not raise HDL-P number, which may be a reflection of pharmacologically improved HDL functionality (i.e., reverse cholesterol transport or other beneficial HDL properties) (244).

The Coronary Drug Project (CDP) was the only sizable trial where niacin monotherapy was utilized (245). The niacin-treated group had mean total cholesterol and triglyceride reductions of 10% and 26%, respectively, compared to placebo, and treatment was associated with statistically significant reductions in nonfatal MI (–27%, *P*<.005), nonfatal MI and CAD death (–14%, *P*<.05), stroke (26%, *P*<.05), need for coronary artery bypass graft (67%, *P*<.005), and need for any cardiac surgery (–60%, *P*<.005). However, the number of patients in the CDP niacin-treatment group (n = 1,119) was relatively small. The total mortality reduction at 9-year follow-up after the trial was 11% (*P*<.0004). Compliance issues occurred with crystalline niacin. Therefore, the statistically significant therapeutic benefits that were achieved in the CDP niacin group resulted from a mean dose that was much less than the prescribed 3,000 mg/day. Based on the actual 26% triglyceride reduction, the estimated average dose utilized was likely <2,000 mg/day. Niacin ER has substantially fewer side effects and can only be taken once a day without the frequent predose aspirin required with rapid-release dosing schedules (246).

In a meta-analysis of 11 trials (n = 9,959 patients), niacin use was associated with a significant reduction (34%, *P* = .007) in the composite endpoints of any CVD event and a significant reduction (12%, *P* = .02) of major CHD events (247). The magnitude of HDL-C difference between treatment arms was not significantly associated with the magnitude of the effect of niacin on outcomes. Thus, the observed reduction of CVD events by niacin may occur through a mechanism independent of HDL-C changes. Niacin targets atherogenic dyslipidemia associated with T2DM. Niacin use, as monotherapy, at a mean dose of 2,580 mg/day in 28 patients with T2DM reversed dyslipidemia associated with insulin resistance; for example, lowering triglycerides from 192 mg/dL to 99 mg/dL and raising HDL-C from 41 mg/dL to 57 mg/dL (105).

Two recent trials were designed to evaluate the potential additive CVD benefits of niacin, in particular, to test the HDL-C-raising hypothesis. The AIM-HIGH trial involved patients (n = 3,414) with established CAD, the majority (92%) of whom had previously been aggressively managed for years with statins and other antilipid therapies. At randomization, all participants were placed on simvastatin 40 mg/day and then randomly assigned to receive 1,500 mg to 2,000 mg/day niacin ER or placebo-niacin (containing 50-200 mg crystalline niacin). Niacin ER significantly increased median HDL-C (from 35 mg/dL to 42 mg/dL), lowered patients' mildly elevated triglycerides (from 164 mg/dL to 122 mg/dL), and lowered LDL-C (from 74 mg/dL to 62 mg/dL). It reduced median non-HDL-C (from 108 mg/dL to 90 mg/dL) and median apo B (from 81 mg/dL to 69 mg/dL). The placebo or statin-only group at trial end had a median HDL-C of 38 mg/dL, triglycerides of 152 mg/dL, LDL-C of 67 mg/dL, non-HDL-C of 99 mg/dL, and apo B of 77 mg/dL. The trial was stopped prematurely after a mean follow-up of 3 years due to a lack of efficacy, with preliminary data suggesting increased stroke in the niacin group (237).

The HPS2-Treatment of HDL to Reduce the Incidence of Vascular Events (THRIVE) trial tested the benefits of added niacin in combination with laropiprant, a DP1 receptor blocker that reduces flushing symptoms, rendering niacin more tolerable (154). Patients (n = 25,673) with elevated cardiovascular risk were enrolled in a randomized controlled trial of statin +/- ezetimibe + placebo-niacin versus statin +/- ezetimibe + niacin/laropiprant. Mean patient lipid levels at baseline (in mg/dL), on statin +/-ezetimibe, were as follows (all mg/dL): total cholesterol, 128; LDL-C, 63; non-HDL-C, 84; apo B, 68; triglycerides, 120; and HDL-C, 44. After 3.9 years, niacin ER failed to demonstrate any benefit for the primary endpoints of CHD deaths, nonfatal MI, cerebrovascular accident, or need for revascularization (154,248).

In summary, AIM-HIGH and HPS2-THRIVE patients were already at or below desirable targets for the atherogenic markers (LDL-C, non-HDL-C, or apo B) before randomization to niacin ER, which possibly and unintentionally introduced futility into any expectation of additional cardiovascular benefits. However, niacin remains a viable pharmacologic agent for statin-intolerant individuals, those patients who are not yet at goal on statin, and particularly those patients who meet the dyslipidemia indication (high triglyceride and low HDL-C) suggested by the 2002 ATP-III (84).

Niacin can cause flushing side effects. Because of this, niacin ER is usually started at 500 mg at bedtime and titrated monthly, usually by 500 mg. Flushing can be minimized if the drug is taken with or after meals and if aspirin is administered before the niacin. Other adverse effects of niacin are gastrointestinal, including nausea, vomiting, diarrhea, flatulence, dyspepsia, and peptic ulcer. Concern about raising blood glucose levels in patients with T2DM has probably limited its use. While some patients may experience profound blood glucose effects, the majority do not. Niacin's beneficial effects on cardiovascular events and mortality appear to be greatest among those with the highest baseline glucose levels and among those with metabolic syndrome (106).

Omega-3 Fish Oils

Dietary intake of fish and fish oil is associated with reduced risk for total mortality, sudden death, and CAD. Eating fish once a week compared to eating less fish was associated with a 16% lower risk of fatal CHD in a meta-analysis (249). The mechanisms of action of omega-3 fatty acids with regard to triglyceride levels include a reduction in the availability of hepatic fatty acids for VLDL-triglyceride synthesis and an increase in the clearance of triglycerides from circulating VLDL and IDL particles. Other potential biochemical pathways and physiological and cardiovascular effects of omega-3 fatty acids and effects on clinical endpoints and dietary guidelines have been reviewed. Two favorable studies utilized relatively low-dose (1,000 mg/day) omega-3 fish oils in patients with CAD but without hypertriglyceridemia (250). One randomized controlled intervention trial, the GISSI-Prevenzione trial, suggested that fish and fish oil (1,000 mg DHA-EPA) reduced the primary endpoints of death, nonfatal MI, and stroke (251). A large Japanese open-label clinical trial (n = 18,645) investigated the effects of a highly purified (>98%) fish-derived ethyl EPA on CAD (109). Fifteen percent of subjects had T2DM. All patients received statin alone (pravastatin 10 mg/day or simvastatin 5 mg/day) or the same dose with EPA. EPA had no significant effect on total cholesterol or LDL-C levels, indicating that EPA can lower CAD risk by mechanisms other than LDL-C lowering. The primary endpoint (any major CVD event, including sudden cardiac death, fatal and nonfatal MI, and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting) was reduced with EPA by 19% ($P = .011$). In the higher-risk group (triglycerides >150 mg/dL and HDL-C <40 mg/dL), EPA treatment reduced CAD risk by 53% ($P = .043$) (108). Among the patients with impaired fasting glucose or T2DM, EPA decreased the incidence of CAD events by 22% ($P = .048$) (107).

It is important to distinguish studies of low-dose omega-3 ethyl ester (i.e., <1,000 mg) as an enrichment supplement, from doses (<4,000 mg) indicated to treat very high triglycerides (>500 mg/dL). While a 4,000-mg/day dose of prescription-grade omega-3 fatty acids is indicated for the management of severe hypertriglyceridemia in T2DM to prevent pancreatitis, the CVD benefits of EPA and DHA, either separately or in combination, are currently unknown. No trial has yet been designed to evaluate the triglyceride-lowering benefits of omega-3 ethyl ester in a dedicated population of moderate to severe hypertriglyceridemic patients. Even The Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT) (252), which will evaluate the effectiveness of an exclusive EPA-containing omega-3 in reducing first major cardiovascular events in a high-risk patient population on statin therapy, has inclusion criteria permiting TG levels as low as 150 mg/dL.

Summary

If LDL-C targets have not yet been reached after the implementation of TLC and intensification of statin therapy to a maximally tolerated dosage, the addition of ezetimibe, colesevelam, niacin, or various combinations may be required. If LDL-C has reached a desirable level, but non-HDL-C is not optimal, triglyceride-lowering by adding omega-3 fatty acids, fibrates, niacin, or various combinations can be utilized. Patients with T2DM, insulin resistance, metabolic syndrome, and/or hypertriglyceridemia are the mostly likely populations to have persistently elevated apo B or LDL-P, even when LDL-C and non-HDL-C are at goal levels. Following intensification with statins, the addition of ezetimibe, colesevelam, niacin, or combination therapy can be useful in reducing apo B or LDL-P to desirable levels. Patients with both T2DM and previous CVD events may require very aggressive management using multiple classes of lipid-modifying agents, even to levels below those recommended for high-risk patients with T2DM. However, no large clinical trials have evaluated this approach. When TLC is intensifed or new pharmacologic treatments are added, it is important to regularly assess therapeutic adequacy and tolerability using focused laboratory evaluations and close patient follow-up.

DISCLOSURE

Dr. Alan J. Garber reports that he is on the Advisory Board for Novo Nordisk, Merck, Halozyme, Janssen, Takeda, and Vivus. He is a speaker for Novo Nordisk, Merck, Santarus, Janssen, and Vivus. He is also a consultant for Novo Nordisk, Merck, Santarus, Takeda, Tethys, and Vivus.

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Dr. Michael H. Davidson has no multiplicity of interests to disclose.

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AACE COMPREHENSIVE DIABETES MANAGEMENT ALGORITHM 2013

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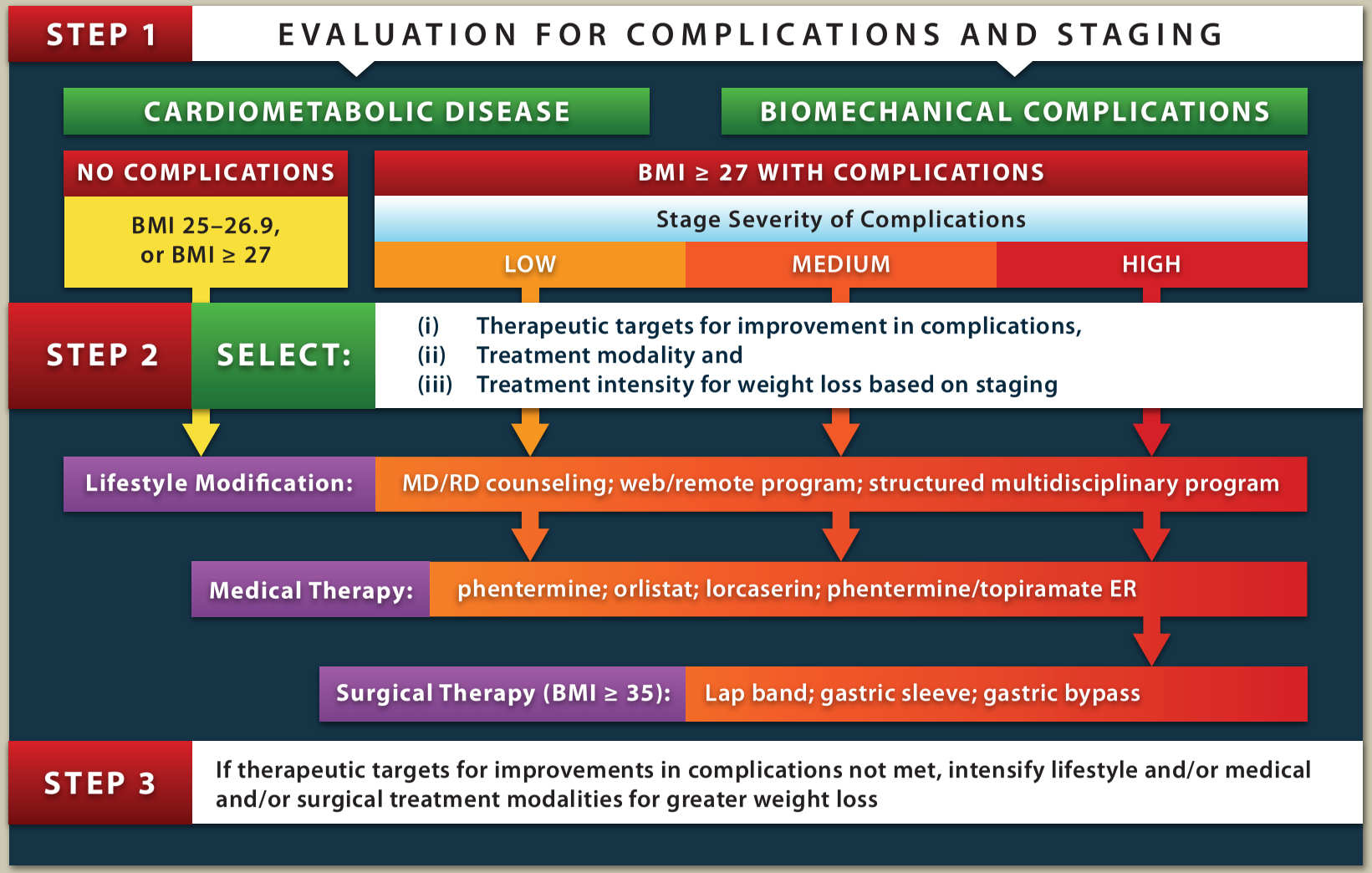
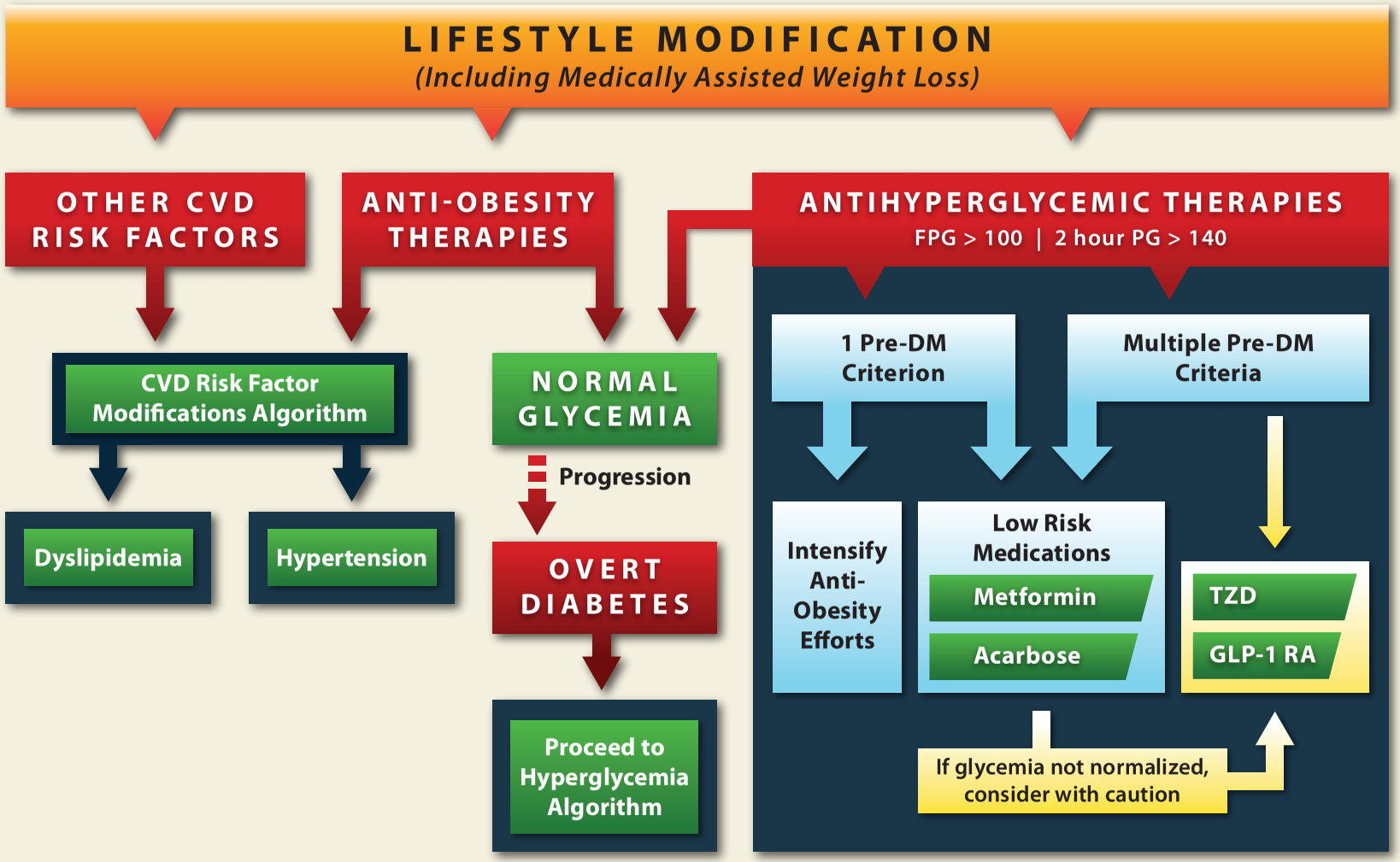
Complications-Centric Model for Care of the Overweight/Obese Patient



Prediabetes Algorithm

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2005)



Goals for Glycemic Control

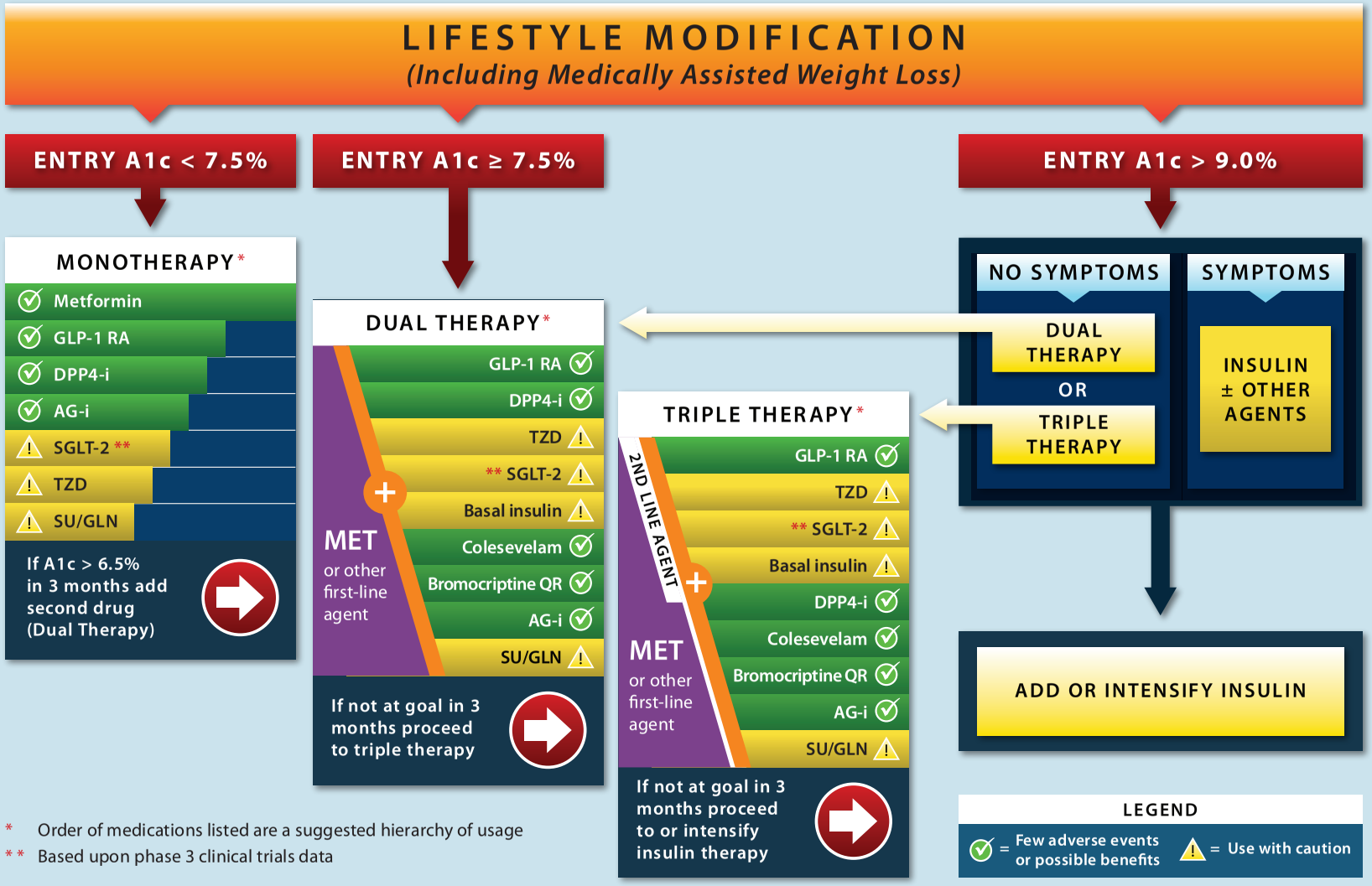
A1c ≤ 6.5%

For healthy patients without concurrent illness and at low hypoglycemic risk

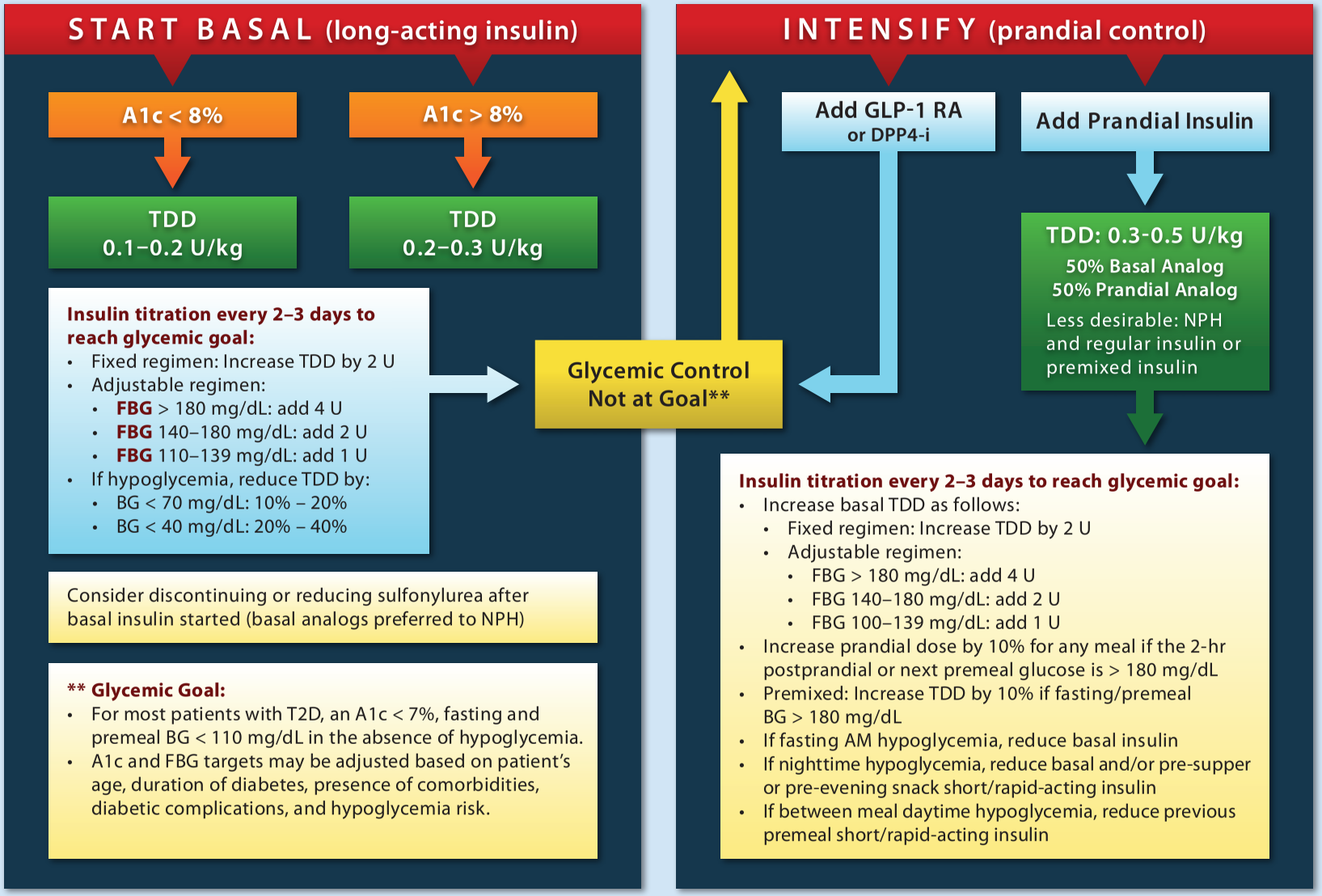
A1c > 6.5%

Individualize goals for patients with concurrent illness and at risk for hypoglycemia

Glycemic Control Algorithm



Algorithm for Adding/Intensifying Insulin



CVD Risk Factor Modifications Algorithm

DYSLIPIDEMIA

THERAPEUTIC LIFESTYLE CHANGES *(See Obesity Algorithm)*

LIPID PANEL: Assess CVD Risk

Statin Therapy

If TG > 500 mg/dL, fibrates, omega-3 ethyl esters, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C-lowering therapies → Repeat lipid panel; assess adequacy, tolerance of therapy → Intensify therapies to attain goals according to risk levels

RISK LEVELS	MODERATE DM but no other major risk and/or age <40	HIGH DM + major CVD risk(s) (HTN, Fam Hx, low HDL-C, smoking) or CVD*
	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70
Non-HDL-C (mg/dL)	<130	<100
TG (mg/dL)	<150	<150
TC/HDL-C	<3.5	<3.0
Apo B (mg/dL)	<90	<80
LDL-P (nmol/L)	<1200	<1000

If not at desirable levels: Intensify TLC (weight loss, physical activity, dietary changes) and glycemic control; Consider additional therapy

To lower LDL-C: Intensify statin, add ezetimibe &/or colesevelam &/or niacin
To lower Non-HDL-C, TG: Intensify statin &/or add OM3EE &/or fibrates &/or niacin
To lower Apo B, LDL-P: Intensify statin &/or ezetimibe &/or colesevelam &/or niacin

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* even more intensive therapy might be warranted

HYPERTENSION

GOAL: SYSTOLIC ~130, DIASTOLIC ~80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg: Dual therapy

ACEi or ARB + Thiazide ✓ / Calcium Channel Blocker ✓ / ß-blocker ✓

If not at goal (2–3 months)

Add ß-blocker or calcium channel blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, spironolactone)

Achievement of target blood pressure is critical

Profiles of Antidiabetic Medications

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

Few adverse events or possible benefits — Use with caution — Likelihood of adverse effects

Principles of the AACE Algorithm for the Treatment of Type 2 Diabetes

1) Lifestyle optimization is essential for all patients with diabetes. This is multifaceted, ongoing, and engages the entire diabetes team. However, such efforts should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on the response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it.
2) The A1c target must be individualized, based on numerous factors, such as age, co-morbid conditions, duration of diabetes, risk of hypoglycemia, patient motivation, adherence, life expectancy, etc. An A1c of 6.5% or less is still considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate and may change in a given individual over time.
3) Glycemic control targets include fasting and postprandial glucose as determined by self blood glucose monitoring.
4) The choice of therapies must be individualized based on attributes of the patient (as above) and the medications themselves (see *Profiles of Anti-Diabetic Medications*). Attributes of medications that affect their choice include: risk of inducing hypoglycemia, risk of weight gain, ease of use, cost, and safety impact of kidney, heart, or liver disease. This algorithm includes every FDA-approved class of medications for diabetes. This algorithm also stratifies choice of therapies based on initial A1c.
5) Minimizing risk of hypoglycemia is a priority. It is a matter of safety, adherence, and cost.
6) Minimizing risk of weight gain is a priority. It too is a matter of safety, adherence, and cost.
7) The algorithm provides guidance to what therapies to initiate and add, but respects individual circumstances that would make different choices.
8) Therapies with complementary mechanisms of action must typically be used in combinations for optimum glycemic control.
9) Effectiveness of therapy must be evaluated frequently until stable (e.g. every 3 months) using multiple criteria including A1c, SMBG records including both fasting and post-prandial data, documented and suspected hypoglycemia, and monitoring for other potential adverse events (weight gain, fluid retention, hepatic, renal, or cardiac disease), and monitoring of co-morbidities, relevant laboratory data, concomitant drug administration, diabetic complications, and psycho-social factors affecting patient care.
10) Safety and efficacy should be given higher priorities than initial acquisition cost of medications per se since cost of medications is only a small part of the total cost of care of diabetes. In determining the cost of a medication, consideration should be given to monitoring requirements, risk of hypoglycemia and weight gain, etc.
11) The algorithm should be as simple as possible to gain physician acceptance and improve its utility and usability in clinical practice.
12) The algorithm should serve to help educate the clinician as well as to guide therapy at the point of care.
13) The algorithm should conform, as nearly as possible, to a consensus for current standard of practice 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.
14) The algorithm should be as specific as possible, and provide guidance to the physician with prioritization and a rationale for selection of any particular regimen.
15) Rapid-acting insulin analogs are superior to Regular because they are more predictable.
16) Long-acting insulin analogs are superior to NPH insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency both between subjects and within subjects, with a corresponding reduction in the risk of hypoglycemia.

This document represents the official position of the American Association of Clinical Endocrinologists and the American College of Endocrinology. Where there were no RCTs or specific FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Many details that could not be included in the graphic summary (Figure) are described in the text.