

## Comprehensive Management of Patients with Type 2 Diabetes: Establishing Priorities of Care

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### **Abstract**

Type 2 diabetes is a complex metabolic disorder characterized by elevated blood glucose levels and a marked increase in the risk of cardiovascular disease (CVD). The increased CVD risk is caused by a unique cluster of metabolic abnormalities, including dyslipidemia, hypertension, insulin resistance, and hyperglycemia.

To reduce the risk of cardiovascular complications in patients with type 2 diabetes, comprehensive management of risk factors is essential. Aggressive treatment of dyslipidemia and hypertension is known to benefit patients with type 2 diabetes. In addition, intensive glycemic control and targeted treatment of insulin resistance can further reduce the enormous burden of CVD in this high-risk population. Increasing evidence suggests that insulin resistance is one of the earliest markers of risk for both CVD and diabetes, and it is known that insulin resistance alone can significantly increase the risk of CVD. Type 2 diabetes and insulin resistance are both associated with disordered lipid metabolism, manifest in elevated triglyceride levels, low levels of high-density lipoprotein cholesterol, and small, dense low-density lipoprotein cholesterol particles. Patients with type 2 diabetes and insulin resistance have an increased risk of hypertension, which further contributes to their CVD risk. Each of these factors can also contribute to the risk of microvascular disease.

To ensure that patients with type 2 diabetes receive comprehensive, high-quality care, specific standards have been developed. These standards can help providers establish clear treatment targets, identify specific priorities of care, and use therapies of known efficacy to reduce the risk of complications. This review summarizes the current standards of care for patients with type 2 diabetes, with an emphasis on treatments that reduce the cardiovascular risk factors. Using a case study approach, it reviews the essential components of diabetes care and proposes a rational approach to these complex cases—an approach that should result in consistent, high-quality care.

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Type 2 diabetes has emerged as one of the most important public health concerns of the 21st century. The incidence and prevalence of type 2 diabetes are increasing,<sup>1,2</sup> and the morbidity and mortality attributable to this disease is staggering. Diabetes care currently absorbs approximately \$1 of every \$7 US healthcare dollars. Most of the morbidity, mortality, and cost of diabetes care is a direct result of treatment of potentially preventable complications.<sup>3-6</sup> Cost of care for those with diabetes is 4 times higher than for the population without diabetes.<sup>5</sup> However, practitioners now have at their disposal effective interventions which, when applied systematically, can markedly reduce the medical and financial burden of type 2 diabetes.

Limiting the risk of diabetes-related complications requires much more than intensive glycemic control. Good glycemic control can reduce microvascular complications of the eyes, kidneys, and nerves. Cardiovascular disease (CVD), however, is arguably the most common and clinically important secondary complication in adults with diabetes.<sup>7,8</sup> CVD affects up to 80% of those with diabetes and accounts for approximately 70% of mortality in diabetes patients.<sup>9</sup> Diabetes increases the risk of CVD 2 to 4 times,<sup>10</sup> and the risk is greatest for women.<sup>11</sup> Recent data suggest that individuals with diabetes have a risk of CVD events that is comparable

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with that of individuals without diabetes who have preexisting CVD.<sup>7,12</sup> Much of this increased risk is a consequence of an increase in classic CVD risk factors.<sup>13</sup> In addition, the negative impact of any given risk factor is amplified in the patient with diabetes. For example, abnormalities in blood pressure or lipids will have a greater negative impact on diabetes patients than on those without diabetes.<sup>14</sup> Given these findings, type 2 diabetes should not be regarded simply as a metabolic syndrome, but as a vascular syndrome with metabolic consequences, including hyperglycemia and insulin resistance. Indeed, type 2 diabetes generally arises in the same metabolic setting as CVD. Obesity, hypertension, dyslipidemia, and insulin resistance are common to both conditions.<sup>11,13,14</sup> This fact and the presence of modifiable risk factors in patients with diabetes suggest that early and aggressive treatment can significantly reduce the risk of heart disease.

### Standards of Care for Patients with Diabetes

Hyperglycemia is universal, while dyslipidemia occurs in up to three fourths of those with diabetes.<sup>15</sup> Hypertension is present in up to 70% of patients,<sup>16</sup> and insulin resistance is reported to be present in 75% to 90% of patients with type 2 diabetes.<sup>13,17</sup>

Healthcare providers, diabetes educators, and patients all share a common goal: preventing or minimizing secondary complications. Fortunately, several interventions—intensive glycemic control, management of dyslipidemia and hypertension, and specific therapies for insulin resistance—have been shown to significantly reduce the rates of both microvascular and macrovascular disease. **Table 1** (based on data from published clinical trials) summarizes some specific therapies used in patients with type 2 diabetes and describes the potential impact of these therapies on rates of microvascular and macrovascular disease.

A set of common and essential medical processes and outcomes for adult patients with diabetes has been identified and embraced by health management organizations and healthcare practitioners. These standards of care were recently published by the American Medical Association, the Joint Commission on Accreditation of Healthcare Organizations, and the National Committee for Quality Assurance in a consensus statement titled *Coordinated Performance Measurement for the Management of Adult Diabetes*.<sup>18</sup> This publication outlines evidence-based criteria for specific interventions that are consistent with recommendations by the American Association of Clinical Endocrinologists and the American Diabetes Association (ADA).<sup>19</sup> By using these specific measures, health management systems can now collect and report on an expanded, comprehensive set of outcomes. This information will allow health plans and medical practitioners to benchmark their results against those of others. The standards of care advocated in this review include specific treatment targets and interventions, all based on published data.

**Table 1.** Therapeutic Areas in Diabetes Management: Potential Impact on Macrovascular Risk and Microvascular Complications in Type 2 Diabetes

Risk Factor	Intervention	Prevalence	Reduction in Cardiovascular Disease Risk	Reduction in Microvascular Risk
<b>Hyperglycemia</b>	Intensive glycemic control	100%	? 16% <sup>1</sup>	20%-50% <sup>20,21</sup> (with HbA <sub>1c</sub> target < 7%)
<b>Dyslipidemia</b>		~75%		
LDL-C,	Statins		25%-50% <sup>39-41</sup>	? Modest benefit
Trigs, HDL-C	Fibrates		25% <sup>42-43</sup>	—
	Glitazones		Unknown	—
<b>Hypertension</b>	Multidrug therapy	~70%	20%-55% <sup>50-59</sup>	25% <sup>50-51</sup>
<b>Insulin Resistance</b>	Glitazones Metformin	75%-90%	Unknown ? 39% <sup>20</sup>	Unknown

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; trigs = triglycerides; ? = final data not yet available.

Source: References 1, 20, 21, 39-43, 50-59. Reprinted with permission from International Diabetes Center. Copyright 2001, International Diabetes Center, Minneapolis, MN.

### Case Study

A 53-year-old woman presented to a diabetes clinic at the request of her primary physician to discuss treatment options for type 2 diabetes. Her diabetes had been diagnosed 8 years earlier and treated with a combination of metformin and glyburide. Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) values had ranged from 6.9% to 7.6% in the past year. Despite a modest elevation in morning blood glucose values (130 to 178 mg/dL in the 4 weeks prior to evaluation), the patient was experiencing daytime hypoglycemia. Blood glucose values lower than 60 mg/dL occurred up to 5 times weekly. She had received instruction on carbohydrate counting and was attempting to follow a consistent meal plan. The patient did not participate in regular physical activity because of persistent knee pain from osteoarthritis.

The patient was concerned about the potential for CVD because 3 of her 4 siblings had type 2 diabetes. Two of them had died of CVD in their 50s. The patient's medical history showed hypertension of 3 years' duration, currently being treated with angiotensin-converting enzyme (ACE) inhibitor therapy (lisinopril 10 mg/day). Her elevated low-density lipoprotein cholesterol (LDL-C) was currently being treated with cerivastatin sodium, 0.4 mg/day. She was maintained on daily aspirin therapy (325 mg/day). System review was otherwise negative. She reported a history of oligomenorrhea dating back more than 20 years. She had never been pregnant. She had no history of peripheral neuropathy or retinopathy. She said she had no history of chest pain, shortness of breath, or other anginal symptoms. Neither a dilated-eye examination nor a comprehensive foot examination had been performed within the past year.

Physical examination was remarkable for central obesity. The patient's weight was 260 lb (118 kg); her body mass index was 44 kg/m<sup>2</sup>. Blood pres-

sure was 148/88 mm Hg. No additional abnormalities were noted on physical examination.

In initial laboratory studies, HbA<sub>1c</sub> value was 7.0%. Lipid values on cerivastatin therapy were as follows: total cholesterol, 189 mg/dL; high-density lipoprotein cholesterol (HDL-C), 39 mg/dL; triglycerides, 240 mg/dL; LDL-C, 102 mg/dL. A random urine sample obtained 1 year earlier revealed an albumin/creatinine ratio of 122 mg/g. Serum creatinine values, liver function studies, and electrolyte levels were normal.

Despite the absence of specific cardiovascular symptoms, the patient and her primary physician wanted an evaluation with imaging exercise stress testing. Given the patient's family history and the presence of multiple CVD risk factors, exercise Sestimibi stress imaging was performed. It revealed a large, reversible anterior defect. Subsequent coronary angiography revealed total occlusion of the left anterior descending artery and a 70% stenosis of the right coronary artery. A number of distal lesions (<40% stenosis) were also noted. Given these findings, coronary bypass surgery was advised. The patient underwent successful 3-vessel coronary artery bypass grafting.

### Comprehensive Management of Type 2 Diabetes

This case study underscores the need for complex management of patients with type 2 diabetes. The discovery of previously undiagnosed CVD emphasizes the importance of comprehensive CVD risk factor assessment and treatment. In this case, it is clear that the primary focus of care should be to reduce the risk of cardiovascular events. However, glycemic control and the potential microvascular complications cannot be ignored. In caring for such a patient, healthcare providers must first identify any modifiable risk factors that contribute to the

complications risk. In addition, the patient must be educated about specific pharmacologic and nonpharmacologic therapies.

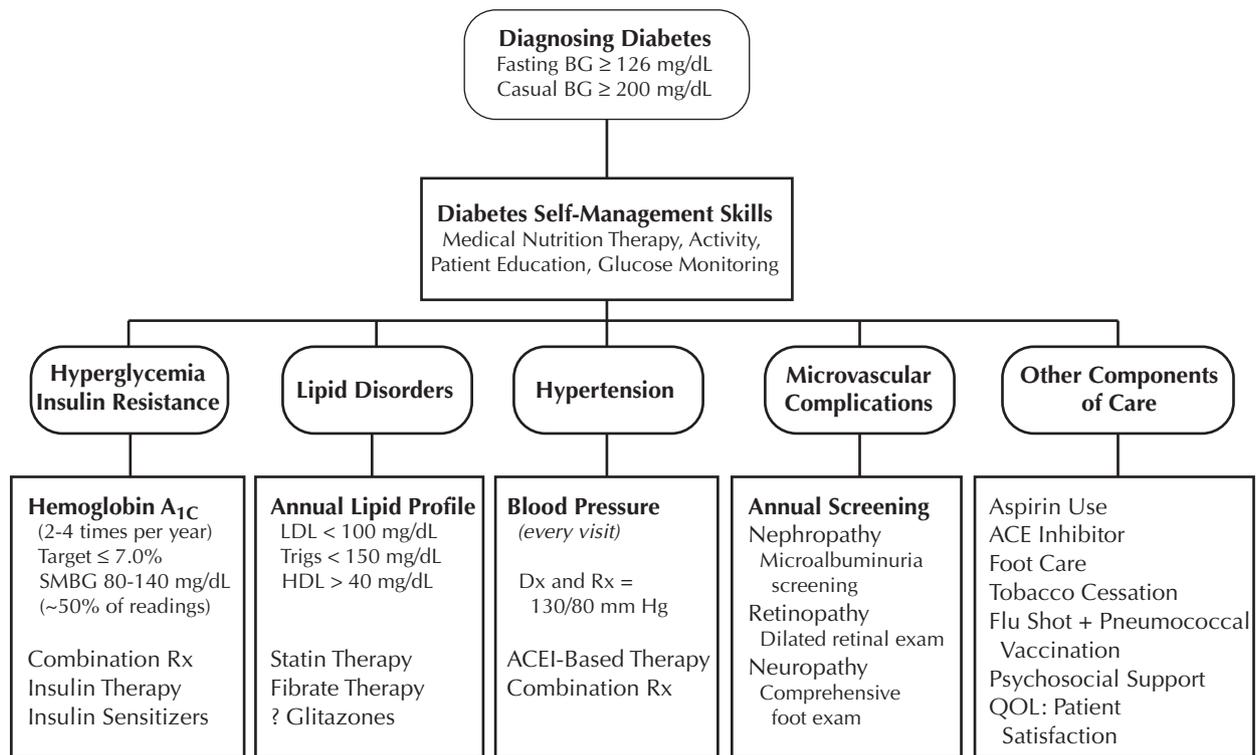
**Figure 1** outlines a straightforward, comprehensive approach to caring for adults with diabetes. The management of type 2 diabetes is multifaceted. This graphic summarizes the central theme of our review. It includes criteria for diagnosis of diabetes, elements of patient education, and the specific components of care necessary to limit the risk of complications. Glucose control, recently confirmed by the United Kingdom Prospective Diabetes Study (UKPDS) as a critical determinant of microvascular disease risk, is only one component of care.<sup>20,21</sup> Comprehensive care also includes

identification and treatment of lipid disorders and hypertension; treatment of insulin resistance; the prevention, screening, and treatment of microvascular complications; and attention to other components of clinical care that have special significance in people with diabetes.<sup>18</sup> Other reviews have discussed the importance of early diagnosis of diabetes and the potential benefit of early treatment of insulin resistance.<sup>22,23</sup>

**Priorities of Care in Adults with Diabetes**

**Diagnosis of Diabetes.** Although our clinical case does not specifically emphasize the importance of early diagnosis, comprehensive diabetes care begins with

**Figure 1.** Priorities of Care for Adults with Diabetes



ACEI = angiotensin-converting enzyme inhibitor; BG = blood glucose; DX = diagnosis; HDL = high-density lipoproteins; LDL = low-density lipoprotein; QOL = quality of life; RX = prescription drug; SMBG = self-monitoring blood glucose; trigs = triglycerides; ? = final data not yet available.

a timely diagnosis. In 1997, an expert committee from the ADA revised the National Diabetes Data Group/World Health Organization 1979 classification and diagnosis standards.<sup>24,25</sup> Type 2 diabetes (formerly called non-insulin-dependent diabetes) now represents 90% to 95% of diabetes diagnoses—the remainder being type 1 diabetes. The key to making this diagnosis is to identify and screen high-risk populations. These high-risk groups include people of specific ethnic backgrounds (Hispanic Americans, American Indians, African Americans), individuals who have a family history of type 2 diabetes, women with a history of gestational diabetes, and individuals with other components of the insulin-resistance syndrome (hypertension, dyslipidemia, impaired fasting glucose).<sup>13</sup> Patients with known CVD are also at higher risk for type 2 diabetes.<sup>17</sup> After the diagnosis of diabetes is established, patient education is paramount, and specific, targeted therapies can be considered for each component of this syndrome.

***Self-Management Training: Education and Team Management.*** In recent years, diabetes care has emphasized the growing importance of self-management education and behavior change. Diabetes care must begin with the education of the patient. A number of studies have demonstrated the benefit of diabetes education,<sup>26-29</sup> although most of them conclude that education alone cannot affect all areas of diabetes care.<sup>30,31</sup>

Education is intended to enhance the patient's understanding of diabetes and to provide the patient with detailed training about nonpharmacologic interventions. More important, education is critical if patients are to change behavior. It is well understood that improved outcomes in diabetes depend upon a sustained change in patient behavior.<sup>32,33</sup> These changes include adherence to medications and to the nondrug components of care, including self-monitoring of blood glucose levels, education about nutrition, and physical activity. Education programs can

establish and reinforce treatment targets for each intervention and ensure that these targets are clearly understood and agreed to by the patient.

Diabetes education is an ongoing process. The goal of such education is to help patients better understand the importance of the many components of diabetes care, such as the importance of ongoing monitoring of blood glucose and regular measurement of HbA<sub>1c</sub> values. Education teams can identify patients who may need interval monitoring for lipid disorders and hypertension. In addition, those on the education teams can assist primary providers in ensuring that regular eye examinations, microalbumin screening tests, and comprehensive foot examinations are performed. With increased awareness, patients are more likely to adhere to all aspects of treatment.

#### **Targeting Risk Factors**

Dyslipidemia, hypertension, hyperglycemia, and insulin resistance contribute significantly to the increased CVD risk in diabetes patients. **Figure 2** is a timeline showing the probable onset sequence of components of the type 2 diabetes syndrome. The figure illustrates the CVD risk identified at the time of diagnosis of diabetes. The data indicate that hyperglycemia may be one of the last metabolic abnormalities to appear in these patients. Hyperglycemia contributes significantly to microvascular disease. The combination of insulin resistance, dyslipidemia, and hypertension contributes to CVD risk even before glucose intolerance develops. Insulin resistance is usually one of the earliest markers of the disease. However, whether early treatment of insulin resistance can have a significant impact on CVD risk remains to be determined.

***Dyslipidemia.*** Dyslipidemia is common in adults with diabetes, and treatment of lipid disorders has clear benefits. It is estimated that up to 70% of adults with diabetes have clinically significant lipid abnormalities, the most common

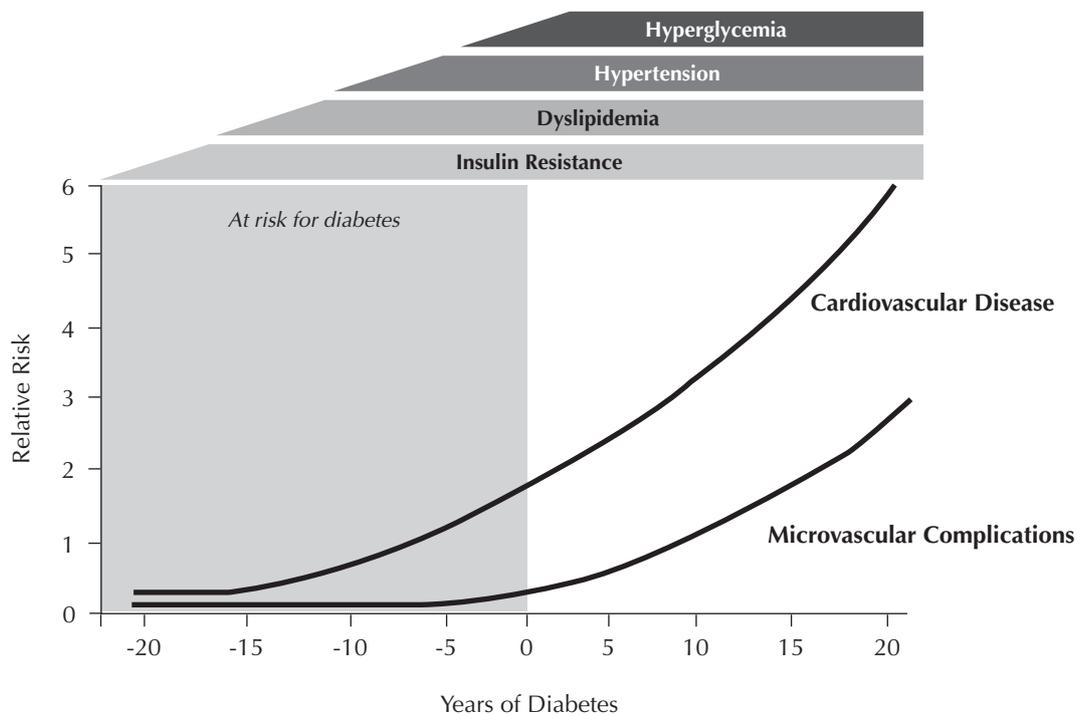
being high triglyceride levels and low levels of HDL-C.<sup>16</sup> Our clinical case outlines a common scenario: The patient has known coronary disease with an elevated LDL-C level, a high triglyceride level, and a low HDL-C level.<sup>34-36</sup>

**Figure 3** describes a practical, systematic approach to the management of lipid disorders in diabetes. This algorithm identifies the common clinical decisions considered in diabetes management; it emphasizes specific therapies with known clinical benefit. The figure lists steps that might follow the annual determination of fractionated lipids, a standard test in diabetes management. After dyslipidemia is identified, aggressive treatment must be considered because of the associated increase in CVD risk with any lipid abnormality. First-line treatment should emphasize nonpharmacologic interventions such as dietary fat and carbohydrate

restrictions, increased physical activity, and moderate weight loss.<sup>37</sup> If treatment targets are not met, pharmacologic therapy should be considered for all types of lipid disorders.

Elevations in LDL-C levels are no more common in diabetes patients than in the general population, but they are of greater clinical importance in this group of patients. An elevation in LDL-C is known to have a greater “negative” effect when it appears with diabetes.<sup>38</sup> Data from several clinical trials indicate that patients with diabetes can reduce their CVD risk by aggressively lowering their LDL-C levels. In several studies, lowering of elevated LDL-C levels (>100 mg/dL) with 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitor (statin) therapy resulted in a 25% to 55% reduction in CVD risk in patients with diabetes and known heart disease.<sup>39-41</sup> Patients

**Figure 2.** Theoretical Timeline for the Onset of Insulin Resistance Syndrome, Type 2 Diabetes, and the Complications of Diabetes



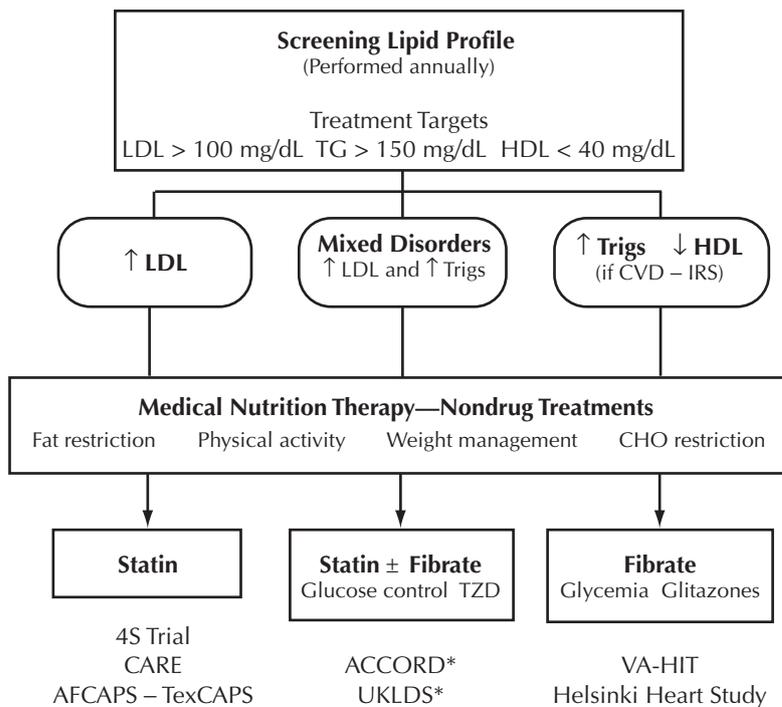
Source: David M. Kendall. Adapted in part from references 13, 14, 17, 23, 34, 35, 37, 45, 74.

with diabetes achieved a comparable or greater benefit when compared with the population without diabetes. Statin therapy may be useful in up to 70% of patients with diabetes.

As the clinical case shows, the lowering of LDL-C levels is beneficial, but it does not address the most common lipid disorder in patients with diabetes: high triglyceride levels and low HDL-C levels. Recent evidence has confirmed that treatment of an elevated triglyceride level and a low HDL-C level with fibric acid derivatives (fibrates) can lower the risk of recurrent coronary events in patients with diabetes.<sup>42-44</sup> In addition, the Helsinki Heart

Study suggests that fibrate therapy may be of particular benefit to patients with diabetes<sup>42</sup> and to those with markers of the insulin-resistance syndrome.<sup>45</sup> Other treatment options for patients with high triglycerides and low HDL-C include high-dose statin therapy and insulin-sensitizing medications. Furthermore, combination therapy with statins and fibrates can be considered for individuals with mixed lipid disorders, although the benefit of this combination has not yet been fully evaluated in clinical trials. In statin-fibrate therapy, the potential risk of drug-associated myopathy must be weighed against the potential benefit of

**Figure 3.** Diagnosis and Treatment of Lipid Disorders in Diabetes



ACCORD = Action to Control Cardiovascular Risk in Diabetes; AFCAPS-TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE = Cholesterol and Recurrent Events Trial; CHO = carbohydrate; CVD = cardiovascular disease; HDL = high-density lipoproteins; IRS = insulin resistance syndrome; LDL = low-density lipoprotein; 4S = Scandinavian Simvastatin Survival Trial; TG = triglycerides; TZD = thiazolidinedione; UKLDS = United Kingdom Lipids in Diabetes Study; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial.

\*Trial is still ongoing with final conclusions not yet available.

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the combination treatment. Two clinical trials—the National Institutes of Health-supported study called Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the United Kingdom Lipids in Diabetes Study (UKLDS)—are under way to determine the potential benefit of combination therapy with statins and fibrates.

Drugs that favorably affect insulin resistance may also improve lipoprotein profiles in patients with diabetes. The thiazolidinediones or glitazones (pioglitazone, rosiglitazone) have been reported to favorably affect triglycerides, HDL-C, or both. Several publications have detailed many of the unique lipid effects of the glitazones,<sup>46,47</sup> and their ability to reduce levels of free fatty acids. Both pioglitazone and rosiglitazone can increase HDL-C levels. Clinical trial results about the effect of the glitazones on triglycerides differ for the 2 agents. Pioglitazone therapy is associated with a significant reduction in triglyceride levels. Rosiglitazone is reported to have a neutral or variable effect on triglycerides: Some studies demonstrate a reduction and others studies show an increase. Rosiglitazone may significantly increase LDL-C levels; studies with piogli-

tazone indicate that it has no negative effect on LDL-C concentration. Both agents appear to reduce a fraction of small, dense LDL-C particles. Although glitazone therapy is not indicated for the primary treatment of lipid disorders, these agents may be a useful adjunct in managing patients with low HDL-C and high triglyceride levels. Current data suggest that one clinical approach to statin-treated patients with low HDL-C or modest elevation in triglyceride levels might be the addition of a glitazone agent (in lieu of combination therapy with fibrates). Glitazone therapy may be of particular benefit to patients with low HDL-C levels. **Table 2** summarizes some treatment options for lipid disorders in diabetes. Further head-to-head studies will be needed to determine the effect of these agents on lipid disorders over a wide range of baseline triglyceride and glucose levels.

Lastly, any assessment of dyslipidemia in diabetes would be incomplete without reference to the cost efficiency of the interventions. Given the high baseline risk of heart disease, the treatment of lipid disorders in diabetes is likely to have a favorable cost-benefit ratio. Cost-modeling analyses of data from the Scandinavian Simvastatin Survival Study and the Cholesterol and Recurrent Events Trial show statin treatment to be at least as or more cost efficient in diabetes patients as it is in a high-risk population without diabetes.<sup>48,49</sup> Although none of these findings are from randomized clinical trials, results of ongoing studies, including the UKLDS and the ACCORD trial, may clarify the cost benefit of lipid-lowering treatments in the diabetes population.

**Table 2.** Clinical Approaches to the Treatment of Dyslipidemia in Patients with Diabetes

	TG <150 mg/dL (Optimal)	TG 150-400 mg/dL* (Elevated)	TG >400 mg/dL* (Marked Elevated)
<b>LDL-C &lt;100 mg/dL</b> (Optimal)	Emphasize glycemic control	Fibrate therapy Pioglitazone	Fibrate therapy Glitazone
<b>LDL-C &gt;100 mg/dL</b>	Statin	Statin Fenofibrate Statin + fibrate Statin + pioglitazone	Statin + fibrate Fenofibrate Niacin Statin + pioglitazone

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.  
\*If TG >150 mg/dL medical nutrition is essential (limit total carbohydrates, reduce fat and alcohol intake). If HDL-C is very low, strongly consider glitazone or niacin therapy.

**Case Study (continued)**

After recovering from bypass surgery, the patient returned to the diabetes clinic to discuss treatment options. She remained on cerivastatin therapy. Her glucose-lowering medications were unchanged. With further attention to her meal plan, she had improved her blood glucose data. HbA<sub>1c</sub> was modestly lower at 6.5%. Fractionated lipids were as follows: total cholesterol, 163 mg/dL;

triglycerides, 213 mg/dL; HDL-C, 38 mg/dL; LDL-C, 82 mg/dL. A number of treatment options were discussed, including the addition of fibrate therapy. However, given the persistence of daytime hypoglycemia and the potential impact of glitazone therapy on her mixed lipid disorder, pioglitazone (30 mg/day) was substituted for glyburide. Follow-up HbA<sub>1c</sub> and lipid values are shown in **Table 3**, with subsequent therapeutic changes noted. Substitution of glitazone therapy eliminated daytime hypoglycemia, although HbA<sub>1c</sub> values increased modestly over the next several months. Given this change and the onset of moderate lower-extremity edema, the pioglitazone dose was reduced. Glipizide GITS (2.5 mg/day) was started and metformin was continued at 1000 mg twice daily. Continued improvement in HbA<sub>1c</sub>, triglyceride, and HDL-C levels was noted thereafter. LDL-C values remained at or near the target value of 100 mg/dL.

Glitazone therapy markedly improved both triglyceride and HDL-C levels in this patient. Overall glycemic control was also markedly improved.

**Hypertension.** Hypertension is common in adults with diabetes, and it increases the risk of both microvascular and macrovascular disease. Data from the National Health and Nutrition Examination Survey database<sup>15</sup> suggest that approximately 70% of adults with diabetes have blood pressure values above the current target of 130/80 mm Hg. A wide variety of antihypertensive agents can be used to reduce this risk.<sup>50-60</sup> Data from the UKPDS suggest that even modest elevations in blood pressure are associated with a marked increase in the risk of complications.<sup>59</sup> These data and data from several other clinical trials were the basis for the new lower standard of 130/80 mm Hg as the diagnostic threshold for hypertension and as the current treatment target goal for diabetes patients.<sup>61</sup> Blood pressure

**Table 3.** Case Study of a Patient with Diabetes

	HbA <sub>1c</sub> (%)	Triglycerides (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	Therapeutic Considerations
<b>Baseline Visit</b>	7.0	240	39	102	CABG performed
<b>2 months*</b>	6.5	213	38	82	Pioglitazone substituted for glyburide
<b>4 months*</b>	7.6				Pioglitazone increased to 45 mg/day
<b>6 months*</b>	7.3	177	42	94	Edema noted Pioglitazone reduced to 15 mg/day; glipizide GITS 2.5 mg/day initiated
<b>9 months*</b>	6.5	209	41	105	—
<b>12 months*</b>	6.1	157	46	86	—

CABG = coronary artery bypass graft; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; — = no change in therapy.

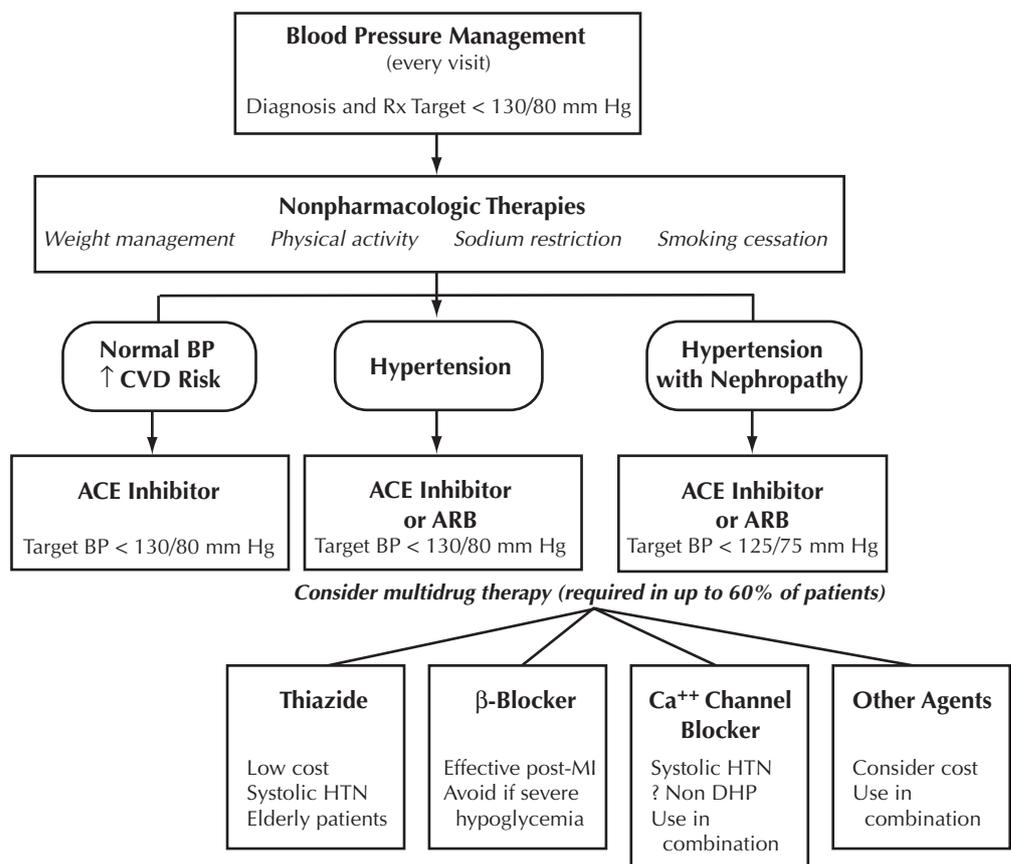
\*Indicates months of follow up from baseline visit.

should be measured at each clinic visit in a patient with diabetes, and aggressive treatment of elevated blood pressure should be considered an important standard of care.

Diabetes patients with hypertension can be treated with pharmacologic and nonpharmacologic therapies. **Figure 4** outlines one way to manage hypertension in the patient with diabetes. Regular physical activity, sodium restriction, and modest weight loss can lower blood pressure in some individuals. For many patients, pharmacologic therapy is also required. Some treatment trials that focused specifically on high-risk patients with diabetes

showed a significant reduction in rates of microvascular and macrovascular complications when more intensive blood pressure control was achieved.<sup>50-60</sup> Many different antihypertensive agents—including ACE inhibitors, beta-blockers, thiazide diuretics, and calcium channel blockers—were shown to be effective. However, it is generally accepted that ACE inhibitors are the preferred initial therapy for the treatment of hypertension in diabetes patients. This preference stems from the findings of several trials that demonstrated greater reduction in CVD risk when ACE inhibitor therapy was used.<sup>53-56,58</sup> ACE inhibitors can also slow the progression of renal dis-

**Figure 4.** Treatment Decisions for Managing Hypertension in Diabetes



HTN = hypertension; DHP = dihydropyridine; BP = blood pressure; CVD = cardiovascular disease; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; MI = myocardial infarction; ? = final data not yet available.

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ease. In addition, the Heart Outcomes Prevention Evaluation Study demonstrated that normotensive diabetes patients at high risk for CVD who were treated with ACE inhibitor therapy (ramipril) significantly reduced that risk.<sup>53,54</sup> Angiotensin II receptor blockers (ARBs) are considered an acceptable alternative for patients who do not tolerate ACE inhibitors well, although many of the benefits of ACE inhibitors have not yet been proved with ARBs.

Patients with type 2 diabetes usually require multidrug therapy to achieve blood pressure targets of <130/80 mm Hg.<sup>50,51,58</sup> Given the effectiveness of many other agents, practitioners may choose a second-line agent based on the presence or absence of other clinical markers. Beta-blockers have been shown to be as effective as ACE inhibitor therapy in reducing microvascular disease risk<sup>51</sup>; they may be useful in a patient with established coronary disease or symptomatic angina. Beta-blockers should, however, be avoided in patients who have a history of severe hypoglycemia. Thiazide diuretics may be of particular benefit to older patients and those with systolic hypertension.<sup>52</sup> In addition, diuretic therapy may be useful in patients who find the cost of therapy a concern. Despite earlier evidence that calcium channel blockers might be associated with higher rates of CVD than those associated with ACE inhibitors, calcium channel blockers have proved effective for treatment of systolic hypertension in people with diabetes, both alone and in combination with ACE inhibitors.<sup>57,58</sup> Some studies suggest that the nondihydropyridine agents are preferred if a calcium channel blocker is considered. However, the recent Systolic Hypertension in Europe Trial suggested that aggressive blood pressure treatment with a dihydropyridine agent also effectively reduces CVD risk.<sup>57</sup>

Ideal blood pressure targets for patients with diabetes remain controversial. Although the current target is 130/80 mm Hg, even lower blood pressure targets have been proposed for patients with established renal disease (125/75 mm Hg). Newer studies—including the ACCORD

trial and the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial—have been better designed to define the ideal blood pressure treatment target for high-risk patients with diabetes, but their results are not in yet.<sup>62</sup>

#### Case Study (continued)

Blood pressure control was discussed at the patient's follow-up visits. Given the patient's modest lower extremity edema and systolic blood pressure values above 130 mm Hg, low-dose hydrochlorothiazide was initiated, 12.5 mg/day. Microalbumin/creatinine ratio remained modestly elevated at 54 mg/g. Lisinopril was subsequently increased to 20 mg/day. Follow-up blood pressure readings averaged 124/74 mm Hg and microalbumin/creatinine ratio was normalized to 12.2 mg/g.

**Insulin Resistance.** Insulin resistance is a central defect that contributes to both hyperglycemia and CVD risk in patients with type 2 diabetes. Dyslipidemia and hypertension are 2 components of the insulin-resistance syndrome that contribute to increased CVD risk and to vascular abnormalities. Vascular abnormalities include impaired vascular reactivity, significant procoagulant tendencies (with elevations in plasminogen activator inhibitor, fibrinogen, and increased platelet aggregation), and abnormalities in endothelial function. Therapies that target insulin resistance, including weight loss, increased physical activity, and glitazones, not only improve glucose control and lipid disorders but may also improve these vascular abnormalities. Specifically, glitazone therapy has been shown to limit vascular smooth-muscle growth and intimal hyperplasia<sup>63</sup> and improve vascular reactivity.<sup>64</sup> Both rosiglitazone and pioglitazone lower blood pressure modestly,<sup>65-67</sup> and they may reduce urinary protein excretion.<sup>68,69</sup> Whether the addition of insulin-sensitizing therapy will eventually play a greater clinical role in CVD risk management for patients with type 2 diabetes and insulin resistance is not yet known. However, these intriguing effects will probably be

the focus of future studies. Further mechanistic studies and large-scale cardiovascular outcome trials will be needed to establish clearly whether glitazone therapy has a cardiovascular benefit in addition to its metabolic effects.

#### ***Glycemia and Complications Risk.***

Achieving and sustaining glucose control is another priority for patients with diabetes. Intensive glycemic control reduces the risk of microvascular complications in both type 1 and type 2 diabetes.<sup>20,21,70-72</sup> The relationship between glucose lowering and the lowering of complication risk is continuous, which suggests that there will be a benefit from any lowering of blood glucose. This benefit is maximized as HbA<sub>1c</sub> levels approach normal. However, for patients with type 2 diabetes, achieving and sustaining intensive glucose control can be difficult. Data from the UKPDS suggest that even if patients receive early pharmacologic treatment, glucose control may deteriorate over time.<sup>20,73</sup>

Patients with type 2 diabetes now have access to 7 classes of medications. The natural history of diabetes, which combines insulin resistance and progressive insulin deficiency,<sup>13,73,74</sup> suggests that any single agent is unlikely to achieve and sustain good glycemic control for more than a few years. A single oral agent is successful in sustaining HbA<sub>1c</sub> levels at <7% in less than 25% of patients with diabetes.<sup>20,75</sup> A combination of 2 oral agents will lower HbA<sub>1c</sub> even further (by up to 3.5%), but studies show that even maximal doses of metformin and a sulfonylurea achieved target glucose readings in only 70% of patients.<sup>75</sup> Data on the effectiveness of 3-drug oral agent therapy are beginning to accumulate.<sup>76,77</sup> Combinations of oral agents are effectively used earlier in the course of type 2 diabetes, and it appears the combination of oral agents (particularly insulin sensitizers) with insulin may also be effective.<sup>78-80</sup> As more intensive treatment targets are sought, aggressive use of multidrug therapy should be considered the standard for most patients with type 2 diabetes. Our case study emphasizes the potential benefit of such

combinations: This patient achieved near-normal HbA<sub>1c</sub> values with aggressive 3-drug therapy.

At present, the impact of blood-glucose lowering on the risk of macrovascular disease is not fully understood, but a recent analysis of data from the UKPDS suggested that more aggressive blood glucose lowering may be associated with reduced rates of CVD.<sup>21</sup> These data also suggest that the maximal benefit from glucose lowering is realized as HbA<sub>1c</sub> levels approach 6%. Some new approaches combine existing drugs with insulin, and some use new medications to enhance the action of insulin. Which combination of glucose-lowering therapies will be of greatest benefit remains to be determined. Long-term studies, although costly, must be conducted to clarify how important glycemic control is to the reduction of cardiovascular complications in type 2 diabetes.

#### **Complications Screening and Other Components of Care**

Another important component of comprehensive diabetes care is to screen for, prevent, and treat microvascular complications of diabetes. Specific standards for screening have been established. Appropriate diabetes management must include these simple, clinically useful tests. Limiting the occurrence of retinopathy, nephropathy, and neuropathy can significantly improve the quality of life for patients with diabetes.<sup>80</sup>

Annual dilated-eye exams are necessary to identify early changes that signal diabetic retinopathy. Intensive glycemic control and aggressive treatment of hypertension combined with early and aggressive treatment of established retinopathy can prevent blindness, which may result from uncontrolled diabetes.<sup>81</sup> Early use of photocoagulation therapy can markedly reduce rates of vision-threatening eye disease.<sup>82</sup> In this era of cost-effective approaches to management, the most appropriate intervals for retinopathy screening are being reexamined.<sup>83</sup>

Early renal disease can be detected with the annual microalbumin test. The

most practical microalbumin screening test is a random measurement of the albumin to creatinine ratio.<sup>84</sup> If the test is positive (>30 mg of albumin/g of creatinine), it is repeated. If it is positive on 2 of 3 occasions, ACE inhibitor therapy is recommended.<sup>85,86</sup> Microalbuminuria in patients with type 2 diabetes is associated with an increased CVD risk. Patients with diabetes who have microalbuminuria are 2 to 4 times more likely to get CVD than individuals who do not demonstrate microalbuminuria.<sup>87</sup> This suggests that aggressive CVD risk reduction is appropriate for any adult patient with microalbuminuria.

Basic screening for peripheral neuropathy includes a comprehensive foot exam. The exam involves inspection for skin changes and deformities, assessment of circulation (posterior tibial and dorsalis pedis pulses and, if indicated, ankle brachial index), and a neurologic evaluation. One simple, effective way to do the neurologic evaluation of the foot is to test vibration sense with a 128-Hz tuning fork. The vibration test is the most sensitive test for early abnormalities in nerve function. If the test results show anything abnormal, providers should follow up by testing pressure sensation with a 10-g monofilament. If the monofilament testing is also abnormal, the foot is at a higher risk for undetected skin lesions and neurogenic arthropathy. The patient may need to get specially fitted footwear and do daily foot inspections. Podiatric care for any open lesion or significant deformity is imperative. In addition to conducting an annual examination, physicians should ask patients with diabetes a set of questions each year regarding autonomic nerve function. These should include questions that identify symptoms of enteropathy (early satiety, recurrent nausea, diarrhea), orthostasis, bladder atony, sexual dysfunction, and gustatory sweating.

#### Other Components of Care

In addition to the diabetes-specific therapies described here, physicians should be sure that their patients with diabetes receive good general medical care.

Given the high rate of CVD and the presence of multiple CVD risk factors, aspirin therapy is likely to be of significant benefit for many people with diabetes.<sup>88,89</sup> A recent report suggested that up to 98% of adults with diabetes are candidates for aspirin therapy.<sup>89</sup> A dose of 81 to 325 mg/day is recommended for all high-risk patients with diabetes who are older than 35 years.

Other components of care include appropriate instructions about foot care and interval vaccinations, including vaccines against influenza and pneumococcal disease.<sup>90,91</sup> Tobacco use remains a critical cardiac risk factor in those with diabetes.<sup>92</sup> As such, tobacco cessation counseling must also be a component of diabetes care for those patients with diabetes who smoke. A recent report confirmed that tobacco cessation efforts are a useful component of diabetes care programs.<sup>93</sup> Ultimately, the inclusion of tobacco cessation efforts into formal diabetes education programs may further improve the rate of patients with diabetes who stop smoking.

In addition to direct medical interventions, physicians should carefully review the psychosocial factors that can affect their patients' day-to-day diabetes management.<sup>94</sup> Furthermore, the new ADA standards require that providers monitor patient adherence to these medical therapies and patient understanding of and satisfaction with diabetes care.

#### Case Study (continued)

The patient continues to do well. She has had no cardiac symptoms since the surgery. Her most recent HbA<sub>1c</sub> level was 6.4%. Interestingly, the patient reported normalization of menstrual cycles after approximately 6 months of pioglitazone therapy. No specific markers of insulin resistance were studied, but the restoration of normal menses suggests that the therapy this patient received may have addressed another component of the insulin resistance syndrome—namely the polycystic ovarian syndrome (PCOS). Both metformin and the glitazones have been shown to lower androgen levels in

women with PCOS, so normalization of menses and ovulation can occur in some women.<sup>95,96</sup> Women with oligomenorrhea or anovulation should be told that the use of glitazones or metformin can restore ovulation, so that they can consider contraceptive measures.

Comprehensive management of this patient involved combined therapy for the treatment of dyslipidemia (statin plus glitazone), combination therapy for the treatment of hypertension and microalbuminuria (ACE inhibitor plus hydrochlorothiazide), and multidrug therapy for intensive glycemic control. At present, all of the patient's numerous CVD risk factors are well controlled.

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