Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome

The Primary Care Guide to Diagnosis and Management

By

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Series Editor’s Introduction

_Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Care Guide to Diagnosis and Management_ is an important addition to the literature for primary care physicians. It covers concisely and with attention to clinical relevance the full spectrum of insulin resistance and diabetes. This book gives a practical, no-nonsense approach to understanding the basic pathophysiology of diabetes and the metabolic syndrome, an approach to treatment with oral agents and insulin, and an approach to risk factor management. By putting all this information in one readable text, Dr. Codario provides a service to us all, facilitating the understanding of a body of knowledge that cannot be obtained through any attempt to read portions of much larger textbooks in the field.

This textbook will serve as a resource for medical students, residents in family medicine and internal medicine, and attending physicians who wish to update and improve their knowledge in the field of diabetes and the newly emerging science of the metabolic syndrome. In addition, it allows attending physicians the opportunity to obtain Continuing Medical Education credits while performing self-directed learning. After reading _Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Care Guide to Diagnosis and Management_, the physician should feel comfortable and confident that they have acquired a solid understanding of the latest information in the field, and by so doing, should be better able to take excellent care of patients with diabetes and the metabolic syndrome.

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Several factors can be involved in the deterioration in β-cell function, including progressive β-cell exhaustion owing to dietary indiscretion, prolonged glucose toxicity, and preprogrammed genetic abnormalities in β-cell function. Nonetheless, it is the progressive β-cell deterioration that results in worsening of the hyperglycemic state in the type 2 diabetic patient. The majority of type 2 diabetic patients are overweight and hyperinsulinemic at the time of diagnosis. The subsequent conversion from the impaired glucose-tolerant state to type 2 diabetes is influenced by concomitant medical conditions, distributions of body fat, degree of obesity, ethnicity, sedentary lifestyle, and aging. Thus, one can see that the type 2 diabetic patient is at the end of a progressive triad of metabolic defects whose interrelationships directly affect the natural history and progress of the disease (see Fig. 1) (12).

The impaired glucose-tolerant state is characterized by mild postprandial hyperglycemia, compensatory hyperinsulinemia, and insulin resistance. Clearly, insulin resistance can be present for many years before an individual becomes diabetic. Even at these stages, blood sugar levels are not necessarily elevated.

Understanding the natural history of the disease is important both for the early identification of patients at risk for developing diabetes, and for developing an effective treatment plan including diet and exercise with weight reduction to prevent or delay the development of the disease. Additionally, because insulin resistance is one of the major factors in the prediabetic state and persists in the frankly diabetic individual, improvements in insulin sensitivity with medications like thiazolidinediones and biguanides may be invaluable as first-line agents in early treatment. As we will see in Chapter 6, the glitazones can be invaluable not only in preserving β-cell function but also in regenerating β-cell tissue (13).

Early recognition and treatment is of tremendous advantage because macrovascular disease begins with impaired glucose tolerance and microvascular disease begins with diabetic levels of hyperglycemia. Clearly, patients will die from their macrovascular disease but suffer from their microvascular disease.

Of critical importance is an understanding of how damaging the hyperglycemic state is at the tissue level. At the cellular level, various critical and damaging signaling pathways can be affected by abnormal glucose tolerance. These damaging pathways can be
The criteria for impaired glucose tolerance (IGT) include postprandial sugars on two 75-g oral glucose tolerance test values greater than 140 mg/dL or less than 200 mg/dL (7.8–11 mmol).

IGT is not defined by clinical signs and symptoms but strictly by plasma glucose levels alone. This state has also been referred to as chemical diabetes, borderline diabetes, or prediabetes. Although these patients do not yet have the microvascular complications of diabetes mellitus they are at risk for, and begin to develop, macrovascular complications caused by arteriosclerotic deposition secondary to the hyperglycemic state and are at significant risk for developing diabetes, especially when associated with concomitant risk factors of hypertension, body mass index (BMI) greater than 25 kg/m², sedentary lifestyle, dyslipidemia (especially increased small, dense low-density lipoproteins [LDL] and increased triglycerides), history of gestational diabetes, polycystic ovaries and associated ethnicity (African American, Latin American, Native American, and Pacific Islanders) (13).

In the United States alone, close to 15 million adults (40–74 years old) have impaired glucose tolerance and close to 10 million have IFG. Curiously, minimal overlap between the two impaired states exists, with only 16% of individuals possessing both IFG and IGT, whereas 23% have IFG alone and 60% have IGT alone. Individuals with IGT have a 3.6–8.7%/year chance of developing diabetes. These individuals frequently have the metabolic syndrome that will be discussed in detail in Chapter 5.

SCREENING RECOMMENDATIONS (4)

**Strongly Recommended**

Screening is strongly recommended in individuals over 45 years of age with BMI greater than 25 kg/m² or 20% above ideal weight; waist size greater than 35 inches in women and 40 inches in men; high-density lipoprotein (HDL) less than 40 mg/dL in men or 50 mg/dL in women; triglycerides more than 150 mg/dL, especially in association with increased small, dense LDL.

**Recommended**

Screening is recommended in individuals less than 45 years old with BMI greater than 25 kg/m² with one of the following risk factors:

1. Family history of diabetes (i.e., parents or sibling with diabetes).
2. Physical inactivity.
3. At-risk ethnic group (African American, Hispanic American, Native American, Asian American, and Pacific Islander).
4. Impaired fasting tolerance and/or IGT.
5. History of gestational diabetes or delivery of high-birthweight infant (>9 lb).
6. Polycystic ovary syndrome.
7. Arteriosclerotic vascular disease.
8. Hypertension.
9. HDL less than 35 mg/dL.
10. Triglycerides greater than 150 mg/dL.

Although fasting glucoses have been used for many years as the sole screening test for diabetes, strong consideration must be given to preferably using the postprandial
β-blockers and exercise stress-test findings of ischemia can have a bearing on the maximum desirable heart rate. Interestingly, β-blockers usually do not prevent the training effects on muscle strength and aerobic capacities.

**PRECAUTIONS**

Stress testing is imperative before embarking on an exercise program. Blood pressure should be controlled and guided by the response to exercise testing. Self-monitoring of blood glucose is particularly important in patients taking insulin. Although exercise does not normally aggravate diabetic neuropathy and may even reduce or delay the risk of ophthalmic complications, training, as seen in heavy resistance training, should be avoided by those with proliferative retinopathy because of the increased risk of vitreous hemorrhage and retinal detachment. It is not known whether patients who have undergone laser procedures can tolerate more aggressive resistance activity (13).

Common misconceptions about exercise are discussed in the following subheadings (14).

**Morning Exercise vs Evening Exercise**

Research has shown that exercise before bedtime can alter sleep patterns for deconditioned but not fit people, but regular exercise actually helps normalize sleep quality over a longer period. There is no evidence to support the thought that morning exercise boosts the metabolic rate better than evening exercise.

**Exercise and Appetite**

In general, exercise neither stimulates nor suppresses appetite. In uncontrolled patients with diabetes or impaired glucose tolerance, by enhancing insulin activity, particularly in the postprandial period, glycemic excursions are reduced, and these excursions can play a role in stimulating appetite. For those with postprandial hyperglycemia, a brisk walk 1–2 h after eating can enhance glycemic control. In fact, exercising in a fasting state may result in increased eating after the workout, thus these individuals would be better advised to pursue the postprandial exercise approach.

**Exercise and Weight Loss**

Exercise is more important in maintaining muscle tone and strength, whereas dieting results in weight loss. Studies comparing the effects of exercise to diet for weight loss have shown that dieting results in more robust weight reduction. Exercise can be associated with an increase in muscle mass and muscle is heavier than fat. Thus, resistance training is usually associated with gaining more muscle than aerobic activity.

**Duration vs Intensity**

Research has shown that it is the duration not the intensity of the workout that correlates best with glycemic control and reductions in insulin resistance. Therefore, patients should choose an activity that they enjoy and that is convenient for them to perform. The more that exercise becomes a chore and a job the more likely it will become a bore and a flop. Patients should exercise for 30–35 minutes four to five times a week for maximum benefit.
CME Questions

1. True or False? The Diabetes Prevention Study showed that diet alone reduced the risk of developing diabetes.
   a. True.
   b. False.

2. Which of the following is not true concerning ω-3 fatty acids?
   a. They can reduce triglycerides.
   b. They have antiarrhythmic properties.
   c. They are uniformly pure.
   d. They can have antiplatelet effects.

3. True or False? Diets rich in saturated fats and cholesterol have not been shown to increase the risk of arteriosclerotic cardiovascular disease.
   a. True.
   b. False.

4. Which of the following supplements have been shown to improve insulin sensitivity in some clinical studies?
   a. Chromium.
   b. Selenium.
   c. Iron.
   d. Cobalt.
   e. Zinc.

5. Which of the following foods can raise serum triglycerides?
   a. Pasta.
   b. Bread.
   c. Rice.
   d. Potatoes.
   e. All of the above.
   f. A, B, C only.

6. True or False? Weight loss is a major focus of diet therapy in obese patients with diabetes.
   a. True.
   b. False.

7. True or False? Long-term compliance with a weight-loss diet is more likely if the caloric restriction is not too stringent.
   a. True.
   b. False.

8. True or False? Metformin works better to reduce the risk of diabetes than diet and exercise in patients with impaired glucose tolerance.
   a. True.
   b. False.

9. Which of the following is not used as a non-nutritive sweetener?
   a. Saccharin.
   b. Aspartame.
   c. Sucralose.
   d. Acesulfame-K.
   e. Cinnamon.

10. True or False? The clearly positive reasons for patients with diabetes to consume alcohol are few.
    a. True.
    b. False.
2. Orlistat (Xenical). This lipase inhibitor decreases absorption of fat from the gastrointestinal tract. Adverse effects include flatulence and oily spotting with discharge and fecal urgency.

3. Cybutrimine (Meridia). This drug is a serotonin, norepinephrine, and dopamine reuptake inhibitor. This medication has been used to safely promote weight loss over a prolonged period. Side effects include hypertension, dry mouth, and insomnia. Cybutrimine should not be used with selective serotonin reuptake inhibitors (SSRIs).

4. SSRIs. Although some reports indicate that these drugs may cause weight gain, other studies show weight loss. This can be seen especially with those patients who tend to eat when depressed. Sexual dysfunction and decreased libido remain the major problems with this class.

5. Bupropion (Wellbutrin SR). This non-SSRI has been modestly effective in promoting weight loss in doses of 300–400 mg/day. This drug is generally well-tolerated but can increase the risk of seizures (this is less likely with the sustained-release preparation).

6. Zonisamide (Zonegran). This antiepileptic drug causes weight loss as a side effect. In a 16-week trial of 60 patients with a mean BMI of 36.3, average weight loss was 5.9 kg compared with 0.9 kg in the placebo group. A 16-week extension study showed a further 3.3 kg weight loss compared with 1.5 kg in the placebo group. Cognitive problems, difficulty concentrating, and rare reports of Stevens–Johnson syndrome have been reported.

7. Topiramate (Topamax). This antiepileptic drug was evaluated in a double-blind trial in 385 patients on a reduced-calorie diet. 64–384 mg/day of topiramate for 6 months led to a 4.8–6.3% weight loss compared with 2.0% for placebo. Paresthesias, somnolence, and difficulty in concentration and memory were reported side effects.

8. Metformin (Glucophage). In the Biguanides and the Prevention of the Risk of Obesity (BIGPRO) trial evaluated this drug in nondiabetic patients and found similar weight loss with this product in that population. This drug has not been formally approved for use in impaired glucose tolerance or for weight loss in nondiabetic patients.

Surgery for weight reduction includes the following:

1. Roux-en-Y gastric bypass. This procedure is the treatment of choice for patients more than 100 lb over desired weight or who have a BMI greater than 40. The first portion (20–30 mL) of the stomach is clipped with staples and anastomosed to the jejunum, bypassing most of the stomach, the entire duodenum and the first 15–20 cm of the jejunum. With this procedure mean weight loss is 65–75% or 35% of initial weight. This procedure can reverse the glycemia of type 2 diabetes if performed early. Perioperative mortality is less than 1%, with deficiencies of calcium, iron, vitamin D, and B12 because of malabsorption. Dumping syndrome and wound infections have been reported, with life-long follow-up necessary to prevent and treat deficiencies and the complications of ulcerations at the gastroenterostomy stoma and the duodenum.

2. Vertical banded gastroplasty. Staples are used to create a 15–20 mL gastric pouch in the upper stomach, with a small calibrated opening in the rest of the stomach. Mean weight loss is as high as 60% in the initial postoperative period, although many patients can regain lost weight over 5–10 years. Complications include reflux, stenosis, and staple-line breakdown, with 15–20% of patients requiring a second procedure to correct outlet stenosis or severe reflux. There is no malabsorption with this technique and perioperative mortality is less than 1%. This procedure is the least efficacious, with only short-term weight loss of 35–50%. Reoperation rates are high as a result of reservoir breakdown or component deterioration.
3. Biliopancreatic bypass with duodenal switch. This procedure can lead to 75–80% weight loss, restricts the stomach, and causes malabsorption. The greater curvature of the stomach is resected, leaving a small gastric pouch (100–250 mL), and the proximal duodenum is anastomosed to the distal 250 cm of ileum, bypassing the duodenum, the entire jejunum, and the rest of the ileum. Perioperative mortality is 1% higher than the other procedures, and metabolic malabsorption problems of anemia, fat-soluble deficiencies, and protein-calorie malnutrition can result.

In treating the obese patient, recognition and determination of goals is critical. Commitment of the patient to a practically designed program is critical to success. Realistic goals need to be set to avoid patient frustration. Positive reinforcement behavior modification, increased physical activity, and judicious use of pharmacotherapy all play an important role.

Modification of eating and activity habits following a set of principals and techniques can be used in an efficacious way in helping patients battle with obesity. Patients should constantly be reminded of the consequences of being overweight and of dietary indiscretion, although the physician should avoid being dictatorial or dogmatic.

In their review and practical dieting outline, VanWarmer and Boucher list the five “As” for weight-management counseling. These include (37):

1. Assessing the patient by identifying any biological, genetic, or behavioral risk factors (including accurate measurements of height, weight, waist circumference, and BMI), and identifying the presence of any other behavioral mediators, such as barriers to weight loss, social support, or change of status or occupation.

2. Advising the patient, including recommending a weight-management program and reviewing the recommendations, particularly for the patient with diabetes and patients with specific dietary habits, and recommending helpful stress-management techniques. It is important for the physician to give clear respectful advice and to link these recommendations with outcome data.

3. Agreement. Setting up an agreement with the patient for both short-term goals (including calorie restriction, glucose monitoring, and exercise) and long-term goals (hemoglobin A1-C, lipid profiles, and weight reduction), and collaborating on acceptable approaches to changing the patient’s lifestyle and stressing achievable goals.

4. Assisting the patient with motivation and any problems they may be having and discussing all available resources to aid the patient in their struggle, sometimes presenting treatment options that have worked for other patients, including group sessions.

5. Arranging follow-up to insure proper adherence to techniques and to receive feedback from the patients on their success or lack of success with the program (38).

VanWarmer and Boucher recommend key messages in any type of counseling program. The first is to emphasize that tight glycemic control is the top priority for patients with diabetes, not necessarily weight management. Although weight loss may improve glycemic control, better control in some patients may lead to weight gain.

Explaining the pathophysiology of the disease is important to maintain patient compliance, as well as self-monitoring of the patient’s blood glucose, which can give individuals important insight as to how the foods they are ingesting will affect their state of glycemia. Physical activity is always to be encouraged, assuming that the individual is capable of such activity. Moderate levels of physical activity for 30–45 minutes, 3–5 days/week are optimal in many exercise protocols.

It is the duration of physical activity, not the intensity, that correlates with benefit. Physical activity will reduce abdominal fat and improve insulin sensitivity and overall
present with acute myocardial ischemia and/or infarction while taking sulfonylureas. Concern about the first-generation sulfonylureas was originally raised as early as the 1970s, with the University Group Diabetes Study casting aspersions on tolbutamide use and its worsening prognosis in macrovascular disease.

In general, all sulfonylureas are equally effective in terms of their hypoglycemic potency, although a recent trial has indicated that glimepiride (Amaryl) may be slightly more efficacious than the others. One can expect a 1.5–2% drop in hemoglobin A1-C with entry A1-C greater than 9% in most patients. Generally, the greater the fasting plasma glucose on initiation of therapy, the greater the benefit (3).

Sulfonylureas depend on good β-cell function and the absence of antibodies to glutamic acid decarboxylase or islet-cell for their efficacy. Many patients, particularly those with an entry hemoglobin A1-C greater than 8%, will require the addition of a second oral agent, usually a sensitizer or insulin. Disappointingly, patients on oral agents, although achieving an initial drop in A1-C, experience progressive A1-C and fasting glucose elevations caused by progressive β-cell deterioration over a period of 2–4 years.

Table 1
Mechanism of Action of Oral Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of action</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretagogues</td>
<td>• Sulfonylureas</td>
<td>Glipizide, glyburide, glimepiride</td>
</tr>
<tr>
<td></td>
<td>• Increase insulin secretion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stimulate pancreatic β-cell</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td>Repaglinide</td>
</tr>
<tr>
<td>Phenylalanines</td>
<td>• Decrease hepatic glucose production</td>
<td>Nateglinide</td>
</tr>
<tr>
<td>Biguanides</td>
<td>• Decrease intestinal glucose absorption</td>
<td>Metformin</td>
</tr>
<tr>
<td></td>
<td>• Increase peripheral glucose uptake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increase insulin sensitivity</td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>• Delay carbohydrate digestion</td>
<td>Acarbose, miglitol</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>• Increase insulin sensitivity</td>
<td>Pioglitazone, rosiglitazone</td>
</tr>
<tr>
<td></td>
<td>• Preserve β-cell function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May regenerate β-cells</td>
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From ref. 22.

Despite their efficacy in causing insulin release from the pancreas, sulfonylureas have not been shown to preserve β-cell function. Weight gain, lack of exercise, and dietary indiscretion are also associated with failures on sulfonylureas. Side effects with these medications are generally mild and reversible with discontinuation of therapy, with less than 2% of patients discontinuing therapy because of adverse affects. The major problem is hypoglycemia, which is more common in agents with longer duration, such as glyburide and chlorpropamide (4).

Sulfonylureas are metabolized hepatically and excreted renally; therefore, any patients with renal insufficiency may have trouble with hypoglycemia with all sulfonylureas (except for glipizide, whose hepatic metabolites are not active, thus there is no dosage decrease necessary in patients with renal insufficiency and taking glipizide).
with associated hypotension, hypothermia, and cardiac arrhythmia in more severe cases. Prompt withdrawal of metformin should be undertaken when these symptoms present themselves. Lactic acidosis can be suspected in any diabetic patient who presents with a metabolic acidosis in the absence of ketonuria, ketonemia, and ketoacidosis.

Lactic acidosis is a medical emergency and requires prompt medical attention. Cimetidine is the only known drug shown to reduce the renal clearance of metformin, although other products can have the potential to decrease its renal excretion, namely amiloride, digoxin, quinidine, vancomycin, procainamide, morphine, ranitidine, and quinine. Metformin is also available in a combination product with glipizide (Metaglip), glyburide (Glucovance), or rosiglitazone (Avandamet). Metformin is also available as a liquid preparation for those patients who have trouble swallowing pills.

**The α-Glucosidase Inhibitors**

The nonsystemic α-glucosidase inhibitors are used primarily to control postprandial hyperglycemia by delaying the absorption of polysaccharides and disaccharides in the intestinal brush border. They can be used as initial agents or in combination therapy. Recent trials have indicated that patients placed on acarbose can reduce their risk of developing cardiovascular events.

Acarbose (Precose) was approved for use in the United States in 1995 and miglitol (Glycet) was approved for use in 1996. Acarbose and miglitol do not decrease, but only delay the overall absorption of carbohydrates, thus producing a smaller postprandial peak in serum glucose concentrations, which results in a more prolonged carbohydrate absorption curve. This allows the β-cell to have a greater opportunity to match insulin responses to subsequent glucose demands, enabling the available insulin to better metabolize circulating glucose in the postprandial state.

Miglitol has been shown to inhibit sucrase and α-amylase (responsible for the metabolism of sucrose and starch, respectively) in the lumen of the small intestine. α-Amylase facilitates the breakdown of starch into dextrins, maltotriose, and maltose; whereas sucrase inhibits the breakdown of sucrose. Miglitol’s inhibition of the enzymes delays subsequent carbohydrate degradation, attenuating postprandial plasma glucose elevation by delaying glucose uptake.

α-Glucosidase inhibitors are modestly effective in treating diabetes with hemoglobin A1-C reductions of 0.5–1% and can be particularly effective in patients who consume high-carbohydrate diets. Adverse effects of α-glucosidase inhibitors are gastrointestinal and include abdominal bloating, pain, diarrhea, and flatulence, occurring in up to 70% of patients. Although these adverse effects tend to dissipate in 4–6 weeks, they are to be a major reason for discontinuation of medications.

High doses of acarbose have been shown to elevate transaminases, whereas miglitol has been shown to be less irritating hepatically. Miglitol has been shown to decrease the bioavailability of propranolol and ranitidine. α-Glucosidase-inhibitor activity can be impaired with concomitant administration of intestinal absorbants, such as cholestyramine and digestive enzyme preparations (particularly those containing carbohydrate-splitting enzymes).

Acarbose is contraindicated in patients with cirrhosis, whereas miglitol is not contraindicated in patients with liver disease. α-Glucosidase inhibitors are not indicated in patients with severe renal insufficiency or in patients with inflammatory bowel disease or pre-existing bowel obstruction.
combination; it is available with metformin as Avandamet. Glucose-lowering potency of pioglitazone and rosiglitazone seems to be equivalent. When used in triple-agent therapy, reductions in hemoglobin A1-C of up to 1.3% have been reported.

From a physiological point of view, the TZDs offer some significant advantages at the cellular level because of their anti-inflammatory and antiatherogenic effects. The small adipocytes are responsible for the production of adiponectin (which decreases insulin resistance), whereas the large adipocytes produce leptin-releasing free fatty acids (which can enhance insulin resistance). Both rosiglitazone and pioglitazone have been shown to reduce free fatty acid concentrations and increase adiponectin levels.

Pioglitazone is the only available TZD with effects on both PPAR-γ and PPAR-α (18).

The weight gain with rosiglitazone and pioglitazone primarily results from an increase in subcutaneous fat content and a decrease in intra-abdominal fat, with a subsequent decline in triglycerides and free fatty acid concentrations. Rosiglitazone and pioglitazone also cause decreases in intramuscular fat content. Animal models indicate that thiazolidinediones help preserve β-cell function.

Significant drug-induced hepatotoxicity has been reported with both rosiglitazone and pioglitazone, but these cases are rare and usually confined to individuals that are consuming alcohol or taking other hepatotoxic drugs, such as acetaminophen, in large quantities. When taken as directed, TZDs are far safer to the liver than their precursor, troglitazone. Because of concerns regarding hepatotoxicity, liver-function tests should be performed before starting TZD therapy and every 2–3 months during the first year of therapy thereafter.

If liver function tests rise to more than three times the upper limit of normal, the thiazolidinedione should be stopped. Slight decreases in hemoglobin and hematocrit resulting from fluid retention and the dilutional effect of expansions in plasma volume have also been reported.

Edema occurs in 2–4% of patients with monotherapy and 4–6% of patients receiving combination therapy, although the incidence of edema can be as high as 10–15% in individuals taking insulin. Thiazolidinediones are contraindicated in diabetic patients with New York Heart Association class III and class IV cardiac status.

Pioglitazone is strictly a once-daily drug, whereas rosiglitazone can be administered twice daily.

Because rosiglitazone and pioglitazone have various sites of metabolism within the cytochrome P-450 system, drug interactions of any significance have not been reported. Although the drugs are protein bound, there have been no drug interactions reported with highly protein-bound drugs.

**ORAL AGENT COMBINATIONS**

Less than 20% of patients with type 2 diabetes presenting to primary care physicians offices with an initial glucose of 200–240 mg/dL (hemoglobin A1-C of 9–10%) will be able to reach a hemoglobin A1-C of less than 7% if treated with maximal doses of a sulfonylurea or metformin alone. With newer guidelines lowering the desired goal for hemoglobin A1-C to 6.5%, the majority of patients seen in primary care offices with this degree of hyperglycemia will require combination therapy to achieve the 6.5% A1-C goal. Even patients with initially good responses to a single agent will subsequently require a second or even a third agent in the future because of the progressive nature of type 2 diabetes, dietary indiscretion, and noncompliance.
A4 enzyme system, drugs that are metabolized through this system (Rifampin, barbiturates, carbamazepine, certain statin drugs, amiodarone, benzodiazepines, sildenafil (Viagra), theophylline, and certain selective serotonin reuptake inhibitors) may increase repaglinide metabolism (19). Although in vitro data indicate that repaglinide metabolism may be inhibited by antifungal agents (such as ketoconazole and miconazole) or antibacterial agents (such as clarithromycin), systematically acquired data is not available on increased or decreased plasma levels with other cytochrome P-450 3-A4 inhibitors or inducers.

Risk of hypoglycemia is increased with the metformin/repaglinide combination compared with either agent alone. Repaglinide is not indicated for combination use with any sulfonylurea and should be avoided in the elderly, debilitated, or malnourished patients, or in patients with adrenal or pulmonary insufficiency. Repaglinide should not be used in patients with severe liver disease and should be used only with caution in patients with impaired hepatic function.

**Metformin and Nateglinide**

Nateglinide is metabolized in the liver primarily by cytochrome P-450 2-C9 (70%) and 3-A4 (30%), and its metabolites are excreted renally. Therefore, no dose adjustment is necessary in patients with renal or hepatic insufficiency. Nateglinide is indicated for combination therapy with metformin in patients whose diabetes has not been adequately controlled with either agent alone. Patients whose diabetes has not been controlled by sulfonylureas or metformin should not be switched to nateglinide alone.

Although nateglinide is not appropriate in patients with advanced diabetes, especially where fasting blood glucose levels are greater than 200 mg/dL, it can be used very effectively in combination with metformin to enhance insulin sensitivity. A recent trial presented at the American Diabetes Association Scientific Sessions showed that nateglinide reduced postprandial glucose levels from 195 to 150 mg/dL in monotherapy and from 209 to 160 mg/dL in combination therapy with metformin and nateglinide. A1-C levels dropped an additional 0.8% when nateglinide was given to patients inadequately controlled on metformin monotherapy (20).

Other trials have shown more robust reduction of A1-C levels by 1.4% with the nateglinide/metformin combination, with fasting glucose reductions of 40 mg/dL. The nateglinide/metformin combination is ideal for overweight patients whose primary disturbance is postprandial hyperglycemia with A1-C less than 8%.

**Repaglinide and Thiazolidinedione**

The repaglinide and TZD combination demonstrated a reduction in A1-C of 1.3% when repaglinide was added to Troglitazone (Rezulin). Current studies with pioglitazone and rosiglitazone have demonstrated a synergistic effect that reduced A1-C levels by 1.3% after 6 months. Because repaglinide and pioglitazone and, to a certain extent, nateglinide, are metabolized in cytochrome P-450 3-A4, a potential for drug interaction exists although none has yet been described (19).

**Sulfonylurea and Thiazolidinedione**

Clinical trials evaluating the addition of pioglitazone or rosiglitazone to poorly controlled, sulfonylurea-treated type 2 diabetic patients have shown synergistic effects, with
lowering fasting or premeal glucose, although the glinides and the α-glucosidase inhibitors specifically target postprandial excursions.

2. Levels of postprandial glucose are regulated by preprandial glucose levels, insulin sensitivity, and bolus or first-phase insulin release. Oral agents effective in reducing postprandial hyperglycemia include the glinides (repaglinide and nateglinide), α-glucosidase inhibitors, and, to a lesser extent, the TZDs and biguanides.

The following is a recommended treatment strategy (4):

1. For fasting glucoses that are slightly elevated (126–160 mg/dL, A1-C < 8%) insulin resistance predominates and plasma insulin levels are usually elevated. A good approach would be to use diet and exercise with either the insulin sensitizers (alone or in combination) or sulfonylureas as initial therapy.

2. For fasting glucoses of 160–180 mg/dL (A1-C: 8–9%), combination therapy with a sensitizer (metformin and/or TZD) and a secretagogue, sulfonylurea, nateglinide, or repaglinide will usually be necessary. Combination drugs involving a sulfonylurea and biguanide can be ideal for this purpose, starting with the lowest dose (1.25 mg) of sulfonylurea and 250 mg of metformin and titrating upwards. Nateglinide and repaglinide should not be used in combination with a sulfonylurea.

3. Patients with fasting glucose levels in excess of 180–200 mg/dL (A1-C levels > 9%) will require a combination therapy with a sulfonylurea and a sensitizer (Biguanide, TZD) either alone or in combination with another sensitizer. Patients failing to achieve an A1-C of less than 6.5% may require secretagogues, with different fat catabolic mechanisms of action; usually including a sulfonylurea, metformin, and TZD. These patients may also respond to the addition of a bedtime intermediate-acting insulin.

The new rosiglitazone/metformin combination affords the physician the opportunity of using two sensitizing agents with different and synergistic mechanisms of action in one pill. Ultimately, the majority of patients with type 2 diabetes will require insulin either alone or in combination with oral agents or other insulin. Chapter 7 addresses insulin use and the use of insulin with various oral-agent combinations.

REFERENCES

This concept of faster and better control can be applied to acutely ill patients, who will also require rapid control of their blood glucose with insulin. Recent outcomes data have supported better prognoses in acutely ill patients with insulin-treated hyperglycemia than those in whom hyperglycemia is casually treated.

Thin patients with type 2 diabetes tend to be less sensitive to oral regimens because they tend to primarily have insulin-secretion problems rather than insulin resistance. A trial of dietary therapy, exercise, and oral agents can be acceptable provided that the patient is not in the toxic glucose range on a consistent basis. Even patients with latent autoimmune diabetes can remain controlled for short periods on oral agents. Weight gain is always a large patient concern with the use of insulin, which has also been another major factor in patients’ resistance to taking insulin. In the United Kingdom Prospective Diabetes Study (UKPDS) (7), weight gain was more common with patients taking insulin, where they gaining an average of approximately 4 kg compared with 2.6 kg for patients on sulfonylurea therapy.

However, patients in the intensive control group also had fewer microvascular complications as a result of tighter diabetic control. As discussed in Chapter 6, the use of metformin will tend to attenuate weight gain in any treatment modality, whether it be in thin or oral agents. Because of the connection with insulin resistance, cardiovascular risk factors, and elevated insulin levels, the UKPDS compared with cardiovascular events among patients with diet control and conventional therapy with patients on sulfonylureas, metformin, or insulin (8). Patients taking insulin did not experience any increase in adverse cardiovascular events. Studies by Van den Bergh (9) and DIGAMI (10) both proved that tighter glycemic control in acutely ill patients and patients with myocardial infarctions led to a significant reduction in mortality, particularly in patients with a high cardiovascular-risk profile and in patients who were insulin-naive compared with other patients.

Another concern has been the incidence of hypoglycemia with the use of insulin. In the Diabetes Control and Complications Trial (DCCT) (11), in patients with type 1 diabetes, tighter control of glycemia did increase the risk of hypoglycemia threefold over conventional therapy. However, there was also a significant improvement in microvascular events and neurological complications.

In the Kumamoto study (12) with patients with type 2 diabetes, average hemoglobin A1C values were 7.1 and 9.4% for tightly controlled and conventional groups, respectively. Only mild hypoglycemic reactions, with similar rates, were seen in both groups. In the UKPDS trial, the rate of hypoglycemic episodes was 2.3% in patients taking insulin compared with less than 1% with other agents.

Although there is an increased risk of hypoglycemia with tighter glycemic control, aggressive therapy is extremely important to minimize risks. Newer insulin analogs tend to mitigate the risk of hypoglycemia and better mimic natural insulin patterns.

Another strategy that physicians can use to encourage patients to accept insulin use include turning fears into motivators, such as asking the patient about: their family history of diabetes and its complications; employment issues relative to common diabetic complications; and their work duties, vision problems, personal concerns, responsibilities, sexual dysfunction, exercise capacity, and symptoms.

It is critically important to have patients understand that improving the hemoglobin A1C with tighter control will reduce their risk of complications, and that even if tighter control means more medication and/or the use of insulin it is worthwhile on a long-term basis. Making the transition from oral agents to insulin is often a great challenge when patients are very resistant to the idea.
glargine is injected into the subcutaneous tissue, neutralization of the acidic solution is achieved. This causes the formation of microprecipitates from the small amounts of glargine that are slowly released and result in a consistent concentration time profile over 24 hours with essentially no peak, allowing for once-a-day dosing. Glargine has an equivalent glucose-lowering effect to human insulin on a molar basis. The longer duration of action of glargine is directly related to its slower absorption rate.

Glargine insulin cannot be diluted or mixed with other insulins or solutions. This newer long-acting analog insulin also has lower intersubject and intrasubject variability than NPH or Ultralente. Glargine closely mimics continuous subcutaneous insulin infusion, which remains the gold standard for insulin replacement.

Studies by LePore in 2000 (28) confirm glargine’s close comparison with continuous subcutaneous insulin infusion. In head-to-head comparisons with NPH insulin, glargine insulin had a lower incidence of nocturnal hypoglycemia in both type 2 and type 1 diabetic patients than NPH (31 vs 40% in type 2 diabetic patients, and 18 vs 27% in type 1 diabetic patients), whereas fasting plasma glucose levels were reduced from baseline to a greater extent in patients with type 2 diabetes than with type 1 diabetes with insulin glargine (from 32 to 22% for type 2 diabetic patients and from 31 to 6% for patients with type 1 diabetes) (28).

In the LePore studies, final hemoglobin A1-C levels were comparable. A1-C levels achieved were 7.9% with NPH insulin and 7.49% with glargine in patients with type 1 diabetes, and in patients with type 2 diabetes A1-C levels were 6.49% with NPH and 7.54% with glargine. Studies published in Diabetes Care in 2001 by Hinella Yki-Jarvinen et al. showed a lower residual hypoglycemia and better postprandial dinner glucose control with a bedtime insulin glargine regimen compared with bedtime NPH insulin for patients with type 2 diabetes (29).

The consistent absorption of glargine allows for lower risk of mistakes and allows bedtime administration to do a better job controlling the dawn phenomenon without risking hypoglycemia. This permits greater flexibility of lifestyle and less worry about variability. Additionally, patients find fewer short-acting insulin requirements and fewer postprandial excursions when using glargine.

When combined with short-acting insulins to cover postprandial hyperglycemia, the ideal basal/bolus therapeutic concept can be achieved. A large, randomized, controlled clinical study compared a basal–bolus regimen of glargine once daily at bedtime vs Humulin NPH insulin administered once or twice daily along with regular human insulin before meals as needed in both groups. Glargine had similar effectiveness as NPH (which was given once or twice daily) in reducing A1-C and fasting glucose, and showed less hypoglycemia.

Dosage of glargine should always be individualized, with lower starting doses required if oral agents are retained. Patients taking maximal oral agents can usually be started on low-dose, once-a-day administration of glargine (5–10 U initially, with weekly increasing 2-U titration to achieve a fasting blood sugar <100 mg/dL).

Glargine dosage must be individualized with each patient. The principal is to start low and increase slowly when using glargine. In patients who are switched from once-daily mixed or intermediate insulins, a 1:1 conversion can be used. If intermediate or mixed insulins are administered on a twice-daily basis, then two-thirds of the total daily dose of the mixed insulins can be used as a starting dose for glargine. Because of its true
Use of the analog insulins has resulted in less overall insulin use in a 24-hour period, with even fewer episodes of less hypoglycemia. In the DCCT trial (11) with patients with type 1 diabetes, the incidence of severe hypoglycemia was three times greater in the group receiving intensive therapy than in the group receiving conventional therapy, but less than in the group receiving multiple-dose injections. The reduction in insulin requirements, better pharmacological delivery of insulin, and the minimal weight gain with insulin pumps (22) makes short-acting insulin analogs extremely appealing.

When pump therapy is started, the total daily insulin dose should be reduced by 25–30% in adults with half of the total daily dose used as the basal dose and the other half as the total bolus dose. Dividing the basal dose by 24 calculates the units per hour that can be entered as a single basal rate. Both bolus and basal doses are adjusted according to the patient’s blood glucose measurements taken preprandially, postprandially, and at bedtime.

The basal rate is adjusted to avoid glucose excursions greater than 30 mg from baseline. The basal rate should only be adjusted during the day if there are significant glucose excursions more than 4 hours after a mealtime bolus. Bolus doses are adjusted according to glucose measurements, which can be taken either preprandially or postprandially. Using the preprandial approach, patients are given guidelines for their carbohydrate to insulin ratio.

The carbohydrate to insulin ratio may vary among individuals from 1 U of insulin per 5 g of carbohydrate up to 1 U of insulin per 5–15 g of carbohydrate; an average ratio is 1 U of insulin for every 10–15 g of carbohydrate. Because of both the interperson variability and the unknown carbohydrate content of various foods, postprandial glucose measurements (particularly with the use of rapid-acting insulin analogs) may be more practical.

When the patient still does not achieve A1C goals, the clinician must examine the frequency of the patient’s monitoring and the patient’s diet recording and knowledge of food intake, and determine whether the basal rate is set properly, whether the patient is using the proper correction bolus factor to treat blood sugars, and whether the patient is pre-emptively counting carbohydrates in appropriate fashion.

For some people a postemptive or postmeal approach may be more efficient. Clearly, the future of insulin-pump therapy is promising. Newer designs with remote control devices and machines that can administer insulin according to measured levels of glucose with minimal patient interference seem to provide some important breakthroughs for future endeavors. Although the ease of use and important benefits from glargine insulin has limited pump therapy to primarily patients with type 1 diabetes, there are some type 2 diabetic patients who can genuinely derive benefits from pump therapy.

NOVEL THERAPEUTICS

Implantable insulin pumps have not yet been approved for use in the United States. Generally, patients using these pumps are more satisfied with their treatment and experience less weight gain. This technique delivers insulin directly into the abdominal cavity, closely resembling normal insulin physiology and production even more than subcutaneous injections. This technology, along with an implantable glucose sensor, may provide an important breakthrough and advance in insulin-pump therapy.

Pancreatic transplantation is becoming another option at several medical centers to restore insulin secretion in selective patients. Many areas are using islet-cell transplantation in lieu of whole pancreas organ donations. Further research is ongoing to genetically engineer β-cells and to investigate the use of fetal islet cells or isolation of
events. This data has shown that CHD mortality rates are higher in individuals with impaired glucose tolerance than in individuals with normal tolerance. The risk of CHD is 2.5 times greater in individuals with type 2 diabetes than nondiabetic patients, and 1.9 times greater in individuals with impaired glucose tolerance. Elevated hemoglobin A1-C was found to be a predictor for CHD in patients with type 2 diabetes.

One study looked at 1069 patients with diabetes, evaluating the incidence of CHD mortality and all events during a 3.5-year period. Patients in the highest A1-C tertile had a significantly higher incidence of CHD mortality than the lowest A1-C tertile. Incidence of fatal and nonfatal myocardial infarction was 0.4% for patients without diabetes but rose to 14.8% among patients with diabetes. The highest tertile for coronary artery disease mortality and for all CHD events was with hemoglobin A1-C greater than 7.9% (9).

Curiously, in the United Kingdom Prospective Diabetes Study (UKPDS) (10) and Diabetes Control and Complications Trial (DCCT) (11) patients with type 2 and type 1 diabetes, respectively, although tight glycemic control reduced the risk of MI, it did not reduce the risk to a significant degree. This can be appreciated when one understands the multiple risk factors underlying vascular disease in general and coronary artery disease in particular; including dyslipidemia, hypertension, impaired endothelial function, cigarette smoking, lifestyle, hyperinsulinemia, insulin resistance, oxidative stress, obesity, hyperhomocysteinemia, lipoprotein (a) elevations, and vascular inflammation. Risk of vascular disease can only be improved with a comprehensive plan addressing these risk factors (see Table 1).

The presence of more than one risk factor exponentially increases cardiovascular risk. There are some risk factors that are associated with more increased risk than others. The UKPDS trial showed that the most important risk factor for myocardial infarction was low-density lipoprotein (LDL) cholesterol level, followed by diastolic blood pressure, cigarette smoking, low HDL level, and high hemoglobin A1-C level. In addition to identification of risk factors, early recognition and management is important.

Although these factors may vary in their importance in different patients, a top priority should include blood pressure, lipid, and glucose control when addressing coagulopathy disorders.

Cigarette smoking doubles the risk of macrovascular disease in diabetic patients and significantly increases the likelihood of developing and aggravating microvascular disease. This is because cigarette smoking promotes endothelial dysfunction, arteriosclerotic deposition, and is a source of advanced glycosylation end products, which promote diabetic vascular complications. Cigarette smoking also increases oxidation of LDL cholesterol, enhancing its deposition within the intima.

### Table 1

**Risk Factors for Macrovascular Disease in Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Smoking</th>
<th>The metabolic syndrome</th>
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</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Peripheral arteriosclerotic vascular disease</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Coronary arteriosclerotic vascular disease</td>
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<tr>
<td>Hypercoagulability</td>
<td>Carotid arteriosclerotic vascular disease</td>
</tr>
</tbody>
</table>

From ref. 8.
CONTENTS

INTRODUCTION
RETINOPATHY
DIABETIC NEUROPATHY
DIABETIC NEPHROPATHY
SUMMARY
REFERENCES
CME QUESTIONS

INTRODUCTION

The microvascular complications of diabetes include the following:
1. Retinopathy.
2. Nephropathy.
3. Neuropathy, including mononeuropathy, diabetic amyotrophy, symmetrical distal neuropathy, diabetic gastroparesis, diabetic diarrhea, neurogenic bladder, impaired cardiovascular reflexes, and sexual dysfunction.

Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Perspective Diabetes Study (UKPDS) have shown the importance of tight glycemic control in preventing microvascular disease. The DCCT and UKPDS trials also showed that the benefits of treating microvascular disease did not have a threshold at A1-C levels of 6.5%, but formed a continuum; that is, reductions in A1-C levels below 6.5% continued to demonstrate additional benefits.

RETINOPATHY

Diabetes is the leading cause of new cases of blindness in individuals between the ages of 20 and 74 years. Ninety percent of patients with diabetes will have retinopathy after 15 years of known duration of disease, and 21% of patients will have retinopathy at the time of diagnosis. Retinopathy is responsible for 12,000–24,000 cases of blindness each year. It is critical for the primary care physician to realize that waiting until the diabetic patient complains of blurred vision may be too late, because permanent retinal injury with visual loss may have already occurred.

There are several interesting theories as to how hyperglycemia wreaks havoc on the retina. These include the following:

1. Neovascularization. In response to local tissue ischemia, vascular endothelial growth factor (VEGF) stimulates the growth of new blood vessels in nonperfused areas.
neovascularization causes blood vessels to grow between the internal surface of the retina and the vitreous gel.

2. Capillary occlusion. In the hyperglycemic state, the white blood cells may express more molecules on their surfaces, called integrins. Integrins can interact with the capillary endothelial cells that express intercellular adhesion molecules (ICAMS), which make the white cells adhere to the capillary walls. This adhesion causes the capillaries to become plugged and interferes with white-cell passage, progressively depriving larger areas of the retina of perfusion. Initially, surrounding capillaries can compensate by accepting increased flow, but this autoregulation eventually fails and wider retinal areas become compromised.

3. Exudative edema and leakage. White cells that have adhered to the endothelial surface release products that increase permeability. With increased permeability of the endothelium, production of VEGF is increased, which allows fluid to leak into the retina, resulting in tissue edema. This edematous fluid and cholesterol begins to accumulate in the retina, impairing visual acuity.

4. Fibrosis. With neovascularization there is a proliferation of fibrous tissue, which causes local and widespread vitreous gel retraction, tearing additional blood vessels and resulting in hemorrhage between the vitreous gel and the retina. This can result in floaters or diffuse visual loss. Hemorrhaging can produce more fibrosis, which can cause further retinal distortion and detachment and additional visual loss.

Diabetic retinopathy can be divided into background and proliferative retinopathy. Background retinopathy involves microaneurysms, intraretinal hemorrhages, clinically significant maculopadema, beading, cotton-wool spots, intraretinal microvascular abnormalities, and circinate retinal abnormalities. Proliferative diabetic neuropathy can include surface neovascularization, diffuse neovascularization, and subsequent complications of proliferation (including vitreous hemorrhaging and fraction retinal detachments). Although the retina may appear to be normal on clinical examination, several biological and physiological changes are occurring at the cellular level, accompanied by alterations in retinal blood flow and leukocyte adhesion.

Diabetic retinopathy tends to progress from the mild nonproliferative form, simply manifesting increased vascular permeability, to the moderate and severe nonproliferative form, which involves vascular alterations closer to the finer proliferative form, and is characterized by neovascularizations on the retina and the posterior portion of the vitreous.

Visual loss from diabetic retinopathy can occur as a result of preretinal or vitreous hemorrhaging from neovascularization, distortion of the retina from new blood vessel formation and contraction of fibrous tissue resulting in retinal detachment and subsequent irreversible vision loss, and capillary nonperfusion or macular edema (5).

The primary physician should understand the importance of preventing or delaying the onset of progression of diabetic retinopathy, particularly while the individual is asymptomatic. Referral to an ophthalmologist is important at the time of diagnosis of diabetes. Timely intervention with laser photocoagulation can prevent visual loss in a large percentage of patients who have severe nonproliferative or early proliferative diabetic retinopathy.

Clinical presentations of diabetic retinopathy can be varied, with the most common presentation being asymptomatic individuals. However, other presentations can include sudden visual loss, marked retinal lipid exudation in association with increased hyperlipidemia, marked vascular narrowing in small vessels (usually asso-
Diabetic Retinopathy Study (ETDRS) (9) revealed that argon laser photocoagulation applied locally can be extremely effective in stabilizing vision and treating macular edema.

Photocoagulation has slowed the progression of visual loss in cases of macular edema and improved vision by as much as 50% when used as a preventative measure. Patients with proliferative retinopathy and high-risk characteristics are usually given panretinal laser treatments with a scattered pattern of 1200–1600 burns applied uniformly throughout the periphery of the retina, avoiding the macular area (10).

Significant retinal detachments and large vitreous hemorrhages may require vitrectomy. This is usually reserved for patients with poor vision. Hypertension can be a significant independent risk factor in causing and aggravating retinopathy in patients with type 2 diabetes as well as increasing the risk for macular edema.

Clinical trials have shown that elevated systolic blood pressure may significantly increase the risk of retinopathy in patients with type 2 diabetes. Most studies confirm an association not only with systolic but also with diastolic hypertension. In the UKPDS trial, blood pressure decreases of 10 mmHg systolic and 5 mmHg diastolic reduced diabetic microvascular complications after approximately 8 years by 35%.

Several mechanisms are postulated for the aggravation and acceleration of diabetic retinopathy by hypertension. These include the following:

1. Increased retinal endothelial damage.
2. Loss of retinal vascular autoregulation.
3. Increased expression of VEGF, resulting in proliferation of small vessels and worsening of retinopathy.

Several clinical trials have confirmed that microalbuminuria, macroalbuminuria, and/or proteinuria is related to progression of retinopathy. Close to 70% of patients with type 2 diabetes on dialysis have some form of retinopathy. This is important to keep in mind, particularly in patients with impaired renal function, because retinopathy may also be progressing (11).

An interesting association has been found between anemia and retinopathy, particularly because anemia is more common in patients with renal failure. Next to hyperglycemia, anemia has now been found to be the second highest risk factor for subsequent development of diabetic retinopathy; patients with hemoglobins less than 12 were twice as likely to develop diabetic retinopathy in a recently completed Finnish trial.

The ETDRS trial (9) showed that severe visual loss and iris peripheral retinopathy were associated with a low hematocrit, and that increases in hematocrit from 29.6 to 39.5% after treatment with erythropoietin (Procrit, Epogen) resolved macular edema in three of five patients evaluated.

Although there is some literature to support the association between smoking and diabetic retinopathy, the association is much stronger with macrovascular disease and nephropathy. Lipid disturbances can also aggravate prognosis in diabetic retinopathy; elevated triglyceride levels were associated with vision loss and proliferative diabetic retinopathy in the ETDRS trial.

All intensive glucose therapeutic maneuvers (except for chlorpropamide) were associated with a clear reduction in the risk of diabetic retinopathy progression in the UKPDS trial. Lisinopril has been beneficial in slowing retinopathy progression in patients with type 1 diabetes; and captopril and the β-blocker atenolol were beneficial in patients with type 2 diabetes in the UKPDS trial.
increases the intraglomerular pressure by narrowing the renal efferent arterials, which subsequently increases the glomerular capillary pressure, putting significant pressure on the walls.

Angiotensin II may also cause disruption of the supporting cells within the renal glomerulus, causing small amounts of protein to leak through the capillary walls. Thus, blocking the effect of angiotensin II and decreasing its production has had direct beneficial effects, decreasing the production of interstitial and glomerular matrix protein, reducing proteinuria, and lowering both systemic and glomerular hypertension.

ACE inhibitors block the synthesis of angiotensin II and inhibit ACE along with inhibiting the degradation of vasodilatory bradykinin, increasing nitric oxide levels. Approximately 50% of the angiotensin II produced in the body goes through ACE with 90% of that produced in the tissues. ARBs prevent the binding of angiotensin II to its type II receptor site, preventing its vasoconstrictor effects (45).

Of patients with type 2 diabetes, 30% are hypertensive when the diagnosis is made and 70% are hypertensive when nephropathy develops. Renovascular arteriosclerotic disease is present in up to 40% of patients with overt nephropathy and contributes to 20% of patients with hypertension. ACE inhibitors have established themselves as hypertensive and renal protective agents in patients with diabetes and are particularly effective in decreasing the risk of development or progression of nephropathy.

ACE inhibitors are particularly effective in decreasing intraglomerular pressure by selectively dilating glomerular efferent arterioles. This renal protective effect can delay or prevent the development of glomerulosclerosis and, in some instances, can be independent of its antihypertensive effect. Captopril (Capoten) was shown to slow the progression of nephropathy by 50% in patients with type 1 diabetes, despite the fact that median blood pressures in the captopril group and the placebo group were comparable throughout the trial. These individuals had urinary protein excretions greater than 500 mg/day (46).

Over a 7-year period, enalapril was evaluated in 94 patients with type 2 diabetes and microalbuminuria with normal blood pressure. Albumin excretion and serum creatinine levels remained stable over the 7-year course of time in individuals taking the ACE inhibitor, with a subsequent reduction of the absolute risk of nephropathy by approximately 42%. This was in sharp contrast to patients who did not take the ACE inhibitor, in whom albumin rates steadily climbed. When the placebo-treated patients were switched to enalapril (Vasotec), the albumin excretion stabilized for the final 2 years and, interestingly, began to rise again in the enalapril-treated patients who declined treatment after the first 5 years. This served as evidence that the ACE inhibitors can stabilize renal function in previously untreated patients and can offer some significant long-term protection.

The diabetic substudy of the Heart Outcomes Prevention Evaluation (HOPE) study (also called the MICRO-HOPE trial (47)) showed that, compared with placebo at equivalent blood pressures, ramipril decreased the rate of progression to overt nephropathy by 24% in patients who were either normal albuminuric or had microalbuminuria. Although the most significant benefits in the MICRO-HOPE trial were in the cardiovascular area, the combined microvascular outcomes, including the need for dialysis, retinopathy laser therapy, or overt nephropathy was reduced by 16% in the ramipril group, with a reduction in overall proteinuria regardless of the presence of microalbuminuria at entry (48).


choice for raising HDL is either niacin or fibrates. The thiazolidinediones (TZDs) and metformin are also effective in raising the HDL and are particularly efficacious because of their dual efficacy in diabetic patients in achieving glycemic and lipid goals. The TZDs, however, will change LDL composition from the more atherogenic, small, dense LDL to the fluffy, less atherogenic, buoyant, and larger LDL molecule. The TZDs have also been demonstrated to have anti-inflammatory effects (8).

The next priorities are triglyceride lowering and lowering the non-HDL cholesterol. Here, glycemic control with dietary interventions can have a dramatic effect. Fibric acid derivatives or fibrates, such as gemfibrozil and fenofibrate, are extremely effective in lowering triglyceride. Niacin is also extremely effective in triglyceride lowering, with the newer extended-release niacin less likely to interfere with glycemic control than the intermediate or crystalline and sustained-release derivatives. Pioglitazone (but not rosiglitazone) can also be effective in triglyceride-lowering.

Statins, particularly rosuvastatin, lipitor, fluvastatin, extended-release lovastatin, and simvastatin can be effective for hypertriglyceridemic patients but do not seem to be as potent in lowering triglycerides as the fibric acid derivatives (fibrates) or niacin.

The most potent of the statins is the newest member of the class, rosuvastatin (Crestor) with recent data from the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin Trial (9) indicating greater efficacy in reducing non-HDL cholesterol than the other statins across the dosing spectrum. This randomized open-label 6-week trial in 2431 patients with LDL cholesterol at entry of 160–250 mg/dL and triglycerides less than 400 mg/dL found that rosuvastatin at 10 mg/day, 20 mg/day, and 40 mg/day reduced LDL by 46–55%, compared with 37–51% with atorvastatin (10–80 mg), 28–46% with simvastatin (10–80 mg), and 20–30% with pravastatin (10–40 mg). Rosuvastatin (10–40 mg) also increased the HDL cholesterol by 7.7–9.6%, compared with 2.1–5.7% with atorvastatin (10–80 mg), 5.2–6.8% with simvastatin (10–80 mg), and 3.2–5.6% with pravastatin (10–40 mg) (2).

More impressive was the fact that at the 10-mg dose, rosuvastatin was associated with a 42% decrease in non-HDL cholesterol, compared with reductions of 34, 26, and 19% with 10 mg of atorvastatin, simvastatin, and pravastatin, respectively. At the 40-mg dose, rosuvastatin decreased the non-HDL cholesterol by 51%, compared with 45% and 48% among patients treated with 40 and 80 mg of atorvastatin, respectively, and 35% and 42% among patients receiving 40 mg and 80 mg of simvastatin, respectively (10).

Of the study population in the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin Trial, 35% had hypertriglyceridemia at baseline. Looking at this subset of people, treatment with 10 mg of rosuvastatin was able to get 80–84% of patients to their LDL and non-HDL cholesterol goals.

A randomized trial of 156 patients with triglycerides of 300–800 mg/dL found that treatment with rosuvastatin reduced triglycerides by 37% with 10–20 mg doses and by 40% with 40–80 mg doses. Pooled analyses of five randomized double-blinded trials have shown that 10 mg/day of rosuvastatin lowered triglycerides as effectively as 10 mg of atorvastatin and more effectively than 20 mg of simvastatin (9).

A double-blinded trial reported by Capuzzi in Preventative Cardiology in 2004 of 216 patients with type 2 diabetes and triglyceride levels of 310–372 mg/dL found that 10 mg/day of rosuvastatin plus 67 mg of fenofibrate three times daily lowered triglycerides by 47%, compared with 30% with 40 mg of rosuvastatin alone and 34% with fenofibrate alone. An open-label, 24-week trial in 270 patients with hypertriglyceridemia and low
A recent trial compared the effects of the combination of atorvastatin and 200 mg/day of micronized fenofibrate for 24 weeks on 120 patients without coronary disease. The LDL decreased by 46%, with 97.5% of the patients reaching their LDL goal. Triglycerides decreased by 50%, and 100% of the patients achieved triglyceride levels less than 200 mg/dL. Additionally, 60% of the patients reached optimal HDL goals, with HDL levels increasing by 22%.

A similar study using fenofibrate and fluvastatin in 333 patients with mixed lipidemia and coronary disease showed similar benefits; with HDL increasing by 22%, triglycerides falling by 38%, and LDL falling by 24%. There were no clinically relevant liver or muscular abnormalities reported. Although adding a fibrate to a statin is a common approach for people with mixed lipidemia, particularly in diabetes, no large-scale controlled trials have confirmed the safety of this combination or established clear-cut efficacy in reducing cardiovascular events (20).

Currently available data seems to be very promising in pointing the way toward future approaches and perhaps toward a softening of the warning on combination use (particularly in the case of fenofibrate, which is metabolized in a different area of the liver than the cytochrome P-450 system and involves glucuronidation in the liver). This is important because the risk for potential toxicity increases when statins are combined with other potentially myotoxic drugs.

Pravastatin is not metabolized through the cytochrome P-450 system, whereas fluvastatin and rosuvastatin do not have any significant metabolism through cytochrome P-450 3-A4. Other agents, such as atorvastatin, lovastatin, and simvastatin, are metabolized mainly through the cytochrome P-450 3-A4, with simvastatin significantly metabolized in the first pass through the liver, through 3-A4. Atorvastatin also is metabolized via 2-C9 (21).

The major concern with gemfibrozil interaction with the statins and the reason for the increased area under the curve is largely because of the area of the liver where gemfibrozil is metabolized. Gemfibrozil is glucuronidized in a similar area of the liver to all of the statins, with the exception of pravastatin and fluvastatin. This is why the area under the curve is increased for all the statins except those two. Thus, the risk of myopathy is increased with gemfibrozil as compared with fenofibrate (22). However, fibrate therapy can impair liver function independently, thus patients with impaired liver function should not receive a combination of statin + fibrate.

Adding a bile-acid sequestrant to statin therapy has been shown to enhance LDL reduction, however, the combination can raise triglycerides, particularly in the earlier preparations, such as cholestyramine. The newer preparations, such as colesevelam (Wel-Chol), do not seem to have a significant triglyceride elevation effect and have been shown to be synergistic in LDL reduction. ω-3 fatty acids can reduce the triglyceride concentration by 20–50%, depending on the dose, and will not increase the risk of myopathy if used in combination with a statin. Small studies have demonstrated that the addition of ω-3 fatty acids to atorvastatin increased the HDL and decreased the concentration of small, dense LDL compared with baseline. Of concern, however, is the purity of these products, and particularly the toxic chemical load of oily fish. This has been raised recently through a controversial study in Science Magazine that pointed out high levels of polychlorinated biphenyl (PCB) and dioxins in some preparations of oily fish, surprisingly highest in the farm-grown fish. Because of these concerns, ω-3 fatty acid therapy should be used cautiously and with some safety considerations until further data can prove their purity.
Combination therapy remains extremely attractive in managing the diabetic patient, who usually presents to the primary care physician with a multiplicity of lipid abnormalities, including high triglycerides, low HDL, high total cholesterol, a preponderance of small, dense LDL, and lipoprotein (a) elevations. For these individuals, the benefits of combination therapy have to be weighed and may be greater than the risk for adverse events (23).

The benefits of combination therapy include the following:

1. Synergistic activity in lowering LDL triglyceride and raising HDL.
2. Reduction of lipoprotein (a), especially with niacin, and to some extent, fenofibrate, and estrogen.
3. Change in LDL particle size to a less atherogenic, larger, and fluffy-type molecule.
4. Decreases in fibrinogen.
5. Regression of arteriosclerotic vascular disease.
6. Better tolerance with lower doses of medication, particularly with the statins, minimizing drug interaction and side effects.

The disadvantages of combination therapy include the following:

1. Added cost and copayments of taking two medications.
2. Increased risk of adverse side effects, including rhabdomyolysis, particularly with the combination of statin and gemfibrozil.
3. Paucity of outcome data and less compliance with the added medications.

Generally, when faced with the dilemma of mixed hyperlipemia, the physician must treat the LDL first by starting with a statin. If the LDL is still above goal while on statin therapy, either a higher dose or adding a second agent should be considered. Increasing the dose of the statin increases the risk for statin drug interaction and side effects (24).

Framingham data (24) clearly shows that body mass index was directly associated with blood pressure, blood glucose, and total cholesterol. Therefore, nonpharmacological adjunctive treatment of dyslipidemia involves increased physical activity, smoking cessation, weight reduction, and dietary modification (reducing the intake of trans fatty acids, cholesterol, and saturated fat in the diet).

The HDL-Atherosclerosis Treatment Study (HATS) (25) showed the safety of the combination of simvastatin and niacin in improving arteriosclerotic progression, outcomes, and lipid profiles in composite clinical events. The HATS trial compared treatment regimens with lipid-modifying therapy and antioxidant vitamin therapy. This 3-year, double-blind trial included 160 patients with coronary disease, low levels of HDL, and near normal levels of LDL. Patients were evaluated with the following:

1. Simvastatin and niacin.
2. Antioxidants.
3. Placebo.
4. Niacin, simvastatin, and antioxidants.

In all groups, crystalline or immediate-release niacin was used. The patients were a mean age of 53 years, with a mean HDL of 31 mg/dL, mean LDL of 125 mg/dL, and mean triglycerides of 213 mg/dL (26).

Treatment with a combination of niacin and simvastatin decreased LDL by 43%, triglycerides by 38%, and lipoprotein (a) by 15%, with a 29% increase of HDL from baseline. For the primary angiographic end point, stenosis progressed with placebo or antioxidants and regressed with the combination of simvastatin and niacin (25).

The composite clinical end point included CHD death, nonfatal myocardial infarction, stroke, or revascularization for worsening ischemia. Combination of niacin and
dose \((p = 0.048)\), whereas the changes with the 1000 mg dose were comparable to placebo. Fasting glucoses rose between 4 and 8 weeks and returned to baseline by 16 weeks. ADVENT also demonstrated a dose-related reduction in high-sensitivity C-reactive protein of 12% with the 1000-mg dose and 20% with the 1500-mg dose, compared with 2% with placebo. Niaspan reduced the concentration of the smaller, dense LDL particles by 50–60% and increased the concentration of the larger, less atherogenic LDL particles \((37)\).

Humans obtain cholesterol from two sources, \textit{de novo} synthesis in the extrahepatic tissues in the liver, and ingested saturated fats and cholesterol. The total amount of cholesterol that is synthesized or in the diet must be excreted. Approximately 300 mg of cholesterol is derived from the diet, whereas 800 mg is synthesized on a daily basis, thus this combined amount of 1100 mg must be excreted as fecal sterols.

Cholesterol in the extrahepatic tissues is delivered to the liver in HDL, the majority of which is derived from in vivo synthesis. HDL is taken up by the liver through the scavenger receptor. Cholesterol produced in the liver has two major fates, most is returned to the liver (being taken up by the extrahepatic tissue), and the remainder is reintroduced into the systemic circulation as VLDL particles (which are subsequently metabolized to LDL), because the intestinal reabsorption of chylomicrons and the intestinal absorption of cholesterol from diet and bile play an important role in cholesterol metabolism. These represent key targets for cholesterol lowering therapy.

The bile–acid sequestrants, such as cholestyramine, colestipol, and colesevelam, inhibit intestinal reabsorption of bile acids. The plant stanols and sterols along with the selective cholesterol absorptive inhibitors, such as ezetimibe, prevent intestinal absorption of cholesterol.

Ezetimibe is the newest agent in this class of selective cholesterol intestinal absorptive inhibitors and does not affect the absorption of other lipid-soluble nutrients. This newer class of medications affects cholesterol by several distinct mechanisms. Bile–acid sequestrants reduce bile–acid reabsorption in the ileum, causing hepatic bile–acid deficiency. This subsequent deficiency results in an increase in the synthesis of bile–acid from hepatic cholesterol, which is subsequently replenished through an increased hepatic uptake of LDL and chylomicrons, along with an increased hepatic cholesterol synthesis.

Through this increased clearance of LDL particles by the liver, bile–acid sequestrants reduce the LDL concentration. The plant stanols and sterols displace cholesterol from micelles, preventing their reuptake at the brush border and subsequently reducing the cholesterol that is transported to the liver, thereby increasing the clearance of LDL from plasma.

Ezetimibe acts by decreasing the absorption of cholesterol in the bile and from the diet, inhibiting its uptake into the cholesterol of the micelles and the intestinal epithelial cells. This enhances LDL clearance by the liver and reduces LDL levels. This action is achieved by a selective inhibition of the intestinal epithelial sterol transporter \((39)\).

Stanol esters lower LDL by up to 14%, triglycerides by up to 10%, and have no significant effect on HDL and triglycerides. They can be taken two or three times daily as a spread, and can be effective as adjunctive therapy. Stanol esters are well-tolerated and palatable, with no significant laboratory abnormalities, and are safe to use in combination with statins and safe to use in patients with diabetes.

The major side effects of the bile–acid sequestrants include decreased absorption of the fat-soluble vitamins A, D, and K, gastrointestinal distress and constipation, and triglyceride elevations with cholestyramine but not with colesevelam. Despite the known
An important therapeutic decision in managing the hypertensive patient with diabetes is the role of β-blockers, and at what point in therapy they should be used. Clearly, for patients who have had a recent myocardial infarction, β-blockers should be added to the regimen.

In a study of diabetic patients with unstable angina, β-blockers improved the 3-month mortality from 8.6 to 2.5% and the 6-month mortality from 16.8 to 8.6%. Cardiac mortality was reduced by 42% and cardiac events declined from 14 to 7.8% after 3 years of β-blocker use in diabetic subjects (10).

β-blockers have several beneficial effects on the cardiovascular system in the myocardium. When the heart rate decreases, diastolic filling time is prolonged, thereby increasing the blood flow to the myocardial tissue. By decreasing heart rate and blood pressure, β-blockers are responsible for reducing cardiac workload. These agents can also increase vagal tone, lessening the likelihood of arrhythmia and having an antiatherogenic effect by decreasing arterial shear stress, improving endothelial function, decreasing inflammation within the atheromatous plaques, and inhibiting platelet aggregation.

β-blockers are also effective in decreasing the hepatic production and myocardial use of free fatty acids, increasing myocardial glucose utilization. The subsequent decrease in myocardial oxygen consumption decreases the frequency of myocardial ischemia and results in fewer cardiac arrhythmias. β-blockers also lower the levels of C-reactive protein and β-blockers have been shown to both prevent and reverse myocardial remodeling (11).

Third-generation β-blockers, such as carvedilol, enhance vasodilation and maintain cardiac output, resulting in better outcomes in patients with congestive failure. Additionally, the third-generation β-blockers, such as carvedilol, reduce insulin resistance, which is not the case for the first-generation β-blockers (propranolol and timolol) or the second-generation β-blockers (metoprolol and bisoprolol) (12).

Carvedilol has improved left ventricular ejection fractions and decreased mortality rates in both diabetic and nondiabetic patients with congestive heart failure. In a double-blind, randomized trial, the effects of the ACE inhibitor, perindopril (Aceon) on blood pressure and endothelial function were compared with carvedilol in 26 diabetic patients with hypertension. Both perindopril and carvedilol significantly reduced mean blood pressure and increased leg blood flow to the same extent.

Interestingly, carvedilol reduced platelet aggregation significantly but this effect was not seen with perindopril. In other controlled trial, the metabolic and cardiovascular effects of carvedilol and atenolol in 45 hypertensive patients with type 2 diabetes were evaluated. Mean fasting glucose, insulin, and hemoglobin A1-C concentrations decreased during carvedilol treatment and increased during atenolol treatment (p < 0.01 between the two groups) (12).

The Appropriate Blood Pressure Control in Type II Diabetes (ABCD) (13) trial was primarily designed to evaluate renal end points with intensive hypertension control in patients with type 2 diabetes. In this study, 470 patients with hypertension and diabetes were assigned to one of two treatment goals, a target diastolic blood pressure of 80–89 mmHg or of 75 mmHg. In the intensive hypertension control group, a mean blood pressure level of 132/78 mmHg was achieved compared with 138/86 mmHg in the moderate hypertension control group. After 5 years of follow-up, the groups did not differ in progression of normal albuminuria or microalbuminuria, diabetic retinopathy, or neuropathy. However, total mortality was 5.5% in the intensively controlled group and 10.7% in the moderately controlled group.
Various studies have evaluated the effects of specific classes of drugs in the management of hypertension in patients with diabetes. Some studies compared ACE inhibitors with CCBs.

In a substudy of the ABCD trial (14), 470 hypertensive patients with diabetes were randomly assigned to treatment with either nisoldipine or enalapril. Equivalent blood pressures were achieved, but the nisoldipine group had a substantially higher rate of myocardial infarction.

The Fosinopril vs. Amlodipine Cardiovascular Events Trial (FACET) was an open label study that randomized 380 patients with type 2 diabetes to receive either fosinopril or amlodipine. At the conclusion of the study, systolic blood pressure control was better in the amlodipine group, and diastolic pressures were similar. Fosinopril had significantly fewer combined cardiovascular events, despite having higher systolic blood pressures, although total mortality and changes in albumin secretions did not differ (15).

In the Swedish Trial in Old Patients with Hypertension (STOP II), three drug groups were evaluated: CCBs, ACE inhibitors, and β-blockers plus diuretics. In a post hoc analysis of patients in the group with type 2 diabetes, blood pressure was equal in all treatment groups and cardiovascular events and total mortality were similar. Interestingly, as seen in the ABCD trial, risk for myocardial infarction was lower in patients treated with the ACE inhibitors than with the CCBs (16).

The ALLHAT trial showed that in a prespecified subgroup analysis of 12,000 patients with type 2 diabetes, there was no significant difference between treatment with ACE inhibitors, CCBs, or thiazide diuretics in the primary outcomes of nonfatal myocardial infarction or coronary heart disease death or all-cause mortality. However, the risk for heart failure was lowest in the diuretic group.

In comparison to the STOP II and ALLHAT trials, two studies compared traditional β-blocker or diuretic base therapy with ACE inhibitors. The Captopril Prevention Project trial (CAPP) (17) randomly assigned patients with hypertension to treatment with β-blockers or diuretics and captopril, with target diastolic blood pressure being less than 90 mmHg. In this hypertensive group, 572 patients had diabetes. Although blood pressure control was similar in both groups, in the captopril group, the risk for myocardial infarction, all-cause mortality, and cardiovascular events was lower. The UKPDS trial also included a subanalysis in which patients in the intensive control group with blood pressures less than 150/85 mmHg were randomly assigned to atenolol or captopril. In contrast to the Captopril Prevention Project trial, there were no differences in any of the aggregated or individual macrovascular or microvascular events between the two groups (12).

In addition to ALLHAT and STOP II, two other studies directly compared traditional treatment with β-blockers or diuretics to CCBs. The Nordic Diltiazem Trial (NORDIL) (18) compared treatment with β-blockers or diuretics to diltiazem. Blood pressure was similarly reduced in both groups, but in the subgroup analysis of 727 patients with type 2 diabetes, no differences were seen in total mortality or combined cardiovascular end points. The International Nifedipine Study Intervention as a Goal in Hypertensive Treatment Trial (INSIGHT) (19) compared treatment with thiazide diuretics and a long-acting nifedipine. Once again, blood pressure reductions were similar in both groups but in the subanalysis of 1302 patients with diabetes, there was no difference in the risk for total mortality or cardiovascular end points.
Comprehensive risk reduction involves careful attention of the primary care physician to the following four categories (1):

1. Glycemic control, including control of the hemoglobin A1-C to less than 6.5%, fasting glucose less than 100 mg/dL, and postprandial sugars less than 140 mg/dL.
2. Lipid control, including LDL less than 100 mg/dL, HDL greater than 45 mg/dL in men and 55 mg/dL in women, triglycerides less than 150 mg/dL, and non-HDL cholesterol less than 130 mg/dL.
3. Blood pressure less than 130/85 mmHg, or 125/75 mmHg with any evidence of end-organ disease (retinopathy, neuropathy, or nephropathy).
4. Inhibition of platelet aggregation with aspirin.

**GLYCEMIC CONTROL**

In the United Kingdom Prospective Diabetes Study (UKPDS), the metformin-intensive group showed a 32% reduction in any diabetes-related endpoint, a 42% reduction in diabetes-related deaths, a 36% reduction in all-cause mortality, a 39% reduction in myocardial infarction, a 41% reduction in stroke, and a 29% reduction in microvascular disease. The sulfonylurea insulin-sensitive group had less reduction in diabetes-related endpoints (7%), in diabetes-related deaths (20%), in all-cause mortality (8%), and in myocardial infarction (21%), none of which were statistically significant (2).

**LIPID CONTROL**

For lipid control, there have been several important primary-prevention and secondary-prevention trials.

For primary prevention, seven studies with diabetic patients are noteworthy:

1. The Prevention Study/Texas Coronary Atherosclerosis Prevention Study (3). This study randomly assigned patients with average cholesterol levels of 221 mg/dL, LDL of 150 mg/dL, and lower than normal HDL of 36 mg/dL for men and 40 mg/dL for women, to 20–40 mg/day of lovastatin or placebo, and followed them for an average of 5.2 years. Of these patients, 155 were diabetic. In this study, lovastatin led to a relative risk (RR) reduction of 0.56% for any arteriosclerotic event (fatal or nonfatal myocardial infarction, unstable angina, or sudden death) and an absolute risk reduction of 0.04. Despite LDL levels of 115 mg/dL and HDL levels of 39 mg/dL at the end of the study, the differences in the patients with diabetes were not statistically significant.

2. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial (ALLHAT-LLT) (4) randomly assigned patients 55 years and older who had hypertension and at least one other risk factor to 40 mg/day of pravastatin or to placebo. There were 3638 patients with diabetes in the subgroup analysis. The relative risk reduction was 0.89 for coronary heart disease (CHD).

3. The Helsinki Heart Study (5) randomly assigned men aged 40–55 years with elevated non-HDL cholesterol levels to 600 mg of gemfibrozil twice daily or to placebo. The starting mean total cholesterol was 290 mg/dL and the mean HDL was 47.6 mg/dL. There were 135 patients with diabetes in this study, and the incidence of CHD was 3.45% in the gemfibrozil group and 10.5% in the placebo group at 5 years. The relative risk was 0.32 and the absolute risk was 0.07; neither was statistically significant.

4. The landmark Heart Protection Study (HPS) (6) included both primary-prevention and secondary-prevention data in patients with diabetes who were at risk for cardiovascular disease. The objective was to study the effects of a fixed dose of simvastatin across a
baseline with a mean age of 60 years; 72% of these patients were male. In this diabetic
group, 12% were treated with insulin, 39% were on oral hyperglycemic drugs, and 50% 
were on diet therapy alone. Mean baseline glucose levels were 154.9 mg/dL in the 
placebo group and 154.2 mg/dL in the simvastatin group. Total cholesterol was 259.9 
mg/dL in the placebo group and 259.5 mg/dL in the simvastatin group; LDL was 185.6 
mg/dL in the placebo group and 186.0 mg/dL in the simvastatin group; and triglycerides 
were 157.7 mg/dL in the placebo group and 149.7 mg/dL in the simvastatin group (10).

Over the course of the trial, the simvastatin-treated diabetic patients had a reduction 
of 27% in total cholesterol, a reduction of 36% in LDL cholesterol, an increase of 7% 
in HDL, and a reduction of 11% in triglycerides. The major revelation was the reduction 
in coronary events: the risk of major CHD events was significantly reduced by 54% in 
patients with diabetes, with a $p$ value of 0.002!

There were equally significant reductions for the risk of any CHD events ($p = 0.015$), 
and of any atherosclerotic event ($p = 0.018$). The 6-year probability of escaping a major 
coronary disease event was 50.7% in the placebo group and 75.1% in the simvastatin 
group, representing a 55% risk reduction in the diabetic cohort, even more impressive 
than the 32% risk reduction in the nondiabetic cohort. The risk of major CHD events was 
significantly reduced in patients with diabetes and the risk of any CHD events was substan-
tially reduced (to a statistically significant degree). The diabetic patients included in the 
4S tended to have a longer duration of CHD and a higher prevalence of chest pain on 
exertion than their nondiabetic cohorts (10).

Based on the data from the 4S, the potential benefit of simvastatin treatment for 6 
years in 100 patients would be an expected major CHD event in 9 of 29 nondiabetic 
patients, compared with 24 of 49 patients with diabetes. Thus, there is a significant 
benefit in addition to the lipid lowering effects, in using simvastatin in the diabetic 
patient population.

This post hoc subgroup analysis on patients with diabetes provided the first trial-
based evidence that cholesterol lowering significantly and convincingly reduced the risk 
of major CHD events and other atherosclerotic events in diabetic patients (10).

The treatment effect did not seem to depend on baseline total cholesterol or LDL 
cholesterol levels. This data has suggested that the clinical benefit was greater in diabetic 
patients than nondiabetic patients because of their underlying increased risk.

In addition to the 4S, an expanded 4S diabetes post hoc subgroup analysis trial was 
published by Haffner (11) in the Journal of Diabetes Care. In this study, subjects with 
known baseline fasting glucoses were evaluated using updated 1997 American Diabetes 
Association diagnostic criteria. This added an additional 281 subjects to the diabetic 
subcohort. In addition to the 202 diabetes subjects previously identified, an additional 
281 subjects met the American Diabetes Association criteria of having fasting glucoses 
greater than 126 mg/dL. Of the remaining individuals, 678 met the criteria for impaired 
fasting glucose (fasting glucose between 110 mg/dL and 125 mg/dL) and 3237 patients 
still were within the normal range. Interestingly, the event rate in the placebo groups 
was similar to the data obtained in previous cohorts, showing that the patients with normal 
fasting glucoses had a 5-year event rate of approximately 26%. Patients with impaired 
fasting glucose had an event rate of 30%, patients with diabetes with elevated fasting 
glucoses had an event rate of 32%, and patients who were known to have diabetes had 
a 5-year event rate of 45%.

Compared with the 335 placebo-treated, impaired fasting glucose subjects, the 343 
simvastatin-treated, impaired fasting glucose subjects had significantly reduced coro-
nary mortality; with a relative risk reduction of 56%, a relative risk reduction in total 
mortality of 46%, a 40% risk reduction of major coronary events, and a 43% risk reduc-
Clopidogrel (75 mg/day), was as effective as 325 mg/day of aspirin in reducing the risk of ischemic stroke, vascular death, or myocardial infarction in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events trial (38). A subgroup analysis of the patients with diabetes in this trial revealed an annual combined vascular event rate of 17.7% for aspirin and 15.6% for clopidogrel (38).

Presently, prophylactic use of anticoagulants or fibrinolytics in patients with type 2 diabetes is not supported in the literature; low-dose warfarin failed to benefit diabetic patients in the Post-Coronary Artery Bypass Graft Trial (38).

Aspirin is currently indicated for the reduction of the combined risk of death in nonfatal myocardial infarction in patients with a previous infarct, unstable angina, or diabetes; reduction of the combined risk of sudden death and myocardial infarction in patients with chronic stable angina; and reduction of vascular death in patients with suspected acute myocardial infarction. It is also indicated for the reduction of death and stroke in patients who have had an ischemic stroke or transient ischemia of the brain caused by fibrin platelet emboli.

MULTIPLE RISK-FACTOR REDUCTION

Control of blood pressure plays a critical role in preventing the macrovascular and microvascular complications of diabetes and is a major contributor to excess mortality and morbidity caused by end-stage renal disease, stroke, and cardiovascular catastrophe.

The Hypertensive Optimal Treatment trial (37) evaluated the effect of calcium-channel blockers in 18,790 hypertensive patients (8% of whom had diabetes). Overall, the results showed that patients with intensive blood pressure control randomized to the goal of less than 80 mmHg did much better than those randomized to less than 90 mmHg. The study demonstrated significant improvements in major cardiovascular events for the diabetes subgroup, with reduction of major cardiovascular events from 24.4% in the group with diastolic blood pressures less than 90 mmHg to 11.9% in the group with diastolic blood pressures equal to or less than 80 mmHg.

This was the first significant trial that showed that lowering of diastolic blood pressure was statistically significant in a diabetic subcohort. In patients with diabetes, when blood

<table>
<thead>
<tr>
<th>End point</th>
<th>HOPE</th>
<th>MICRO-HOPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>26</td>
<td>37</td>
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<tr>
<td>All-cause mortality</td>
<td>16</td>
<td>24</td>
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From ref. 10.

Ramipril is indicated to reduce the risk of stroke, myocardial infarction, and death from cardiovascular causes in patients 55 yr or older who are at increased risk for these events.

HOPE, Heart Outcomes Prevention Trial; MICRO-HOPE, HOPE substudy.
known coronary disease had a lower amount of risk reduction, but still received significant benefit.

Physicians should not delay in starting treatment with statins in the diabetic patient, and can consider the use of fibrate therapy for patients with low LDL cholesterols and low HDL levels without being on statins. Meta-analysis released by the American College of Physicians showed that statin use reduced major cardiovascular events by 22–24% in patients with diabetes, with similar relative risk reductions in primary and secondary prevention, but double the absolute risk reduction for patients with known CHD.

For the primary-prevention trials reviewed, the number needed to treat to prevent one cardiovascular event over an average of 4.3 years was 34.5. The number needed to treat was 13.8 for 4.9 years in a secondary-prevention situation.

In the UKPDS trial, the stratification priorities for CHD risk reduction were as follows:

1. LDL.
2. HDL.
3. Hemoglobin A1-C.
4. Systolic blood pressure.
5. Smoking.

Patients with diabetes are at increased risk for all forms of ischemic stroke but, interestingly, no high-quality evidence supports stroke-risk reduction with improved glycemic control. Three major randomized trials have demonstrated no significant reduction in the risk of ischemic stroke or any macrovascular outcome when glucose control alone was used as a target. Multifactorial risk reduction strategies are important for stroke reduction for all patients, especially for the diabetic subset (51).

Multifactorial risk reduction strategies involve the following:

1. Therapeutic lifestyle changes, especially smoking cessation, avoidance of excessive alcohol, and regular exercise.
2. Hypertensive control. Effective control of systolic and diastolic blood pressure will reduce stroke risk.
3. Lipid-lowering therapy. Treatment with statins reduces the risk of stroke in patients with diabetes.
4. Antiplatelet medication. the Food and Drug Administration recommends aspirin doses of 50–325 mg/day for primary stroke prevention, with aspirin combined with extended-release dipyridamole or clopidogrel for secondary prevention.
5. Tight glycemic control-reducing fasting glucose below 100 mg/dL, 2 hour postprandial glucose below 140 mg/dL, and HbA1C below 6.5.

The Steno-2 study enrolled 160 patients from Denmark with type 2 diabetes and microalbuminuria. The patients, with an average age of 55 years, were placed in two management groups—conventional and intensive therapy. The intensive group all received ACE inhibitors, aspirin, dietary intervention, more than 30 minutes of exercise weekly, smoking cessation, and tight control of glucose (A1-C < 6.5%), blood pressure (< 130/80 mmHg), and lipids (total cholesterol < 175 mg/day and triglycerides < 150 mg/day). Most outcomes in the intensive strategy group were consistently better than the conventionally managed patients. The primary outcomes of composite cardiovascular death, nonfatal myocardial infarction, coronary revascularization, nonfatal stroke, amputation, or peripheral vascular surgery was reduced by 53% in the intensive strategy.
Resources

American Association of Diabetes Educators
444 N. Michigan Avenue, Suite 1240, Chicago, IL 60611
Phone: 312-644-2233 or 800-338-3633
Website: www.diabetesnet.com/aade.html

American Diabetes Association (ADA)
ADA National Service Center
1600 Duke Street, Alexandria, VA 22314
Phone: 703-549-1500 or 800-342-2383
Website: www.diabetes.org

American Dietetic Association
216 W. Jackson Boulevard, Chicago, IL 60606-6995
Phone: 800-877-1600 or 312-899-0040
Website: www.eatright.org

American Heart Association
7320 Greenville Avenue, Dallas, TX 75231
Phone: 800-242-1793
Website: www.americanheart.org

Diabetes Action Research and Education Foundation
426 C Street, NE, Washington, DC 20002
Phone: 202-333-4520
Fax: 202-785-9595
Website: www.daref.org

Division of Diabetes Translation National Center for Chronic Disease Prevention and Health Promotion; Centers for Disease Control and Prevention
Mail Stop K-10, 4770 Buford Highway NE, Atlanta, GA 30341-3717
Phone: 770-488-5000
Website: www.cdc.gov/diabetes

Diabetes Exercise and Sports Association
(formerly known as the International Diabetic Athletes Association)
8001 Montcastle Drive, Nashville, TN 37221
Phone: 800-898-4322
Fax: 615-673-2077
desa@diabetes-exercise.org

From: Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Guide to Diagnosis and Management
By: R. A. Codario © Humana Press Inc., Totowa, NJ
Index

A

ABCD trial. See Appropriate Blood Pressure Control in Type 2 Diabetes (ABCD) trial
Ablify (Aripiprazol) and IGT/diabetes risk, 17
α-Blockers, contraindications, 177
Acarbose (Precose)
and cardiovascular risk reduction, 197
contraindications, 82
described, 82
and sulfonylureas, 88
ACE inhibitors. See also individual drug by name
and angiotensin II, 183
and blood pressure control, 174, 178, 181, 211, 212, 215
and calcium channel blockers, 179, 180
and hyperkalemia, 177, 183
for hypertension, 145, 180, 217
and left ventricular dysfunction, 121
for nephropathy, 148
for neuropathy, 142
side effects of, 183
and stroke risk, 129, 181
and valsartan, 184
Acetaminophen
and TZDs, 85
Acetohexamide (Dymelor)
described, 79
Actose (Pioglitazone). See Pioglitazone (Actose)
Adenosine and blood flow, 33
Adipocytes, function of, 121
Adiponectin levels
and metformin (Glucophage), 81
in obesity, 64
ADMIT (Arterial Disease Multiple Intervention Trial) on niacin monotherapy, 164
Adolescents, diabetes risk factors in, 16
Advanced glycation end products (AGE)
formation of, 7
in tissue damage, 6
ADVENT (Assessment of Diabetes Control and Evaluation Trial) on niacin monotherapy, 164–165
Aerobic exercise
benefits of, 36
described, 35
and insulin sensitivity, 30
intensity, monitoring, 30
AGE. See Advanced glycation end products (AGE)
Age and diabetes onset, 15–16
Agent Orange and diabetes, 18
α-Glucosidase inhibitors
case study of, 112
described, 82–83
and hemoglobin A1-C, 193
mechanism of action, 75, 77
and sulfonylureas, 88
Albuminaria, clinical, 146
Alcohol
and diabetes management, 52
in metabolic syndrome, 60
and TZDs, 85
Aldose reductase inhibitors and microvascular disease, 6
β-Lipoic acid
benefits of, 51
for neuropathy, 142
ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial)
on blood pressure reduction, 173, 175, 178–179, 181
ALLHAT-LLT described, 206
American Diabetes Association
carbohydrate terms, recommended, 42
exercise guidelines, 29
fat consumption recommendations, 45–46
American Heart Association on fatty acid consumption, 47
Amitriptyline for neuropathy, 142, 144
Amlodipine for blood pressure control, 175, 177, 179, 181
Amputation and nerve damage, 138, 140
Amylin therapy, 110–111
Anemia and retinopathy, 136
Angina, therapy for, 124, 174
Angioedema
and ACE inhibitors, 183
ARBs and, 185
Angioplasty
benefits of, 123, 124
indications for, 127
Angiotensin II
ACE inhibitors and, 183
and blood pressure control, 211
in diabetic nephropathy, 148, 182
heart, effects on, 182
kidneys, effects on, 183
and tissue injury, 211
Angiotensin receptor blockers (ARBs)
and angioedema, 185
captopril (Capoten), 179, 211, 215
clofibrate for, 173
diltiazem for, 175, 177, 179
fosinopril for, 175, 178
indapamide (Lozol), 185
lisinopril for, 173
Nordic Diltiazem Trial (NORDIL) on, 175
olmesartan (Benicar) for, 184
overview, 211–213, 218
UKPDS study on, 171, 175, 177, 186, 215
in diabetes, 147
diabetic coronary artery disease and, 172
dysfunction described, 29
function, assessing, 34–35
lowering, 178, 214–215
and metabolic syndrome, 64
microvascular complications and, 172
systolic and diabetes-related complications, 172, 178
Body Mass Index (BMI)
and blood pressure, 162
calculating, 68
Bolus insulin. See Insulin, bolus
Bone structure abnormalities in diabetics, 218
Borderline diabetes. See Impaired glucose tolerance (IGT)
Brunek study on insulin resistance, 66
Bupropion (Wellbutrin SR) for weight control, 69
C
Cactus (Opuntia streptacantha), benefits of, 52
Calcium channel blockers
and ACE inhibitors, 179, 180
benefits of, 179
for blood pressure reduction, 175, 177–180, 214
dihydropyridine
for blood pressure control, 179, 180
for nephropathy, 150
vs nondihydropyridines, 180
Cambridge Heart Antioxidant Study on vitamin E in diabetes management, 50
Candesartan (Atacand) for hypertension, 184
Capillary occlusion theory described, 134
CAPRIE trial on clopidogrel therapy, 121
Capsaicin for neuropathy, 143
Captopril (Capoten)
for blood pressure control, 179, 211, 215
and nephropathy, 148, 150, 181
Captopril Prevention Project trial (CAPPP) on cardiac event mortality reduction, 175
Carbamazepine for trigeminal neuralgia, 143
Carbohydrates
absorption and proteins, 44
ADA recommended terms, 42
in diabetes described, 42–44
to insulin ratio, 109
restriction and ketosis, 68
zinc deficiency and intolerance, 50
CARDIA. See Coronary Artery Risk Development in Young Adults (CARDIA)
Cardiac autonomic neuropathy, 140
Cardiovascular disease
and exercise, 32
glucose tolerance and, 193
hyperhomocysteinemia and, 50, 122
and impaired glucose tolerance (IGT), 194
insulin sensitivity and, 36
and nephropathy, 178, 216–218
predicting, 36, 199–200
risk reduction, 197, 207, 209
Carpal tunnel syndrome, 139, 140
Carvedilol (Coreg)
benefits of, 174
and heart failure complications, 123
Case studies, 112–114
Cerebral arteriosclerotic vascular disease, 118, 128–129
Charcot’s neuroarthropathy, 139
Chemical diabetes. See Impaired glucose tolerance (IGT)
Children, diabetes risk factors in, 16
Chlorpropamide (Diabinese) described, 79
and retinopathy, 136
side effects of, 78
Chlorthalidone for blood pressure reduction, 173
Cholesterol
HDL and CHD, 62–63
fibates and, 158, 217
increasing, 67, 157–158
and Metformin (Glucophage), 81, 158
niacin and, 158, 161
and hypertriglyceridemia, 62, 120
LDL
atherogenicity of, 157
levels calculating, 156
goals for, 151
normal, 157
in myocardial infarction, 119
stanol esters and, 165
and weight control, 67
LDL/HDL ratio, 63
and metformin, 81, 158
non-HDL
calculating, 157
normal levels of, 62
reduction of, 64
obtaining, 165
reduction, 47, 160, 161, 165, 166
Cholesterol and Recurrent Events Trial described, 159–160, 209
Cholesterlamine and triglyceride levels, 161
Chrominum and glycemic control, 50–51
Chromium picolinate and glycemic control, 50–51
Chronotropic index described, 33–35
Cilostazol (Pletal)
contraindications, 127
for PAD, 125, 127
Clinical trials, 159–167, 171–173, 191–200. See also
individual study by name
Clonidine for gastroenteropathy, 144
Clopidogrel (Plavix)
described, 122
for retinopathy, 137
and stroke reduction, 214
as therapy, 121, 128
Clozapine (Clozaril) and IGT/diabetes risk, 17
Clozaril (Clozapine) and IGT/diabetes risk, 17
Colestipol and niacin, 164
Collaborative Atorvastatin Diabetes Study (CARDAS)
described, 207
Congestive heart disease (CHD)
and cilostazol, 127
lovastatin for, 160, 209
predictors of, 62–63, 66, 155
risk reduction, UKPDS study data on, 217
triglycerides and, 62, 129
Coronary arteriosclerotic disease, risk factors for, 62
Coronary artery disease
described, 117–124
diastolic blood pressure and, 172
ST-segment depression and, 32
Coronary Artery Risk Development in Young Adults
(CARDIA) on exercise and diabetes risk factors, 36–37
Counseling patients, 28–29, 70, 107
Coxsackie virus and type I diabetes, 13–14
C-Reactive protein (CRP)
as heart attack predictor, 122
and statin therapy, 123
Cybutrimine (Meridia) for weight control, 69
Cyclosporine and ezetimibe, 166
Cytokines, adipose tissue expression of, 64
D
Da Quing study described, 20–21
DART. See Diet and Re-Infarction Trial (DART)
Dawn phenomenon described, 108
DCCT. See Diabetes Control and Complications Trial
(DCCT)
DECODE. See Diabetes Epidemiology: Collaborative
Analysis of Diagnostic Criteria in Europe (DECODE)
Depuytren contractures, formation of, 7
Dexamethasone and glycemic control, 18
Diabeta. See Glyburide (Micronase, Glynase,
Diabeta)
Diabetes Arteriosclerosis Intervention Study
described, 160
Diabetes Control and Complications Trial (DCCT)
on hypoglycemia and glucose control, 96, 133,
191, 193
on infusion pumps, 108, 109
on myocardial infarction risk, 119, 197–198
on neuropathy treatment, 142
Diabetes Epidemiology: Collaborative Analysis of
Diagnostic Criteria in Europe (DECODE)
described, 192
on diabetes testing, 22
on mortality predictions, 196–197
Diabetes Mellitus Insulin Glucose Infusion and Acute
Myocardial Infarction (DIGAMI)
on diabetes mortality, 78
on hyperglycemia, 195
Diabetes Prevention Program trial described, 27, 67
Diabetes Prevention Study
described, 20
on lifestyle modification benefits, 63–64
Diabetes type 1, 13–14
Diabetes type 2
associated factors, other, 17–18
cardiac mortality in, 118
causes of, 1, 4
described, 14–17
development of, 29–30
economic impact of, 205
macrovacular complications of, 118
metabolic targets for, 2
natural history of, 3–9
risk factors for, 16
Diabetes type A, 140, 144, 145
Diastolic dysfunction described, 29
Diastolic function, assessing, 34–35
Diet
efficacy in diabetes management, 20–22, 159, 217
and hypertension management, 172–173
and insulin preparations, 107
management, goals of, 41–42
principles of, 49, 71
recommendations, 43
therapy and metabolic profile, 47
types of, 67–68
Diet and Reinfarction Trial (DART) on fatty acid
consumption, 46
DIGAMI trial
on diabetes mortality, 78
on hyperglycemia, 195
Diltiazem for blood pressure reduction, 175, 177, 179
Dioxin (TCDD) and diabetes, 18
Dipyridamole
and blood flow, 33
as therapy, 128, 129
Diuretics. See also Thiazide diuretics
hypokalemia and, 185
mechanism of action, 185
side effects of, 185
Division of Diabetes Translation initiatives described, 15
Dobutamine and ischemia, 33
Domperidone for gastroenteropathy, 144
Drug therapy targets, 121–122
Duke treadmill score described, 24

Dawn phenomenon described, 108
DCCT. See Diabetes Control and Complications Trial
(DCCT)
DECODE. See Diabetes Epidemiology: Collaborative
Analysis of Diagnostic Criteria in Europe (DECODE)
Depuytren contractures, formation of, 7
Dexamethasone and glycemic control, 18
Diabeta. See Glyburide (Micronase, Glynase,
Diabeta)
Diabetes Arteriosclerosis Intervention Study
described, 160
Diabetes Control and Complications Trial (DCCT)
on hypoglycemia and glucose control, 96, 133,
191, 193
on infusion pumps, 108, 109
on myocardial infarction risk, 119, 197–198
on neuropathy treatment, 142
Diabetes Epidemiology: Collaborative Analysis of
Diagnostic Criteria in Europe (DECODE)
described, 192
on diabetes testing, 22
on mortality predictions, 196–197
Diabetes Mellitus Insulin Glucose Infusion and Acute
Myocardial Infarction (DIGAMI)
on diabetes mortality, 78
on hyperglycemia, 195
Diabetes Prevention Program trial described, 27, 67
Diabetes Prevention Study
described, 20
on lifestyle modification benefits, 63–64
Diabetes type 1, 13–14
Diabetes type 2
associated factors, other, 17–18
cardiac mortality in, 118
causes of, 1, 4
described, 14–17
development of, 29–30
economic impact of, 205
macrovascular complications of, 118
metabolic targets for, 2
natural history of, 3–9
risk factors for, 16
Diabetes type A, 140, 144, 145
Diastolic dysfunction described, 29
Diastolic function, assessing, 34–35
Diet
efficacy in diabetes management, 20–22, 159, 217
and hypertension management, 172–173
and insulin preparations, 107
management, goals of, 41–42
principles of, 49, 71
recommendations, 43
therapy and metabolic profile, 47
types of, 67–68
Diet and Reinfarction Trial (DART) on fatty acid
consumption, 46
DIGAMI trial
on diabetes mortality, 78
on hyperglycemia, 195
Diltiazem for blood pressure reduction, 175, 177, 179
Dioxin (TCDD) and diabetes, 18
Dipyridamole
and blood flow, 33
as therapy, 128, 129
Diuretics. See also Thiazide diuretics
hypokalemia and, 185
mechanism of action, 185
side effects of, 185
Division of Diabetes Translation initiatives described, 15
Dobutamine and ischemia, 33
Domperidone for gastroenteropathy, 144
Drug therapy targets, 121–122
Duke treadmill score described, 34
South Beach diet described, 68
SPECT. See Single photon emission computed
tomography (SPECT)
SSRIs for weight control, 69
Stanol esters and LDL cholesterol, 165
Starch
and glycemia, 43
and postprandial glucose, 44
Statin therapy. See also individual drug by name
and bile acid sequestrants, 161
and CRP, 123
for dyslipidemia, 150, 157
and gemfibrozil, 161
and triglyceride levels, 158
Steno-2 study described, 217–218
Stents
and heart failure complications, 123, 124
indications for, 127
Steroids and glycemic control, 18
STOP-NIDDM. See Study to Prevent Noninsulin-
dependent Diabetes (STOP-NIDDM)
Stress echocardiography
contraindications, 34
in exercise evaluation, 33, 34
Stress testing, purpose of, 30
Stroke
and dyslipidemia, 156
preventing, 122, 128, 217
reduction, 129, 130
ST-segment depression and coronary artery disease,
Study of Hypertension and the Efficacy of Lotril in
Diabetes Trial (SHIELD) described, 177–178
Study to Prevent Noninsulin-dependent Diabetes
(STOP-NIDDM) described, 20
Sucrose and glycemia, 43
Sugar alcohols, and postprandial glucose response, 44
Sulfonylureas
acarbose and, 88
cardiotoxicity of, 199
classification of, 79
described, 76–79
and drug interactions, 78, 113
α-glucosidase inhibitors and, 88
and hypoglycemia, 78
mechanism of action, 75, 105
metformin and, 86, 106
miglitol and, 88
and the potassium channel, 78
and renal insufficiency, 76
and TZDs, 87–88
Superoxide anion production in hyperglycemia, 9
Surgery for retinopathy, 137
Sympathomimetic amines for weight control, 68
Tadalafil (Cialis) described, 145
Taurine uptake, 6
TCDD. See Dioxin (TCDD) and diabetes
Tea and diabetes management, 52–53
Telmisartan, dosage regimen, 184
Testing for diabetes
indications for, 15
recommendations, 19–20, 22
TRIPOD study, 21
Thallium 203 and myocardial perfusion assessment, 33
Thiazide diuretics. See also Diuretics
and hyperglycemia, 18
mechanism of action, 176, 185, 186
and NSAIDs, 185
side effects of, 185
Thiazolidinediones (TZD)
advantages of, 85, 121
contraindications, 76, 83, 85
described, 83–85
and edema, 84, 85, 106, 113
and HDL cholesterol levels, 158
hypoglycemia, 84
and insulin, 106
insulin sensitivity of, 5, 63, 75
macrophage accumulation in tissue, 216
mechanism of action, 77
peripheral neuropathy, 143
and polycystic ovary syndrome, 113
PPARs and, 216
and retinopathy, 137
sulfonylureas and, 87–88
and weight gain, 106
Thrombosis prevention, 213–214
Ticlopidine in stroke prevention, 122
Tinel’s sign, 140
Tissues, damage to
by hyperglycemia, 5–9
in insulin resistance, 210–211
Tolazimide (Tolinase) described, 79
Tolbutamide (Orinase) described, 79
Topiramate (Topamax)
for neuropathy, 143
for weight control, 69
Tramadol for neuropathy, 143
Trandolopril
for coronary event reduction, 183
for nephropathy, 181
for neuropathy, 142
Tricor (Fenofibrate) for triglyceride levels, 158, 160, 161
Tricyclic antidepressants for neuropathy, 142
Triglycerides
and CHD, 62, 129
insulin resistance, identifying, 63
reducing, 46–47, 62, 158–161
TRIPOD study. See Troglitazone in the Prevention of
Diabetes (TRIPOD) study
Troglitazone in the Prevention of Diabetes (TRIPOD)
study described, 21–22
on thiazolidinediones, 63
Troglitazone (Rezulin) and liver injury, 76
TZD. See Thiazolidinediones (TZD)