Pharmacologic Management of the Patient with Newly Diagnosed Type 2 Diabetes

Case Study and Commentary, M. Angelyn Bethel, MD, and Mark N. Feinglos, MD, CM

Abstract

• **Objective:** To review appropriate pharmacologic management for patients with newly diagnosed type 2 diabetes.
• **Methods:** Qualitative assessment of the literature.
• **Results:** Intensive control of blood glucose in patients with type 2 diabetes has been shown to reduce the prevalence and incidence of microvascular disease but may not be sufficient to reduce cardiovascular events. Few oral antidiabetic agents have been evaluated for effect on cardiovascular outcomes; however, metformin and acarbose are both associated with reduced morbidity and, in the case of metformin, mortality related to cardiovascular disease. Aggressive management of lipids and blood pressure have also been shown to reduce cardiovascular morbidity and mortality in patients with type 2 diabetes.
• **Conclusions:** In patients early in the course of type 2 diabetes, choice of pharmacologic agent to control blood glucose can often be guided by determination of cardiovascular risk status. Most patients will require combination therapy to control blood glucose, blood pressure, and lipid levels.

The approach to care of any patient with diabetes must address 2 major issues: glucose control and cardiovascular risk. Cardiovascular disease accounts for 65% of deaths in patients with diabetes [1]. Similarly, diabetes is the leading cause of blindness, end-stage renal disease, and nontraumatic amputations, mediated by the microvascular complications of the disease (retinopathy, nephropathy, and neuropathy). The United Kingdom Prospective Diabetes Study (UKPDS) has clearly demonstrated that intensive blood glucose control, whether with oral antidiabetic agents or insulin, is associated with significant reductions in the microvascular complications of diabetes. Patients randomized to intensive blood glucose control had a 12% reduction in any diabetes-related endpoint ($P = 0.03$) and 25% reduction in all microvascular endpoints ($P < 0.001$) [2]. However, there is currently no conclusive evidence indicating that blood glucose control alone is sufficient to reduce cardiovascular risk. Instead, patients with diabetes require aggressive management of multiple cardiovascular risk factors, including blood pressure and lipid levels.

**CASE STUDY**

**Initial Presentation**

A 57-year-old man presents to his physician for evaluation of his type 2 diabetes. He was diagnosed with diabetes 9 months ago when routine screening revealed an elevated fasting plasma glucose of 135 mg/dL. His physician recommended that he attend a group diabetes education class that included appropriate dietary and exercise recommendations, which he has implemented. His physician also prescribed glyburide 10 mg daily, which he is currently taking. He has always lived a “healthy lifestyle,” is a nonsmoker, and continues to exercise 5 to 6 times weekly. He has lost 5 lb since his diagnosis, which he attributes to decreased portion sizes and increased vegetable consumption. The patient has a family history significant for a father and 2 brothers with type 2 diabetes diagnosed in their late 40s. Additionally, the patient’s father had a myocardial infarction (MI) at age 52, and one of his brothers required coronary artery bypass grafting at age 50. The patient would like advice on a regimen appropriate to control his blood glucose and to address his increased risk of cardiovascular disease.

**Physical Examination**

Physical examination reveals a blood pressure of 148/88 mm Hg, pulse of 82 bpm, weight of 210 lb, and height of 5 ft 10 in. Body mass index is 30.1 kg/m². Other than obesity, results from the physical examination are normal. There is no acanthosis nigricans or pathologic striae. Laboratory evaluation reveals hemoglobin A₁c (HbA₁c) of 7.8%, no microalbuminuria, normal renal function, total cholesterol of 215 mg/dL, triglyceride level of 188 mg/dL, high-density lipoprotein (HDL) level of 38 mg/dL, and low-density lipoprotein (LDL) level of 120 mg/dL.

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HbA<sub>1c</sub> measurement in this patient reveals that his diabetes is not well controlled (current American Diabetes Association [ADA] guidelines recommend a target Hba1c < 7%) [3]. At this level of glucose elevation, an oral antidiabetic agent is appropriate for glucose control. Although the mechanism of action of various oral antidiabetic agents can be considered, this patient’s cardiovascular risk and comorbid conditions are important factors in the determination of the choice of diabetes therapy.

**Oral Antidiabetic Agents**

There are currently 5 major classes of oral antidiabetic agents available for diabetes control: sulfonylureas (SUs), biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and non-SU secretagogues. With the exception of alpha-glucosidase inhibitors and nateglinide (a non-SU secretagogue), the classes have equal efficacy in reducing HbA<sub>1c</sub> by 1% to 2% (Table) [4,5]. Alpha-glucosidase inhibitors and nateglinide lower HbA<sub>1c</sub> by 0.5% to 1% [6,7].

Among SUs, both first-generation agents (chlorpropamide, tolbutamide, acetohexamide, and tolazamide) and second-generation agents (glyburide, glipizide, and glimepiride) are available. The second-generation agents are more potent, have fewer drug interactions, and are probably safer than the first-generation drugs [4] but are of equal efficacy. However, there is an increasing body of evidence that glyburide may not be an appropriate choice for patients at high risk for cardiovascular disease. Glyburide has been shown to block the protective effects of ischemic preconditioning, a phenomenon whereby the heart adapts to repeated ischemic episodes, resulting in a reduced area of myocardial damage. Glimepiride, an agent with more specific binding to ATP-dependent potassium channels in the pancreas compared with the myocardium, seems to have a neutral effect on ischemic preconditioning [8]. On the other hand, the UKPDS, which used glyburide, did not demonstrate any excess cardiovascular morbidity or mortality attributable to SU therapy [2]. Given these conflicting data, it seems prudent to avoid glyburide in favor of agents not implicated in the blockade of ischemic preconditioning (ie, glimepiride, metformin, thiazolidinediones, or insulin) [9]. Additionally, glyburide offers no advantages over other SUs and is associated with more significant hypoglycemia, leading some authors to suggest that its use should be discouraged in all patients.

For this patient, a better choice for an initial oral antidiabetic agent might be metformin. Metformin offers equivalent HbA<sub>1c</sub> reduction, has a lower risk of hypoglycemia, and is considered first-line therapy for obese patients with diabetes [10]. Metformin is well tolerated in most patients when titrated slowly to avoid gastrointestinal side effects, but under current guidelines it should be avoided in patients with renal insufficiency or states of low cardiac output because of the purported risk of lactic acidosis [11]. Although a documented problem with phenformin, the incidence of lactic acidosis with metformin is debated and, at most, extremely rare. Additionally, metformin is the only oral antidiabetic agent to have a demonstrated cardiovascular benefit in patients with type 2 diabetes, particularly in overweight patients. Metformin was included as a randomization option in the UKPDS, initially only for overweight patients, but as the study progressed metformin was also used for patients demonstrating poor control on SU therapy alone. Overweight patients assigned to the metformin arm had a 32% lower risk of developing any diabetes-related endpoint ($p = 0.0023$) and a 36% lower risk of all-cause mortality ($p = 0.011$) compared with those in the conventional arm [12]. Additionally, the risk reduction in these endpoints was greater than that seen in intensive treatment groups using SU or insulin therapy. Assignment to the metformin group was

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**Table. Efficacy of Oral Agents for the Treatment of Newly Diagnosed Type 2 Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Hemoglobin A&lt;sub&gt;1c&lt;/sub&gt; Reduction, %*</th>
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<tbody>
<tr>
<td>Sulfonylureas</td>
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<tr>
<td>Glyburide</td>
<td>1.5–2.0</td>
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<tr>
<td>Glipizide</td>
<td>1.5–2.0</td>
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<tr>
<td>Glipizide GITS</td>
<td>1.5–2.0</td>
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<tr>
<td>Glimepiride</td>
<td>1.5–2.0</td>
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<tr>
<td>Nonsulfonylurea secretagogues</td>
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<tr>
<td>Repaglinide</td>
<td>1.5–2.0</td>
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<tr>
<td>Nateglinide</td>
<td>0.5–1.0</td>
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<tr>
<td>Biguanides</td>
<td></td>
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<tr>
<td>Metformin</td>
<td>1.5–2.0</td>
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<tr>
<td>Glucophage XR</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
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<tr>
<td>Rosiglitazone</td>
<td>1.5</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>1.5</td>
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<tr>
<td>Alpha-glucosidase inhibitors</td>
<td></td>
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<tr>
<td>Acarbose</td>
<td>0.5–1.0</td>
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</table>


*Approximate hemoglobin A<sub>1c</sub> reduction versus placebo at maximally effective dose.

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associated with lower risk of diabetes-related death, MI, and all macrovascular disease compared with the conventional group, a result not different from the insulin and SU groups. However, when a combined analysis was performed among all patients receiving metformin (overweight and normal weight), there was no additional benefit for metformin in all-cause mortality, diabetes-related death, or MI.

The only other oral antidiabetic agent to demonstrate a cardiovascular benefit is acarbose, an alpha-glucosidase inhibitor. In the Study to Prevent Non–Insulin-Dependent Diabetes (STOP-NIDDM), acarbose was used in high-risk patients with impaired glucose tolerance (IGT) to prevent conversion to type 2 diabetes [13]. The acarbose group had a lower risk of conversion to diabetes (32% versus 42%), and post-hoc analysis showed that patients randomized to receive acarbose had a significantly reduced risk of developing any cardiovascular event, including MI, angina, cardiovascular death, congestive heart failure, stroke, and peripheral vascular disease (hazard ratio [HR], 0.51 [95% confidence interval [CI], 0.28–0.95], P = 0.03) [14]. However, these data were not derived from a prospectively defined outcome, were obtained in a different population (IGT versus diabetes), were limited by a small number of events (15 in the acarbose group and 32 in the placebo group), and were derived in the setting of a lack of statistical adjustment for testing multiple hypotheses. In addition, the trial had a 24% discontinuation rate for the drug, predominantly related to gastrointestinal side effects (93 patients in the acarbose group, 18 patients in the placebo group), a common adverse reaction that limits the clinical utility of acarbose.

Thiazolidinediones

Thiazolidinediones (pioglitazone and rosiglitazone) are also approved for initial therapy for patients with type 2 diabetes. Although proven to lower blood glucose, their use is limited in patients with established cardiovascular disease and altered myocardial function due to their propensity to trigger significant weight gain and peripheral edema. Thiazolidinediones may cause exacerbations of heart failure and are contraindicated in patients with class III or IV congestive heart failure. They should be used with caution and careful monitoring in all patients with congestive heart failure. However, as with many other classes of oral antidiabetic agents, there remains a paucity of data demonstrating the effect of thiazolidinediones on cardiovascular outcomes. A meta-analysis of 23 randomized trials of either pioglitazone or rosiglitazone versus placebo demonstrated that both drugs result in similar degrees of HbA1c lowering and similar increases in body weight (3.0 kg). Pioglitazone therapy resulted in a more favorable lipid profile compared with rosiglitazone (decreased triglycerides, increased HDL, no LDL increase) [15].

To date, only 1 large multicenter trial powered to address the effects of thiazolidinediones on both glycemic control and cardiovascular event reduction has been completed. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) recruited 5238 patients with type 2 diabetes and a history of macrovascular disease and randomized them to receive pioglitazone or placebo [16]. After a mean observation of 34.5 months, patients in the pioglitazone group did not differ significantly from the placebo group in the primary composite endpoint (all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, peripheral vascular disease, and amputation). However, the pioglitazone group had an increased incidence in the main secondary composite endpoint (all-cause mortality, nonfatal MI, and stroke) (HR, 0.84 [95% CI, 0.72–0.98]; P = 0.03) [17]. Unfortunately, this benefit in cardiovascular morbidity and mortality occurred in the setting of an increased incidence of heart failure, edema, and weight gain, which were poorly quantified in the study because these events were categorized as adverse effects, not measured and adjudicated endpoints [18]. Further study is needed to determine the balance of risk and benefit for thiazolidinedione therapy, particularly for patients with known cardiovascular disease.

Results of the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial may help to shed further light on thiazolidinedione use, particularly early in the course of diabetes. DREAM is a randomized, double-blind, controlled trial that will enroll at least 4000 participants with IGT and 1000 participants with isolated impaired fasting glucose [19]. The subjects will be randomized to ramipril and/or rosiglitazone in a 2 × 2 factorial design. Follow-up is planned for at least 3 years. The primary outcomes will be all-cause mortality and new-onset diabetes. Secondary outcomes include MI, congestive heart failure, revascularization, and renal events.

Nateglinide

One other oral antidiabetic agent is under evaluation for its effects on cardiovascular outcomes. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial is an ongoing study designed to examine the time to development of diabetes in a group of patients with IGT. Patients in the trial will be randomized in a 2 × 2 factorial design. Follow-up is planned for at least 3 years. The primary outcomes will be all-cause mortality and new-onset diabetes. Secondary outcomes include MI, congestive heart failure, revascularization, and renal events.

Insulin

Insulin could also be used in the case patient to obtain glucose control. Some data support use of insulin soon after diagnosis to improve beta cell function. Alvarsson et al [20]
drug therapy for type 2 diabetes

Demonstrated that treatment with twice daily premixed insulin in patients whose diabetes was diagnosed within the past 2 years resulted in improved parameters of beta cell function compared with glyburide. Patients treated with insulin over a 2-year period demonstrated improved HbA\textsubscript{1c} and improved insulin response to glucagon stimulation testing without significant differences in weight gain or quality of life [20]. These data support the idea that insulin treatment provides relative beta cell “rest,” resulting in preserved beta cell function. Similarly, follow-up data from the Diabetes Control and Complications Trial (DCCT), performed in patients with type 1 diabetes, have shown that even 7 years after the end of the study, patients randomized to intensive control (achieving an HbA\textsubscript{1c} of 7.3% compared with 9.1% in the conventional group during the DCCT) have a lower rate of progression of microvascular complications even though differences in HbA\textsubscript{1c} levels between the groups are no longer statistically significant [4]. The only large-scale randomized trial available to prospectively evaluate early insulin use for treatment of type 2 diabetes is the UKPDS. Patients in the UKPDS randomized to oral agents demonstrated a progressive loss of beta cell function; however, beta cell function in patients randomized to insulin therapy was not assessed due to ongoing insulin treatment. In contrast to Alvarsson’s data, the UKPDS patients randomized to insulin had similar increases in HbA\textsubscript{1c}, compared with oral agents [2]. Proponents of early insulin use have suggested that the UKPDS results differ due to less aggressive insulin titration and titration schema based solely on fasting plasma glucose, ignoring the impact of postprandial hyperglycemia [20].

- Is there a benefit to more aggressive blood glucose lowering?

According to current ADA recommendations, the goal HbA\textsubscript{1c} for patients with diabetes is less than 7% [3]. However, epidemiologic evidence indicates that individual patients may derive benefit from more aggressive blood glucose lowering, with the aim of achieving a normal (< 6.0%) HbA\textsubscript{1c}; unfortunately, no randomized controlled trials have been completed to evaluate the balance of risk and benefit for this approach. In this healthy patient with few contraindications to aggressive glucose lowering, an HbA\textsubscript{1c} goal of 6% seems achievable and reasonable.

- What interventions are appropriate to address blood pressure control in this patient?

In the patient with newly diagnosed diabetes, it is essential to evaluate and treat other cardiovascular risk factors. There is a large body of evidence suggesting that improved blood pressure in patients with diabetes improves cardiovascular outcomes. The UKPDS randomized 1148 patients with both diabetes and hypertension into treatment groups with goal blood pressures of 150/85 versus 180/105 mm Hg [21]. Patients in the “tight” control group had a lower risk of all-cause mortality (relative risk [RR], 0.82; P = 0.17), MI (RR, 0.79; P = 0.13), and stroke (RR, 0.56; P = 0.013). In fact, the impact of blood pressure control was more profound than that of blood glucose control. Patients in the tight control group received regimens based either on captopril or atenolol; both therapies were equivalent with respect to clinical endpoints.

Since the publication of the UKPDS, a number of trials have compared the efficacy of different antihypertensive agents. Although some of the newer classes (ie, angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]) continue to grow in popularity, no clear superiority of these agents for cardiovascular event prevention has been demonstrated. Neither the Captopril Prevention Project (CAPPP), the Swedish Trial in Old Patients with Hypertension-2 (STOP-2), nor the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated a clear benefit of ACE inhibitor therapy to prevent cardiovascular events. CAPPP randomized 10,985 hypertensive patients to either captopril or β blocker with or without thiazide diuretic [22]. The trial failed to demonstrate a significant difference between groups, including the diabetes subgroup, in the composite endpoint of fatal or nonfatal MI, stroke, and other cardiovascular deaths (RR, 1.05; P = 0.52). However, the captopril group did demonstrate a statistically significant increase in fatal and nonfatal stroke (RR, 1.25; P = 0.044). Some of this increased risk may have been due to the slightly higher blood pressures in the captopril group at baseline and throughout the study or because more patients in the captopril group (43 versus 35 in the control group) had a history of transient ischemic attack.

In contrast, STOP-2 did not demonstrate a difference in stroke outcomes between treatment groups. The study randomized 6614 patients (719 with diabetes) with hypertension to treatment with conventional antihypertensive agents (β blocker, diuretics), ACE inhibitors, or calcium channel blockers [23]. There was no difference in prevention of cardiovascular death between the groups, including the subgroup with diabetes. However, patients in the ACE inhibitor group did demonstrate significantly fewer fatal and nonfatal MIs (RR, 0.77; P = 0.016) compared with those receiving calcium channel blockers. This difference was not seen between the ACE inhibitor group and the β blocker/diuretic group (RR, 0.99; P = 0.38). However, it should be noted that
this study performed more than 48 statistical comparisons
without adjustment for multiple comparisons.

ALLHAT also examined the effect of multiple classes of
antihypertensive agents on cardiovascular morbidity and
mortality [24]. Patients (n = 33,357; 12,063 with diabetes)
with stage I or II hypertension and 1 other cardiovascular
risk factor were randomized to chlorthalidone, amlodipine,
lisinopril, or doxazosin (an α blocker). Early in the trial,
chlorthalidone was found to be superior to doxazosin,
resulting in the discontinuation of that treatment arm. There
were no differences between the groups, including the
diabetes subgroup, in the primary outcome (combined fatal
coronary heart disease or nonfatal MI). However, several dif-
fferences in the secondary outcomes were noted. Amlodipine
resulted in a 38% higher risk of heart failure compared with
chlorthalidone (P < 0.001). Lisinopril conferred a 15% higher
risk of stroke (P = 0.02), particularly for African American
patients, and a 10% higher risk of combined cardiovascular
disease (P < 0.001), including higher risk of heart failure and
higher risk of coronary revascularization, when compared with
chlorthalidone. The results of this trial underscore the
beneﬁts of the diuretic chlorthalidone, which was super-
ior in blood pressure lowering as well as heart failure and
stroke prevention.

Insight into effect of calcium channel blockers and
diuretics was obtained from the International Verapamil-
Trandolapril Study (INVEST). INVEST randomized 22,576
patients (6400 with diabetes) with hypertension and known
coronary artery disease to receive either a calcium channel
blocker–based regimen (verapamil ± trandolapril and hy-
drochlorothiazide) or a non–calcium channel blocker strat-
egy (atenolol ± trandolapril and hydrochlorothiazide) [25].
There were no differences noted between groups, including
the diabetes subgroup, in the primary composite outcome of
all-cause mortality, nonfatal MI, or nonfatal stroke. Like-
wise, no differences were seen in each of the components
comprising the composite endpoint.

More recently, the Valsartan Antihypertensive Long-term
Use Evaluation (VALUE) trial randomized 15,245 hypertensive
patients (31.7% with diabetes) at high risk for cardiac events
to receive either amlodipine or valsartan [26]. The study did not
demonstrate a difference between groups, including the di-
betes subgroup, in the primary composite outcome of sudden
cardiac death, fatal MI, cardiovascular death, or cardiovascu-
ar morbidity (including heart failure). Amlodipine achieved
a small but statistically signiﬁcant increase in blood pressure
lowering effect. Valsartan was associated with an increase
in MI (HR, 1.19; P = 0.02), but outcomes for heart failure and
stroke were not different.

In summary, diuretics, β blockers, calcium channel block-
ers, ACE inhibitors, and ARBs have all been demonstrated to
reduce adverse clinical events in patients with diabetes and
hypertension. The choice of drug can be tailored to prevent
speciﬁc complications present in any individual patient. 
β Blockers and calcium channel blockers should be used in
patients with angina based on data supporting deﬁnitive
antianginal effects and possible beneﬁts for atherosclerosis
[27,28]. Diuretics, ACE inhibitors, and β blockers have all
been shown to beneﬁt patients with heart failure [29,30].
Despite some evidence that β-blocker treatment is associated
with increased risk of conversion to diabetes [31], β blockers
should not be withheld from patients with diabetes and prior
MI due to its proven beneﬁts in secondary cardiovascular
event prevention [32]. Likewise, although various studies
with calcium channel blockers, ACE inhibitors, and ARBs
have demonstrated decreased incidence of conversion to dia-
betes [24–26,33,34], the difference was seen in secondary or
post-hoc analyses with little rigor applied to detecting dia-
betes. There is no clear evidence to support a preference among
these agents with regard to glucose lowering. Calcium chan-
nel blockers and diuretics appear beneﬁcial to prevent stroke
[24,35], and ACE inhibitors and ARBs have both been shown
to preserve renal function in patients with diabetic nephrop-
athy [36–38]. Combination therapy is commonly required
to achieve the ADA goal of blood pressure less than 130/
80 mm Hg, allowing the use of multiple agents shown to
simultaneously reduce cardiovascular risk and treat other
comorbidities [3].

• What interventions are appropriate to address lipid
control in this patient?

ADA recommendations for lipid goals are as follows: LDL
lower than 100 mg/dL, triglycerides lower than 150 mg/dL,
and HDL higher than 40 mg/dL [3]. Although lifestyle in-
terventions, including medical nutrition therapy (to reduce
saturated fats, cholesterol, transunsaturated fats, and car-
bohydrates in the case of hypertriglyceridemia), smoking
cessation, increased physical activity, and weight loss, can
help patients to reach these goals, many will require phar-
macologic therapy. Data from the Heart Protection Study
demonstrated that in patients older than 40 years with dia-
betes and total cholesterol greater than 135 mg/dL, treatment
with simvastatin resulted in a 30% reduction of LDL, which
was associated with a 25% decreased rate of cardiovascular
events, regardless of baseline LDL level [39]. Likewise, the
Collaborative Atorvastatin Diabetes Study (CARDS) showed a
37% reduction in major cardiovascular events in patients
with type 2 diabetes, regardless of initial LDL cholesterol level
[40]. Consequently, current recommendations are not only a
goal LDL level lower than 100 mg/dL but also consideration
of statin therapy in patients with type 2 diabetes over age
40 with total cholesterol greater than 135 mg/dL, regardless of initial LDL level.

Recent data from the PROVE-IT [41] trial have been used to suggest that LDL goals for patients with known cardiovascular disease should be lower than 70 mg/dL. PROVE-IT randomized 4162 patients with acute coronary syndrome, 17.6% of whom had diabetes, to receive either 40 mg pravastatin or 80 mg atorvastatin. LDL was lowered from mean 106 mg/dL in both groups to 95 mg/dL in the pravastatin group compared with 62 mg/dL in the atorvastatin group. The atorvastatin group had a 16% relative risk reduction in the composite endpoint of death, MI, revascularization, or stroke.

The TNT trial, which randomized 10,003 patients with LDL lower than 130 mg/dL and stable coronary heart disease to receive either 10 mg or 80 mg of atorvastatin, demonstrated LDL lowering to 77 mg/dL in the 80-mg atorvastatin group, compared with 101 mg/dL in the 10-mg atorvastatin group [42]. The group receiving atorvastatin 80 mg showed a 22% reduction in the composite endpoint of cardiovascular death, nonfatal MI, fatal or nonfatal stroke, or resuscitation after cardiac arrest. The compilation of these data has resulted in ADA recommendations to consider an LDL goal of lower than 70 mg/dL in high-risk patients with overt cardiovascular disease [3].

**Approach to Treatment in this Patient**

As the initial intervention for all patients with diabetes should focus on lifestyle changes, including nutrition modification, a program of regular exercise, and smoking cessation when necessary, the physician reinforces the importance of the patient maintaining his “healthy lifestyle” habits. In addition, because the patient is older than 40 years and at increased cardiovascular risk, primary cardiovascular event prevention with aspirin (75–162 mg/day) is prescribed [3,43]. Due to the patient’s increased cardiovascular risk, the drug regimen is changed to eliminate glyburide in favor of another agent, in this case, glimepiride. An ACE inhibitor is prescribed, and statin therapy is also initiated, with a target LDL goal of less than 100 mg/dL. The patient is unlikely to require pharmacotherapy for elevated triglyceride levels as improved glucose control will likely bring them into the target range.

- **What if satisfactory glucose control is not achieved?**

If a single agent is insufficient to achieve satisfactory glucose control, a second oral agent should be added. There is little evidence to suggest that switching from one oral antidiabetic agent to another provides benefit, and combination therapy is often required to achieve glycemic goals [44]. The addition of metformin will enhance glycemic control, will not result in additional weight gain, and may be beneficial to the cardiovascular risk profile; alternatively, the addition of insulin therapy will not increase cardiovascular risk and is likely to normalize HbA1c. Details of insulin strategies are beyond the scope of this review but have been described elsewhere [45].

**SUMMARY**

In treating patients with diabetes, glycemic control is not enough. Patients with diabetes are at a two- to fourfold increased risk of stroke and death from heart disease [46–48]. As yet, there are no data that lowering blood glucose in patients with type 2 diabetes is sufficient to reduce cardiovascular risk. However, there are limited data that some oral antidiabetic agents, such as metformin and acarbose, may provide cardiovascular benefit. As more data become available on the cardiovascular risk profiles of other oral antidiabetic agents, an evidence-based approach to diabetes therapy with attention to cardiovascular risk reduction will be possible. However, modification of cardiovascular risk factors, including blood pressure, lipid levels, and smoking status, remains a critical component of patient care.

**References**

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