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Managing Type 2 Diabetes: Going Beyond Glycemic Control

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*Mark W. Stolar, MD; Byron J. Hoogwerf, MD; Stephen M. Gorshow, MD, FACP;
Patrick J. Boyle, MD; and Dirk O. Wales, MD, PsyD*

Learning Objectives

After studying this supplement, participants should be able to do the following:

1. Discuss the clinical and economic rationale for aggressive management and treatment of type 2 diabetes;
2. Recognize the role of disease pathophysiology in establishing appropriate diabetes management strategies;
3. Review the current American Diabetes Association (ADA) algorithm and the recommended treatments for hyperglycemia in type 2 diabetes;
4. Establish the importance of the glycemic and nonglycemic benefits of currently available treatment agents in the overall management of patients with type 2 diabetes.

(Note: This supplement is not associated with either continuing pharmacy or medical education credit.)

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Managing Type 2 Diabetes: Going Beyond Glycemic Control

Mark W. Stolar, MD; Byron J. Hoogwerf, MD; Stephen M. Gorshow, MD, FACP;
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ABSTRACT

BACKGROUND: Aggressive management of type 2 diabetes is necessary to achieve glycemic and nonglycemic treatment goals. Attainment of treatment goals is associated with a decreased risk of diabetes-related complications, costs, and health care utilization.

OBJECTIVE: To review the advantages and disadvantages of different glucose-lowering agents, with an emphasis on the role of thiazolidinediones (TZDs).

SUMMARY: Diabetes has become increasingly prevalent, particularly among younger age groups in the United States, accounting for approximately 15% of health care expenditures by managed care organizations. Reducing a patient's glycated hemoglobin (A1C) has been shown to decrease the risk of diabetes-related complications, as well as reduce medical costs and health care utilization. Despite this knowledge, achievement of the American Diabetes Association (ADA) goal A1C of <7% is suboptimal, and <1 in 10 patients also reach the ADA targets for cholesterol (low-density lipoprotein <100 mg per dL) and blood pressure (<130/80 mm Hg). To ensure that all ADA treatment goals are met, clinicians need to closely monitor patients and adjust therapy as needed, taking into consideration both a drug's glycemic and nonglycemic effects when selecting medication therapy. Four basic defects contribute to type 2 diabetes: insulin resistance, decreased insulin secretion, increased hepatic glucose production, and reduced glucagon-like peptide-1 levels. Unlike metformin, sulfonylureas, and insulin that address only 1 or 2 physiologic defects, TZDs uniquely address 3 of these defects at the adipocyte. Metformin is recommended for initial drug therapy; TZDs, sulfonylureas, and insulin are useful options as add-on therapy for patients whose A1C levels remain $\geq 7\%$ despite treatment with metformin and lifestyle interventions. It has been suggested that TZDs, when used either as add-on therapy or when appropriate as monotherapy, may conserve pancreatic beta-cell function over an observed 3- to 5-year period of time and sustain a decrease in A1C ranging from 0.5%-1.5%. Although rarely associated with hypoglycemia, TZDs may cause total body weight gain that is most commonly caused by volume expansion, which may manifest as new or worsened heart failure in susceptible individuals. Pioglitazone and rosiglitazone, the 2 TZDs available in the United States, contain black box label warnings about their potential to cause or exacerbate congestive heart failure; additional data have suggested a link to ischemic cardiac events. Recent data also suggest that TZDs may reduce bone density. Conversely, pioglitazone may have some vasculoprotective effect related to elevation of high-density lipoprotein and lessened progression of carotid intima-media thickness; however, any effect on macrovascular clinical outcomes is unknown. Other drug options are available for the treatment of type 2 diabetes, such as incretin-based therapies. Yet despite their favorable effects on glycemia, they have not been included to date in the ADA treatment algorithm.

CONCLUSIONS: Proper glycemic control and attainment of other nonglycemic management targets (e.g., blood pressure, lipids, body weight) are essential to the prevention of long-term complications of diabetes and to reduction of overall disease management costs. Therefore, patients with diabetes should be followed closely to ensure that they achieve and maintain both glycemic and nonglycemic treatment goals. Most patients will not sustain an adequate level of control using nondrug or single-drug therapeutic approaches. When choosing among treatment options, consideration should be given to the nonglycemic as well as glycemic effects of various glucose-lowering agents.

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Diabetes has become an increasingly prevalent and costly chronic disease state and presents a significant medical and economic burden to the U.S. health care system. The increasing prevalence of diabetes has been most pronounced among younger age groups.¹ Much of the morbidity and cost is attributable to long-term, diabetes-related complications, particularly cardiovascular disease (CVD). Prevention of these complications requires a management strategy that addresses multiple physiologic conditions including hyperglycemia, dyslipidemia, and hypertension. Despite numerous observational studies and 2 large intervention trials demonstrating the benefits of aggressive management of diabetes, most patients are not attaining their treatment goals. While clinicians need to closely monitor diabetic patients and take active steps to adjust therapy when needed to reach goals for glycemic control, lipids, blood pressure, and other disease markers, this situation is increasingly problematic in current health care delivery systems. The ideal pharmacologic agent for treatment of diabetes would address all of the underlying pathophysiologic defects that lead to disease progression while also positively affecting both glycemic and nonglycemic end-points of interest. However, it is clear that multiple medications are required from an early stage of the disease to achieve targeted goals and reduce long-term complications and health care costs.

Incidence and Prevalence

According to the most recent data from the Centers for Disease Control and Prevention (CDC), nearly 15 million people in the United States, or 5% of the population, have been diagnosed with diabetes, with an additional 6 million cases, as yet, undiagnosed.² Type 2 diabetes mellitus (type 2 diabetes) accounts for

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FIGURE 1 Total Percentage of Adults With Diagnosed Diabetes by State, 2004

Taken from the Centers for Disease Control and Prevention (2007).³

approximately 90%-95% of all diagnosed diabetes cases.² Within the United States, the prevalence of diabetes varies from state to state, with higher rates generally observed in the southern and eastern states (Figure 1).³

The prevalence of diabetes in the United States has increased significantly over the past 25 years,³ with 1.5 million new cases of diabetes diagnosed in adults in 2005 alone.² Diabetes is particularly prevalent among older adults and is present in approximately 6 million individuals aged ≥ 65 years.³ However, the prevalence of type 2 diabetes is increasing in younger adults.³ Additionally, data from the CDC show that both non-Hispanic

black adults and Hispanic/Latino Americans have increased diabetes prevalence rates compared with non-Hispanic white adults (13.3%, 9.5%, and 8.7%, respectively).² The increasing rate of diabetes is expected to continue, with projections of 29 million total diagnosed cases by 2020 and 48 million cases by 2050.⁴ The increasing prevalence among younger age groups may cause a disproportionate increase in the overall health care burden because these patients will live longer with diabetes and, therefore, accrue cardiovascular and other costly complications of type 2 diabetes over a longer period of time than those previously diagnosed at an older age.

FIGURE 2 Economic Consequences of Diabetes in the United States

Taken from the American Diabetes Association (2003).⁷

^aApproximate 2002 dollars.

FIGURE 3 Estimated Cumulative Cost (Average per Patient) of Managing Complications of Type 2 Diabetes According to Type of Complication

Taken from Caro et al. (2002).⁸

The prevalence of obesity and overweight, which are significant risk factors for type 2 diabetes, has also increased. According to the National Health and Nutritional Examination Survey (NHANES), the prevalence of obesity among adults aged 20-74 years was 15%

based on data from the 1976-1980 survey and 33% according to 2003-2004 data. A similar trend was noted in the prevalence of overweight children and adolescents. In the NHANES 1976-1980 survey, the prevalence of overweight children aged 2-5, 6-11, and 12-19 years was 5%, 6.5%, and 5%, respectively. In the 2003-2004 NHANES survey, these percentages were 13.9% for children aged 2-5 years, 18.8% for those aged 6-11 years, and 17.4% among 12- to 19-year-olds.⁵ If this growth rate continues, it is estimated that nearly every American adult will be overweight by 2040.⁶ Considering the link between obesity and type 2 diabetes, as well as the comorbidities and disabilities that frequently accompany both conditions, these trends have very serious implications for future health care costs.

Burden of Illness

Annual expenditures for diabetes in the United States have been conservatively estimated at \$132 billion in direct and indirect costs (Figure 2), with costs only expected to increase as the prevalence of diabetes continues to rise.⁷ Direct costs constitute \$92 billion of this total, with annual per capita expenditures of \$13,243 compared with \$2,560 for individuals without diabetes. Patients aged ≥ 65 years account for 52% of expenditures, but costs for patients aged < 45 years are also significant, constituting 14% of the total or nearly \$13 billion per year. As greater numbers of individuals are diagnosed with diabetes at an earlier age, payers could see a potential shift in diabetes-related claims whereby more resources are devoted to managing and treating patients aged < 45 years. More than \$1 of every \$10 spent in the United States on health care services that were analyzed in this study was attributable to diabetes and diabetes-related complications, with approximately \$40 billion spent annually for hospital inpatient care, \$14 billion for nursing home care, and \$10 billion for physician office visits. For some categories of U.S. health care, costs attributable to diabetes represent a large portion of total expenditures, accounting for 18% of total home health costs, 15% of nursing home costs, and 14% of costs associated with hospice care. Chronic complications of diabetes account for 27% of expenses, with CVD presenting itself as the greatest contributor by far, accounting for 24% of inpatient days, 21% of physician office visits, and 15% of nursing home days.

Cumulative costs of diabetes-related complications, particularly macrovascular complications, rise substantially as time elapses since the original diagnosis (Figure 3).⁸ Data from a Michigan health maintenance organization (HMO) show that complications significantly increase the annual costs associated with type 2 diabetes.⁹ Each of the following increased direct medical costs by 10%-30% per member per year: a 10-kg/m² increase in body mass index, treatment with oral antidiabetic or antihypertensive agents, kidney disease, cerebrovascular disease, or peripheral vascular disease. Independent increases of 60%-90% were seen with insulin treatment, angina, and myocardial infarction (MI), and dialysis was associated with an 11-fold increase in annual

member costs for type 2 diabetes. Adding to these findings, another study found that approximately one third of diabetes-related hospital admissions were caused by uncontrolled diabetes, resulting in estimated charges of \$2.8 billion in 2004.¹⁰ Nearly 40% of these hospitalizations occurred in individuals aged <25 years.

The employer perspective on diabetes-related costs was assessed by evaluating a claims database from a self-insured national Fortune 100 manufacturer with >100,000 medical plan beneficiaries.¹¹ Expenses captured included both medical and work productivity costs. Mean annual per capita costs were significantly higher for beneficiaries with diabetes than those without (\$7,778±\$16,176 vs. \$3,367±\$8,783; $P<0.001$). Increased costs were seen in all age groups, with the highest incremental cost in the 18- to 35-year-old cohort, which had a differential cost of \$4,671 per year. Over the course of 1 year, employees with diabetes had an average of 3.4 claims for inpatient services, 5.5 claims for outpatient services, and 9.1 claims for office services compared with 1.3, 2.9, and 4.9 claims, respectively, for employees without diabetes. Approximately one third of diabetic beneficiaries filed at least 1 disability claim during the study year compared with one fifth of nondiabetic beneficiaries. The average duration of each disability claim was 41±98 days for diabetic employees and 22±73 days for nondiabetic employees ($P<0.001$).

Costs of diabetes to managed care organizations (MCOs) have recently been reviewed.¹² Diabetic patients are estimated to account for approximately 15% of MCO health care expenditures. Expressed in 2005 dollars, the mean annual cost per member ranged from \$4,614 to \$6,532 in MCOs with diabetes disease management programs and was as high as \$9,046 in MCOs without such programs. In one closed-model HMO, diabetic patients received an average of 20-24 prescription drugs per year for diabetes and other medical conditions. Pharmacy expenditures accounted for 10%-65% of overall costs, with approximately 30% of prescription costs directly related to glycemic control and the balance allotted to manage diabetes-related complications and common comorbidities (e.g., hyperlipidemia, hypertension). Thus, it is important that MCOs implement aggressive strategies that improve the overall care provided to those with diabetes while reducing the economic burden to both patients and payers. The National Committee for Quality Assurance (NCQA) estimated in 2006 that failure to deliver appropriate care to diabetic patients in MCOs results in an annual toll of 7,100-15,900 avoidable deaths, \$1.3-\$1.7 billion in avoidable hospital costs, and 10.9 million avoidable sick days.¹³

Indirect costs of diabetes, including lost productivity, disability, and premature mortality, are estimated at \$40 billion per year in the United States.⁷ During the year of this study, there were 176,000 new cases of permanent disability related to diabetes, with each case resulting in average lost earnings of \$42,462 per year. As of January 2002, 122,000 individuals aged 18-64 years who were receiving Social Security Disability Insurance benefits

listed diabetes as their primary disability, and an additional 109,000 individuals listed diabetes as a secondary disability. Lost productivity due to 186,000 premature deaths in 2002 contributed \$21.6 billion to total indirect costs. CVD was the leading cause of diabetes-related mortality, accounting for 58% of deaths. Of all cardiovascular-related mortality in the United States, approximately 19% is attributable to diabetes. Compared with individuals without diabetes, men and women with diabetes have 3.1 and 0.6 more lost workdays per year, respectively. Men and women with diabetes also have 7.9 and 8.1 more bed days per year, respectively. An additional study found that workers with diabetes are more likely to have self-reported work limitations than workers without diabetes.¹⁴ Improved glycemic control has also been shown to have a positive impact on patient quality of life, improving physical and cognitive function, mood, and overall sense of well being.^{15,16}

Value of Aggressive Management

Adequate glycemic control is a critical component in preventing microvascular complications associated with type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a 25% reduction in the risk of microvascular endpoints in patients with type 2 diabetes who were treated using an intensive glucose-lowering strategy compared with a conventional approach.¹⁷ Subsequent observational analyses from the UKPDS trial showed reductions in mortality and other diabetes-related complications, including cardiovascular complications.¹⁸ For example, a 1% decrease in glycated hemoglobin (A1C) was associated with a 14% reduction in the incidence of MI (Table 1). There were no A1C thresholds above or below which benefit was not seen; however, the greatest benefit appeared to accrue in individuals with an A1C >8%.

Reductions in A1C have also been shown to decrease medical costs and health care utilization.¹⁹⁻²² For example, Shetty et al. reported that, among diabetic patients in a large MCO, those who achieved a target A1C ≤7% had costs that were 32% lower after 1 year of follow-up than those who did not reach the target (\$1,171 vs. \$1,540).¹⁹ Another study followed individuals enrolled in a Minnesota health plan to determine the effect of baseline A1C, CVD, and depression in predicting subsequent health care costs among those with diabetes.²⁰ In their 3-year analysis, the authors found that for every 1% rise in A1C levels, there was an associated increase in costs for diabetes patients. Furthermore, these costs were significantly higher in diabetes patients who had higher A1C levels, as well as concomitant heart disease, hypertension, heart disease and hypertension, and depression.²⁰ Diabetic patients with heart disease or hypertension had significantly higher 3-year costs than patients without either of those conditions. Once A1C was <7.5% in this study, it ceased to be a predictor of increased costs; consequently, the authors concluded that once this level of glycemic control is achieved, it may be more cost-effective to focus efforts on prevention of cardiovascular

TABLE 1 Relationship Between Glycemic Control and Diabetes-Related Complications

Endpoint	Decrease in Risk (%) per 1% Decrease in A1C (95% CI) ^a	P Value
All-cause mortality	14 (9-19)	<0.001
Any diabetes-related endpoint	21 (17-24)	<0.001
Diabetes-related mortality	21 (15-27)	<0.001
Myocardial infarction	14 (8-21)	<0.001
Stroke	12 (1-21)	0.035
Lower extremity amputation or fatal peripheral vascular disease	43 (31-53)	<0.001
Heart failure	16 (3-26)	0.016
Microvascular disease	37 (33-41)	<0.001
Cataract extraction	19 (11-26)	<0.001

Taken from Stratton et al. (2000).¹⁸

^aResults are based on an observational analysis of the association between glycemic exposure and diabetes complications. For their analysis, the authors measured A1C values at baseline and as an updated mean, which was based on annual measurements of A1C concentrations calculated for each individual from baseline to each year of follow-up. Results were also controlled for factors such as age of diabetes diagnosis, sex, ethnicity, smoking, albuminuria, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides.

A1C=glycated hemoglobin.

events. An ideal management strategy for diabetes would address both glycemic control and reduction of cardiovascular risk.

Despite the clear benefits of proper glycemic control, many patients are not achieving adequate A1C reduction. In a study of primary care patients with type 2 diabetes, only 41% of patients achieved a target A1C level of <7%, which is the goal recommended by the American Diabetes Association (ADA).²³ Despite the availability of newer and potentially more efficacious drugs that work by new pharmacologic mechanisms, the number of patients with poor glycemic goal has not substantially decreased over the past 10 years.¹³ The 2007 "State of Health Care" report from the NCQA states that 30% of diabetic patients who were enrolled in commercial MCOs, 27% in Medicare, and 49% in Medicaid had poor glycemic control, defined as an A1C >9%.¹³ Furthermore, in a study of modestly controlled patients (range in mean A1C from 7.9% to 8.8%) who were managed with a sulfonylurea and/or metformin, patients spent an average of 14.5-25.6 months with A1C values >8% before a therapeutic change was made.²⁴ Only 35.3% and 44.6% of patients treated with sulfonylurea and metformin monotherapy, respectively, were switched to a new regimen as soon as, or before, the A1C exceeded 8%. Only 18.6% of patients treated with a combination of these agents were switched upon reaching this threshold. These results suggest that patients are being left with relatively uncontrolled hyperglycemia for too long before more aggressive therapy is initiated and that new therapeutic options are either

being underutilized or incorrectly prescribed too late in the disease process to best maximize therapeutic efficacy.

Although glycemic control is a very important predictor of complications and costs associated with type 2 diabetes, non-glycemic risk factors are far more important in determining global CVD risk and outcomes. Because of the significant contribution of cardiovascular comorbidities to patient outcomes and costs, it is important to evaluate endpoints and markers related to cardiovascular health. Specific recommendations are made by the ADA for management of hypertension and dyslipidemia²⁵; however, only 7% of primary care patients with type 2 diabetes have been shown to reach all 3 of the ADA goals for A1C (<7%), blood pressure (<130/80 mm Hg), and low-density lipoprotein (LDL) cholesterol (<100 mg per dL).²³ The aforementioned NCQA document reported that 57% of diabetic patients in commercial MCOs, 53% in Medicare, and 69% in Medicaid have an LDL ≥100 mg per dL.¹³ Additional biochemical markers, such as C-reactive protein and fibrinogen, have been proposed for assessing an individual patient's cardiovascular risk, but they are not as important as targeting LDL in determining outcomes.^{26,27} Drugs used in the glycemic management of type 2 diabetes may have significantly different effects on cardiometabolic risk factors and, therefore, should be evaluated with respect to these effects as well as to glycemic parameters.²⁷ This evaluation should also take into account the patient's treatment goals based on baseline A1C levels, duration of disease, and comorbidities to optimize the potential benefits of these agents and minimize the risk of intensifying any cardiovascular risk factors.

The goal of A1C levels <7%, as suggested by the ADA, is based on established evidence that this level of blood glucose control reduces the risk of microvascular disease (e.g., retinopathy, neuropathy, nephropathy) in people with type 1 or type 2 diabetes and the risk of CVD for those with type 1 diabetes. It should be advised that intensive blood glucose-lowering beyond established A1C goals in patients with type 2 diabetes and CVD may result in adverse cardiovascular outcomes, as seen with preliminary results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.²⁸ The ACCORD study was designed to evaluate whether CVD rates could be reduced in patients with type 2 diabetes who were at high risk for CVD events. The study was designed to intensively treat 3 CVD factors: hyperglycemia, dyslipidemia, and elevated blood pressure. In this study, primary outcome measures were first occurrence of a major cardiovascular event, which consisted of a composite of nonfatal MI, nonfatal stroke, or cardiovascular death.

Regarding the glycemia portion of the ACCORD study, an A1C goal of <6% was targeted for those receiving intensive treatment, while an A1C target of 7.0%-7.9% was established for the standard treatment group. Patients in both groups received all currently available antihyperglycemic agents, including metformin, sulfonylureas, meglitinides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, insulin, and insulin analogues,

along with lifestyle intervention.²⁹ Preliminary results from this study of 10,251 subjects showed that those assigned to intensive glycemic treatment (median A1C 6.4%) had a greater number of deaths compared with those in the standard treatment (median A1C 7.5%) group (257 vs. 203, respectively, or 14 vs. 11 deaths per 1,000 patients per year).³⁰ The study also found that one half of the deaths that occurred in the intensive treatment group were due to cardiovascular events, such as heart attack, sudden cardiac death, stroke, heart failure (HF), or another cardiovascular disease condition.³¹ It should be noted that, although the death rate seen in the intensive treatment group was higher than the standard treatment group, it was still lower than the death rates reported in other type 2 diabetes studies.³¹ Additionally, the incidence of nonfatal cardiovascular events (e.g., MI) was reduced by 10% among those in the intensive treatment group.³⁰ Concerned about the increased number of deaths, the National Heart, Lung, and Blood Institute (NHLBI) stopped the intensive glycemic control treatment arm of this study and switched patients to a more standard treatment regimen.²⁸ Results from this study are scheduled for publication sometime this year.

■ Pathophysiology and the Rationale for Aggressive Management Techniques

A basic understanding of the natural history and pathophysiology of type 2 diabetes is important when determining appropriate management strategies. Four intrinsic defects are present in individuals with type 2 diabetes: (1) insulin resistance in muscle and adipose tissue, (2) decreased insulin production by pancreatic beta cells, (3) increased production of glucose by the liver (Figure 4),³²⁻³⁴ and (4) decreased glucagon-like peptide-1 (GLP-1) levels.³⁵ The most significant site of insulin resistance is muscle tissue, which accounts for approximately 75% of glucose disposal in nondiabetic subjects.³² Insulin resistance in muscle is the major cause of postprandial hyperglycemia.^{32,34}

Many experts believe that insulin resistance is the primary defect present in type 2 diabetes, but that this defect is initially compensated for by an increase in insulin secretion by the pancreas.^{33,34} Individuals destined to develop diabetes, however, are genetically predisposed to eventual deterioration of beta-cell function, manifesting initially as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), or to prediabetes, with further deterioration to overt type 2 diabetes in most individuals over time.^{32-34,36} Loss of beta-cell function is gradual, and individuals generally have <20% of normal beta-cell function by the time they are diagnosed with diabetes.³⁷ Debate continues regarding the causes of beta-cell dysfunction, but possible mechanisms include chronic exposure to hyperglycemia (glucotoxicity) and/or free fatty acids (lipotoxicity).^{32-34,38} Some data suggest that chronic insulin resistance places increased secretory demands on beta cells, resulting in progressive beta-cell dysfunction.^{39,40} This hypothesis is supported by studies showing that TZDs, which decrease insulin resistance, can preserve beta-cell function over time.^{39,40}

FIGURE 4 Natural History of Type 2 Diabetes

Taken from Ramlo-Halsted and Edelman (2000).^{33,34}

The third defect of type 2 diabetes is increased hepatic glucose production, which is a result of hepatic insulin resistance.³² Hepatic glucose production is not a significant cause of hyperglycemia early in the disease course of diabetics with postprandial hyperglycemia, but it is important in maintaining the established diabetic state, especially contributing to fasting hyperglycemia.³² GLP-1 is an incretin hormone that is secreted from the gastrointestinal tract during food intake.⁴¹ GLP-1 enhances glucose-dependent insulin secretion and activates insulin biosynthesis and gene transcription to restore cellular insulin supplies for subsequent release. Additionally, GLP-1 suppresses inappropriate glucagon production from pancreatic alpha cells, slows gastric emptying (which reduces postprandial hyperglycemia), and suppresses food intake (which results in weight loss).⁴¹⁻⁴³ It has been shown that secretion of GLP-1 is decreased in individuals with type 2 diabetes. Dipeptidyl peptidase 4 (DPP-4) is an amino acid that is widely distributed in numerous tissues as well as in T cells, B cells, and natural killer cells.⁴¹ DPP-4 rapidly degrades endogenous GLP-1 levels (half-life <2 minutes).⁴¹⁻⁴³ DPP-4 inhibitors prevent the breakdown of endogenous GLP-1, thus leading to reduced glucose production from the liver by inhibiting glucagon release from pancreatic alpha cells and increasing insulin production.⁴¹ Importantly, animal studies have shown that GLP-1 preserves or enhances beta-cell function resulting from beta-cell proliferation and neogenesis, as well as inhibition of apoptosis.⁴¹ The ideal treatment strategy would address all 4 defects resulting in type 2 diabetes: reduced disposal of glucose by muscle

FIGURE 5 Algorithm for Management of Type 2 Diabetes

^a Check A1C every 3 months until $\leq 7\%$ and then at least every 6 months.

Taken from Nathan et al. (2006).⁴⁴

A1C=glycated hemoglobin.

and other tissues, impaired function of pancreatic beta cells, increased hepatic glucose production, and reduced GLP-1 levels.

Currently Recommended Treatments

The ADA and the European Association for the Study of Diabetes (EASD) have published consensus guidelines for the management of hyperglycemia in type 2 diabetes (Figure 5).⁴⁴ Initial management of both IGT and diabetes should always include lifestyle modifications, such as exercise and weight loss; however, long-term efficacy of lifestyle modification alone is limited, often requiring the addition of drug therapy to reach or maintain the goal A1C of $<7\%$. The benefits of intensive lifestyle modification of 5%-10% weight loss and 150 minutes of exercise/week were

well demonstrated in the Diabetes Prevention Program (DPP) study of patients with IGT. Current ADA guidelines recommend that individuals with IGT or IFG lose 5%-10% of their body weight and increase their physical activity to at least 150 minutes per week of moderate activity (such as walking) to prevent or delay the onset of type 2 diabetes.⁴⁵ Conventionally implemented nonintensive lifestyle management programs that do not entail regular ongoing patient educational reinforcement have not been as successful in maintaining glucose lowering.

In addition to promoting lifestyle modifications, the ADA-EASD guidelines recommend use of metformin for initial pharmacotherapy. A1C should be monitored every 3 months until the target goal is reached and every 6 months thereafter. Because of

the progressive nature of type 2 diabetes, addition of medications is the rule rather than the exception. Consequently, insulin, a sulfonylurea, and/or a TZD should be added within 2-3 months when more intensive therapy is required due to either failure of maximally tolerated doses of metformin or at any time when goal A1C is not reached, although incretin-based therapies could also be considered. Selection of a specific agent is based in part on the existing level of glycemia, with preferential consideration given to insulin for the patient who is symptomatic or has an A1C >8.5%. Other considerations when choosing a specific agent may include tolerability, nonglycemic effects, adherence, and cost.

Although the ADA-EASD algorithm provides sound guidance for the management of patients with type 2 diabetes in an evidence-based design, it does contain some significant limitations. Primary among these is that treatment recommendations are not explicitly based on the underlying pathophysiology of type 2 diabetes in a given patient, and step-care decisions are not based on fasting versus postprandial loss of glycemic control. Many of the drugs recommended for first- and second-line management address 1 but not all of the defects that cause type 2 diabetes: insulin resistance, beta-cell dysfunction, increased hepatic glucose production, and decreased GLP-1 levels. Similarly, consideration is not given to the individual patient's duration of diabetes when recommending therapy. For example, TZDs and DPP-4 inhibitors require the presence of sufficient beta-cell function to work properly and, therefore, may be more effective when administered earlier in the disease before beta-cell function has completely deteriorated. In addition, treatment recommendations are based exclusively on the patient's ability to achieve adequate glycemic control and do not give strong consideration to the propensity of glucose-lowering agents to either positively or negatively influence common comorbidities, particularly CVD. Monitoring A1C every 3 months, as recommended in the guidelines, would allow for appropriate intensification of therapy. However, Brown et al. noted up to a 3-year delay in practice before step-care was implemented in patients showing progressive hyperglycemia on monotherapy.²⁴ Thus, the guidelines, if not intensively implemented, may allow for significant periods of inadequately controlled glycemia before adjustments are made to the treatment regimen and do not require that the treating physician change the regimen after failure to achieve the target. As is the case with many step-care approaches to progressive chronic diseases, the guidelines treat to fail (i.e., allow disease progression) rather than treat to succeed (i.e., disease modification) if the treating physician's strategy lags behind the rate of disease progression.

Treatment Options

Metformin

Metformin is the only available biguanide glucose-lowering agent and is a well accepted first-line agent for treatment of type 2 diabetes.⁴⁴ Its major mechanism of action is to decrease hepatic glucose production, thus decreasing fasting hyperglycemia.^{27,44}

In addition, metformin reduces insulin resistance in muscle tissue and the liver, decreasing postprandial hyperglycemia.²⁷ When used as monotherapy, metformin typically reduces A1C by about 1.5%.⁴⁴ It is generally body-weight neutral or modestly weight lowering, is rarely associated with hypoglycemia, and may have modestly favorable effects on cardiovascular risk factors, such as triglycerides and plasminogen activator inhibitor-1, as well as possible effects on cardiovascular event rates.^{27,44} However, the frequency of gastrointestinal adverse events may limit the ability to reach maximally effective doses, with rates of diarrhea and nausea/vomiting of up to 53% and 26% of patients, respectively.⁴⁶ In addition, metformin has been associated with rare cases of fatal lactic acidosis and is contraindicated in patients with renal dysfunction.⁴⁶ Furthermore, a study by Ting et al. noted that metformin use was associated with a risk of vitamin B₁₂ deficiency. This risk increased with each 1-g-per-day metformin dose increment, as well as >3 years' duration of metformin therapy, and was consistent whether the analysis included or excluded individuals with borderline B₁₂ deficiency. The authors concluded that, for patients on long-term or high-dose metformin therapy, screening for B₁₂ deficiency should be considered.⁴⁷ Caution must be exercised when using metformin in a number of other patient populations, including those with impaired hepatic function or requiring drug therapy for HF, and metformin should be temporarily discontinued prior to surgical procedures or intravascular radiocontrast studies.⁴⁶ Because of its efficacy, infrequency of weight gain or hypoglycemia, and low cost, metformin has been recommended by the ADA-EASD as first-line pharmacotherapy for type 2 diabetes.⁴⁴ However, the durability of metformin's effectiveness as monotherapy is limited, with only 44% of patients maintaining an A1C <7% 3 years after starting therapy and only 13% with an A1C <7% after 9 years,⁴⁸ a result consistent with the progressive loss of beta-cell function seen in type 2 diabetes.⁴⁹

Sulfonylureas

Sulfonylureas are the oldest class of oral glucose-lowering agents and include the second-generation agents glipizide, glyburide, and glimepiride, as well as the first-generation agents acetohexamide, chlorpropamide, tolazamide, and tolbutamide. Sulfonylureas work as insulin secretagogues, enhancing insulin secretion by binding to a unique receptor on pancreatic beta cells and having their greatest effect on fasting hyperglycemia.^{27,44} When used as monotherapy, sulfonylureas generally result in A1C improvements of a magnitude similar to metformin (1.5%).⁴⁴ Unlike metformin, however, sulfonylureas are commonly associated with hypoglycemia and a mean weight gain of 2 kg. Although some studies, particularly those using first-generation sulfonylureas, have reported an increased risk of cardiovascular events associated with this class, more recent data suggest neither cardiovascular harm, nor benefit, with sulfonylurea agents.²⁷ Based on long experience, efficacy, and low cost, sulfonylureas are

recommended by the ADA-EASD as options for second-step pharmacotherapy in patients whose A1C remains elevated on metformin.⁴⁴ However, sulfonylureas are also hindered by limited durability of effect, with 3- and 9-year failure rates similar to those described for metformin,⁴⁸ which is again consistent with progressive beta-cell failure.⁴⁹

Insulin

Insulin administration is the most effective means of restoring glycemic control; because there is no maximum dose, any A1C level can be reduced to the target range if insulin is dosed adequately.⁴⁴ However, insulin has a number of possible limitations. It is typically administered by subcutaneous injection, often requiring multiple injections per day. Insulin carries a tangible risk of hypoglycemia, and regular self-monitoring of blood glucose is usually required.⁴⁴ Like sulfonylureas, insulin therapy is typically associated with a weight gain of 2 kg-4 kg.⁴⁴ Weight gain may be significantly higher in patients on intensive insulin therapy, with a mean weight gain of 8.7 kg in 1 study.⁵⁰ Weight gain may adversely influence a patient's cardiovascular risk. The ADA-EASD guidelines recommend addition of insulin as a second-step option for patients who are not adequately controlled on metformin monotherapy or as a third-step option for patients who still do not reach the A1C target goal on oral combination therapy.⁴⁴ Insulin is also the treatment of choice for patients with severely uncontrolled or symptomatic diabetes.⁴⁴ Some stigma may be associated with insulin use because some patients dislike giving themselves injections and because many view the drug as a treatment of "last resort" when other regimens have failed.^{51,52} Basal insulin allows clinicians to add insulin with less hyperglycemia, thus potentially reducing glucose-induced beta-cell dysfunction. However, because the need for insulin at stage 2 or 3 of treatment reflects significant beta-cell loss and, therefore, poor postprandial control, basal insulin fails to address that defect. Postprandial monitoring is not frequently used in the primary care setting; if basal insulin is used, physicians and patients must be advised to monitor efficacy with postprandial glucose monitoring. Patients on basal insulin who still have significant glycemic excursions should be considered for more intensive management with short-acting insulins, such as lispro, aspart, or glulisine.

Thiazolidinediones

TZDs, or glitazones, currently include pioglitazone and rosiglitazone. TZDs improve insulin sensitivity in muscle and adipose tissue and in the liver by activating peroxisome proliferator-activated receptor- γ (PPAR- γ).^{27,44,53} TZDs have also been shown to improve beta-cell function, probably as a result of PPAR- γ -mediated decreases in insulin resistance and beta-cell fatty acid concentrations.⁵³ TZDs have demonstrated the ability to conserve beta-cell function, delaying or preventing the development of type 2 diabetes in a high-risk population of women with

gestational diabetes in the TRIPOD (TRoglitazone In the Prevention Of Diabetes) and PIPOD (Pioglitazone In the Prevention Of Diabetes) studies.^{39,40} In the TRIPOD trial, administration of the older TZD troglitazone resulted in a 55% reduction in the incidence of diabetes at the trial's conclusion from 12.1% per year for women receiving placebo to 5.4% per year with troglitazone ($P<0.01$).³⁹ This benefit was associated with preservation of the beta-cell compensatory response to insulin resistance. Protective effects persisted even after troglitazone was discontinued, with a 92% risk reduction approximately 8 months after therapy, from a type 2 diabetes incidence of 21.2% per year in women who had received placebo to 3.1% per year in women who had received troglitazone ($P=0.030$). This suggests that troglitazone influenced the underlying defects that result in progression of beta-cell dysfunction rather than merely masking hyperglycemia. When troglitazone was withdrawn from clinical use in 2000, a follow-up study (PIPOD) was conducted using pioglitazone.⁴⁰ Pioglitazone arrested the decline in beta-cell function that occurred in women who received placebo during TRIPOD and maintained the stable beta-cell function that was present in those treated with troglitazone, with an annual incidence of diabetes of 4.6% after >3 years of follow-up.

The positive effects of TZDs on beta-cell function are somewhat supported by the ADOPT (A Diabetes Outcome Progression Trial) study.⁵⁴ In ADOPT, 40% of patients with type 2 diabetes who were initially treated with rosiglitazone monotherapy had an A1C of <7% after 4 years compared with 36% of patients treated with metformin ($P=0.030$) and 26% treated with glyburide ($P<0.001$). Thus, it appears that the ability to conserve beta-cell function through a reduction in insulin secretory demands is a class effect of TZDs, although the relatively modest improvement in progression over metformin at 5 years suggests that beta-cell stabilization with the TZD class, while important, is not complete. Over the 5-year study period, the rosiglitazone group experienced a mean weight gain of 4.8 kg, while the metformin group had a mean decline of 2.9 kg; those in the glyburide group had a 1.6-kg weight gain in the first year, which then stabilized for the remainder of the study. Rosiglitazone was also more frequently associated with edema and the use of loop diuretics than the other treatments. However, the risk of congestive heart failure (CHF) for rosiglitazone and metformin was similar (1.5% vs. 1.3%, respectively), but was significantly lower in the glyburide group (0.6%).⁵⁴

When used as monotherapy, TZDs provide a sustained decrease in A1C that ranges from 0.5%-1.5%, and they reduce both fasting and postprandial hyperglycemia while maintaining a low incidence of hypoglycemia.^{44,53,55} The most common adverse events associated with the TZD class are weight gain and fluid retention.⁴⁴ Weight gain of 3 kg-5 kg is typical, but unlike weight increases seen due to lifestyle choices, TZD-associated weight gain is actually accompanied by improvements in glycemic control^{34,53} and is mostly secondary to volume expansion and not to

fat accumulation in the majority of patients.⁵³ Weight changes reflect, in part, a redistribution of fat within the body, with increases in subcutaneous fat and decreases in the more insulin-resistant visceral fat.^{34,53} Unique to TZD therapy is fat-cell insulin sensitization, leading to improved peripheral insulin resistance and decreased free fatty acid flux, which is an important defect in the diabetic patient.^{34,53} This improvement in insulin sensitivity is due to the stimulation of fatty acid uptake, oxidation, and oxidative phosphorylation in the subcutaneous fat, but not skeletal tissue, of diabetics.⁵⁶ Fluid retention most often presents as peripheral edema but can also manifest as new or worsened HF.^{27,44}

Product labeling for both pioglitazone and rosiglitazone includes black box warnings regarding the potential for these agents to cause or exacerbate CHF in some patients, and both are contraindicated in patients with New York Heart Association class III or IV HF.^{57,58} It is recommended that patients on TZDs must be carefully observed for signs and symptoms of HF (i.e., excessive, rapid weight gain; dyspnea; and/or edema); if these signs and symptoms develop, they should be managed in accordance with current standards of care for HF. Additionally, reduction in dose or discontinuation of therapy should be considered.^{57,58} The TZD class has also been associated with an increased risk of bone loss and fractures in women, and fractures are included among the precautions in rosiglitazone's product labeling.^{58,59} A recent retrospective study conducted in the United Kingdom concluded that long-term use of TZDs was associated with an increased risk of hip and wrist fractures,⁶⁰ however, it should be noted that the mechanism for this occurrence is not fully understood and that the U.S. Food and Drug Administration (FDA) has not considered this issue to date.

In contrast to the risk of CHF, TZDs have been associated with a number of potentially beneficial effects on other cardiometabolic risk factors and events (Table 2).^{27,61-63} Agent-specific differences have been observed between pioglitazone and rosiglitazone with respect to some cardiovascular endpoints. Goldberg et al. determined that, relative to rosiglitazone, pioglitazone resulted in significant improvements in triglycerides, high-density lipoprotein (HDL) cholesterol, and LDL particle concentration and size (Figure 6).⁶³ Pioglitazone also was associated with smaller increases in total and LDL cholesterol and with no significant change in apolipoprotein B (ApoB) compared with an 11% increase in ApoB with rosiglitazone. Additionally, results from the CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) trial demonstrated that, compared with glimepiride, pioglitazone reduced the progression of carotid intima-media thickness (CIMT), a surrogate marker for coronary artery disease and cardiovascular risk. After 72 weeks of treatment, the mean CIMT progression was -0.001 mm compared with a progression of +0.012 mm with glimepiride, a difference in absolute change from baseline of -0.013 mm ($P=0.020$).⁶⁴

Pioglitazone has also demonstrated a beneficial effect on the incidence of ischemic cardiovascular events. The PROactive

TABLE 2 Effect of Thiazolidinediones on Cardiovascular Risk Markers

Risk Marker	Effect ^a	
Lipids ^b	↓/↑ total cholesterol ²⁷ ↑ LDL ^{27,61,62} ↑ HDL ^{27,61-63} ↓ TG ^{27,61-63}	↔/↑ ApoB ⁶³ ↓ LDL oxidation ^{27,61,62} ↑ LDL particle size ^{27,61,62} ↓ Free fatty acids ^{27,61,62}
Coagulation and fibrinolysis	↓ PAI-1 ^{27,61,62} ↓ Fibrinogen ^{27,61-63}	↑ TPA ²⁷ ↔/↓ Platelet aggregation ²⁷
Direct vascular effects	↓ Intima-media thickness ²⁷ ↓ Blood pressure ^{27,61,62} ↑ Cardiac output ^{27,61,62} ↑ Stroke volume ^{27,61,62} ↓ Peripheral vascular resistance ^{27,61,62} ↓ Vascular smooth muscle migration ^{27,61,62}	↓ Calcium influx and vascular contractility ^{27,61,62} ↓ Carotid intimal inflammation ^{27,61,62} ↑ Endothelial reactivity ^{27,61,62} ↓ Vascular cell adhesion molecules ²⁷ ↓ Oxidative stress ²⁷
Others	↓ Visceral adiposity ^{27,61,62} ↓ CRP ^{27,61,62}	↓ Hyperinsulinemia ^{27,61,62}

Taken from Uwaifo and Ratner (2007),²⁷ Gilling et al. (2002),⁶¹ Kelly and Bank (2007),⁶² and Goldberg et al. (2005).⁶³

^a ↓ = decreased; ↑ = increased; ↔ = no appreciable change. ApoB = apolipoprotein B; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor-1; TG = triglycerides; TPA = tissue plasminogen activator.

^b See text and Figure 7 for specific differences between pioglitazone and rosiglitazone.

(PROspective pioglitazone Clinical Trial In macroVascular Events) trial enrolled patients with type 2 diabetes and prior evidence of extensive CVD.⁶⁵ Patients were randomly assigned to receive pioglitazone (N=2,605) or placebo (N=2,633) in addition to other antidiabetic, lipid-lowering, antiplatelet, and antihypertensive medications. The primary endpoint was a composite of all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle; the main prespecified secondary endpoint was the composite of all-cause mortality, nonfatal MI, and stroke. Although pioglitazone did not achieve a statistically significant reduction in the primary endpoint (HR 0.90, 95% CI=0.80-1.02; $P=0.095$), it was associated with a 16% reduction in the main secondary endpoint (HR 0.84, 95% CI=0.72-0.98; $P=0.027$) after a mean follow-up period of 34.5 months (Figure 7). In a prespecified subgroup analysis of patients who had a previous MI (n=1,230 in the pioglitazone group, n=1,215 in the placebo group), pioglitazone patients had a 28% reduction in the risk of subsequent fatal or nonfatal MI ($P=0.045$) and a 37% reduction in the risk of acute coronary syndrome ($P=0.035$).⁶⁶ In an

FIGURE 6 Effects of Pioglitazone and Rosiglitazone on Lipids

Differences for all parameters showed statistical significance of $P < 0.001$ except for LDL particle size, which showed a statistical significance of $P = 0.005$.

Taken from Goldberg et al. (2005).⁶³

ApoB=apolipoprotein B; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TG=triglycerides.

additional subgroup analysis of patients who had a history of previous stroke ($n=486$ in the pioglitazone group, $n=498$ in the placebo group), pioglitazone decreased the incidence of recurrent stroke by 47% ($HR=0.53$, 95% $CI=0.34-0.85$; $P<0.009$).⁶⁷

In the original PROactive study, 281 patients (10.8%) in the pioglitazone group experienced HF compared with 198 (7.5%) in the placebo group ($P<0.001$). In addition, 5.1% ($n=132$) of pioglitazone-treated patients had nonserious HF compared with 3.4% ($n=90$) for placebo ($P=0.003$), and 5.7% ($n=149$) of pioglitazone patients had a serious HF event requiring hospitalization compared with 4.1% ($n=108$) for placebo ($P=0.007$). However, results demonstrated that fatal HF between the 2 groups was similar (approximately 1% in both groups; $P=0.634$).⁶⁵ These data were confirmed in subsequent analyses of the same cohort. A study by

Erdmann et al. in patients with type 2 diabetes and pre-existing CVD found that, although 5.7% of pioglitazone patients in the overall PROactive study population developed serious HF compared with 4.1% of placebo patients ($HR=1.41$, 95% $CI=1.10-1.80$; $P=0.007$), fatal HF events occurred in only 0.96% and 0.84% of patients, respectively ($HR=1.15$, 95% $CI=0.65-2.03$; $P=0.639$).⁶⁸ Among patients developing serious HF, more patients in the pioglitazone ($n=149$, 34.2%) group developed edema prior to serious HF compared with the placebo group ($n=108$, 24.1%). Furthermore, patients receiving pioglitazone in this study experienced significantly higher rates of nonserious HF (6.4%) compared with placebo (4.3%, $P<0.001$) as well as serious or nonserious edema (21.6% vs. 13.0%, $P<0.001$).⁶⁸ However, there was no significant difference in the proportion of pioglitazone

patients with serious HF that went on to have an event in the primary composite endpoint (47.7%) compared with placebo (57.4%) (HR=0.72, 95% CI=0.51-1.01; $P=0.059$). For the secondary composite endpoint, which included all-cause mortality, nonfatal MI, and stroke, slightly fewer pioglitazone patients with serious HF experienced death or cardiovascular events compared with placebo patients (HR=0.64, 95% CI=0.44-0.95; $P=0.025$).⁶⁸ This study has been criticized because the primary composite endpoint (all-cause mortality, nonfatal MI [including silent MI], stroke, acute coronary syndrome, leg amputation, coronary revascularization, or revascularization of the leg) did not reach statistical significance for pioglitazone versus placebo.

The potentially modest beneficial effect of pioglitazone on ischemic cardiovascular events is supported by a recent meta-analysis that included 19 randomized controlled trials (RCTs) of pioglitazone, enrolling 16,390 patients.⁶⁹ This analysis showed that pioglitazone was associated with a reduction in the incidence of death, MI, or stroke compared with controls (HR=0.82, 95% CI=0.72-0.94; $P=0.005$). The authors concluded that, “although fluid retention and heart failure are more frequent with pioglitazone treatment, the offsetting risks do not appear to negate the beneficial effects of the drug on irreversible ischemic and fatal end points.” While many noted limitations are apparent when using meta-analyses to interpret data, the effects of pioglitazone on ischemic heart disease (favorable) and HF (unfavorable) were consistent between this meta-analysis and the PROactive trial.

In contrast, 2 meta-analyses have suggested that rosiglitazone is associated with an increased risk of both ischemic cardiovascular events and HF. Nissen et al. conducted a meta-analysis that included 42 RCTs of rosiglitazone, which enrolled a total of 27,847 patients.⁷⁰ Compared with control patients, rosiglitazone was associated with an increased incidence of MI (OR=1.43, 95% CI=1.03-1.98; $P=0.030$). In an editorial in the *New England Journal of Medicine*, Psaty and Furberg noted that the Nissen meta-analysis had several important limitations that should be taken into account.⁷¹ One of these limitations was the use of trial summary-level data rather than patient-level data, which precluded any time-to-event analyses. The eligible trials used in the meta-analysis included comparisons to both active treatments and placebo, and no standard method was used to identify or validate outcomes; thus, events in eligible and ineligible trials may have been missed or misclassified. In addition, the authors pointed out that the total number of events was relatively small and, therefore, had no power to detect potential differences among the trials. They added that these weaknesses were substantial and that a few events occurring in either way could have changed the findings observed for MI and death from cardiovascular causes.⁷¹

A subsequent meta-analysis included only rosiglitazone RCTs that had at least 12 months of follow-up and stated an explicit intention to monitor cardiovascular adverse events;⁷² 4 trials, including 14,291 patients, met inclusion criteria. Similar to the

FIGURE 7 Kaplan-Meier Curve of Time to the Main Secondary Endpoint^a in the PROactive Trial

Numbers at Risk

Pioglitazone	2,536	2,487	2,435	2,381	2,336	396
Placebo	2,566	2,504	2,442	2,371	2,315	390

Taken from Dormandy et al. (2005).⁶⁵

^aComposite second endpoint of all-cause mortality, nonfatal MI, and stroke. There was no difference between pioglitazone and placebo in the primary endpoint of composite of all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle ($P=0.095$).

CI=confidence interval; HR=hazard ratio; MI=myocardial infarction;

PROactive=PROspective pioglitazone Clinical Trial in macroVascular Events.

previous meta-analysis, rosiglitazone was associated with a 42% increased risk of MI (RR=1.42, 95% CI=1.06-1.91; $P=0.020$). In addition, the relative risk of HF with rosiglitazone was 2.09 (95% CI=1.52-2.88; $P<0.001$). Meta-analyses have limitations, as noted earlier. Although the relative risk with rosiglitazone was increased, absolute risk remained quite small.

Additionally, a retrospective cohort study utilizing a large U.S. health care claims database suggested a differential effect of TZDs on ischemic cardiovascular events.⁷³ Among the 29,911 eligible patients, pioglitazone was associated with a decreased risk of hospitalization for MI relative to rosiglitazone (adjusted HR=0.78, 95% CI=0.63-0.96) (Figure 8). Pioglitazone also reduced the risk of the secondary endpoint, a composite of hospitalization for MI and coronary revascularization, with an adjusted HR of 0.85 (95% CI=0.75-0.98). A subsequent meta-analysis by Lago et al. failed to confirm these findings, determining that neither pioglitazone (RR=1.01, 95% CI=0.51-2.01; $P=0.98$) nor rosiglitazone (RR=0.91, 95% CI=0.63-1.32; $P=0.63$) increased the risk of cardiovascular death.⁷⁴ Both TZDs increased the risk of HF, and the difference between the 2 drugs did not reach statistical significance ($P=0.07$): RR=2.18, 95% CI=1.44-3.32, $P<0.001$ for

FIGURE 8 Risk of Hospitalization for Myocardial Infarction With Pioglitazone and Rosiglitazone

Taken from Gerrits et al. (2007).⁷³
MI=myocardial infarction.

rosiglitazone versus placebo and $RR=1.32$, 95% $CI=1.04-1.68$, $P=0.02$ for pioglitazone versus placebo.

In response to these findings, the FDA has recently included additional language in the rosiglitazone boxed warning that describes the potentially increased risk of heart attack.⁵⁸ In addition, the label was changed to contain warnings that rosiglitazone is not recommended for use in patients who are taking insulin or nitrates.⁵⁸ No such warnings have been required for pioglitazone.

In an editorial explaining the FDA's rationale for their decision, Clifford J. Rosen, MD, chair of the FDA Advisory Committee that conducted the hearing, noted that their conclusions were based on 3 independently conducted meta-analyses that investigated the incidence of myocardial ischemic events with rosiglitazone. Presentations from FDA staff members also suggested that there was a subgroup of type 2 diabetes patients (those with long-term nitrate use and those receiving concomitant insulin) who were at a higher risk for myocardial ischemic events. However, the subcommittee was mindful of the limitations that are often inherent in meta-analyses. In this case, the clinical trial limitations included a duration of only 6 months, the relatively small number of overall myocardial events, and differences in the adjudication of ischemic events. Additionally, the subcommittee received conflicting data comparing the rates of acute MI with pioglitazone versus rosiglitazone from studies including Gerrits (discussed earlier),⁷³ the WellPoint Observation Study, and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study.⁷⁵

In the WellPoint study, data from >160,000 patients were collected regarding the incidence of acute MI or acute MI/unstable angina in patients taking rosiglitazone ($N=22,050$), pioglitazone ($N=23,768$), or other antidiabetic agents ($N=120,771$). Their analysis found that the incidence for acute MI per 100,000 patient-years was similar among the 3 groups, with rates of 0.73, 0.74, and 0.72, respectively. Rates of acute MI or unstable angina found a similar trend, with incidences of 1.43, 1.33, and 1.34 per 100,000 patient-years in those taking rosiglitazone, pioglitazone, and other antidiabetic agents, respectively.⁷⁵ An interim analysis of the RECORD study was conducted that evaluated 4,447 patients who had inadequate glycemic control with metformin or a sulfonylurea. These patients were randomized to receive add-on rosiglitazone therapy or combination therapy with metformin and a sulfonylurea. The primary endpoint of this study was hospitalization or death from cardiovascular causes. Results demonstrated that the rate of hospitalization between the 2 groups was similar: 212 patients for the rosiglitazone group and 202 patients in the control group ($HR=1.08$, 95% $CI=0.89-1.31$). However, patients in the rosiglitazone group did experience a greater incidence of HF compared with controls ($HR=2.15$, 95% $CI=1.30-3.57$). Due to a mean follow-up of only 3.75 years, the authors noted that their analysis had limited statistical power to detect treatment differences.⁷⁶

TZDs are recommended by the ADA-EASD as an alternative agent in second-step therapy after metformin failure.⁴⁴ Although more expensive than generic versions of metformin and sulfonylureas, TZDs possess several characteristics suggesting that they may be better utilized at an earlier stage of type 2 diabetes.⁷⁷ TZDs have a positive effect on 3 of the 4 intrinsic pathophysiologic defects that cause type 2 diabetes. Increasing the insulin sensitivity of adipocytes, a mechanism unique to TZDs and the liver, results in improved glucose disposal and decreased hepatic glucose production, respectively.⁵³ TZDs also improve insulin secretory function and conserve beta-cell function, delaying disease progression and the onset of insulin as a permanent requirement in patients with established diabetes.^{39,40,53,65} As insulin-sensitizing agents, TZDs require the presence of insulin to work; therefore, it may be sensible to use TZDs at an earlier stage of disease progression before beta-cell function has completely deteriorated.

When used in combination with sulfonylureas, metformin, or insulin, TZDs can achieve additional A1C reductions of 0.9%-1.3%, 0.8%-1.0%, and 0.7-1.0%, respectively.^{57,58} In patients with poor glycemic control while on metformin or sulfonylurea monotherapy, addition of pioglitazone has been shown to decrease A1C by 0.6%-1.3% compared with placebo, in which increases in A1C values of 0.1%-0.2% were observed.^{78,79} Treatment regimens containing pioglitazone as add-on therapy can improve glycemic control in patients who are on existing therapy with metformin or a sulfonylurea. Over a 2-year period, the addition of pioglitazone to existing metformin therapy resulted in a reduction of

1.0% compared with a decrease of 0.8% in A1C values in patients who received add-on gliclazide therapy to metformin. In patients receiving existing gliclazide therapy, the addition of pioglitazone or metformin resulted in A1C reductions of 1.1% and 1.2%, respectively. It should be noted, however, that patients receiving add-on therapy with either metformin or gliclazide experienced rapid reductions in A1C within the first 24 weeks of the study followed by an attenuation of effect, whereas pioglitazone-treated patients had more moderate A1C reductions that were mostly sustained throughout the 2-year study.⁸⁰ This study also found that the percentages of patients who achieved target A1C levels of <7% were similar among the 3 study drugs. When pioglitazone was added to the regimen of patients who failed metformin monotherapy, 30.6% achieved target A1C values <7% after 2 years compared with 25.2% of patients who added a sulfonylurea ($P=0.128$).⁸⁰ Similarly, in patients who were failing sulfonylurea monotherapy, 30.2% who added pioglitazone were at target A1C values after 2 years compared with 28.4% of those who added metformin ($P=0.635$).⁸⁰

For patients who do not achieve adequate glycemic control while taking 2 glucose-lowering agents, the ADA-EASD recommend addition of either insulin or a third oral agent. Compared with a 2-drug regimen, a regimen of pioglitazone plus metformin and a sulfonylurea resulted in a reduction in A1C.⁸¹ In a small head-to-head study, investigators compared the effects of add-on therapy with either pioglitazone ($n=30$) or NPH insulin ($n=28$) in patients who were inadequately controlled with a dual regimen of metformin and a sulfonylurea. In this randomized 16-week study, baseline A1C values were 9.7% and 10.1% for the groups receiving add-on pioglitazone and add-on insulin, respectively. At the end of the study, patients receiving the combination of pioglitazone plus metformin and a sulfonylurea had A1C reductions of 1.9% compared with a 2.3% decrease in A1C in those receiving insulin plus metformin and a sulfonylurea ($P=0.32$).⁸¹ In each group, a similar proportion of patients achieved A1C values <7% after 16 weeks (23% for the pioglitazone group vs. 21% for the NPH insulin group, $P=0.86$).⁸¹ Nineteen patients (68%) receiving add-on insulin therapy experienced hypoglycemia compared with 11 patients (37%) receiving pioglitazone ($P=0.02$). No significant differences were found between the pioglitazone and insulin groups in blood pressure, total cholesterol, LDL cholesterol, and triglycerides, but there was significant improvement in HDL cholesterol levels (4 mg per dL [pioglitazone] vs. 0 mg per dL [NPH insulin]; $P=0.02$).⁸¹

Because metformin, sulfonylureas, and TZDs all achieve similar reductions in A1C,⁴⁴ the effect of these drugs on other disease markers should also be considered. Risk factors related to CVD are of particular concern. Pioglitazone has been shown to have a positive influence on multiple risk factors and endpoints related to ischemic cardiovascular events.^{63,65,67,69} Considering the significant impact of CVD on the morbidity, mortality, and costs associated with type 2 diabetes, the use of a drug that both

improves glycemic control and may modestly reduce the incidence of cardiovascular events might offer advantages over agents that lower glucose alone. However, glycemic therapies must be viewed primarily for their ability to sustain glucose lowering over time, with any cardiovascular benefit being a secondary and still weakly documented consideration.

Several other available treatment options were not specifically recommended in the ADA-EASD treatment algorithm. Omission of these treatment options are most often due to a relative lack of experience with and higher cost of these agents.

Meglitinides

The meglitinides, repaglinide and nateglinide, are nonsulfonylurea insulin secretagogues that must be dosed multiple times per day.⁴⁴

Alpha-glucosidase inhibitors

The alpha-glucosidase inhibitors, acarbose and miglitol, inhibit digestion of carbohydrates. They also must be dosed multiple times per day and are associated with frequent gastrointestinal side effects.⁴⁴

Incretins

Pramlintide is a human amylin analogue, and exenatide is an incretin mimetic, activating the receptor for GLP-1. Circulating levels of amylin and GLP-1 are normally increased in response to food intake. Both amylin and GLP-1 inhibit gastric emptying and glucagon secretion and reduce food intake; GLP-1 also stimulates insulin secretion.⁴³ When used in combination with metformin, sulfonylureas, TZDs, or metformin plus a sulfonylurea, exenatide has been shown to result in weight loss ranging from 0.9 kg-2.8 kg (approximately 2 lbs-6 lbs).⁸² These drugs must be administered by injection multiple times per day and frequently cause gastrointestinal adverse events.⁴⁴ Sitagliptin is a well tolerated, orally administered inhibitor of DPP-4, the enzyme responsible for rapid degradation of GLP-1.^{42,43} DPP-4 inhibitors prevent the rapid degradation of incretin hormones, improving glycemic control by increasing levels of biologically intact GLP-1, resulting in a reduction in hepatic glucose output and increase in insulin production. Due to its mechanism of action, it has been suggested that DPP-4s may potentially improve beta-cell function in humans. In addition, these agents appear to be weight neutral when used as monotherapy or in combination with other agents.⁴¹ The alpha-glucosidase inhibitors, pramlintide, and DPP-4 inhibitors generally result in smaller reductions in A1C than treatment options recommended by the ADA-EASD.^{42,44} A comparison of available glucose-lowering agents is presented in Table 3.

Combination Therapy Options

It may be practical to combine metformin (which decreases hepatic glucose production) with a sulfonylurea (an insulin secretagogue) in patients who cannot achieve adequate glycemic

TABLE 3 Comparison of Glucose-Lowering Agents

Class	Examples	Primary Mode of Action	Route of Glycemic Control	Adverse Events	Effect on Weight	Effect on Beta-Cell Function
Alpha-glucosidase inhibitors	Acarbose, miglitol ^{26,27}	Inhibit enzyme central to digestion of carbohydrates ^{26,27,44}	Postprandial glucose ^{26,27,44}	Diarrhea, abdominal pain, flatulence, ↑transaminases ²⁷	— ⁴³	?
Biguanides	Metformin ²⁷	↓ Hepatic glucose production, ↑ muscle sensitivity to insulin ^{26,27,44}	Fasting glucose, insulin sensitivity ²⁶	Diarrhea, nausea, lactic acidosis ^{27,44}	— ^{26,27,44}	?
DPP-4 inhibitors	Sitagliptin ²⁷	Inhibition of DPP-4 results in ↑ GLP-1 ^{26,27,53}	Postprandial glucose ^{26,27}	Upper respiratory infection, nasopharyngitis, headache ⁸⁷	— ^{42,87}	↑ ^{42,43}
Meglitinides	Nateglinide, repaglinide ^{26,27}	Beta-cell secretagogue ^{26,27}	Postprandial glucose ^{26,27}	Hypoglycemia ^{27,44}	— ^{27,43,44}	?
Sulfonylureas	Glimepiride, glipizide, glyburide ^{26,27}	Beta-cell secretagogue ^{26,27,44}	Fasting and postprandial glucose ^{26,53}	Hypoglycemia, weight gain ^{27,43,44}	↑ ^{43,44}	?
Thiazolidinediones	Pioglitazone, rosiglitazone ^{26,27}	Enhanced peripheral insulin sensitivity, improved hepatic insulin sensitivity ^{26,27,44}	Insulin sensitivity, postprandial and fasting glucose ^{26,53}	Fluid retention, weight gain, heart failure ^{27,43,44,53}	↑ ^{27,43,44,53}	↑ ^{27,44}
Amylin analogues	Pramlintide ²⁷	↓ Glucagon secretion, gastric emptying, and food intake ^{27,43}	Postprandial glucose ^{27,43}	Nausea, hypoglycemia ⁴³	↓ ^{27,43}	— ⁴³
Incretin mimetics	Exenatide ²⁷	↓ Glucagon secretion, gastric emptying, and food intake; ↑ insulin secretion ^{27,43}	Postprandial glucose ²⁷	Nausea, diarrhea, hypoglycemia, pancreatitis ^{43,88}	↓ ⁴³	↑ ²⁷
Insulin	—	—	Fasting and postprandial glucose ⁴³	Hypoglycemia, weight gain ^{43,44}	↑ ^{43,44}	?

Taken from American Association of Clinical Endocrinologists (2007),²⁶ Uwaifo and Ratner (2007),²⁷ Ahren (2007),⁴² Riddle and Drucker (2006),⁴³ Nathan et al. (2006),⁴⁴ Ahmed et al. (2007),⁵³ Lyseng-Williamson (2007),⁸⁷ and U.S. Food and Drug Administration (2007).⁸⁸

↓=decreased; ↑=increased; DPP-4=dipeptidyl peptidase 4; GLP-1= glucagon-like peptide-1.

control with monotherapy. These drugs are also complementary in terms of their potential to cause weight changes and hypoglycemia. The combination of metformin with a sulfonylurea can decrease A1C by 1.5%-2% compared with either drug alone with no significant increase in adverse events.⁸³ In patients failing monotherapy with either agent alone, <30% of patients treated with the combination of metformin and a sulfonylurea achieve an A1C of <7% after 2 years of treatment.⁸⁰ In another study, only 33% of patients achieved an A1C of <7% after 3 years of metformin and sulfonylurea combination therapy.⁸⁴ While effective and generally well tolerated, this combination remains limited by its inability to prevent progressive beta-cell dysfunction, thus requiring eventual addition of other glucose-lowering drugs, including insulin.

Treatment Considerations

Much of the burden of type 2 diabetes in terms of health status, direct and indirect financial costs, and quality of life is

attributable to diabetes-related complications, particularly CVD. Numerous studies have proven the benefits of adequate glycemic control on reducing the incidence of complications, and the ADA also recommends aggressive management of dyslipidemia and hypertension to further reduce the risk of cardiovascular events. Despite clear target recommendations from the ADA,²⁵ the majority of patients fail to attain an A1C <7%, an LDL <100 mg per dL, or other treatment goals. In addition, due to the progressive nature of type 2 diabetes, most patients who initially reach target levels of glycemic control will eventually experience deterioration that results in treatment failure. Consequently, it is critical that diabetic patients have regular follow-up visits to ensure that treatment goals are achieved and maintained.

The ADA-EASD recommend that A1C levels be checked every 3 months until the target goal of <7% is reached; levels should be checked at least every 6 months thereafter.⁴⁴ Metformin is recommended as initial drug therapy for most patients, but a second drug should be added within 2-3 months for patients who fail

to reach or maintain the target A1C. Medications that may be considered at this time include insulin, a sulfonylurea, or a TZD. Because TZDs address the “triple defect” of insulin resistance, beta-cell dysfunction, and hepatic glucose production and have been shown to preserve beta-cell function, they are effective options for early drug management. In addition, pioglitazone has been shown to potentially influence a variety of cardiovascular risk factors and endpoints, with favorable effects on lipids, as well as the potential to improve ischemic cardiovascular events. A recent economic analysis based on the results of the PROactive trial concluded that pioglitazone increased quality-adjusted life expectancy and was cost-effective in both short- and long-term analyses based on quality-adjusted life-years gained.⁸⁵ However, more definitive data are needed to clearly substantiate the effects of pioglitazone on cardiovascular risk factors, particularly relative to rosiglitazone. Given the conflicting evidence surrounding the risk of MI with TZD use, it is advised that caution be exercised when prescribing these agents because they can lead to fluid retention and weight gain, as well as cause or exacerbate CHF.

Summary and Conclusions

The prevalence of diabetes has been increasing in the United States and is expected to continue to rise over the next 50 years.^{3,4} The accompanying increase in the prevalence of diabetes-related complications and the occurrence of diabetes among younger adults, children, and adolescents is likely to have a substantial impact on health care costs. Total direct and indirect costs associated with diabetes have been estimated at \$132 billion per year, with CVD and other chronic complications of diabetes accounting for more than one quarter of all direct expenses.⁷ Diabetes is also associated with significant indirect costs, attributable in part to lost productivity, disability, and premature mortality.⁷ Proper glycemic control has been shown to reduce mortality, diabetes-related complications, medical costs, and health care utilization,¹⁷⁻²² but many diabetic patients do not reach or maintain their target A1C level.^{10,13,23,24} Many patients also fail to achieve treatment goals for the prevention of CVD.^{13,23}

Type 2 diabetes is the result of a combined defect in insulin resistance, beta-cell dysfunction, increased hepatic glucose dysfunction, and reduced GLP-1 levels.³²⁻³⁴ Numerous drug options are now available for the management of type 2 diabetes, but all are associated with limitations and most do not address all aspects of the “quadruple defect.” Treatment guidelines are available from the ADA-EASD,⁴⁴ but these recommendations also present limitations. TZDs influence 3 of 4 components of the quadruple defect,^{27,44,53} and pioglitazone has been shown to modestly improve dyslipidemia and possibly ischemic cardiovascular endpoints;^{63,65,67,69,73} however, both pioglitazone and rosiglitazone increase the risk of HF.^{65,69} Because patients eventually lose the ability to compensate for the pathophysiologic mechanisms behind the quadruple defect, there is a high secondary failure rate for pharmacologic therapy. The addition of TZDs to met-

formin, which also offers modest lipid and cardiovascular effects, is mechanistically attractive for diabetic patients at high risk of progression, especially those who fail initial therapy or initial combination therapy. Recognition of the significant beta-cell dysfunction that presents early in type 2 diabetes and the progressive decline in both beta-cell function and mass that follows should lead to more aggressive disease-modifying management strategies.

In conclusion, diabetes and diabetes-related complications represent a large burden to health care in terms of both direct and indirect costs. Proper glycemic control and attainment of other nonglycemic management targets are essential to the prevention of long-term complications of diabetes and to reduction of overall disease management costs. Therefore, patients with diabetes should be followed closely to ensure that they achieve and maintain both glycemic and nonglycemic treatment objectives. Most patients will not sustain an adequate level of control using nondrug or single-drug therapeutic approaches. Given the loss of 80% of beta-cell function at diagnosis of diabetes, as well as the 50% prevalence of pre-existing coronary heart disease at diagnosis, a more aggressive approach from the earliest stages of disease is clearly indicated.^{37,86}

DISCLOSURES

Author Patrick J. Boyle, MD, is a speaker for Amylin, Eli Lilly, and Takeda Pharmaceuticals North America, Inc. Author Stephen M. Gorshow, MD, FACP, is a consultant for Takeda Pharmaceuticals North America, Inc. Author Byron J. Hoogwerf, MD, is a grant recipient from Amylin and Eli Lilly; a speaker for Amylin, Eli Lilly, and Takeda Pharmaceuticals North America, Inc.; and an advisor for Amylin and Takeda Pharmaceuticals North America, Inc. Author Mark W. Stolar, MD, is a stockholder of Takeda Pharmaceuticals North America, Inc., and a speaker for Eli Lilly, Merck, and Takeda Pharmaceuticals North America, Inc. Author Dirk O. Wales, MD, PsyD, discloses no potential bias or conflict of interest relating to this article.

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Supplement