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The Impact of Diabetes and Associated Cardiometabolic Risk Factors on Members: Strategies for Optimizing Outcomes

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FACULTY

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Target Audience
Managed health care professionals with an interest in optimizing members' outcomes in metabolic syndrome, understanding the impact of cardiometabolic risk factors, and determining the role of new technologies and pharmacotherapeutic agents

Learning Objectives
After completing this activity, participants should be able to do the following:

1. Evaluate current guidelines for diagnosis and identification of metabolic syndrome.
2. Identify appropriate pharmacologic interventions in patients with cardiometabolic risk factors, including prediabetes and obesity.
3. Examine the relationship between insulin resistance and obesity as well as its role in advancing cardiometabolic risk.
4. Recognize the financial implications of cardiometabolic risk and the economic impact associated with treatment.

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The Impact of Diabetes and Associated Cardiometabolic Risk Factors on Members: Strategies for Optimizing Outcomes

Thomas J. Hoerger, PhD, MA, and Andrew J. Ahmann, MD, MS

ABSTRACT

BACKGROUND: In the past decade, the prevalence of obesity, diabetes, and metabolic syndrome has increased exponentially. Estimated national spending on direct costs related to these conditions exceeds $90 billion for overweight and obesity, $90 billion for diabetes, and $250 billion for cardiovascular disease (CVD). Spending on prescription drugs that are used to modify cardiometabolic risk (CMR) is both a major component of all spending on prescription drugs and a leading cause of the increase in such spending. Also, spending on antihyperglycemic agents is projected to become the largest single component of all spending on prescription drugs in the near future. As the use of antihyperglycemic agents continues to increase, there is a growing need to evaluate the relative and comparative cost-effectiveness of these products. As new antihyperglycemic agents appear, physicians and health plans may begin differentiating products in this category not only on the basis of their use in achieving glycemic control, but also in the context of their effect on global CMR factor modification.

OBJECTIVE: To describe the effect of overall CMR on clinical outcomes and costs in patients with diabetes.

SUMMARY: Metabolic syndrome is defined as a clustering of risk factors that identify those at increased risk of CVD and diabetes. Although the exact definition and clinical use of the term "metabolic syndrome" are debated, the clinical community is united in identifying its individual risk factors as important contributors to the development of cardiometabolic disease. Two of the most important points of consensus are that diabetes significantly increases the risk of CVD and that the CVD risk associated with metabolic syndrome is greater than the sum of its measured risk factors. Therefore, it is increasingly recognized that the risk of CVD is greater in patients with diabetes and other CMR factors than in those with diabetes alone.

Diabetes treatment goals extend beyond glycemic control to include other risk factor modifications, such as blood pressure control, lipid management, weight management, and smoking cessation. However, a significant percentage of patients do not reach their treatment targets. To improve the quality of diabetes care, treatment algorithms have been developed to provide specific recommendations for each line of treatment and to suggest prompt reevaluation. Also, new antihyperglycemic agents, such as incretin-related therapies, have the potential to address the unmet needs associated with conventional antihyperglycemic agents, including the improvement of glycemic control with either weight maintenance or weight loss and the modification of CMR factors.

Economic analyses demonstrate that CMR modification in patients with diabetes can reduce the costs of complications. Among chronic complications of diabetes, CVD treatment generates the greatest expenses, particularly in the early stages of disease progression. Health plan spending related to diabetes can be affected by a number of patient attributes, including age, glycemic control, complications, and CMR. It has also been shown that diabetes spending increases substantially in the presence of various CMR factors (e.g., obesity, hypertension, and dyslipidemia), independent of the presence of other chronic complications.

Increasing differences among antihyperglycemic agents have made apparent the need for models in cost-effectiveness analysis. Pharmacoeconomic models have been developed and validated that simulate the treatment benefits not just of glycemic control, but of comprehensive diabetes management. These models can assist in demonstrating the importance of CMR modification in patients with diabetes.

CONCLUSION: Growing evidence indicates that the evaluation of diabetes treatment strategies should incorporate considerations of their effect on global CMR. Macrovascular disease is one of the major factors in diabetes costs and resource use, both medical and pharmaceutical. Various economic analyses indicate that global CMR should be reduced to control costs in this population. Newer antihyperglycemic agents with a favorable overall metabolic profile may offer a cost-effective approach to managing diabetes.

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Managed care professionals are quite concerned about the management of diabetes, obesity, and the clustering of cardiometabolic risk (CMR) factors referred to as metabolic or cardiometabolic syndrome, because of the increased prevalence of CMR factors and the increasing number of Americans with cardiovascular disease (CVD) and/or diabetes. In particular, the growing costs—especially pharmaceutical costs—of these diseases are of great concern. As our understanding of the clinical and economic impact of CMR evolves, it is becoming clear that the strategy for controlling these costs must involve modification of the global CMR, even in patients who have already developed CVD or diabetes.

This supplement presents clinical and economic considerations related to the modification of CMR in patients with diabetes. A general discussion of controversies and established evidence regarding CMR is followed by a review of recommendations for diabetes management and an evaluation of antihyperglycemic agents in the context of CMR modification. Also reviewed are the pharmacoeconomic issues that should be considered in developing effective benefit design and coverage policies in the area of diabetes care.

Heightened Focus on Diabetes and Associated CMR Factors in the Managed Care Setting

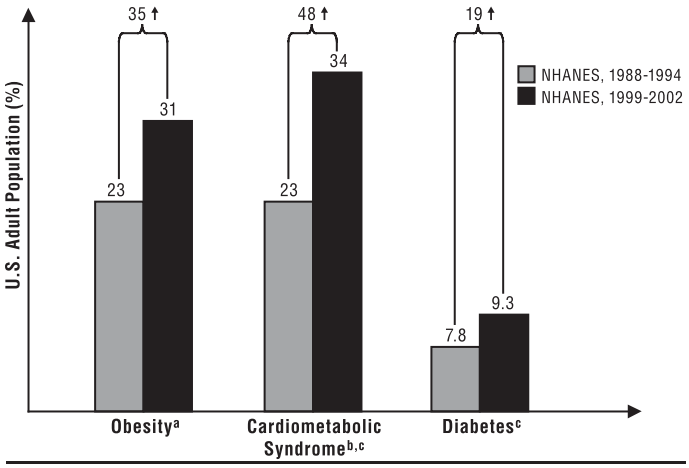
For the past decade, the managed care community has faced a growing burden from cardiometabolic disease. The increasing prevalence of obesity and other individual CMR factors has been identified as the main cause of this trend.[1] Moreover, the increasing prevalence of metabolic syndrome contributes to an increase in the prevalence of CVD and diabetes.[2] Various studies based on the results of the National Health and Nutrition Examination Survey (NHANES) indicate that over a 10- to 15-year period, the prevalence of obesity, metabolic syndrome, and diabetes has increased by 35%, 48%, and 19%, respectively (Figure 1).[3-6] Current estimates show that approximately 1 in every 3-4 American adults is obese and has metabolic syndrome and/or impaired fasting glucose, a precursor of diabetes.[3,5,6] Diabetes affects approximately 10% of American adults, and its prevalence increases to 21% among those aged 60 and over.[7]

The increasing prevalence of CVD and diabetes also leads to an increase in associated complications that result in morbidity and mortality.[2] In the United States, diabetes complications now contribute to 810 deaths, 230 amputations, 120 cases of kidney failure, and 55 cases of blindness daily.[7] Among people with diabetes, CVD is the leading cause of death, while heart disease and stroke account for about 65% of all deaths.[7] Both the use of resources and the spending associated with the clinical consequences of cardiometabolic disease and the modification of its risk factors are enormous. For example, health care spending related to just 1 CMR factor (i.e., overweight or obesity) has been estimated at $92.6 billion per year (Figure 2).[8-10] Nationwide, annual spending on direct costs related to diabetes and CVD is $90 billion and $250 billion, respectively.[9-10] The annual cost of CVD reportedly ranges from $8,200 to $13,100 per person, depending on the presence of diabetes.[11] In general, spending on individuals with diabetes is substantially higher than spending on those without diabetes. The American Diabetes Association (ADA) estimated that, in 2002, annual per capita medical expenditures were 2.4 times higher for people with diabetes than for similar people without diabetes.[9] From an employer perspective, it has been determined that workers with diabetes generate an average of $4,410 more in medical and productivity costs annually than do those without diabetes.[12]

The managed care pharmacy community has seen the increasing prevalence of CMR factors, CVD, and diabetes reflected in the steady increase in cardiovascular and diabetes therapeutic categories.[13] The growing use of 3 drug classes (i.e., lipid-lowering, antihyperglycemic, and antihypertensive agents) is the result of a larger treatment population and more aggressive treatment goals.[11,13] According to the Medco Drug Trend Reports, in the past 3 years, the increase in the rate of use of these 3 drug classes has been greater than the average increase of 2.7% for all prescription drugs.[13-16]

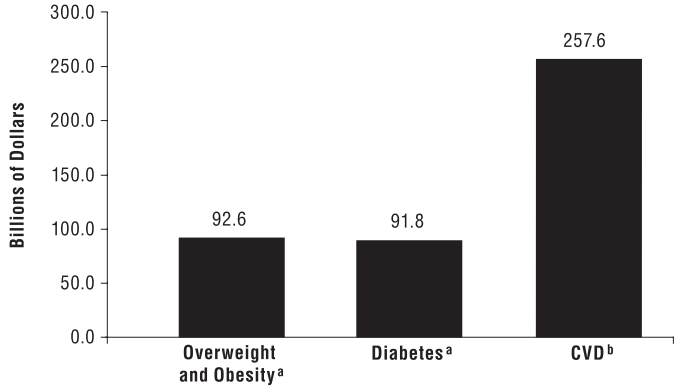
In 2006, the rates of use of lipid-lowering and antihyperglycemic agents increased by 6.2% and 5.1%, respectively. Although the overall use of antihypertensive agents has declined slightly, the decline primarily reflects the shift in therapy toward combination products; use of combination antihypertensive products increased by 9.2% in 2006. Still, spending on prescription drugs that are used to reduce CMR is both a major component of all spending on prescription drugs and a leading cause of the increase in such spending[13]; in 2006, it accounted for approximately 30% of Medco's drug spending. In particular, spending on lipid-lowering and antihyperglycemic agents was a major factor

FIGURE 1 Trends in Prevalence of Obesity, Metabolic Syndrome, and Diabetes in the U.S. Adult Population[3-6]



[a] *Age-adjusted prevalence rate.*
[b] *Prevalence of metabolic syndrome was estimated according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).*
[c] *Crude prevalence rate.*
NHANES=National Health and Nutrition Examination Survey.

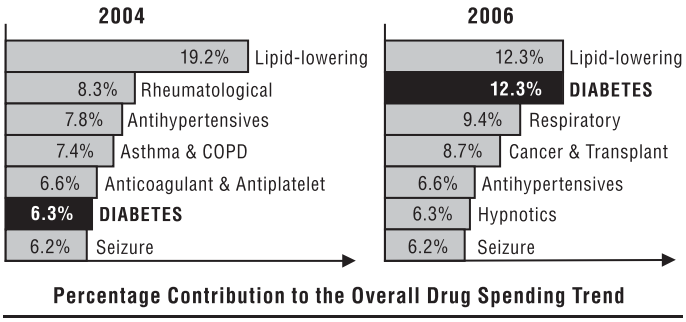
FIGURE 2 National Health Care Expenditures Attributable to Overweight and Obesity, Diabetes, and Cardiovascular Disease[8-10]



[a] *2002 dollars.*
[b] *2006 dollars.*
CVD=cardiovascular disease.

in all spending on prescription drugs and in the increase in such spending in 2006. However, while spending on lipid-lowering agents declined from 19.2% of all prescription drug spending in 2004 to 12.3% in 2006, spending on antidiabetic agents increased from 6.3% of all prescription drug spending in 2004 to 12.3% in 2006. Spending on antidiabetic drugs may exceed spending on any other prescription drugs in the near future (Figure 3).[13,15]

FIGURE 3 Trends in Top 7 Therapeutic Classes Contributing to Drug Trend[13,15]



COPD=chronic obstructive pulmonary disease.

Current Trends in the Coverage of Antihyperglycemic Agents

The antihyperglycemic category has been affected by rapidly changing market dynamics. After several years of stagnation in the marketplace, the U.S. Food and Drug Administration (FDA) approved 9 new products in the last 2 years (Table 1).[13,17] The newly marketed products are either a mix of existing classes (e.g., insulins and thiazolidinedione [TZD]/metformin combination products) or belong to new therapeutic classes (e.g., amylin analogs, glucagon-like peptide-1 [GLP-1] receptor agonists, and dipeptidyl peptidase-IV [DPP-IV] inhibitors). In 2006, growth in the antihyperglycemic category was led by select insulin analogs, TZDs, and metformin.[13] These trends may be shifting, however, because several recently approved products are rapidly penetrating the market. Specifically, according to the Medco Drug Trend Report, sales of pioglitazone + metformin (ACTOplus met), rosiglitazone + glimepiride (Avandaryl), and exenatide (Byetta) grew rapidly in 2006.[13] Also, it is expected that the latest market entrant, sitagliptin (Januvia), will reach $680 million in sales in 2007; it is already reducing the market share of TZDs.[18-19] A further shift may occur when the 6 new agents that are expected to receive FDA approval by the end of 2009 are introduced. As indicated by the pipeline projections listed in Table 1, product development is moving toward novel product delivery, such as inhaled insulin, and new therapeutic classes, such as GLP-1 agonists and DPP-IV inhibitors.[13]

As of earlier this year, TZDs were frequently positioned as tier-2 products, while new drugs, such as exenatide and sitagliptin, are typically positioned as tier-3 products. During the educational symposium titled "The Impact of Metabolic Syndrome and Cardiometabolic Risk Factors on Members: Strategies for Optimizing Outcomes" at the Academy of Managed Care Pharmacy's (AMCP) 19th Annual Meeting and Showcase in April 2007, managed care pharmacists and other professionals were polled on trends in commercial benefit coverage of the most recently approved antihyperglycemic agents (Figure 4). Of the 40 responders, 50% stated that their organizations position TZD/metformin combination products in tier 2, and approximately 50% indicated that their organizations position exenatide and sitagliptin in tier 3. Moreover, most plans were adding a prior authorization requirement to the tier-3 positioning of these 2 products.

Although safety issues related to rosiglitazone, including the risk of cardiovascular events, have been widely publicized after the release of a meta-analysis in the June 2007 issue of the *New England Journal of Medicine*, it does not appear that managed care organizations have changed their coverage policies yet as a result of this publicity.[20] Since the release of the meta-analysis, the FDA has been under pressure to reevaluate the cardiovascular risks associated with TZDs. On July 30, 2007, a federal drug advisory committee voted to require the addition of strict warnings to rosiglitazone labeling.[21] On August 14, the FDA announced that an updated label with a boxed warning on the risks of heart failure was needed for the entire TZD class.[17] The FDA's review of rosiglitazone and its possible association with an increased risk of heart attacks is still ongoing.[17] It is unclear how these safety issues will affect formulary positioning of TZDs in the next few years.

It remains to be seen how greater variety and heightened competition will influence benefit design and formulary coverage decisions in the antihyperglycemic category. It is likely that physicians will gradually shift to newer products as additional options become available. Newer agents, especially those with novel mechanisms of action, may provide options to overcome treatment inertia. With more numerous choices, physicians and health plans may also begin differentiating antihyperglycemic agents on the basis of their effects on CMR. The potential for agents to address multiple risk factors offers the opportunity to overcome obstacles in the management of chronic diseases, such as patient adherence, cost, pill burden, and drug interactions. The following sections present a detailed discussion of the differences among available options in the context of CMR modification.

CMR: Controversy Versus Established Evidence

CMR is defined as a clustering of major risk factors, life-habit risk factors, and emerging risk factors that identify those at increased risk of CVD and diabetes.[22] These associated risk factors are sometimes termed metabolic syndrome, cardiometabolic syndrome, or insulin resistance syndrome. Although the mechanisms underlying metabolic syndrome are not fully known, its pathogenesis is believed to be multifactorial.[2,23] The primary underlying risk factors of metabolic syndrome are obesity and

insulin resistance.

Increased waist circumference (i.e., abdominal obesity) is an identifying characteristic of risk associated with obesity. Abdominal obesity is defined by central adiposity and can be measured by waist circumference, waist-to-hip ratio, or determination of visceral adipose tissue (VAT). Compared with the total amount of adipose tissue, excess fat in the abdominal region is a better predictor of coronary heart disease (CHD) and type 2 diabetes and of their risk factors (i.e., dyslipidemia, glucose intolerance, and hyperinsulinemia).[24] Adipose tissue is a complex and highly active metabolic and endocrine organ; therefore, visceral fat accumulation also contributes to CHD risk factors in healthy, nonobese individuals.[24-25] Excess abdominal fat is typically accompanied by increased C-reactive protein, free fatty acids, and cytokines and by decreased adiponectin. These inflammatory mediators may play a role in the pathogenesis of diabetes.[26-29] Substantial evidence exists to support the link between excess VAT and adverse metabolic consequences, including an elevated risk of cardiometabolic disease.[24,30]

Insulin resistance can be secondary to obesity, but it can also have genetic components.[2] Insulin resistance and compensatory hyperinsulinemia play a central role in the pathogenesis of the associated cluster of abnormalities.[31] When insulin-resistant individuals cannot maintain the degree of hyperinsulinemia needed to overcome the resistance, type 2 diabetes develops.[31] However, even when insulin-resistant individuals secrete enough insulin to be considered nondiabetic, they remain at increased risk of developing metabolic risk factors.[31] Several factors further exacerbate the syndrome, including endocrine dysfunction, advancing age, physical inactivity, and genetic aberrations that affect individual risk factors. The prevalence of metabolic syndrome is increasing in the United States and worldwide, and obesity, exacerbated by a sedentary lifestyle, seems to be the primary cause.[2]

Prothrombic and proinflammatory states are also considered risk factors. A prothrombic state indicates abnormalities in procoagulant factors (i.e., increases in fibrinogen and factor VIII), antifibrinolytic factors (i.e., increase in plasminogen activator inhibitor-1), platelet aberrations, and endothelial dysfunction. A proinflammatory state is characterized by elevations of circulating cytokines and acute-phase reactants (e.g., C-reactive protein).[2]

The interrelationship between these 2 factors—abdominal obesity and insulin resistance—remains an area of divergent opinions. The cardiology community believes that abdominal obesity is the main cause of metabolic syndrome, insulin resistance, and prediabetes.[2] The endocrinology community believes that insulin resistance is the main cause of prediabetes/diabetes. Endocrinologists make a distinction between metabolic syndrome and insulin resistance syndrome because, while a great majority of patients with insulin resistance have metabolic syndrome, not all do.[31] Endocrinologists view obesity as a physiologic variable that decreases insulin-mediated glucose disposal rather than a consequence of abnormal insulin metabolism.[31] Both communities agree, however, that metabolic syndrome and insulin resistance lead to an increased risk of cardiometabolic disease.

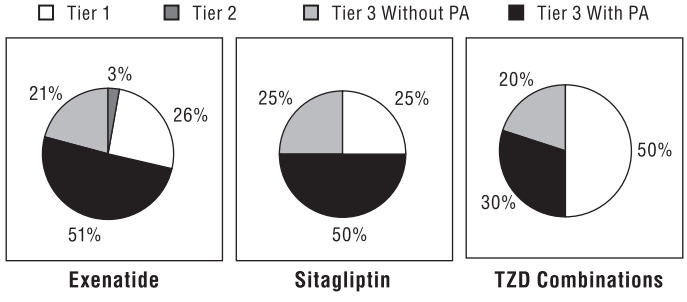
TABLE 1 Recent Hypoglycemic Drug Approvals and Near-Future Projected Pipeline[13,17]

Drug Class	Recent Approvals (January 2005 to June 2007)	Projected Pipeline (June 2007 to December 2009)
TZD combination products	ACTOplus met (pioglitazone and metformin) Avandaryl (rosiglitazone and glimepiride) Duetact (pioglitazone and glimepiride)	
Insulin analogs	Levemir (insulin detemir)	
Inhaled insulin	Exubera[a] (insulin recombinant human)	Inhaled insulin
Amylin analogs	Symlin (pramlintide)	
GLP-1 receptor agonist	Byetta (exenatide)	liraglutide Long-acting-release exenatide
DPP-IV inhibitor/combination products	Januvia (sitagliptin) Janumet (sitagliptin and metformin)	vildagliptin vildagliptin and metformin saxagliptin

DPP-IV=dipeptidyl peptidase-IV; GLP-1=glucagon-like peptide-1; TZD=thiazolidinedione.

[a] *Exubera was voluntarily withdrawn from the U.S. market by the manufacturer in October 2007.*

FIGURE 4 Trends in Coverage of Selected Recently Approved Hypoglycemic Agents[a]



[a] *Based on a sample of 40 responders.*

PA=prior authorization; TZD=thiazolidinedione.

Despite abundant research on the topic, definitions of metabolic syndrome and its various components vary widely. Many organizations have developed criteria to help identify cardiometabolic syndrome. A Diabetes Working Group of the World Health Organization (WHO) has proposed a set of criteria for a clinical diagnosis of metabolic syndrome. Essential for the diagnosis is clinical evidence of insulin resistance, such as impaired glucose tolerance, impaired fasting glucose, or type 2 diabetes. Also required for the diagnosis are 2 other risk factors from

among the following: elevated triglycerides or low high-density lipoprotein (HDL), elevated blood pressure, obesity, and microalbuminemia. The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) simplified the WHO criteria by requiring the presence of 3 or more of the following: increased waist circumference, elevated triglycerides, reduced HDL cholesterol (HDL-C), elevated blood pressure, and elevated glucose. Abdominal obesity was not labeled as a specific requirement for diagnosis because some individuals with insulin resistance have multiple metabolic abnormalities without overt abdominal obesity.[2] Recently, the International Diabetes Federation proposed a set of clinical criteria that are similar to the updated ATP III criteria; the only difference is that the federation requires the waist circumference threshold to be dependent on ethnicity.[2]

Although the exact definition/clinical criteria and clinical use of metabolic syndrome are debated, the clinical/scientific community is united in identifying the syndrome and its individual risk factors as important contributors to the development of cardiometabolic disease. The American Heart Association and the ADA are jointly committed to a reduction in heart disease, stroke, and new-onset diabetes. Recently, they released a joint statement reaffirming the links between CMR factors, diabetes, and CVD. They stated that, despite many unresolved scientific issues, the following CMR factors have been clearly shown to be closely related to diabetes and CVD: fasting/postprandial hyperglycemia, overweight/obesity, elevated systolic and diastolic blood pressure, and dyslipidemia. Because recent evidence suggests that risk assessment and adherence to national guidelines are suboptimal, a renewed effort to prevent and treat these conditions is imperative.[1,32]

In studies evaluating CVD and diabetes in patients with metabolic syndrome, it has been determined that CMR in metabolic syndrome is greater than the sum of its measured risk factors; CMR was associated with higher CVD mortality and higher all-cause mortality (relative risks of 2.6-3.0 and 1.9-2.1, respectively) (Figure 5).[33] Men possessing 4-5 risk factors of metabolic syndrome had a 3.7 times greater risk of CHD and 24.5 times greater risk of diabetes than did men possessing no risk factors (both $P < 0.001$) (Figure 6).[34] Once diabetes develops, CVD risk increases further.[2] Moreover, the risk of CVD is even greater for patients with diabetes and other CMRs than for those with diabetes alone. It is important to understand the factors that put patients at risk so that one can identify those patients effectively and determine the most appropriate intervention.

CMR Factor Modification in Diabetes Management

Diabetes is a chronic illness that requires continuing medical care and patient self-management to modify CMR and prevent complications. The hemoglobin A1C (A1C) goal recommended by the ADA for patients in general is <7%. The A1C goal for the individual patient is an A1C as close to normal (i.e., <6%) as possible without significant hypoglycemia. The American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) recommendation is consistent with that of the ADA (i.e., A1C goal <6.5%).

Treatment goals go beyond glycemic control to include blood pressure control and lipid management, the use of antiplatelet agents to prevent cardiovascular events, and smoking cessation.[35-37] Obesity management is also an important aspect of modifying risk in patients with diabetes.[37] In overweight and obese insulin-resistant individuals, modest weight loss has been shown to reduce insulin resistance. The ADA recommends lifestyle changes as the primary approach to weight loss; they can result in a reduction of as much as 5%-7% of starting weight.[35] However, many patients find it difficult to adhere to suggested lifestyle modifications and are not able to lose weight in this way. This is unfortunate, because even modest weight loss can improve overall health.

Although diabetes management has improved, a significant percentage of patients are not at goal levels for multiple measures including lipids, blood pressure, and A1C. Saaddine et al. used data from the NHANES 1988-1994 and 1999-2002 as well as the Behavioral Risk Factor Surveillance System 2002 to assess changes in the quality of diabetes care.[38] The analysis showed that approximately one third of people with diabetes had reached the low-density lipoprotein (LDL) goal of <100 mg per dL, less than one half had reached the systolic blood pressure goal of <130 mm Hg, and only 42% (a percentage that had not changed in more than a decade) had reached the A1C goal of <7% (Figure 7).[38] Also, epidemiologic studies indicate that 49% of people with diabetes are obese.[39] These findings make clear the need for continued efforts to improve intermediate outcomes.

For type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the benefit of intensive therapy to reduce microvascular and neuropathic complications.[35] Despite the growing array of effective and cost-effective treatments that help prevent or delay diabetes and diabetes complications, improvements in intermediate outcomes (e.g., glycemic control) are not very impressive. Both the ACE/AACE and the ADA have published treatment algorithms for health care practitioners based on current diabetes research (Table 2).[37] AACE 2007 treatment guidelines provide recommendations according to patients' needs based on their presenting A1C and exposure to treatment; these guidelines elucidate the role of newer agents in therapy.[37] The ADA algorithm provides specific recommendations for first-, second-, and third-line treatment and suggests a reevaluation of first-line therapy as early as 3 months after initiation.[40] The algorithm takes into consideration the characteristics of individual interventions, their synergies, and their cost.[35,40]

The Role of Novel Antihyperglycemic Agents in the Modification of CMR

Newer antihyperglycemic agents can play an important role in the modification of CMR factors. There are many problems

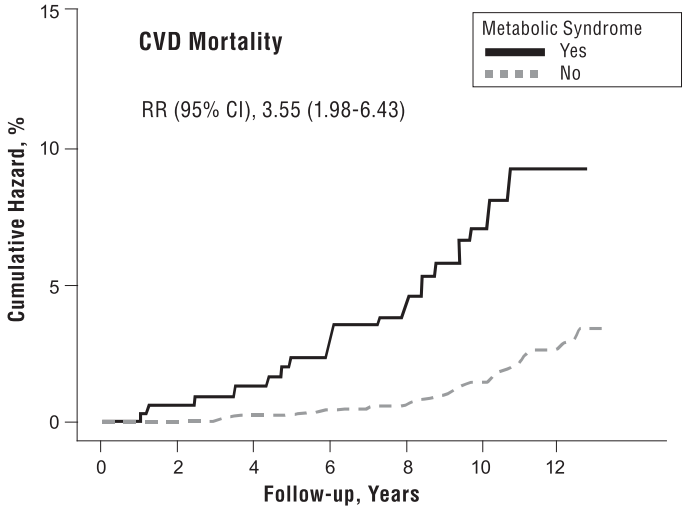
with conventional older antihyperglycemic agents (e.g., adverse metabolic effects, such as weight gain, and worsening of the lipid profile) (Table 3).[40] Also, conventional older agents are associated with the risks of hypoglycemia, gastrointestinal side effects, and edema.[37,40-41] Most important, most therapies fail to maintain long-term glycemic control; wide glycemic fluctuations and postprandial hyperglycemia are relatively common.[42] The following recently available agents address several of these needs.

Insulin analogs—Basal insulin analogs (e.g., insulin glargine and insulin detemir), which have longer nonpeaking profiles, may decrease the risk of hypoglycemia compared with Neutral Protamine Hagedorn insulin. In a number of studies, insulin detemir has been shown to improve glycemic control and induce less weight gain than other insulins.[43-44] Similarly, insulin analogs with very short durations of action, rapid-acting insulins, insulin glulisine, insulin aspart, and insulin lispro may reduce the risk of hypoglycemia compared with regular human insulin.[40]

Pramlintide—Pramlintide is a synthetic analog of the beta-cell hormone amylin. Amylin is colocalized with insulin in the beta-cells and cosecreted with insulin in response to nutrient stimuli. Amylin acts as a neuroendocrine hormone that complements the effects of insulin.[45] Progressive beta-cell dysfunction in insulin-dependent patients with type 2 diabetes leads to impaired postprandial insulin and amylin response.[46] Clinical trials involving the administration of pramlintide to insulin-treated patients with type 2 diabetes demonstrated a reduction of excess postprandial glucagon, a slowed rate of gastric emptying, and improved postprandial glucose excursions.[46] A reduction in A1C of 0.5%-0.7% was achieved without increases in insulin use or significant increases in severe hypoglycemia[40] (Figure 8).[46-47] It has also been shown that pramlintide decreases C-reactive protein and increases adiponectin, both of which are associated with inflammation and insulin resistance. The most common adverse event reported was mild to moderate nausea that dissipated early in treatment. Pramlintide is administered 3 times a day with major meals in conjunction with insulin therapy to improve glycemic control.[47]

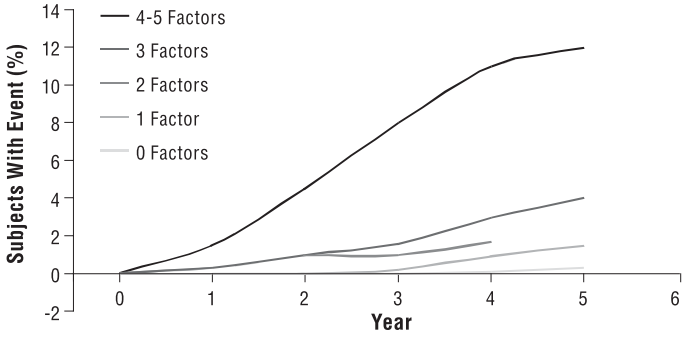
Incretin-related therapies—GLP-1 is secreted in the small and large intestine in response to a meal along with glucose-dependent insulinotropic peptide (GIP).[48] Both regulate blood glucose by stimulating glucose-dependent insulin secretion, inhibiting gastric emptying, and inhibiting glucagon secretion.[49] Therapies targeting GLP-1 have the potential to address many of the unmet needs associated with conventional older antihyperglycemic agents, among them improvement of glycemia with either weight maintenance or weight loss, low risk of inducing hypoglycemia or edema, reduction of postprandial hyperglycemia, reduction in glycemic fluctuations that may be an important contributor to oxidative stress and complications, and maintenance of long-term glycemic control.[49-51] Because GLP-1 is itself rapidly degraded by DPP-IV, there are 2 strategies for receptor activation: enzyme inhibitors and incretin mimetics that stimulate the GLP-1 receptor.[50]

FIGURE 5 Increase in CVD Mortality in Metabolic Syndrome[33]



Adapted with permission from Lakka H et al. (2002).[33]
CI=confidence interval; CVD=cardiovascular disease; RR=relative risk.

FIGURE 6 Diabetes Incidence by Number of Metabolic Syndrome Components[34]



Diabetes risk increases synergistically when at least 4 risk factors are present. Risk factors evaluated comprise metabolic syndrome symptom clusters. Those factors are increased waist circumference, blood pressure, triglycerides, and fasting glucose levels as well as decreased high-density lipoprotein levels.

Adapted with permission from Sattar N et al. (2003).[34]

DPP-IV inhibitors—By inhibiting GLP-1 breakdown, DPP-IV inhibitors increase meal-stimulated active GLP-1 and GIP levels 2-fold to 3-fold.[48] Sitagliptin is currently the only agent in this class that is FDA approved, and studies show that it is effective in improving glycemic control when used alone or in combination with metformin or a TZD. When sitagliptin was added to therapy for type 2 diabetic patients with inadequate glycemic control on a TZD, the percentage of patients achieving the target A1C of <7% was 45% compared with 23% with placebo.[44] Moreover, sitagliptin has a favorable impact on weight compared with other agents. After 54 weeks of therapy, sitagliptin was well tolerated; the change in body weight from baseline (i.e., 95% confidence

TABLE 2 Pharmacologic Regimen Options for the Treatment of Type 2 Diabetes Mellitus [37]

Pharmacologic Treatment Options	Patients Naïve to Pharmacologic Therapy			Patients Currently Treated Pharmacologically
	A1C: 6%-7%	A1C: 7%-10%	A1C: <10%	
Monotherapy				
Metformin	√			
TZD	√			
Secretagogue	√			
DPP-IV inhibitor	√			
Rapid-acting insulin analog		√ (special situations)		
Inhaled insulin		√		
Combination therapy				
Secretagogue + metformin		√		√
Secretagogue + TZD		√		√
Secretagogue + alpha-glucosidase inhibitor		√		√
TZD + metformin		√		√
DPP-IV inhibitor + metformin		√		√
DPP-IV inhibitor + TZD		√		√
Secretagogue + metformin + TZD		√		√
Inhaled insulin + oral agent		√		√
Inhaled insulin + long-acting insulin		√	√	√
Insulin + oral agent(s)		√		√
Premixed insulin analog		√ (special situations)	√	√
Rapid-acting insulin analog + long-acting insulin			√	√
Exenatide + oral agent				√
Pramlintide + prandial insulin				√
Insulin + oral agent(s)				√
Insulin + oral agent + exenatide				√ (A1C: 6.5%-8.5%)
Basal-bolus insulin therapy				√ (A1C: >8.5%)

Adapted from AACE (2007).[37]

DPP-IV=dipeptidyl peptidase-IV; TZD=thiazolidinedione.

interval [CI]) was -0.9 kg compared with 1.5 kg for patients using glipizide.[52] Sitagliptin is administered once daily as monotherapy or administered as combination therapy with metformin or a TZD as an adjunct to diet and exercise.[53]

GLP-1 receptor agonists—Incretin mimetics have become an option for adjunctive treatment in type 2 diabetes. Exenatide is currently the only agent approved in this class; however, a longer-acting formulation of exenatide and liraglutide is in clinical development. In pivotal trials, exenatide has been shown to produce a significant drop in A1C due to a robust effect on postprandial plasma glucose concentrations.[41]

Recent data show that, at 82 weeks (the length of the study extension) and at 2 years (the length of the entire study), A1C reductions from week 30 (-0.9% [0.1%]) were sustained through 2 years (-0.1% [0.1%]; $P < 0.005$ versus baseline), with 50% of the population achieving an A1C <7%. At week 30, exenatide was associated with a significant reduction in weight from baseline (-2.1 [0.2] kg); continued reductions were evident after 2 years (-4.7 [0.3] kg; $P < 0.001$ versus baseline) (Figure 9).[54] At 82 weeks, clinically relevant improvements in blood pressure, HDL-C, and triglycerides were apparent, while the greatest improvement in CVD risk factors occurred among completers with the greatest weight reduction.[54]

On the basis of data demonstrating the efficacy of exenatide when used with a TZD (with or without metformin), exenatide has been approved for use with TZDs. With exenatide, 62% of subjects with elevated A1Cs, despite therapy with TZD (alone or with metformin), achieved an A1C <7% compared with 16% with placebo.[55] The most frequent adverse effect was nausea, which was dose dependent and tended to decline over time. Reductions in weight were shown not to be dependent on nausea because weight loss was also seen in subjects who did not report nausea.[41,56] Exenatide is indicated as adjunctive therapy for patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a TZD, a combination of metformin and a sulfonylurea, or a combination of metformin and a TZD but who have not achieved adequate glycemic control.[57]

The Economic Impact of CMR Among Patients With Diabetes

On the national level, diabetes is associated with a substantial economic burden. It has been estimated that, in 2002, nearly 1 of every 10 health care dollars spent in the United States ($91.8 billion of $865 billion) was associated in some way with diabetes.[9] More than one half of these health care costs were generated by people with diabetes who were at least 65 years old.[9] A closer examination of these costs reveals that only 25% of the direct costs of diabetes is associated with diabetes care. Another 75% is associated with chronic complications (27%) and general medical conditions (48%). Among chronic complications of diabetes, CVD generates the greatest percentage of costs (19%).[9] A recent analysis evaluated the effect of obesity among people with diabetes on total national medical costs.[39] Overall, the 49% of diabetics who are obese generate 56% of the direct medical costs of diabetes.[39]

Lifetime costs associated with diabetes complications have been estimated by Caro et al.[58] They developed a model simulating a cohort of 10,000 patients with diabetes from diagnosis to death, including the occurrence of macrovascular complications (i.e., stroke, transient ischemic attack, myocardial infarction, and angina) and various microvascular complications (i.e., retinopathy, nephropathy, and neuropathy). Risks of complications

used in the model were based on the published findings of several landmark epidemiologic studies, including the UKPDS, the Diabetes Control and Complications Trial, the Rochester Epidemiology Project, the Wisconsin Epidemiologic Study of Diabetic Retinopathy, and the Framingham Heart Study. It was estimated that the 30-year cumulative cost of managing complications in a patient with diabetes was $47,240. Roughly one half of these costs were associated with macrovascular complications.[58] Moreover, it was noted that macrovascular disease is a greater determinant of cost in the early years than are microvascular complications; it accounts for 85% of cumulative costs over the first 5 years and 77% over the first 10 years.[58] These findings suggest that CMR modification in patients with diabetes can reduce the cost of complications of the disease more than modification of microvascular complications.

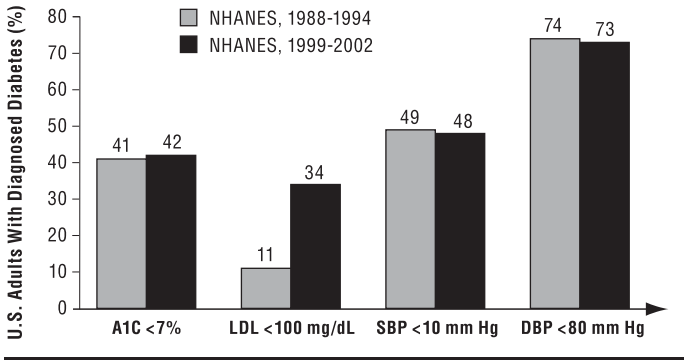
For health plans with a typical mix of members, the average annual cost for a member with diabetes has been reported to be between $4,600 and $9,000, depending on the type of organization and the presence of a diabetes disease management program.[11] Total health plan costs generated by members with diabetes are largely determined by the size and nature of the patient mix. Patient attributes that can affect health plan spending related to diabetes are listed in Table 4.[39,59,60] In the evaluation and management of diabetes costs, managed care professionals should consider specific attributes of this population such as age, glycemic control, complications, and CMR.

The economic impact of glycemic control has been fairly well established.[11] In the latest analysis of predictors of health care costs for adults with diabetes, Gilmer et al. used data from 1999 to demonstrate that higher costs were predicted for patients with an A1C >7.5%.[59] They showed that, depending on the presence and type of comorbid conditions, the cost differential between those with an A1C of 6% and those with an A1C of 10% ranges roughly between $1,500 and $5,000 per year.[59]

Patients with diabetes complications are considered high users; they use a greater number of high-cost services than patients without complications. For example, the Centers for Disease Control and Prevention (CDC) Diabetes in Managed Care Work Group has shown that individuals with multiple complications or comorbidities use significantly more specialty care services (5.8-6.3 times more), make significantly more emergency room visits (3.3-5.5 times more), and have significantly more hospitalizations (3.3-11.9 times more) than do individuals without complications.[61] In another study, Rosenzweig et al. evaluated diabetes-related health care costs based on disease severity, as evidenced by the presence or risk of developing diabetes complications.[60] Their findings indicate that spending related to major complications and comorbidities rises progressively with the increasing severity of diabetes. Moreover, the analysis showed that, among people with diabetes, the 10% with the highest health care costs are more likely to have developed chronic complications than are the other diabetics. Within this subset, the probability of acquiring CVD was higher than that of acquiring any other complication (odds ratio 3.4, 95% CI, 1.7 to 6.7).[60] The stratification of patients with diabetes according to the risk of CVD demonstrates the extent to which the risk of CVD can contribute to medical and pharmaceutical costs (Figure 10).[60]

Independent of the presence of chronic complications, the level of global CMR in patients with diabetes can also contribute significantly to health care spending. Emerging data show that the level of CMR in individuals with diabetes can affect annual and lifetime costs. Gilmer et al. demonstrated that medical costs for patients with diabetes vary, depending on the presence of hypertension, CHD, or both.[59] In this study, the presence of

FIGURE 7 Trends in Quality of Diabetes Care in the United States[a,38]



Adapted from Saaddine JB et al. (2006).[38]

[a] *Estimated for adults between the ages of 18-75 years.*

DBP=diastolic blood pressure; LDL=low-density lipoprotein; NHANES=National Health and Nutrition Examination Survey; SBP=systolic blood pressure.

TABLE 3 Diabetes Drugs[40]

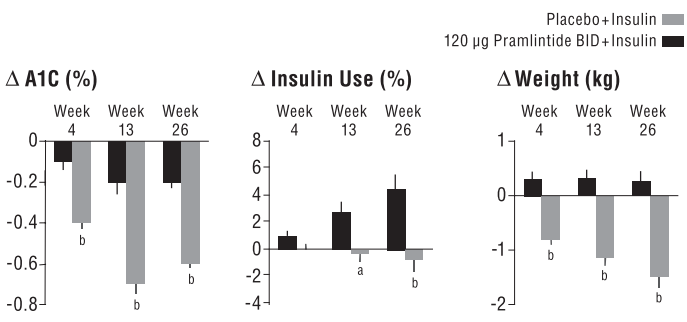
Drug	Hemoglobin A1C Decrease	Weight	Cost/Day[a]	Other CHD Benefits
Lifestyle	1-2	↓		Blood pressure, lipids
Metformin	1.5		<$1	
Insulin	1.5-2.5	↑	Varies	Lipids
Sulfonylureas	1.5	↑	<$1	
Glitazones[b]	0.5-1.4	↑	$5-$6	Lipids
Alpha-glucosidase inhibitors	0.5-0.8		$2.50-$3	
Exenatide	0.5-1	↓	$6.80-$8	
Glinides	1-1.5		$4	
Pramlintide	0.5-1	↓	$6-$8	
Sitagliptin	0.6-0.8		$4.86	

[a] *Based on U.S. average wholesale price values as of October 31, 2007, obtained from www.cardinal.com.*

[b] *Recent evidence demonstrating increased risk of heart failure with thiazolidinediones.*

CHD=coronary heart disease.

FIGURE 8 Pramlintide Clinical Effects: Type 2 Diabetes Combined Pivotals[46,47]



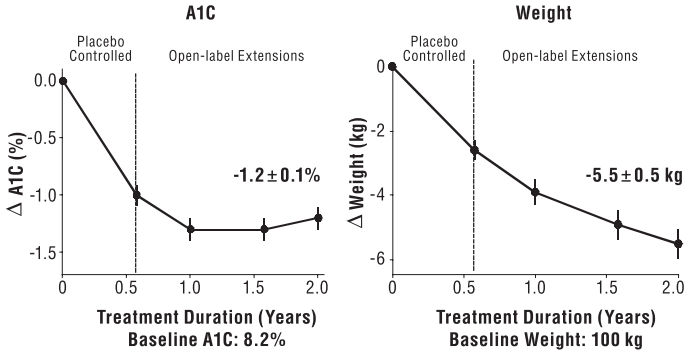
Intent to treat; Mean (SE).

[a] *P<0.01.*

[b] *P<0.0001.*

Placebo+insulin, N=284, baseline A1C=9.3%; Pramlintide+insulin, N=292, baseline A1C=9.1%.

FIGURE 9 A1C and Body Weight Reductions: Patients Treated With Exenatide for 2 Years[a,54]



[a] *2-year data cohort (N=146) mean±SE.*

TABLE 4 Member Attributes That Can Drive Health Care Spending Related to Diabetes[39,59,60]

Attributes Driving Spending	Supporting Evidence
Age	Patients >50 years incur 81% of total direct costs.
State of glycemic control	Patients with an A1C of 10% incur ~$1,500-$5,000 in incremental 3-year costs in comparison with those with an A1C of 6%.
Presence of complications	Top 10% of high-cost patients who incur 60% of the overall costs are more likely to have complications, especially CVD.
Level of CMRs	Patients with obesity ± dyslipidemia incur ~$700-$2,000 in incremental annual costs.

CMR=cardiometabolic risk; CVD=cardiovascular disease.

hypertension and CHD in individuals with diabetes increased 3-year medical costs by about $32,000. A recent analysis conducted by Finkelstein et al. showed that obesity increases the cost of diabetes care by approximately $700 per patient per year.[39] Moreover, the presence of obesity and dyslipidemia in people with diabetes increases costs by up to $2,000 per year. Although incremental costs attributable to obesity in patients with diabetes are constant regardless of age, incremental costs attributable to obesity and dyslipidemia are greater at a younger age. Unfortunately, as mentioned earlier, the prevalence of various CMR factors in people with diabetes is very high. For example, according to the ATP III criteria, abdominal obesity and/or dyslipidemia were found to be prevalent in 50%-83% of individuals with diabetes in the Framingham Offspring Study and Atherosclerosis Risk in Communities cohorts.[62]

Analysis of pharmaceutical spending associated with diabetes reveals similar findings from the standpoint of the relative contribution and breakdown of costs. It has been determined that 70% of pharmaceutical expenses for health plan members with diabetes is spent on the management of diabetes complications and the modification of CMR; only 30% of pharmaceutical expenses is directly related to glycemic control.[11]

Pharmacoeconomic Considerations in the Evaluation of CMR Modification Strategies

The growing array of new antihyperglycemic agents offers the opportunity to individualize care. However, as the use of this therapeutic class continues to expand, there is a growing need to evaluate the relative and comparative cost-effectiveness of these products. Traditionally, diabetes drugs have been judged on their ability to control blood glucose levels, which are typically measured by A1C. When only this parameter is considered, considerable differences are evident among these products (Table 2). However, examination of their overall metabolic effects reveals even greater differences. Three of the mainstays of traditional treatment—sulfonylureas, TZDs, and insulin—are associated with weight gain. In contrast, metformin and some of the new agents either reduce or do not increase weight. Differences also exist with respect to the effect these agents have on blood pressure and lipids.

Finally, cost is an important consideration. Table 3 lists the daily costs of antihyperglycemic agents based on average wholesale pharmacy prices. Although these prices may not reflect the discount prices available to health plans, they offer a good basis for a comparison of costs.

Consideration of the key differences among antihyperglycemic agents prompts the question of how to compare these drugs. This question leads in turn to a variety of more specific pharmacoeconomic questions, such as the following:

- How do products' effects on individual CMR factors affect their overall cost-effectiveness?
- How should metabolic profiles be incorporated into cost-

effectiveness modeling?

- What is the most cost-effective antihyperglycemic agent or combination therapy?
- In which scenarios are specific agents most cost-effective?

There have been a number of efforts to model cost-effectiveness in the area of diabetes management. The challenge in constructing model analyses is to relate the cost of treatment today to clinical outcomes in the future. To avoid end-stage disease (i.e., renal and heart disease) and various chronic complications, resources must be invested in diabetes management today even though their effects may take years or even decades to manifest themselves.

Because clinical trial data rarely offer the opportunity to assess actual outcomes data, pharmacoeconomic models try to simulate patients and treatment patterns over time to extrapolate from the existing evidence. The best models include key diabetes complications in the areas of neuropathy, nephropathy, retinopathy, CHD, and stroke. Their approach is to model the transition probabilities between the various states through which the disease progresses and to estimate how interventions will affect these transition probabilities. Several such validated models have been developed; the most widely used include the following:

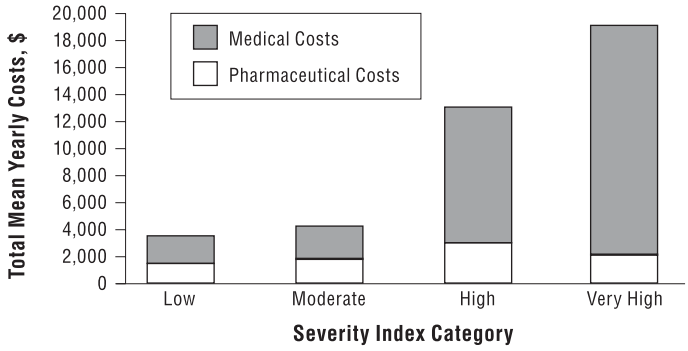
- CDC and Research Triangle Institute International (CDC–RTI) Diabetes Cost-Effectiveness Model
- Center for Outcomes Research (CORE) Diabetes Model
- Global Diabetes Model
- Archimedes Model

One of the primary advantages of these models is that they simulate the benefits of comprehensive diabetes management that accrue over a patient's lifetime. This is an important advantage, because annual transition probabilities for many complications are relatively small. The long-term time horizon used in these models provides the opportunity to evaluate both disease progression and the possibility that treatment will avert complications and their associated costs. However, the models' greatest advantage derives from the level of outcomes and units of effectiveness that they use. Instead of looking solely at intermediate outcomes (e.g., A1C, blood pressure, and LDL levels) or clinical outcomes (e.g., morbidity and mortality), these models use utility outcomes that are adjusted for patient preferences, such as quality-adjusted life-years (QALYs) gained. QALYs provide a common index that can be used to compare the value of treatments across different disease states.

Diabetes cost-effectiveness models typically demonstrate that glycemic control raises total cost but improves outcomes, which produces a positive cost-effectiveness ratio. Although the indicated cost-effectiveness ratios are generally considered attractive, the results produced by the models are always sensitive to the annual cost of treatment, whether the treatment involves a drug or a lifestyle modification. The other major result of using these models has been to emphasize the importance of CMR modification. In some analyses, blood pressure control both lowers total cost and improves outcomes—the most desirable outcome of a cost-effectiveness analysis. Cholesterol reduction usually has a somewhat higher cost-effectiveness ratio.

Results produced by the model developed by the CDC Diabetes Cost-Effectiveness Group are consistent with the aforementioned findings (Table 5).[63] Their model assessed the incremental cost-effectiveness of intensive glycemic control (as

FIGURE 10 Mean Annual Health Care Costs in People With Diabetes by CVD Risk Stratification[60]



Adapted with permission from Rosenzweig JL et al. (2002).[60]
CVD Severity Index: Low—no risk factors, signs and symptoms, or evidence of CVD; Moderate—use of antihypertensive or lipid-lowering medications or 1 CVD risk factor; High—stable CVD; Very High—unstable CVD.
CVD=cardiovascular disease.

TABLE 5 Incremental Cost-Effectiveness of Intensive Glycemic Control, Intensified Hypertension Control, and Cholesterol Reduction for Type 2 Diabetes[63]

Comparison	Change in Costs[a]	Change in QALYs	Incremental Cost-Effectiveness
Intensive vs. conventional glycemic control[b,c]	↑ by $7,927	↑ by 0.1915	$41,384 / QALY
ACEI or beta-blocker vs. diet plus other antihypertensive(s)[c]	↓ by $776	↑ by 0.3962	Cost-saving
Statin vs. no drug therapy[c,d]	↑ by $18,033	↑ by 0.3475	$51,889 / QALY

Adapted from the CDC Diabetes Cost-effectiveness Group (2002).[63]
[a] *Lifetime costs.*
[b] *Intensive glycemic control=sulfonylurea or insulin and a fasting plasma glucose target of 108 mg per dL; conventional glycemic control=diet ± hypoglycemic agent. Efficacy of various treatment options was derived from the UKPDS.*
[c] *Efficacy of hypoglycemic and antihypertensive interventions was derived from the UKPDS.*
[d] *Efficacy of lipid-lowering intervention was derived from the WOSCOPS.*
ACEI=angiotension-converting enzyme inhibitor; CDC=Centers for Disease Control and Prevention; QALY=quality-adjusted life-year; UKPDS=United Kingdom Prospective Diabetes Study; WOSCOPS=West of Scotland Coronary Prevention Study.

defined by the UKPDS), intensified hypertension control with an angiotensin-converting enzyme inhibitor or a beta-blocker, and cholesterol reduction with a statin. Their analysis included fairly high costs for intensive glycemic control and cholesterol reduction, which contributed to the relatively high cost-effectiveness ratios. Nevertheless, these ratios are comparable with those of several frequently adopted health care interventions. Moreover, the results of this model show relatively large improvements in the QALYs associated with both hypertensive control and cholesterol reduction, which highlight the relative importance of managing macrovascular complications. This study has lent support to the increasingly common view that it is essential to address a patient's overall CMR.

CMR Modification in a Cost-Effectiveness Analysis: Exenatide

A recent study demonstrates how diabetes cost-effectiveness models can be used to evaluate the effects of diabetes drugs on CMR factors. Watkins et al. published the findings of a pharmacoeconomic analysis that was used to help formulary decision makers evaluate the long-term outcomes associated with various treatment strategies.[64] They described how an existing sophisticated model (i.e., the CORE Diabetes Model) was used to help the pharmacy staff of Premera Blue Cross determine exenatide's appropriate place in therapy and its formulary positioning.

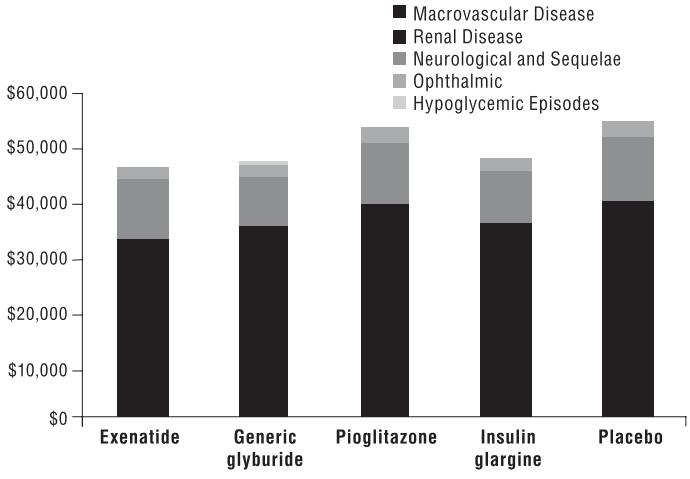
The CORE Diabetes Model was provided to Premera Blue Cross as a part of the AMCP Format dossier to help the company project the cost outcomes of exenatide in combination with metformin. The analysis was designed to evaluate the use of this medication for obese (i.e., body mass index of 35 kg per m^2) patients with uncontrolled A1C (i.e., 8.5%) who were being treated with metformin and who had hypertension (i.e., systolic blood pressure 145 mm Hg) and dyslipidemia (i.e., total cholesterol 217 mg per dL). Some built-in assumptions of the CORE Diabetes Model are that every 10% decrease in body weight results in a 10 mm Hg decrease in blood pressure, a 20 mg per dL decrease in LDL cholesterol, and a 39 mg per dL decrease in triglycerides. One key assumption of the analysis is that exenatide results in a reduction in body weight of up to 8.5%.

The analysis projected that treatment with exenatide and metformin (Figure 11)[64] would produce approximately an 11% reduction in CVD costs compared with continued treatment with metformin monotherapy over a 30-year period (i.e., $27,000 with metformin plus exenatide vs. $30,300 with metformin monotherapy); other therapies were associated with CVD costs that were similar to those with metformin therapy. Results also showed that, if initiated in patients who were inadequately controlled with metformin, exenatide would increase life expectancy by 1.5 years and add 1.7 QALYs over a 30-year period (Table 6).[64] Compared with metformin monotherapy, the incremental cost-effectiveness ratio was calculated to be $16,000 per QALY over a 30-year period.

As with any simulation, this analysis had several limitations; in particular, the assumed 8.5% decrease in body weight was higher than that reported in clinical trials. However, it appears that weight loss with exenatide continues at least through the second year of treatment.[54] The cost-effectiveness ratio was significantly higher for nonobese than for obese individuals. It was also unclear how blood pressure and cholesterol levels would be affected by the baseline treatment. It is possible that these CMR factors could be controlled with antihypertensive and lipid-lowering agents.

The results of this analysis were presented to the Premera Blue Cross pharmacy and therapeutics (P&T) committee. On the basis of the clinical and pharmacoeconomic evidence gathered, the P&T committee positioned exenatide on a 3-tier formulary with step restrictions and required a prior trial with metformin. Because of both practical considerations and the high prevalence

FIGURE 11 Case Study Results: Total 30-Year Treatment Cost in Obese Patients Treated With Metformin ± Add-on Therapy by Type of Complication[a,64]



Adapted from Watkins JB et al. (2006).[64]

[a] *The Center for Outcomes Research (CORE) Diabetes Model was used to estimate costs.*

TABLE 6 Case Study Results: Incremental Cost-Effectiveness of Exenatide Versus Metformin Monotherapy in Patients With Type 2 Diabetes Receiving Metformin[a,64]

Comparison	Change in Costs[a]	Change in QALYs	Incremental Cost-Effectiveness
Exenatide + MTF vs. MTF monotherapy	↑ by $27,000	↑ by 1.7	$16,000 / QALY

Adapted from Watkins JB et al. (2006).[64]

[a] *Data derived from the Center for Outcomes Research (CORE) Diabetes Model simulation with a 30-year time horizon.*

MTF = metformin; QALY = quality-adjusted life-year.

of obesity among plan members with diabetes, it was decided not to limit the use of exenatide to a subset of obese patients.

Summary

The increasing prevalence of diabetes among their members and the increasing use of resources to care for those members have caused managed care organizations to focus on improving the management of members with diabetes. Currently, formulary coverage decisions related to the positioning of antihyperglycemic agents are driven primarily by the value of these agents in achieving glycemic control. However, growing evidence indicates that the evaluation of any diabetes treatment strategy must incorporate considerations of its effect on the global CMR. A clear link between CMR factors and CVD is apparent, especially among patients with diabetes. Macrovascular disease is one of the major factors contributing to diabetes costs and resource use, both medical and pharmaceutical. It has also been shown that diabetes spending increases substantially in the presence of various CMR factors (e.g., obesity, hypertension, and dyslipidemia), independent of the presence of chronic complications. Various economic analyses indicate that global CMR should be reduced to improve quality of care and control costs in this population. Newer antihyperglycemic agents with a favorable overall metabolic profile may offer a cost-effective approach to managing diabetes and improving quality of care.

DISCLOSURES

Author Thomas J. Hoerger reports no financial relationships relating to this article. Author Andrew J. Ahmann is a consultant for the Amylin-Lilly Alliance, sanofi-aventis, and Ortho-Clinical Diagnostics; and is a member of the speakers bureau for Amylin, Merck, Lilly, and sanofi-aventis. Ahmann has financial relationships relating to clinical research for the above entities plus Johnson & Johnson, Bristol-Myers Squibb, Pfizer, and GlaxoSmithKline; and relating to material and document review from the Bimark Center for Medical Education.

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The Impact of Diabetes and Associated Cardiometabolic Risk Factors on Members: Strategies for Optimizing Outcomes

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The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this activity, you must complete the following forms online:

1. Posttest form for this activity, "The Impact of Diabetes and Associated Cardiometabolic Risk Factors on Members: Strategies for Optimizing Outcomes," on the AMCP.org Online Learning Center site. To receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.

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Posttest Worksheet: The Impact of Diabetes and Associated Cardiometabolic Risk Factors on Members: Strategies for Optimizing Outcomes

1. According to the National Health and Nutrition Examination Survey (NHANES), what is the increase in prevalence of obesity, cardiometabolic syndrome, and diabetes, respectively, over the 10- to 15-year period examined?
   a. 35%, 48%, 19%
   b. 19%, 35%, 48%
   c. 48%, 35%, 19%
   d. 35%, 19%, 48%

2. What is the estimated current annual spending on direct costs related to diabetes in the United States?
   a. $40 billion
   b. $90 billion
   c. $250 billion
   d. $550 billion

3. How many new antihyperglycemic agents are expected to enter the market by the end of 2009?
   a. 6
   b. 7
   c. 8
   d. 9

4. Central adiposity is a good predictor of which of the following?
   a. Coronary heart disease (CHD)
   b. Type 2 diabetes
   c. Related risk factors, such as dyslipidemia
   d. All of the above

5. According to the National Cholesterol Education Program Adult Treatment Panel III, which of the following is 1 of the 3 or more criteria that must be present for a clinical diagnosis of cardiometabolic syndrome?
   a. Abdominal obesity
   b. Elevated triglycerides
   c. Microalbuminemia
   d. All of the above

6. According to the American Heart Association and the American Diabetes Association (ADA), which of the following cardiometabolic risk (CMR) factors are closely related to cardiovascular disease (CVD) and diabetes?
   a. Fasting/postprandial hyperglycemia
   b. Overweight/obesity
   c. Elevated blood pressure
   d. All of the above

7. What percentage of diabetics is also obese?
   a. 25%
   b. 36%
   c. 49%
   d. 58%

8. Which of the following are advantages of insulin detemir?
   a. Less weight gain
   b. Slowed rate of gastric emptying
   c. Decrease in C-reactive protein
   d. All of the above

9. Which of the following are advantages of pramlintide?
   a. Improved postprandial glucose excursions
   b. Slowed rate of gastric emptying
   c. Decrease in C-reactive protein
   d. All of the above

10. Which of the following are advantages of incretin-related therapies?
   a. Reduction of postprandial hyperglycemia
   b. Reduction of glycemic fluctuations
   c. Weight maintenance
   d. All of the above

11. In clinical trials, long-acting GLP-agonists have been shown to
   a. produce significant reductions in A1C.
   b. produce minimal reductions in A1C when added to thiazolidinedione (TZD) therapy.
   c. produce the reductions in both A and B.
   d. produce none of the above.

12. What percentage of diabetes costs is associated with chronic complications and general medical costs?
   a. 45%
   b. 60%
   c. 75%
   d. >80%

13. What percentage of the direct medical costs related to diabetes do obese diabetics account for?
   a. 49%
   b. 56%
   c. 67%
   d. 71%

14. What is the annual cost differential between patients with an A1C of 6% and those with an A1C of 10%?
   a. $1,000 to $3,000
   b. $1,250 to $4,000
   c. $1,500 to $5,000
   d. $2,000 to $6,000

15. According to the CDC Diabetes in Managed Care Work Group, diabetics with complications are how many times more likely to be hospitalized?
   a. 3.3 to 5.5
   b. 3.3 to 11.9
   c. 5.8 to 6.3
   d. 5.8 to 11.9

16. Which of the following statements is true regarding health plan members with diabetes?
   a. Seventy percent of pharmaceutical spending is used on diabetes-related complications.
   b. Costs associated with obesity are the same at any age.
   c. Coronary heart disease and hypertension have a minimal impact on diabetes-related costs.
   d. None of the above.

17. Of the following statements, which one best describes findings from diabetes cost-effectiveness models?
   a. A positive cost-effectiveness ratio based on decreased drug costs and improved outcomes
   b. A negative cost-effectiveness ratio based on increased drug costs and improved outcomes
   c. A positive cost-effectiveness ratio based on increased total costs and improved outcomes
   d. A negative cost-effectiveness ratio based on decreased total costs and improved outcomes

18. Results from the CORE Diabetes Model showed which of the following results?
   a. A reduction in CVD costs with metformin plus exenatide versus metformin monotherapy
   b. A reduction in CVD costs with metformin plus exenatide versus metformin plus glyburide
   c. A reduction in CVD costs with metformin plus exenatide versus metformin plus a TZD
   d. All of the above

19. Which of the following is not classified as a CMR factor?
   a. Smoking
   b. Fasting/postprandial hyperglycemia
   c. Dyslipidemia
   d. Overweight/obesity

20. Which of the following agents is/are associated with weight gain?
   a. Metformin
   b. Sulfonylureas
   c. TZDs
   d. Exenatide
   e. All of the above
   f. B and C only

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