DATIS REVIEW OF

MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN PRIMARY CARE
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Preface

This review is intended to provide practical information for healthcare providers regarding the management of type 2 diabetes mellitus. It does not include information regarding the management of type 1 diabetes mellitus or gestational diabetes.

It should be noted that the term ‘oral hypoglycemic’ has not been used in this document. The term ‘oral antihyperglycemic’ was instead chosen as it more accurately reflects the mechanism of action of these agents.

The information contained in this material is derived from a critical analysis of a wide range of evidence-based material in this area of clinical medicine, which is current at the date of publication. Revisions have been made to the original document published in Australia to include more recently published trials and American guidelines. Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.

The DATIS Advisory Board, its individual members, the University of Kentucky, the Repatriation General Hospital of South Australia and the University of Queensland, can accept no responsibility for the use of any of the information or views expressed in this document in any particular individual case.

For additional information about specific drugs, readers are referred to Facts and Comparisons and the American Hospital Formulary Service (AHFS) as well as the approved product information for individual drugs.

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Type 2 diabetes mellitus (formerly known as non-insulin dependent diabetes mellitus, NIDDM or adult-onset diabetes) is the most common form of diabetes. It results from defects in insulin secretion coupled, in most cases, with insulin resistance.\(^1\)

Each year there are nearly 800,000 Americans newly diagnosed with diabetes. In the National Health and Nutrition Evaluation Survey, 1988–1994 (NHANES III) the overall prevalence of diabetes in people over age 20 years was 7.8%.\(^2\) This has increased by 50% since 1990.\(^3\) The prevalence among children and adolescents is also increasing at an alarming rate.\(^4\) At the current rate, by the year 2010, 10% of all Americans will have diabetes.\(^3\) The Centers for Disease Control and Prevention (CDC) is now referring to diabetes as an epidemic.

In addition to the 17 million Americans with diabetes, a further 15.8% have impaired glucose tolerance (IGT) and 9.7% have impaired fasting glucose (IFG).\(^2\) The more commonly used term for IFG and IGT now is pre-diabetes. Importantly, NHANES III reports that of those found to have diabetes, 5.4 million (1/3) were unaware they had it.

In six states including Kentucky, age-adjusted prevalence was at least 50% higher in 2000 than in 1994.\(^3\) Kentucky residents have greatly increased risk for developing diabetes due to increasing age, obesity and sedentary lifestyle. One out of every ten people in Kentucky have diabetes and half are at risk for developing diabetes.\(^5\)

The diagnosis of type 2 diabetes is often delayed by several years because hyperglycemia may not be severe enough to provoke noticeable signs and symptoms. However, the degree of hyperglycemia is generally sufficient to cause pathological and functional changes in various organs, such as the eyes and autonomic nervous system.\(^6\)

In the 1999 Australian Diabetes, Obesity and Lifestyle Study (AusDiab) the prevalence of obesity and hypertriglyceridemia was approximately three times more frequent in the diabetic population compared with those with normal glucose tolerance status. Hypertension and low levels of high density lipoprotein (HDL) cholesterol were approximately twice as common.\(^7\) These conditions, together with diabetes or pre-diabetes (IFG or
IGT), are collectively referred to as the Metabolic Syndrome, and are associated with an increased risk for diabetes and cardiovascular morbidity and mortality. See the Metabolic Syndrome below.

**PRE-DIABETES (IMPAIRED GLUCOSE TOLERANCE AND IMPAIRED FASTING GLUCOSE)**

Pre-diabetes (IGT and IFG) refers to metabolic states that are intermediate between normal glucose regulation and diabetes. The diagnosis is based on plasma glucose concentrations that are greater than the normal expected value but less than the concentration required for diagnosis of diabetes. See glucose concentration values for diagnosis, Figure 1 page 7. Pre-diabetes (IGT and IFG) is a risk factor for the future development of diabetes and/or cardiovascular disease (CVD)^1^,^6^, and perhaps microvascular complications.^8^

**THE METABOLIC SYNDROME**

At present, there are no well-accepted criteria for the diagnosis of the Metabolic Syndrome, which is also referred to as Insulin Resistance Syndrome or Syndrome X.^1^ The World Health Organization (WHO) defines it as a cluster of conditions which must include:^1^

Pre-diabetes (IGT or IFG) or diabetes mellitus and/or insulin resistance, together with two or more of the following components:

- impaired glucose regulation, pre-diabetes (IGT or IFG) or diabetes;
- insulin resistance (under hyperinsulinemic, euglycemic conditions, glucose uptake below lowest quartile for background population under investigation);
- elevated arterial pressure $\geq 135/85$ mmHg;
- elevated plasma triglycerides ($\geq 150$ mg/dL) and/or low HDL cholesterol ($< 40$ mg/dL for men, $< 50$ mg/dL for women);
- central obesity (waist circumference $> 102$ cm ($> 40$ in) for males, 88 cm ($> 35$ in) for females) and/or body mass index (BMI) $> 30$ kg/m$^2$; or
- microalbuminuria (urinary albumin excretion rate $\geq 20$ µg/min or albumin to creatinine ratio $\geq 30$ mg/g).
The National Cholesterol Education Panel Adult Treatment Panel III (ATP III) guidelines define the Metabolic Syndrome as the prevalence of three or more of the following:9

- fasting glucose 110–125 mg/dL;
- blood pressure ≥ 135 mmHg;
- elevated triglycerides and decreased HDL cholesterol as described above in the WHO guidelines;
- abdominal obesity as described above in the WHO guidelines.

Hence, the Metabolic Syndrome includes several recognized risk factors for CVD. This combination of risk factors places the individual at a particularly high risk of macrovascular disease.1, 9

The management of patients with hyperglycemia and features of the Metabolic Syndrome must target strategies to reduce CVD risk factors as well as improve glucose control. Importantly, features of the Metabolic Syndrome may be present for up to 10 years prior to the detection of an abnormality in glucose homeostasis. These patients are at very high risk of developing diabetes in the future. Hence, early intervention and management of the syndrome may significantly impact the prevention of diabetes and CVD.1

**COMPLICATIONS OF TYPE 2 DIABETES**

Diabetes shortens a person’s life expectancy by up to 15 years.7

The long-term complications of diabetes can be divided into two categories: microvascular and macrovascular. Complications of type 2 diabetes are an inevitable consequence; however, the rate of progression and severity can be minimized with appropriate monitoring and management of risk factors.

**Microvascular complications**

Microvascular complications include:

- **Retinopathy** which may lead to impairment of vision and eventual loss of sight if undetected and poorly treated;
- **Nephropathy** which is marked by microalbuminuria, proteinuria and impaired renal function; and
- **Neuropathy** which may involve peripheral and/or autonomic nerves. Peripheral neuropathy increases the risk of foot ulcers and amputation. Autonomic neuropathy may result in a loss of the warning signs of
hypoglycemia and/or affect the urogenital, gastrointestinal or cardiovascular systems.

For further information about microvascular complications, see page 146.

**Macrovascular complications**

Macrovascular complications (large vessel disease) include:

- **Coronary heart disease**
- **Stroke**
- **Peripheral vascular disease**

Macrovascular disease accounts for up to 70% of deaths in people with type 2 diabetes.\(^{10, 11}\) The risk of these complications is also increased in patients with pre-diabetes (IGT or IFG). Lifestyle modification, management of obesity, hypertension, dyslipidemia and hyperglycemia, cessation of smoking, and other pharmacological interventions may reduce the risk of macrovascular complications.

For further information about macrovascular complications, see page 172.

**PREVENTION OF TYPE 2 DIABETES**

Clinical trials have demonstrated that in patients at high risk of developing type 2 diabetes, such as those with pre-diabetes (IGT or IFG), increased BMI or history of gestational diabetes (GDM), lifestyle intervention, such as nutritional modification and/or increased levels of exercise that results in weight loss (even if modest) reduces the incidence of diabetes.\(^{12-14}\) Importantly, the intervention must be maintained long-term, with regular monitoring and reinforcement of the goals of lifestyle intervention. The greater the number of changes successfully undertaken by the at-risk patient, the lower the risk of progression to diabetes will be.

To achieve and maintain life long lifestyle modifications, a multidisciplinary approach utilizing the skills of various health care professionals is the most effective strategy.
SCREENING AND DIAGNOSIS

SCREENING FOR TYPE 2 DIABETES

Individuals with undiagnosed diabetes are at increased risk for coronary heart disease (CHD), stroke and peripheral vascular disease (PVD), and have a greater likelihood of dyslipidemia, hypertension and obesity. Of additional concern is epidemiological evidence that suggests the onset of retinopathy begins at least seven years prior to the diagnosis of type 2 diabetes.6

Asymptomatic patients should be considered for screening starting at age 45 and every three years thereafter if results are normal. Patients with one or more risk factors, as listed below in Table 1, should be considered for screening at a younger age or more frequently. Laboratory measurement of fasting plasma glucose is recommended for screening.15

Table 1. Risk factors for undiagnosed type 2 diabetes.

- Age ≥ 45 years
- Family history of diabetes (e.g. parents or siblings with diabetes)
- Overweight (BMI ≥ 25 kg/m²)*
- Habitual physical inactivity
- Race/ethnicity (e.g. African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
- Previously identified pre-diabetes (IFG or IGT)
- Hypertension (≥ 140/90 mmHg in adults)
- HDL cholesterol ≤ 35 mg/dL and/or a TG level ≥ 250 mg/dL
- History of GDM or delivery of a baby weighing > 9 lbs
- History of vascular disease
- Other clinical conditions associated with insulin resistance (e.g. polycystic ovary syndrome (PCOS) or acanthosis nigricans)

* May not be accurate for certain ethnic groups

HDL = high density lipoprotein; TG = triglyceride; BMI = body mass index
Adapted from Diabetes Care, Volume 27 Supplement 1, January 200416

If the plasma glucose level is abnormal, the test should be repeated on another day, unless unequivocal hyperglycemia with acute metabolic decompensation or obvious symptoms are present.1, 17
When screening for diabetes it is important to consider that certain drug therapies may produce hyperglycemia. See Appendix 2, page 197.

In those individuals with pre-diabetes, appropriate advice regarding risk factor reduction should be provided as these individuals remain at high risk for future development of CVD and type 2 diabetes.\textsuperscript{17}

Routine testing of healthy, low risk individuals is not currently recommended. Likewise, there is insufficient evidence to conclude that community screening is a cost-effective approach to reduce the morbidity and mortality associated with diabetes in presumably healthy individuals.\textsuperscript{15}

**DIAGNOSIS OF TYPE 2 DIABETES AND PRE-DIABETES (IFG AND IGT)**

The diagnosis of diabetes can be made in one of the following three ways.\textsuperscript{1, 17}

- Symptoms of diabetes plus a casual (any time of day regardless of time of last meal) plasma glucose concentration $\geq 200$ mg/dL. Typical symptoms of diabetes include polydipsia, polyuria, recurrent infections, blurred vision and unexplained weight loss.
- Fasting plasma glucose (FPG) $\geq 126$ mg/dL. Fasting is defined as no caloric intake for at least eight hours.
- 2-hour plasma glucose $\geq 200$ mg/dL during an oral glucose tolerance test (OGTT).

Unless unequivocal hyperglycemia with acute metabolic decompensation or obvious symptoms are present, testing should be repeated on another day for confirmation of the diagnosis.\textsuperscript{1, 17} Laboratory measurement of fasting plasma glucose is the preferred test for diagnosis due to ease of use, lower cost, and patient acceptability.\textsuperscript{17}

**Oral glucose tolerance test**

Although an OGTT is not recommended for routine clinical use, it may be necessary for diagnosis when the fasting or casual plasma glucose is normal and diabetes is still suspected or in the evaluation of patients with IFG.\textsuperscript{1, 17}

The OGTT is performed the morning after an overnight fast of 8–14 hours and following three days of unrestricted diet (defined as greater than 150 g of carbohydrates per day) and usual physical activity. The meal consumed
on the evening prior to the test should ideally contain a reasonable amount of carbohydrate, between 30 and 50 g. Smoking is not permitted during the test.

Initially, a fasting blood sample is collected. The patient is then given an oral glucose load equal to 75 g of anhydrous glucose dissolved in 250–300 mL of water and drunk over five minutes. Two hours after the glucose load, a blood sample is collected for measurement of the patient’s venous plasma glucose concentration. A diagnosis of diabetes can be made if the fasting plasma (venous) glucose concentration is ≥ 126 mg/dL or if the two-hour post glucose load concentration is ≥ 200 mg/dL.¹,¹⁷

Figure 1. Criteria for the diagnosis of diabetes.¹⁸

*Diagnosis of diabetes must be confirmed by repeat testing on a different day (in the absence of unequivocal hyperglycemia with acute metabolic decompensation).
MONITORING AND GOALS IN TYPE 2 DIABETES

The chronic and progressive nature of diabetes requires continual medical care together with patient and/or caregiver education, involving a multidisciplinary team of health professionals, to prevent the risk of both acute and long-term complications. When deciding on goals for diabetes, individual patient characteristics should be considered, such as the patient’s capacity to understand and carry out the treatment and monitoring regimen, the patient’s risk of severe hypoglycemia, and other factors that may increase risk or benefit. For example, the presence of a co-morbidity that shortens life expectancy may negate some of the ideal metabolic goals for a patient with diabetes.17

BLOOD GLUCOSE CONCENTRATION

Monitoring of blood glucose status is considered a cornerstone of diabetes management.19 Blood glucose concentrations measured before meals (preprandial) provide information about baseline levels of glycemia, which are affected by several factors, such as weight, diet, level of activity and long-acting antihyperglycemic agents. Concentrations measured after meals (postprandial) provide information about peak glycemia which is influenced by the baseline level of glycemia, food consumed and short-acting antihyperglycemic agents.20

Epidemiological studies suggest that postprandial plasma glucose is a strong predictor for cardiovascular mortality.17 Excessive postprandial glucose concentrations may result in endothelial dysfunction, disrupted coagulation and the generation of free radicals, all of which could contribute to CVD.21 Although yet to be demonstrated in prospective studies, it is hypothesized that reduction in postprandial glucose concentrations may lead to an improvement in cardiovascular outcomes in patients with diabetes and IGT.17 Therefore, self monitoring of blood glucose (SMBG) should include measurements of postprandial glucose concentration (i.e. one to two hours after a meal).

SMBG with a well maintained and calibrated blood glucose monitor allows patients to work toward achieving and maintaining optimal glucose goals. Detailed counseling should be provided regarding the operation and maintenance of the blood glucose monitor, finger-stick procedure, sharps disposal, and the recording and interpretation of results.19
The optimal frequency of SMBG will depend on the needs and goals of individual patients. When therapy is being initiated, modified or discontinued, the frequency of blood glucose monitoring should be increased until the patient is stable. More frequent monitoring is also advisable when a patient is traveling or during an illness.\textsuperscript{17}  

A wide range of blood glucose monitors are available at most pharmacies, with varying functions and levels of sophistication. It is ideal that the patient and/or caregiver play an active role in the choice of blood glucose monitor to ensure it is appropriate for their needs. Pharmacists and diabetes educators can provide individual assessment and advice, taking into consideration factors such as physical dexterity, eyesight and cost, as well as providing training in the use of the glucose monitors.  

In addition to self monitoring of blood glucose, a random plasma glucose concentration, measured by the laboratory, is recommended periodically to assess the accuracy of patient results.\textsuperscript{19} See Table 2, page 11 for the recommended goals for glycemic control.  

**URINE GLUCOSE CONCENTRATION**  
Monitoring of urine glucose concentration is of limited value because of the great variation in urine glucose concentration for given concentrations of blood glucose.\textsuperscript{1} If urine testing is selected, patients should be taught that urine glucose testing provides only a rough estimate of prevailing blood glucose levels and that urine glucose testing provides no information about blood glucose levels below the renal threshold. The average renal threshold for glucose is around 180 mg/dL and therefore is not accurate for detection of hypoglycemia.\textsuperscript{19}  

**GLYCATED HEMOGLOBIN**  
Glycated hemoglobin is a term used to describe a series of stable minor hemoglobin components formed slowly and non-enzymatically from hemoglobin and glucose. Hemoglobin A\textsubscript{1C} (HbA\textsubscript{1C}) is the component usually measured and its rate of formation is directly proportional to the ambient blood glucose concentration. Glucose readily and freely permeates red blood cells. The formation of HbA\textsubscript{1C} was originally thought to be irreversible, reflecting the patient’s glycemic history over the previous 120 days (the average life span of red blood cells). However, the formation of HbA\textsubscript{1C} is now understood to be a slowly reversible process, most accurately reflecting the patient’s glycemic control for the previous two to
three months. HbA$_{1C}$ is the preferred standard for monitoring glycemic control. Both the American College of Endocrinology and the American Diabetes Association (ADA) advocate the term ‘A1C’ for this test.$^{19}$

A1C values have been shown to predict a patient’s risk of developing many of the serious, chronic complications of diabetes, such as retinopathy, nephropathy and possibly neuropathy.$^{19}$ Epidemiological evaluation of the United Kingdom Prospective Diabetes Study (UKPDS) found that for every percentage point decrease in A1C, the risk of microvascular complications was reduced by 37%. The association between reduced A1C and improved macrovascular outcomes is less clear, with a lesser effect on cardiovascular outcomes compared with microvascular outcomes in this study.$^{22}$

Despite these findings, other trials have highlighted a possible deficiency in the A1C value, in that it does not appear to accurately reflect postprandial hyperglycemia.$^{21}$

While it is not a standard measure for the diagnosis of diabetes, it is recommended that A1C be measured at the initial assessment of the newly diagnosed diabetic to document the degree of glycemic control at baseline. Continued monitoring should occur at least every six months in patients with stable glycemic control and who are achieving treatment goals, and every three months in patients whose therapy has been altered or who are not achieving treatment goals. Different laboratory methods exist for measuring A1C; therefore, to aid accurate interpretation of the results, it is recommended that the blood samples be consistently forwarded to the same laboratory.$^{19}$

Table 2, page 11 outlines the recommended goals for glycemic control.$^{17}$
Table 2. Goals for glycemic control in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Average preprandial blood glucose (mg/dL)</th>
<th>Peak postprandial blood glucose (mg/dL)</th>
<th>Additional Action Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>&lt; 110</td>
<td>&lt; 120</td>
<td>Normal</td>
</tr>
<tr>
<td>&lt; 6.5†</td>
<td>&lt; 110†</td>
<td>&lt; 135†</td>
<td>Goals of therapy</td>
</tr>
<tr>
<td>&lt; 7</td>
<td>90–130</td>
<td>&lt; 140†</td>
<td>Minimizes microvascular complications</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>&gt; 150</td>
<td>&gt; 180</td>
<td>Higher values associated with microvascular and macrovascular complications: Indicates need to reevaluate and significantly alter treatment regimen in most cases</td>
</tr>
</tbody>
</table>

Note: Table adapted from American Diabetes Association 2003 Guidelines
* American College of Endocrinology Guidelines
† European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF)

**BLOOD PRESSURE**

In patients with type 2 diabetes, hypertension is an independent contributory risk factor for retinopathy and nephropathy, as well as coronary, cerebrovascular, and peripheral vascular disease and possibly neuropathy. In order to reduce the associated morbidity, early detection through frequent monitoring and active treatment (lifestyle modification and/or pharmacological therapy) to target blood pressure goals is essential. The UKPDS found that for each 10 mmHg decrease in mean systolic blood pressure, the risk of microvascular complications were reduced by 13%, death related to diabetes by 15%, and myocardial infarction (MI) by 11%.

In patients with type 2 diabetes, blood pressure should be measured at each routine diabetes visit. Both sitting and standing blood pressure should be assessed. This is particularly important to detect the presence of autonomic neuropathy as such patients are prone to orthostatic hypotension.
The blood pressure goal for patients with diabetes and no signs of diabetic nephropathy is < 130/80 mmHg. In patients with diabetic nephropathy evidenced by greater than 1 g proteinuria per day, the blood pressure goal is < 125/75 mmHg.

For further information see hypertension, page 94.

**LIPIDS**

Independent of the level of glycemic control, patients with type 2 diabetes have an increased risk for obesity and lipid abnormalities.

The recommended targets for lipid concentrations for patients with diabetes are:

- Total cholesterol < 200 mg/dL
- Triglycerides < 150 mg/dL
- HDL cholesterol > 40 mg/dL (men)
  > 50 mg/dL (women)
- LDL cholesterol < 100 mg/dL
  < 70 mg/dL (optional goal)

It is recommended that a complete fasting lipid profile be done upon diagnosis. According to ATP III recommendations, if the lipid profile is abnormal, medical nutrition therapy (MNT) with or without the addition of drug therapy should be initiated, with periodic monitoring of the lipid profile. If the lipid profile is within normal guidelines, lifestyle modifications should be initiated with lipid profile repeated annually.

For further information see dyslipidemia, page 117.

**WEIGHT**

Type 2 diabetes is strongly associated with weight gain, increased BMI and accumulation of abdominal fat (increased waist circumference). All of these factors are also associated with insulin resistance and pose significant risks for CVD. Regular monitoring of weight (and/or waist circumference) with the goal of reducing weight where appropriate, is a vital step in the management of type 2 diabetes and its complications.

MNT in type 2 diabetes should emphasize lifestyle changes that result in reduced energy intake and increased energy expenditure through physical activity.
activity. The overall goal is to achieve sustainable lifestyle strategies to reduce glycemia, dyslipidemia and hypertension. Such strategies should be initiated upon the diagnosis of diabetes and reinforced at each routine visit.29

For further information see body weight, page 20 and weight loss in type 2 diabetes, page 25.

**EYE EXAMINATION**

Up to 21% of patients with type 2 diabetes have retinopathy at diagnosis. Although laser photocoagulation can prevent severe visual loss in most patients with vision-threatening diabetic retinopathy, it will not restore vision that has already been damaged. Because diabetic retinopathy is often asymptomatic early in the course of the disease, screening is vital in order to prevent visual loss.30

A dilated and comprehensive eye examination by an optometrist or ophthalmologist should be completed at the time of diagnosis and then annually. Once retinopathy is detected, more frequent examinations will be required. Risk factors for development of diabetic retinopathy include gross proteinuria, poor glycemic control, hypertension, hyperlipidemia and smoking.30

For further information see diabetic retinopathy, page 156.

**FOOT EXAMINATION**

Foot problems account for a significant degree of the morbidity, disability (emotional and physical), hospitalizations and amputations associated with diabetes.31 It is estimated that of all amputations in patients with diabetes, 85% are precipitated by a foot ulcer which subsequently deteriorates to a severe infection or gangrene.32 It has been demonstrated that careful screening supported by a multidisciplinary care team can result in significantly fewer amputations in patients with diabetes.33, 34

All patients with diabetes should be examined at diagnosis and at least once a year to identify high risk foot conditions. Patients with demonstrated high risk foot conditions should be examined more often (every 1–6 months) preferably by a podiatrist.35 Risk factors include the presence of sensory neuropathy, foot deformities, bony prominences, signs of peripheral ischemia, and/or previous ulcer or amputation.35 Patients with neuropathy should have a visual inspection of their feet at every visit.31
Foot examination by a health professional should include assessment of foot structure and biomechanics, neuropathy, vascular status, ulcerations and evidence of infection. Footwear should also be assessed, as well as the patient’s level of knowledge and understanding regarding foot care. The necessity of regular foot examinations by a podiatrist should be reinforced.

Peripheral nerve function should be checked at least yearly in the patient with diabetes and should include a quantitative somatosensory threshold test, using the Semmes-Weinstein 5.07 (10 g) monofilament. The presence of PVD should also be assessed as well as joint mobility, gait and balance.

For further information see diabetic neuropathy, page 146; foot care, page 154; and peripheral vascular disease, page 180.

**URINALYSIS**

Monitoring for microalbuminuria is an important step in the early detection of changes in renal function and progression to overt proteinuria and diabetic nephropathy. In patients with type 2 diabetes, albuminuria is also a marker for greatly increased cardiovascular morbidity and mortality. Once clinical albuminuria is detected, the risk of end-stage renal disease (ESRD) is significantly increased in type 2 diabetes.

In type 2 diabetes, the incidence of albuminuria at the time of diagnosis of diabetes ranges from 3–30%. Therefore, a test for microalbuminuria should be performed at diagnosis.

A quick screen for microalbuminuria can be conducted in the clinical setting with reagent tablets or dipsticks specific for microalbumin. These methods have acceptable sensitivity (95%) and specificity (93%) when performed by trained personnel, and can provide a useful snapshot of albumin present in the urine. However, these methods assess urinary albumin by concentration rather than by excretion rate, and they do not correct for creatinine. A diagnosis of microalbuminuria cannot be established with these methods, and all positive tests from reagent strips or tablets should be confirmed by the more specific methods described below.

A diagnosis of microalbuminuria can be made using any of the following three methods of laboratory analysis:

- a measurement of albumin to creatinine ratio in a random spot collection, preferably using the first void or morning collection of urine;
- a timed collection, such as over four hours or overnight; or
• a 24-hour collection with creatinine, allowing simultaneous measurement of creatinine clearance.

The analysis of a spot sample for the albumin-to-creatinine ratio is the preferred method in the office setting and is strongly encouraged.17

If the test for microabumin is positive, it should be repeated twice during the next 6 months. **If two of the three tests are positive for microalbuminuria, treatment should be considered.** If the test for microalbuminuria is negative, re-screening should occur on an annual basis.

**Table 3. Definitions of abnormalities in albumin excretion.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Spot collection (µg/mg creatinine)</th>
<th>24-h collection (mg/24 h)</th>
<th>Timed collection (µg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 30</td>
<td>&lt; 30</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–299</td>
<td>30–299</td>
<td>20–199</td>
</tr>
<tr>
<td>Clinical albuminuria</td>
<td>≥ 300</td>
<td>≥ 300</td>
<td>≥ 200</td>
</tr>
</tbody>
</table>

Several factors have been documented to interfere with the microalbuminuria test results. Short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure and acute febrile illness can all cause transient elevations in urinary albumin excretion.37

For further information see diabetic nephropathy, page 160.

**INFLUENZA AND PNEUMOCOCCAL VACCINATION**

All patients with diabetes are advised to receive the influenza vaccination each year in September. A one-time pneumococcal vaccination is recommended for patients with diabetes. Repeat dosing is indicated, however, in certain circumstances including patients who are > 64 years old and were vaccinated more than 5 years previously. Revaccination is also indicated for diabetic patients with nephrotic syndrome, chronic renal disease and other immunocompromised states (e.g. post-organ transplant).40

**ONGOING PATIENT EDUCATION**

In addition to the laboratory measures and examinations outlined as part of the usual screening procedures for patients with type 2 diabetes, it is important that patient education issues be addressed at each consultation. These issues include lifestyle modification topics such as diet, alcohol
intake, smoking cessation and weight reduction if applicable. To help reinforce the importance of lifestyle interventions, the benefits in terms of long-term morbidity and mortality should be emphasized. The patient’s level of understanding of diabetes and the potential complications should also be reassessed, and reinforced where needed.

Adequate patient understanding of diabetes as a disease state, its subsequent complications and the major role of self-management, is essential for optimal outcomes.

A referral to a diabetes educator and dietitian at diagnosis and as necessary is strongly recommended to reinforce the importance of healthy lifestyle practice.
SUMMARY

Table 4, below summarizes current recommendations for screening and targets for patients with type 2 diabetes.

Table 4. Summary of recommended screening and relevant targets.

| Glycemic control | Frequency of self monitoring depends on patient characteristics and goals. Monitor plasma glucose (laboratory measurement) at diagnosis and every 3–4 months. Monitor A1C at least every 6 months (every 3 months when unstable or treatment is being modified).
| Preprandial: | < 110 mg/dL, * 90–130 mg/dL |
| Peak postprandial: | < 135 mg/dL, † < 140 mg/dL, * < 180 mg/dL |
| A1C: | < 6.5%, * < 7% |

| Blood pressure | Monitor at diagnosis and each consultation
| Goal: | < 130/80 mmHg 25 |
| | < 125/75 mmHg if > 1 g proteinuria per day. 26 |

| Lipid profile | Measure at diagnosis, then annually. 17
| Total cholesterol: | < 200 mg/dL 9 |
| Triglycerides: | < 150 mg/dL 9, 27 |
| HDL cholesterol: | > 40 mg/dL (men) 27 |
| | > 50 mg/dL (women) 27 |
| LDL cholesterol: | < 100 mg/dL 9, 27 |
| | < 70 mg/dL (optional) 28 |

| Weight | Measure at diagnosis and each consultation. 29 |

| Eye examination | At diagnosis, then annually. More frequently if retinopathy is progressing. 17 |

| Foot examination | At diagnosis and then at least annually. More frequently in high risk patients, preferably by a podiatrist. 17 |

| Urinalysis | Perform test for microalbuminuria at diagnosis. If negative, retest annually. If the test is positive, it should be repeated twice during the next 6 months. If two of three tests are positive, consider treatment. 37 |

Adapted from American Diabetes Association 2003 Guidelines 17

*American College of Endocrinology Guidelines 23

† European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) 24
LIFESTYLE INTERVENTIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

The importance of life long lifestyle modifications cannot be overemphasized for patients with type 2 diabetes. Patients should receive ongoing education about appropriate nutrition, exercise, strategies to achieve weight loss and smoking cessation. These measures need to be continually addressed regardless of the need for pharmacological therapy. A multidisciplinary team approach is ideal to enable such changes, bringing together the skills and expertise of various health care professionals, such as diabetes educators and dietitians.

THE EVIDENCE

Evidence to support the importance of lifestyle modification in reducing the risk of type 2 diabetes can be found in two recent randomized controlled trials, the Diabetes Prevention Program Research Group (DPPRG) study and the Finnish Diabetes Prevention Study (FDPS).

The Diabetes Prevention Program Research Group Study

The DPPRG study was a randomized, controlled trial done in the United States to evaluate the effectiveness of lifestyle modifications versus metformin in preventing or delaying the onset of type 2 diabetes. A total of 3234 non-diabetic individuals with elevated fasting glucose (mean 106.5 mg/dL) and post-load plasma glucose (mean 164.6 mg/dL) levels and average BMI of 34 kg/m² were randomly assigned to one of three groups: standard lifestyle modifications plus metformin, standard lifestyle modifications plus placebo, or an intensive lifestyle modification program. Goals of the intensive lifestyle modification program were at least a 7% weight loss and at least 150 minutes of physical activity per week. The average duration of follow-up was 2.8 years.

The incidence of diabetes was reduced by 58% in the intensive lifestyle modification group and 31% in the metformin group as compared to placebo. To prevent one new case of diabetes every 3 years, 6.9 people would have to participate in the lifestyle intervention program and 13.9 people would have to receive metformin.
The Finnish Diabetes Prevention Study

The FDPS was a randomized, controlled trial conducted in Finland designed to observe the effects of lifestyle changes on the prevention of type 2 diabetes. The subjects were randomized into either intervention or control groups. The intervention group received individualized counseling on nutrition (seven sessions with a nutritionist during the first year), weight reduction, and physical activity. The mean duration of follow-up was 3.2 years.\textsuperscript{12}

The risk of type 2 diabetes was reduced by 58% in the intervention group which was directly associated with changes in lifestyle. This study demonstrated that a reduction from baseline body weight of as little as 5% played a substantial role in the prevention of diabetes. To prevent one case of diabetes, 22 subjects with impaired glucose tolerance must follow this program for 1 year (or 5 subjects for 5 years).\textsuperscript{12}

**NUTRITION IN TYPE 2 DIABETES**

MNT in type 2 diabetes involves optimization of body weight and the modification of food intake to a diet low in fat and high in complex carbohydrates.

The goals of MNT include:\textsuperscript{29}
- assisting individuals with diabetes to make changes in nutrition habits that lead to improved metabolic control;
- maintenance of as near-normal blood glucose levels as possible by balancing energy intake with oral antihyperglycemic agents or insulin and physical activity;
- achievement of optimal lipoprotein profile to reduce risk of macrovascular disease;
- achievement of blood pressure levels that reduce the risk of vascular disease;
- prevention of long-term complications of diabetes, such as renal disease, neuropathy, hypertension and CVD;
- improvement of overall health through optimal nutrition and physical activity;
- achievement of a reasonable body weight, defined as the weight an individual health care provider acknowledges as achievable and maintainable over both the short and long-term.
In type 2 diabetes, increased activity and dietary change which reduces total fat and energy intake may often be effective, at least initially, in controlling blood glucose levels. All patients, unless highly symptomatic, should undergo a trial of 1–3 months of nutrition therapy and lifestyle modification prior to the introduction of oral antihyperglycemic agents. These strategies can be enhanced with input from a dietitian to ensure adequate nutrition as well as diabetes management.

Body weight

It is estimated that 65% of adults in the United States are overweight or obese. Obesity increases the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease (CHD), stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and endometrial, breast, prostate and colon cancers. Approximately 36% of people with type 2 diabetes have a BMI of \( \geq 30 \text{ kg/m}^2 \), which is classified as obese. Increased insulin resistance results from increased body adiposity.

Weight loss in overweight or obese individuals reduces risk factors for diabetes and cardiovascular disease. Evidence suggests that even a modest (5–10%) weight loss reduces blood pressure, triglycerides, total cholesterol and LDL cholesterol levels, as well as blood glucose and A1C levels thereby reducing medication needs.

As BMI increases beyond 25 kg/m\(^2\), the risk of metabolic complications increases proportionally. In addition to total body weight or BMI, measurement of abdominal circumference may be used as an indicator of abdominal obesity. It is now recognized that central or abdominal accumulation of fat is associated with a greater risk of type 2 diabetes, CVD and fatty liver than perhaps elevated BMI alone. Table 5, page 21, describes the classification of overweight and obesity and the associated disease risks.
Table 5. Classification of overweight and obesity.

<table>
<thead>
<tr>
<th>Weight Classification$^{46, 47}$</th>
<th>Body Mass Index$^\dagger$ (kg/m$^2$)</th>
<th>Disease Risk$^*$ Relative to Normal Weight and Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Men ≤ 102 cm</strong> (≤ 40 in) <strong>Women ≤ 88 cm</strong> (≤ 35 in) <em><strong>Men &gt; 102 cm</strong></em> (&gt; 40 in) <strong>Women &gt; 88 cm</strong> (&gt; 35 in)</td>
</tr>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Low</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
<td>Average</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obesity Class I</td>
<td>30–34.9</td>
<td>High</td>
</tr>
<tr>
<td>Obesity Class II</td>
<td>35–39.9</td>
<td>Very High</td>
</tr>
<tr>
<td>Obesity Class III</td>
<td>≥ 40</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

Note: Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

* Disease risk for type 2 diabetes, hypertension and CVD.

† Body mass index (BMI) is calculated according to the following equation:
weight (kg) / height$^2$ (m) or weight (lbs) x 702 / height$^2$ (in).

A reasonable body weight may not always be the patient’s ideal body weight. For example, achievement of ideal body weight may not be reasonable given the patient’s co-morbidities and ability to exercise, however, any movement towards that goal will decrease disease risk.$^{12}$

**Nutritional guidelines**

It is important for primary care providers to have an appreciation of the nutritional therapy of type 2 diabetes. However, it is ideal for the patient to be referred to a dietitian and a diabetes educator, if possible, to receive detailed instructions and individualized advice.$^{17}$

The same nutritional guidelines recommended for a healthy lifestyle in the general population also apply to individuals with type 2 diabetes. The emphasis of nutritional therapy for type 2 diabetes should be on lifestyle modifications to reduce hyperglycemia, dyslipidemia, and blood pressure. Moderate amounts of weight loss, particularly of intra-abdominal fat, reduce insulin resistance and can correct dyslipidemia.

The diet should be individually planned with the aim of creating a deficit of at least 500 kcal/day in severely obese patients, (BMI > 35 kg/m$^2$), and at least 300 kcal/day in patients with a BMI between 27 and 35 kg/m$^2$.$^{44}$
**Carbohydrates**

It is recommended that 60–70% of total energy intake be divided between carbohydrates and monounsaturated fat. The relative contribution of carbohydrate and monounsaturated fat should be individualized based on nutritional assessment with a dietitian, metabolic status, weight, and treatment goals.44

Carbohydrates can be classified according to their glycemic index. Glycemic index is used to classify carbohydrates according to their ability to raise postprandial blood glucose concentration.48, 49 The glycemic index of a carbohydrate is influenced by its rate of intestinal absorption, which in turn is influenced by its composition, structure and susceptibility to enzymatic digestion.48 Some concerns surrounding the use of the glycemic index relate to its variability in measurement and the accuracy of this measurement when applied to mixed meals. In addition, the glycemic index of a meal can be influenced by the preceding meal.49 Results of studies of the effect of low-glycemic index diets in patients with type 2 diabetes on glucose and lipid metabolism have been inconsistent. Some have shown improvement while others have shown no difference. In considering the glycemic effect of carbohydrates, the total amount of carbohydrate present in meals or snacks is more important than the source or type. While low-glycemic index foods may reduce postprandial hyperglycemia, there is insufficient evidence of long-term benefit to recommend use of low-glycemic index diets in type 2 diabetes patients.44

Sugar, glucose and foods containing large amounts of refined sugars have traditionally been restricted in the diet of patients with diabetes for fear of hyperglycemia. It is, however, not necessary for patients with type 2 diabetes to eliminate sugar from their diet. Including a small amount of sugar as part of a mixed meal or food has not been shown to adversely affect blood glucose. Patients may prefer to use suitable artificial sweeteners which include aspartame, sucralose, acesulfame potassium, and saccharin.29

**Fat**

An overall reduction in saturated fat and cholesterol intake is important to reduce the risk of CVD. Saturated fats should contribute less than 10% of the total energy intake and cholesterol should be less than 300 mg/day. Patients with LDL cholesterol \( \geq 100 \) mg/dL may benefit from a saturated fat of less than 7% of total energy intake and a cholesterol intake of less than 200 mg/day.44
The overall aim of the reduced fat diet is to substitute saturated fats with polyunsaturated and monounsaturated fats, and to lower overall fat intake by substituting low fat options. For example, fried foods should be avoided. Low fat milk and low fat cheese could be used as substitutes for whole milk and regular cheese, respectively. Reduced fat margarines or alternative spreads, such as cottage or ricotta cheese, could be used instead of standard margarine/butter.

Saturated fats are present in milk, meats, butter, cheese, and vegetable oils extracted from palm and coconut. Polyunsaturated fats are found in fish, fish oils, sunflower, corn and soy oils, and margarines. Monounsaturated fats include avocado, and oils and margarines from canola and olive.

**Protein**

The protein intake recommended for patients with type 2 diabetes and normal renal function is the same as that for the general population, which is 15–20% of total energy intake. Selection of the type of protein should consider the fat content. For example, sources of protein such as beans are very low in fat.

**High protein (high fat)/low carbohydrate diet**

The high protein (high fat)/low carbohydrate diet was first introduced many years ago, and this type of diet is popular once again. Examples include: The Zone Diet, Sugar Busters, Protein Power, and Dr Atkins’ New Revolution Diet. It is claimed that these diets will assist with weight loss, prevent disease, and improve blood glucose levels in people with diabetes. People are attracted to these diets because of the rapid initial weight loss that occurs (which is actually fluid and not fat loss); however, it has not been demonstrated that weight loss can be sustained in the long-term.

Controlled clinical trials showing that the high protein (high fat)/low carbohydrate diet is effective in people with diabetes are lacking. Concerns with this diet include the lack of long-term safety data, and the potential complications. Some potential complications include risks associated with a diet high in saturated fat and low in dietary fiber, vitamins and minerals; dehydration due to excess fluid loss; adverse effects on lipids, bone and kidney function; hyperuricemia; and hyperuricosuria.

Several untoward metabolic consequences have been reported, and the authors of one review concluded that ‘it is not evident that high protein
intake confers any advantage in terms of strength or health’. A particular concern is its use in patients with diabetes who have developed overt nephropathy, as protein restriction may need to be considered in this situation. For more information, see diabetic nephropathy, page 160.

While these diets may produce short-term weight loss and reduce hyperglycemia, the long-term maintenance of these effects and the effect on LDL cholesterol is unclear. The American Dietetic Association does not recommend the high protein (high fat)/low carbohydrate diet as it is often unbalanced and deficient in certain essential nutrients and excessive in others. The American Heart Association has also criticized this diet because of its potential to cause nutritional deficiencies, renal disease and osteoporosis.

**Fiber**

Recommended fiber intake for patients with type 2 diabetes is the same as that for the general population, which is 20–35 g per day. A wide variety of high fiber foods should be promoted from a variety of sources such as whole grains, fruits, and vegetables ensuring that a mixture of soluble and insoluble fiber is consumed. Sources of insoluble fiber include wheat bran, whole wheat bread, vegetables, some fruits, nuts and seeds. Sources of soluble fiber include oat bran, oatmeal, rice bran, fruits, legumes and psyllium seed husks.

**Alcohol**

Alcohol intake should be minimized in patients with type 2 diabetes. The effect of alcohol on blood glucose concentration is not only dependent on the amount of alcohol consumed but also on the relationship to food intake. Alcohol is not metabolized to glucose and inhibits gluconeogenesis. Therefore, if consumed without food by patients treated with insulin or oral antihyperglycemics, hypoglycemia can result. Hypoglycemia can occur at blood alcohol concentrations that do not exceed mild intoxication.

If alcohol is consumed, it should be limited to a daily intake of two standard drinks (consumed with food) per day for men, and one standard drink per day for women, with regular alcohol free days encouraged. A standard drink is defined as: 12 oz. of beer, 5 oz. of wine, or 1.5 oz. of distilled spirits.

By limiting alcohol intake, blood pressure can be substantially reduced in some patients. On average, a reduction of 1 mmHg systolic blood pressure may be seen for each standard drink eliminated per day.
Sodium

Sodium intake should be restricted, particularly in patients with type 2 diabetes and hypertension. The restriction should include the omission of added salt to cooking and high sodium containing foods. Reduced sodium intake benefits both normotensive and hypertensive individuals by lowering blood pressure.

WEIGHT LOSS IN TYPE 2 DIABETES

Patients with type 2 diabetes who are obese are much more refractory to achieving optimal metabolic control compared with patients who are not obese. Weight loss in obese patients with type 2 diabetes by any treatment modality results in a partial reversal of the pathophysiologic mechanisms that account for hyperglycemia. With weight loss, there can be as much as a 165% improvement in insulin resistance. Patients should be advised that only modest weight loss (5–10% of baseline) is needed to result in significant metabolic improvement by way of reduction in both insulin resistance and visceral adiposity. In addition to the beneficial effects on insulin resistance, weight loss has been associated with a 25% reduction in total mortality, and a 28% reduction in CVD and diabetes mortality.

Assessing the patient

Treatment of an overweight or obese person incorporates a two step process: assessment and management. Assessment of a patient should include the evaluation of BMI, waist circumference and overall medical risk (see body weight, page 20). Assessment of a patient’s absolute risk status also requires examination for the presence of disease conditions (e.g. established CHD, atherosclerotic diseases), other obesity associated diseases (e.g. gynecological abnormalities, osteoarthritis, gallstones) and cardiovascular risk factors (e.g. smoking, hypertension, dyslipidemia).

The decision to attempt weight loss treatment should take into consideration the patient’s readiness to make the necessary lifestyle changes. Evaluation of readiness should include the following:

- reasons and motivation for weight reduction;
- previous history of successful and unsuccessful weight loss attempts;
- support expected from family and friends;
- understanding of the causes of obesity and how obesity contributes to several diseases;
• attitude toward physical activity;
• capacity to engage in physical activity;
• time availability for weight loss intervention; and
• financial considerations.

The health care provider plays an important role in patient weight loss motivation. This can be accomplished by stressing the dangers associated with persistent obesity and providing a plan for healthy weight reduction.44

**Goals of treatment**

The general goals of weight loss and management are to reduce body weight, to maintain a lower body weight over the long-term and to prevent further weight gain. An initial weight loss of 10% of body weight achieved over six months is a recommended target. This may equate to a 1 to 2 pound per week weight loss based on a calorie deficit of 500–1000 kcal/day.53 The priority then should be weight maintenance achieved through combined changes in diet, physical activity and behavior. Further weight loss can be considered after a period of weight maintenance.44

Maintenance of weight loss is enhanced by a program consisting of physical activity, nutritional therapy and behavior therapy continued indefinitely.44

**Strategies for weight loss**

A combined intervention of behavior therapy, a controlled energy diet and increased physical activity provides the most successful therapy for weight loss and weight maintenance. This type of intervention should be maintained for at least six months before considering weight-reducing pharmacotherapy.44 Pharmaceutical agents should only be used as part of an overall management strategy with ongoing review and reassessment.

**Medical nutrition therapy**

Controlled energy diets are recommended for weight loss in overweight and obese patients. For further information see nutrition in type 2 diabetes, page 19. Weight reduction diets are unlikely to produce long-term weight loss unless they are part of a structured program which includes lifestyle modifications, education, physical activity and frequent, regular follow-up.29
Physical activity

Physical activity should be an integral part of weight loss therapy and weight maintenance. See exercise in type 2 diabetes, page 28.

Behavior therapy

There is strong evidence that combined interventions of a controlled energy diet, increased physical activity and behavior therapy (generally in a group setting), provide the most successful therapy for weight loss and weight maintenance. There is also suggestive evidence that patient motivation is a key component for success in a weight loss program. Practitioners need to assess the patient’s motivation to begin weight loss therapy, assess the readiness of the patient to implement the plan and then take appropriate steps to motivate the patient for treatment.44 The behavior modification technique involves identifying the eating or related lifestyle behavior to be modified, setting specific goals, modifying determinants of the behavior to be changed and reinforcing the desired behavior.54

Frequent visits to their treating doctor and dietitian early in management also helps to reinforce the desired behavior.

Pharmacotherapy

In carefully selected patients, appropriate drugs can augment controlled energy diets, physical activity and behavior therapy. However, they should never be used without these lifestyle modifications. Continual assessment of drug therapy for efficacy and safety is necessary.44

Research in weight loss pharmacotherapy is focusing on three areas:53
- inhibitors of energy intake (appetite suppressants);
- enhancers of energy expenditure; and
- stimulators of fat mobilization.

Adrenergic agonists

Adrenergic agonists such as diethylpropion (Tenuate®, Tenuate Dospan®), benzphetamine (Didrex®), phendimetrazine (Bontril PDM®, Melfiat-105®, Prelu-2®), and phentermine (Ionamin®,Pro-Fast®, Adipex-P®) have been available for many years. Their clinical use, however, is often limited by amphetamine-like adverse effects including hypertension, tachycardia, insomnia, agitation and dry mouth, and the potential for dependence. These agents are indicated by the Food and Drug Administration (FDA) for short-term weight loss (< 12 weeks) in appropriately selected patients.
Numerous case reports of valvular heart disease and primary pulmonary hypertension (PPH) associated with the use of ‘fen-phen’ (a combination of phentermine and fenfluramine or dexfenfluramine) for weight loss resulted in the voluntary withdrawal of fenfluramine and dexfenfluramine from the US market in 1997. There have been only a few isolated case reports of PPH possibly associated with phentermine monotherapy. No cases of valvular heart disease have been reported with the use of phentermine.64, 65

**Orlistat**

The use of orlistat (Xenical®) for the treatment of obesity in diabetes is discussed in detail in Appendix 3, page 199.

**Sibutramine**

The use of sibutramine (Meridia®) for the treatment of obesity in diabetes is discussed in detail in Appendix 4, page 204.

For more information regarding the use of these agents contact your local DATIS office.

**Weight loss surgery**

Weight loss surgery is an option for carefully selected patients with clinically severe obesity (BMI ≥ 40 or BMI ≥ 35 kg/m² with comorbid conditions) when less invasive methods of weight loss have failed, and the patient is at high risk for obesity associated morbidity or mortality. An integrated program must be in place to provide guidance on diet, physical activity, and behavioral and social support both before and after surgery.47 Studies have found surgery to be very successful in the shorter term (i.e. 85% of individuals had lost at least 50% of their excess weight at four years); however, long-term success is still guided by the individual’s ability to make lifestyle changes, especially in terms of diet and physical activity.66 Nutritional support from a dietitian can assist in long-term weight maintenance and ensure that patients receive a nutritionally balanced diet, as there is a high risk of nutrient deficiencies following weight loss surgery.

**EXERCISE IN TYPE 2 DIABETES**

Physical activity in patients with type 2 diabetes is important, and has been shown to:54, 67

- improve glucose tolerance as insulin sensitivity increases;
- increase energy expenditure resulting in weight loss;
- increase feeling of well being and promote a sense of self control;
• increase work capacity;
• improve blood pressure and lipid profiles;
• possibly decrease abdominal fat; and
• increase cardiorespiratory fitness.

Because cardiovascular risk is high in most patients with type 2 diabetes, the risk of cardiovascular complications with physical activity must be constantly considered.67 Patients on insulin, sulfonylureas or meglitinides need to take special precautions due to the risk of hypoglycemia.68

Initially low-to-moderate levels of physical activity for 10–15 minutes each session, 3–5 days a week, should be encouraged. All adults should set a long-term goal to accumulate at least 30 minutes or more of low-to-moderate intensity physical activity most days of the week, which may be divided into three 10-minute sessions. Walking is one of the best and easiest exercises for patients to do. Resistance training to build muscle mass and reduce intra-abdominal obesity is recommended for motivated patients who have access to the equipment.69

Activity should generally be increased slowly, with care taken to avoid injury.

Preparing for exercise

When prescribing an exercise program, a careful history should be taken. This examination should screen for the presence of macrovascular and microvascular complications that may be worsened by exercise.46, 67

A graded exercise test may need to be performed in some patients based on one of the following criteria prior to starting an exercise program:67
• age > 35 years;
• type 2 diabetes of > 10 years duration;
• type 1 diabetes of > 15 years duration;
• presence of any additional risk factor for CHD;
• presence of microvascular disease;
• peripheral vascular disease;
• autonomic neuropathy.

In addition, the presence of diabetic complications as described below should be taken into consideration prior to initiating an exercise program in patients with type 2 diabetes.
**Presence of diabetic complications**

**Coronary heart disease**

These patients should undergo a supervised evaluation of the ischemic response to exercise, ischemic threshold and the propensity to arrhythmia during exercise.\(^6^7\)

**Retinopathy**

For patients who have proliferative diabetic retinopathy that is active, strenuous activity may precipitate vitreous hemorrhage or traditional retinal detachment. These individuals should avoid strenuous, jarring or pounding activities including weight lifting, jogging and high-impact aerobics. Desirable activities include swimming, walking, low-impact aerobics, stationary cycling and endurance exercises.\(^6^7\)

**Peripheral neuropathy**

Peripheral neuropathy may result in loss of protective sensation in the feet. Significant peripheral neuropathy is an indication to limit weight bearing exercise. Repetitive exercise on insensitive feet can ultimately lead to ulceration and fractures.\(^6^7\) A thorough foot examination is recommended before increasing exercise.

**Autonomic neuropathy**

The presence of autonomic neuropathy may limit an individual’s exercise capacity and increase the risk of an adverse cardiovascular event during exercise. Hypotension and hypertension after vigorous exercise are more likely to develop in patients with autonomic neuropathy, particularly when starting an exercise program.\(^6^7\)

**Risk of hypoglycemia**

During and/or after exercise, there is a risk of hypoglycemia in patients with diabetes requiring insulin, sulfonylureas or meglitinides. There is also potential for delayed effects of exercise on blood glucose levels, in particular delayed hypoglycemia 6–15 hours after cessation of exercise.\(^7^0\) Patients should be educated to increase their carbohydrate intake and/or decrease their insulin dose before exercise, carry quick acting carbohydrates (e.g. glucose tablets, jelly beans) and learn their body’s response to exercise (especially if prolonged or vigorous). It is recommended that patients with diabetes exercise with someone if possible, and that both the patient and their companion know the signs of hypoglycemia (including dizziness,
weakness, sweating, blurred vision and confusion) and what action to take should it occur.  

**Appropriate care of feet**

Appropriate care of feet and appropriate footwear for the type of exercise is important in a patient with diabetes. Patients should be encouraged to carefully monitor for blisters and other potential damage to the feet before, during and after exercise.  

**Type of exercise program**

Exercise programs should include a period of warm-up and cool-down of 5–10 minutes of aerobic activity of low-intensity (e.g. walking, cycling). Moderate resistance training programs that utilize light weights and high repetitions can be used for maintaining or enhancing upper body strength in most patients with diabetes.  

**Other considerations**

It is advisable that patients with diabetes carry identification when exercising, such as their name, diagnosis and emergency telephone number and/or wear medical identification jewelry. It is also important that dehydration is avoided. People should drink two 8-ounce glasses of water about 2 hours before starting to exercise and continue fluid intake frequently throughout the session.  

**SMOKING CESSATION**

Cigarette smoking is the most important source of preventable morbidity and premature mortality in the world. In the United States, smoking accounts for approximately one in every five deaths. Kentucky ranks highest in the nation in prevalence of current cigarette smoking among adults at 30.5% in 2000. Smoking in patients with diabetes significantly increases the risk of CVD, and it contributes to premature mortality and morbidity from macrovascular complications. Smoking is also associated with an increased risk of microvascular complications in patients with diabetes, with studies showing an increased risk for the development and progression of neuropathy, nephropathy, and possibly retinopathy. It may also play a role in the development of type 2 diabetes.
Benefits of smoking cessation in patients with diabetes

Smoking cessation has major and immediate health benefits for smokers of all ages. Well controlled trials evaluating the effect of smoking cessation in patients with diabetes are lacking. However, in people without diabetes, smoking cessation has been associated with reduced cardiovascular mortality and morbidity.\textsuperscript{72, 74}

It is likely that patients with diabetes will benefit from smoking cessation at least as much as people who do not have diabetes but who have other risk factors for CVD.\textsuperscript{74} Therefore, due to the combined risks associated with diabetes and smoking, it is important to advise patients with diabetes who do not smoke of the risks associated with smoking and to encourage them not to begin smoking. For those patients with diabetes who do smoke, they should be given information regarding the adverse effects of smoking and the benefits of quitting, and smoking cessation should be encouraged.\textsuperscript{72}

Strategies to support smoking cessation in patients with diabetes

There is only minimal data on the effectiveness of smoking cessation interventions specifically in diabetes. However, there is no reason to assume that smoking cessation interventions would be less effective in these patients compared with the general population.\textsuperscript{72}

It is estimated that while 70\% of smokers want to quit smoking and 34\% attempt to quit each year, only 2.5\% are successful.\textsuperscript{71} Many people who stop smoking make several attempts to quit before they succeed. Counseling on smoking cessation plays an important role in success rates. More intensive interventions such as > 10 minutes of counseling, problem-solving content and skills training, for multiple sessions over a period of several weeks, are the most effective in long-term smoking cessation.\textsuperscript{72} Primary care providers are the most effective initial source of information and advice. They can help patients quit by providing advice and counseling on smoking cessation, and by providing ongoing follow up and support.

Weight gain is a common concern regarding smoking cessation although most patients gain less than 5 lbs. The benefits of smoking cessation outweigh the risks associated with such a slight weight gain. Patients with diabetes should be educated about the importance of smoking cessation and strategies to help minimize weight gain while quitting should be discussed (e.g. healthy diet and snacks, and regular exercise).\textsuperscript{75}
**Counseling**

Providing counseling, support and follow up for patients is a very important step in successful smoking cessation programs. Randomized controlled trials have shown that counseling by multiple health care professionals, using individual or group counseling, over time, and including problem solving or skills training components with social support, is effective in changing smoking behavior of patients compared with no intervention.\(^72\)

Three types of counseling strategies have been found to be beneficial in smoking cessation success:\(^76\)
- practical counseling (problem-solving, skills training);
- social support as part of treatment; and
- social support outside of treatment.

**Nicotine replacement therapy**

Nicotine replacement therapy (NRT) is considered to be one of the first-line pharmacotherapy’s to increase long-term smoking cessation rates.\(^76\) Studies evaluating the efficacy of NRT specifically in patients with diabetes are lacking. Despite this, the American Diabetes Association recommends that NRT can be considered in this patient group to optimize successful smoking cessation.\(^72\)

The effectiveness of NRT combined with counseling is associated with a greater percentage of success than either one alone.\(^77\) Smoking cessation pharmacotherapy reduces withdrawal effects of nicotine (e.g. craving, anxiety, irritability and hunger) and except in the presence of contraindications, should be used in all patients attempting to stop smoking.\(^72, 76\) The type of NRT that is chosen should take into consideration the needs of the patient, tolerability and cost. Transdermal nicotine patches may be easier to use, are generally better tolerated and have little dependence potential compared with the chewing gum. Whatever form of NRT is used, it is important to reinforce the risks and disadvantages of concurrent NRT and smoking to the patient.

Please refer to the *American Hospital Formulary Service* or the approved product information for dosage and administration information, contraindications, precautions, adverse effects and drug interactions associated with NRT.

In the United States, NRT is available over the counter in the form of chewing gum, lozenges, and transdermal patches. Table 6, page 34, lists the
preparations that are currently available in the US. For information regarding smoking cessation support programs please call your local DATIS office.

Table 6. Nicotine replacement therapies available in the United States.

<table>
<thead>
<tr>
<th>Nicotine replacement therapy (NRT)</th>
<th>Brand name</th>
<th>Strength</th>
<th>Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chewing gum</td>
<td>Nicorette®</td>
<td>2 mg, 4 mg</td>
<td>OTC</td>
</tr>
<tr>
<td>Lozenge</td>
<td>Commit®</td>
<td>2 mg, 4 mg</td>
<td>OTC</td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>Nicoderm CQ®</td>
<td>21 mg/24 hr</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>Habitrol®</td>
<td>14 mg/24 hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 mg/24 hr</td>
<td></td>
</tr>
<tr>
<td>Inhaler</td>
<td>Nicotrol®</td>
<td>15 mg/16 hr</td>
<td>OTC</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>Nicotrol®</td>
<td>10 mg/mL</td>
<td>Rx</td>
</tr>
</tbody>
</table>

**Bupropion (Zyban®)**

Along with NRT, buproprion is considered to be a first-line, non-nicotine agent in smoking cessation. Its mechanism of action to increase the ability of people to quit smoking is not understood, but is thought to be mediated by noradrenergic or dopaminergic mechanisms. Studies evaluating the efficacy of bupropion specifically in patients with diabetes are lacking. A Cochrane review (which included two large published and two smaller unpublished trials) found that at 12 months, 21% of smokers allocated to bupropion 300 mg daily successfully quit compared with 8% in the control group. These trials recruited heavier smokers (≥ 15 cigarettes per day), and all patients received intensive behavioral support.

Bupropion is contraindicated in patients with a current seizure disorder or any history of seizures; in patients with a known central nervous system (CNS) tumor; in patients undergoing abrupt withdrawal from alcohol or benzodiazepines; in patients with a current or previous diagnosis of bulimia or anorexia nervosa; and in patients taking an irreversible monoamine oxidase inhibitor. Patients should be made aware that Zyban® contains the same active ingredient as Wellbutrin® and Wellbutrin SR® and should not be taken with these or any other form of buproprion. Bupropion is associated with a dose related risk of seizures; therefore, the recommended dose must not be exceeded.
There is an increased risk of seizures occurring with the use of bupropion in the presence of predisposing risk factors which lower the seizure threshold. Bupropion must not be used in patients with predisposing risk factors unless there is a compelling clinical justification for which the potential medical benefit of smoking cessation outweighs the potential increased risk of seizure. All patients should be assessed for predisposing risk factors which include: concomitant administration of other drugs known to lower the seizure threshold (e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones, sedating antihistamines); alcohol abuse; history of head trauma; diabetes treated with antihyperglycemics or insulin; and use of stimulant or anorectic products. Bupropion should be discontinued and not restarted in patients who experience a seizure while on treatment.\textsuperscript{78, 80}

The recommended bupropion dose is 150 mg daily for the first three days, increasing to 150 mg twice daily for 7–12 weeks. It is recommended that treatment be started while the patient is still smoking, and that a quit date be set within the first two weeks of treatment (preferably within the second week to allow steady state serum concentrations to be achieved). It is recommended that the dose not exceed 150 mg every other day in patients with severe hepatic impairment.\textsuperscript{78, 80}

Buproprion may be used in combination with nicotine transdermal systems. Monitoring for hypertension during combination treatment is recommended.\textsuperscript{80}

The most common adverse effects associated with the use of bupropion are insomnia and dry mouth. The incidence of seizures associated with the 300 mg daily dose of bupropion is reported to be approximately 0.1%. The more commonly reported problems leading to discontinuation during clinical trials involved nervous system disturbances (primarily tremors) and skin reactions.\textsuperscript{80} Bupropion (Zyban\textsuperscript{®}) is available as 150 mg sustained release tablets.

**Potential drug interactions when using bupropion in patients with type 2 diabetes**

Bupropion is associated with a number of potential drug interactions, which may have importance for patients with type 2 diabetes.

**Pharmacokinetic interactions**

Bupropion and one of its active metabolites are inhibitors of cytochrome P450 2D6 (CYP2D6); therefore, these could increase blood levels and
effects of drugs which are metabolized by this pathway. A number of drugs which may be used in patients with type 2 diabetes are metabolized by CYP2D6 including beta-blockers (e.g. metoprolol, propranolol), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), type 1C antiarrhythmics (e.g. mexiletine, propafenone) and antipsychotics (e.g. haloperidol, risperidone, thioridazine).

**Pharmacodynamic interactions**

The risk of seizures with bupropion may be increased if it is combined with other drugs that lower the seizure threshold, such as antidepressants, antipsychotics and tramadol. Other factors that may increase the risk of seizures include diabetes treated with sulfonylureas, meglitinides, or insulin (as hypoglycemia can result in seizures); alcohol abuse; and the use of stimulants or anorectic products. Care is recommended if using bupropion in these settings, and consideration should be given to using a lower dose (150 mg daily) throughout the treatment period.\(^78, 80\)

**Second-line pharmacotherapies**

Two second-line agents have been found to be efficacious in the treatment of tobacco dependence and are included in the US Public Health Service Clinical Practice Guideline, *Treating Tobacco Use and Dependence*. These drugs which may be considered in the event that first-line therapies fail or are contraindicated, are clonidine and nortriptyline.\(^76\) Clonidine has been used in oral doses of 0.15–0.4 mg/day or 0.2 mg/24-hr transdermal patch for smoking cessation.\(^78\) Several clinical studies have shown that clonidine doubles the abstinence rate compared to placebo.\(^68\) Nortriptyline has been initiated at 25 mg/day then gradually increased to 75–100 mg/day. Therapy should be initiated 10–28 days prior to smoking cessation and continued approximately 12 weeks. These agents are not currently approved for this indication by the US Food and Drug Administration.\(^68\)
ANTIHYPERGLYCEMICS IN THE MANAGEMENT OF TYPE 2 DIABETES

THE EVIDENCE

There are numerous clinical trials demonstrating the ability of currently available antihyperglycemics to lower blood glucose and A1C levels. The results of these trials are summarized in the individual drug group monographs, pages 44 to 92. However, importantly, these measures represent surrogate end points and do not give evidence about the efficacy of these agents in reducing diabetes related morbidity and mortality.

A few randomized clinical studies have assessed whether lowering blood glucose concentrations, with antihyperglycemic agents, is associated with improved outcomes (morbidity and mortality) in type 2 diabetes. The largest and longest such trial was the UKPDS. The UKPDS has been reported in numerous publications. Two important articles that address the effect of good glycemic control on long-term complications are UKPDS 33 & 34.

United Kingdom Prospective Diabetes Study (UKPDS 33 & 34)

UKPDS 33

The UKPDS, which recruited 5102 patients with newly diagnosed type 2 diabetes from 23 centers within the United Kingdom between 1977 and 1991, was conducted to determine whether intensive blood glucose control reduced the risk of macrovascular or microvascular complications, and whether any particular therapy was advantageous.

Non-overweight patients were randomized to intensive treatment with insulin, intensive treatment with a sulfonylurea (either chlorpropamide or glyburide) or conventional treatment with diet. Overweight patients were similarly randomized but with the addition of an intensive treatment with metformin group (see UKPDS 34, page 38). The aim in the intensive group was FPG less than 109 mg/dL. In the conventional group, the aim was the best achievable FPG with diet alone, with drugs added only if there were hyperglycemic symptoms or FPG greater than 273 mg/dL.
Over 10 years, median A1C values were significantly lower in the intensive versus the conventional group (7.0% vs 7.9%). Compared with the conventional group, there was a significant 12% reduction in the risk for any diabetes related end point in the intensive group. This was mainly due to a 25% risk reduction in microvascular end points, most of which was due to fewer cases of retinal photocoagulation.84

No significant differences were observed for any diabetes related deaths and for all-cause mortality, or for any of the other macrovascular end points assessed. There was a borderline significant 16% risk reduction for myocardial infarction (MI) in the intensive versus conventional group.84

No significant differences in efficacy were seen between the three intensive agents (chlorpropamide, glyburide or insulin).84 Patients in the intensive group had more hypoglycemic episodes and gained more weight than those in the conventional group.84

**UKPDS 34**

UKPDS 34 outlined results from two studies involving metformin. The first study was aimed at comparing conventional treatment with intensive treatment with metformin in overweight patients from the original protocol of the UKPDS. This involved comparing 411 overweight patients assigned conventional treatment with 342 overweight patients assigned treatment with metformin. A secondary aim of this study was to compare the group allocated metformin with overweight patients allocated sulfonylureas or insulin (951 patients).85 The target FPG levels and methodology were the same as in UKPDS 33.84

The median A1C during 10 years of follow up was 7.4% in the metformin group versus 8.0% in the conventional group. Body weight change was similar in the metformin group and the conventional group. The risk of weight gain and hypoglycemia was less with metformin than with sulfonylureas or insulin. Compared to the conventional treatment group, patients assigned intensive treatment with metformin had a lower risk of any diabetes related end point (32% risk reduction), diabetes related deaths (42%) and all-cause mortality (36%). Metformin showed a significantly greater effect than sulfonylureas or insulin for any diabetes related end point, all-cause mortality and stroke. There was a non-significant trend for reduced microvascular events with metformin.85

The second study began in 1990 when it was observed that, in UKPDS 33, glycemia was increasing despite maximal sulfonylurea therapy. Following a
protocol amendment, 537 patients, both non-overweight and obese who were treated with maximum dose of sulfonylureas and had a FPG of 111–273 mg/dL, were randomized to either early addition of metformin or continued sulfonylurea alone. The median A1C over four years in the cohort with metformin added was 7.7% compared with 8.2% in the sulfonylurea group alone. Addition of metformin to sulfonylurea was associated with a 96% increased risk of diabetes-related deaths and 60% increased risk of death from any cause.85 This study has been criticized. Most authors agree that further study is needed before changes to the common practice of combining metformin and sulfonylureas are made.86 One author points out that the combined rate of fatal stroke and MI was disproportionately low (0.68%) in the subset of patients receiving sulfonylurea compared with the rate (1%) in those receiving sulfonylurea in the main body of the trial, which may alone invalidate the comparison.87

Conclusions from current evidence

The following conclusions could be made from the UKPDS 33 & 34 results.

- Intensive blood glucose control with insulin or sulfonylureas reduces the risk of microvascular complications compared with conventional treatment (8.6 vs 11.4 events/1000 patient years). This is predominantly due to a reduction in the need for retinal photocoagulation.84
- Intensive blood glucose control with insulin or sulfonylureas does not appear to reduce nor increase the risk of macrovascular complications, diabetes related deaths or all-cause mortality.84
- Intensive treatment with insulin or sulfonylureas is associated with an increased risk of hypoglycemia and weight gain.84
- Intensive treatment of overweight patients with metformin reduces the risk of any diabetes related end point compared with conventional treatment (29.8 vs 43.3 events/1000 patient years) and a number of individual macrovascular end points.85
- Intensive treatment with metformin therapy is not associated with an increased risk of hypoglycemia or weight gain.85
- Multiple agents are often needed to achieve optimal glycemic control.88
- Further study is needed to assess the impact of adding metformin to sulfonylurea therapy, in light of the questionable findings in UKPDS 34.
- Outcome studies involving other antihyperglycemic treatments such as meglitinides, thiazolidinediones and alpha-glucosidase inhibitors are needed.
• An outcome study assessing the benefit of metformin in non-obese patients would be of value.

PRACTICAL POINTS FOR TREATING HYPERGLYCEMIA

In many patients with type 2 diabetes, non-drug measures such as nutrition and exercise can assist in maintaining near normal blood glucose concentrations (at least initially). Therefore, attention to lifestyle modification is essential, even if drug treatment is deemed necessary. For further information see lifestyle interventions in the management of type 2 diabetes, page 17.

Treatment plans must be periodically adjusted to prevent the progressive deterioration of blood glucose control, and multiple agents are often required for achieving optimal blood glucose control.88

For current recommendations regarding target blood glucose levels, see goals for glycemic control in patients with type 2 diabetes, page 11.

It is essential that other cardiovascular risk factors, such as hypertension and dyslipidemia, be addressed along with glycemic control. See reducing cardiovascular risk in type 2 diabetes, page 94.

Patients with diabetes should be educated about sick day management. On sick days blood glucose monitoring should be more frequent and adjustments to antihyperglycemic therapy may be required.17

WHICH ANTIHYPERGLYCEMIC AGENT TO CHOOSE

Choice of drug therapy should be individualized.88 In general, metformin is the initial drug of choice in individuals who are overweight (except where it is contraindicated, see page 56). Sulfonylureas are often considered as the agents of first choice for non-overweight patients.

Factors to consider when choosing an antihyperglycemic agent include the following.

• Patient’s weight. For example, metformin is favored in overweight patients due to UKPDS results, and its neutral or beneficial effects on weight. Thin patients, who are perhaps more likely to be insulin deficient (rather than primarily having insulin resistance) may be more likely to benefit from a sulfonylurea or insulin initially. Many
antihyperglycemic drugs may lead to weight gain including insulin, sulfonylureas, meglitinides, and the thiazolidinediones.

- **Patient’s lipid profile.** The antihyperglycemic agents differ with regard to effects on lipid profile, with metformin and pioglitazone generally having the most favorable effects. See Table 24, page 83.

- **Blood glucose picture.** For example, patients with significant postprandial glucose elevations may benefit from agents which specifically address this issue, such as alpha-glucosidase inhibitors or meglitinides. See Table 24, page 83.

- **Outcome evidence.** For further information see page 37. Favorable outcome data have been demonstrated for glyburide, metformin and insulin. Outcome studies for other agents are currently lacking.

- **Cost.** Many of these medications are quite expensive and may not be covered by third-party payers.

- **Patient characteristics and adverse effect profile of drug.** For example, use of alpha-glucosidase inhibitors may be inappropriate in patients with pre-existing gastrointestinal disorders; patients with renal impairment are at risk of lactic acidosis if given metformin; the risk of hypoglycemia may be a particular concern in the very elderly with sulfonylureas, meglitinides or insulin; and the risk of fluid retention with the thiazolidinediones may rule out their use in someone with severe heart failure. For further information see individual drug group monographs, pages 44 to 92.

- **Drug interaction potential.** See the drug interaction tables in the drug group monographs, pages 44 to 92.

- **Compliance factors.** For example, choice of agent may depend in part on the number of tablets to be taken; frequency of administration; the need for additional monitoring (e.g. regular liver function tests (LFTs) needed for thiazolidinediones); and the ability of the patient to inject insulin.

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**COMBINATION ANTIHYPERGLYCEMIC THERAPY**

Diabetes is a progressive disease, and hence secondary failure of monotherapy should be eventually expected. It is apparent that when glycemic control becomes inadequate with monotherapy, use of a combination of drugs is usually more effective than stopping one agent and substituting another. 41, 89, 90
Most of the currently available classes of oral antihyperglycemic drugs have different modes and sites of action, and hence may be used in combinations to provide more ideal glycemic control for most patients.

The choice of a second agent should be based on individual patient characteristics. For example, obese patients may derive more benefit from the addition of metformin to pre-existing sulfonylurea therapy than from the addition of a thiazolidinedione which is more likely to facilitate weight gain.91 On the other hand, an obese insulin-resistant patient may benefit from the combination of metformin and a thiazolidinedione. A patient currently taking metformin may benefit more from the addition of an alpha-glucosidase inhibitor or meglitinide if the primary defect is postprandial glycemia than by the addition of a long-acting sulfonylurea. The points listed under which antihyperglycemic agent to choose, page 40, are relevant to consider when deciding on the most appropriate second agent.

Historically, the most common combination of oral agents has been with sulfonylureas and metformin. Clinical trials have demonstrated additive antihyperglycemic effects with this combination.92, 93 However, uncertainty about benefit in terms of diabetic related morbidity and mortality with this combination was raised in UKPDS 3485 and awaits further studies for clarification. See UKPDS 34, page 38.

Secondary failure of two drug combinations should also be expected eventually. In some patients three drug combinations may be useful. Alternatively, patients may need the introduction of insulin, alone or in addition to oral antihyperglycemic agents.41, 90

There has also been interest in combining oral antihyperglycemic agents with insulin, with many studies showing that this approach can lead to improved glycemic control and reduced insulin requirements. Insulin has been used successfully in combination with all currently available classes of oral antihyperglycemic drugs in clinical trials.

The rationale for a combination of insulin and an insulin secretagogue (e.g. a sulfonylurea or meglitinide) or insulin sensitizer (e.g. metformin or a thiazolidinedione) assumes that if an evening dose of insulin lowers the fasting glucose to normal by suppressing hepatic glucose output, then the daytime use of the oral antihyperglycemic agent will be more effective in maintaining euglycemia throughout the day.90

Recently, particular interest has been expressed in combining metformin with insulin. For example, one study found bedtime insulin plus metformin to be superior to bedtime insulin plus glyburide or twice daily insulin.94 The
A combination of metformin and insulin appeared to counteract the body weight gain associated with insulin, and was associated with less risk of hypoglycemia than glyburide plus insulin or twice daily insulin.\textsuperscript{94}

Thiazolidinediones have also been used successfully in combination with insulin.\textsuperscript{95-99} However, the risk of edema appears to be increased with such combinations.\textsuperscript{100}

Outcome studies assessing efficacy of various combination regimens on diabetic related morbidity and mortality are generally lacking at present. For further information outlining the combinations which have been subject to clinical trials, see efficacy/role in diabetes in individual drug monographs, pages 44 to 92.

Table 7. Combination antihyperglycemic preparations.

<table>
<thead>
<tr>
<th>Metformin plus sulfonylureas</th>
<th>Metformin plus glitazones</th>
</tr>
</thead>
<tbody>
<tr>
<td>glyburide with metformin 1.25/250, 2.5/500, 5/500 mg Glucovance\textsuperscript{®}</td>
<td>rosiglitazone with metformin 1/500, 2/500, 2/1000, 4/500, 4/1000 mg Avandamet\textsuperscript{®}</td>
</tr>
<tr>
<td>glipizide with metformin 2.5/250, 2.5/500, 5/500 mg Metaglip\textsuperscript{®}</td>
<td></td>
</tr>
</tbody>
</table>

Note: This table outlines more commonly used preparations available as of 05 November 2004.
SULFONYLUREAS

glipizide (Glucotrol®, Glucotrol-XL®), glyburide (Micronase®, Diabeta®, micronized-Glynase®), glimepiride (Amaryl®), acetohexamide (Dymelor®), chlorpropamide (Diabenese®), tolazamide (Tolinase®), tolbutamide (Orinase®)

Mechanism of action

Antihyperglycemic effects

Sulfonylureas are insulin secretagogues. They increase insulin secretion and reduce glycemia over the whole 24-hour period. They act by binding to receptors on the β cells in the pancreas. This results in closure of adenosine triphosphate (ATP) dependent potassium channels (K\textsubscript{ATP}), which in turn gives rise to voltage changes, the influx of calcium ions and, subsequently, the release of insulin. This action does not require the presence of glucose.

Some researchers have suggested that sulfonylureas also act outside of the pancreas to improve insulin sensitivity in peripheral tissues and to decrease hepatic glucose output. However, this remains to be established.

Sulfonylureas generally lower plasma glucose by about 60–71 mg/dL and A1C by 1.5–2.0% in patients with an initial mean A1C of about 10%.

Effects on body weight

Weight gain is common with sulfonylureas. In UKPDS 33, at 10 years, patients assigned sulfonylureas gained approximately 2–3 kg more than patients assigned to conventional therapy.

Effects on lipid profile

In most studies, sulfonylureas have been reported to have neutral or slightly beneficial effects on plasma lipid levels. Changes in lipids observed are most likely secondary to improved glucose control and to changes in insulin levels.
**Pharmacokinetics**

Table 8, below compares the pharmacokinetic characteristics of currently available sulfonylureas.

**Table 8. Pharmacokinetics of the sulfonylureas.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Excretion</th>
<th>Serum $t_{1/2}$ (hours)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glipizide</td>
<td>Extensively metabolized in the liver (in part by CYP2C9). Inactive metabolites.</td>
<td>2–4</td>
<td>10–24</td>
</tr>
<tr>
<td>glyburide</td>
<td>Completely metabolized in the liver (in part by CYP2C9). Two main active metabolites are, in part, renally cleared.</td>
<td>nonmicronized 10 micronized $\approx 4$</td>
<td>nonmicronized 16–24 micronized 12–24</td>
</tr>
<tr>
<td>glimepiride</td>
<td>Completely metabolized in the liver (in part by CYP2C9). One metabolite has 40% activity of parent drug, and is renally cleared.</td>
<td>$\approx 9$</td>
<td>24</td>
</tr>
<tr>
<td><strong>First generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acetohexamide</td>
<td>Metabolized primarily in the liver to hydroxyhexamide, an active metabolite with $t_{1/2}$ of $\approx 6$ hours.</td>
<td>$\approx 6–8$</td>
<td>12–24 hours</td>
</tr>
<tr>
<td>chlorpropamide</td>
<td>Metabolized in the liver to several metabolites whose hypoglycemic activity is unknown.</td>
<td>36</td>
<td>24–60</td>
</tr>
<tr>
<td>tolazamide</td>
<td>Metabolized most probably in the liver to active metabolites.</td>
<td>7</td>
<td>12–24</td>
</tr>
<tr>
<td>tolbutamide</td>
<td>Extensively metabolized by CYP2C9 in the liver. Inactive metabolites.</td>
<td>4.5–6.5</td>
<td>6–12</td>
</tr>
</tbody>
</table>

CYP2C9 = cytochrome P450 2C9
Adapted from Drug Facts and Comparisons & AHFS.68, 78
Efficacy/role in diabetes

Sulfonylureas have been used since the 1950’s. First generation agents fell out of favor after results of the University Group Diabetes Program (UGDP) study reported that tolbutamide was associated with increased risk of cardiovascular mortality. Recently, second-generation sulfonylureas have become popular due to studies demonstrating their benefit.

Sulfonylureas appear to be the most appropriate first choice for patients with type 2 diabetes in whom the predominant cause of hyperglycemia is a defect in insulin secretion rather than insulin resistance. These patients would typically be lean, with lower basal and postprandial insulin levels. In addition, these patients tend to be younger (< 46 years) and are more likely to require insulin therapy eventually. Sulfonylureas have the disadvantage of the potential for causing hypoglycemia and weight gain (making them a less than ideal first choice for obese patients).

Sulfonylureas were found to have favorable effects on microvascular end points in patients with type 2 diabetes in UKPDS 33. For further information see UKPDS 33, page 37.

Clinical trials have not demonstrated superiority of one sulfonylurea over another, in terms of glucose lowering effects, when given in maximally effective doses. The first generation sulfonylureas tend to have longer half-lives and a greater potential for accumulation and side effects. Differences in frequency of administration and risk of hypoglycemia are apparent between the first and second generation agents as well as agents within each class (see Table 9, page 46 and Table 10, page 49).

Sulfonylureas have been useful in combination with metformin, alpha-glucosidase inhibitors, and the thiazolidinediones. While intuitively there would seem little benefit from combining insulin with sulfonylureas, studies have demonstrated that this combination can result in a smaller daily insulin dose and modestly improve glycemic control. The most widely used approach in combining insulin and sulfonylureas is termed BIDS therapy (bedtime insulin daytime sulfonylurea). For further information on combination therapy, see page 41; and for management of type 2 diabetes with antihyperglycemics, see page 37.

Role in other disorders

The sulfonylureas are currently only approved for the treatment of type 2 diabetes.
## Doses and administration

Table 9. Dosing schedules for the sulfonylureas in type 2 diabetes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Dosage forms</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second Generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>glipizide</em></td>
<td>Glucotrol®</td>
<td>Tablet 5 mg, 10 mg</td>
<td>Immediate release: Initially 5 mg once daily (2.5 mg in elderly or liver disease). Increase up to a maximum of 40 mg/day according to response. Divide doses &gt; 15 mg/day. Extended-release: Initially 5 mg/day. Maximum dose 20 mg/day.</td>
</tr>
<tr>
<td></td>
<td>Glucotrol XL®</td>
<td>Tablet (extended-release) 2.5 mg, 5 mg, 10 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablet 2.5 mg, 5 mg, 10 mg</td>
<td></td>
</tr>
<tr>
<td><em>glyburide</em></td>
<td>Diabeta®</td>
<td>Tablet 1.25 mg, 2.5 mg, 5 mg</td>
<td>Initially 2.5–5 mg once daily. Increase up to a maximum of 20 mg/day. Divide doses &gt; 10 mg. Micronized: initially 1.5–3 mg/day. Maximum dose: 12 mg/day.</td>
</tr>
<tr>
<td></td>
<td>Micronase®</td>
<td>Tablet (micronized) 1.5 mg, 3 mg, 4.5 mg, 6 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glynase® micronized</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>glimepiride</em></td>
<td>Amaryl®</td>
<td>Tablet 1 mg, 2 mg, 4 mg</td>
<td>Initially 1–2 mg once daily. Maximum dose: 8 mg daily.</td>
</tr>
<tr>
<td><strong>First Generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>acetohexamide</em></td>
<td>Dymelor®</td>
<td>Tablet 250 mg, 500 mg</td>
<td>Initially 250 mg to 1.5 g/day. BID dosing recommended for doses greater than 1 g/day. Use 100–125 mg/day in hepatic/renal impairment, older, malnourished, debilitated patients.</td>
</tr>
<tr>
<td><em>chlorpropamide</em></td>
<td>Diabinese®</td>
<td>Tablet 100 mg, 250 mg</td>
<td>Initially 250 mg/day. May divide dose if GI intolerance.</td>
</tr>
<tr>
<td><em>tolazamide</em></td>
<td>Tolinase®</td>
<td>Tablet 100 mg, 250 mg, 500 mg</td>
<td>100–250 mg/day initially. If &gt; 500 mg/day required, divide doses twice daily.</td>
</tr>
<tr>
<td><em>tolbutamide</em></td>
<td>Orinase®</td>
<td>Tablet 500 mg</td>
<td>Initially 1–2 g/day. Maximum dose: 3 g/day.</td>
</tr>
</tbody>
</table>

Adapted from Drug Facts and Comparisons®
Important considerations

- Sulfonylureas should be taken with meals to minimize the risk of hypoglycemia (absorption of glipizide is delayed by food).78
- The risk of hypoglycemia appears greatest with long-acting first generation sulfonylureas and glyburide; hence, these should be avoided in high risk patients, such as the elderly and those with renal or hepatic impairment.128
- The long duration of action of glimepiride means that it can be given once daily, which may aid in compliance. However, as a result of its long duration of action, care is warranted in the elderly and those with renal or hepatic impairment due to the risk of hypoglycemia.
- Patients commencing on sulfonylureas need to be educated about the identification, treatment and prevention of hypoglycemic episodes. For further information see hypoglycemia, page 185.
- Start with low doses and increase at weekly intervals until control has been achieved. Increasing the dosage at or above the upper limit of the dose range may achieve little additional hypoglycemic effect.78

Contraindications and precautions

Sulfonylureas are contraindicated in patients with:68, 78
- hypersensitivity to sulfonylureas;
- diabetes complicated by ketoacidosis, with or without coma;
- sole therapy of type 1 diabetes; or
- diabetes when complicated by pregnancy.

Although the reported risk is low, cross sensitivity may occur in individuals who display a type 1 hypersensitivity reaction to sulfonamide agents. Extreme caution is needed when using sulfonylureas in these patients.103

Glyburide should generally be avoided in the elderly, and in those with renal or hepatic impairment, due to its greater risk of hypoglycemia compared to other sulfonylureas.68

The sulfonylureas may be inappropriate in times of stress such as coma, ketoacidosis, severe infection, trauma or other conditions where they are unlikely to control the hyperglycemia; insulin should be administered in such situations.68

Monitoring recommendations

- For information about monitoring glycemic control, see goals for glycemic control in patients with type 2 diabetes, page 11.
## Adverse effects

Table 10. Adverse effects associated with sulfonylureas.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypoglycemia</td>
<td>Hypoglycemia is the most frequent and serious adverse effect of sulfonylureas. The mean proportion of patients per year with any hypoglycemic episode was 10%, 16%, 21% and 28% for patients assigned to conventional nutritional treatment, chlorpropamide, glyburide and insulin, respectively. For major hypoglycemic events, the corresponding figures were 0.7%, 1.0%, 1.4% and 1.8%, respectively. Hypoglycemia can occur in any person, but particularly in the elderly, in patients with renal or hepatic impairment, and in patients who are receiving interacting drugs. Other risk factors include calorie restriction, polypharmacy, alcohol abuse, or intense or prolonged exercise. The incidence of hypoglycemia differs between sulfonylureas mainly due to pharmacokinetic differences. The risk has been found to be highest with glyburide in a number of studies, possibly due to its long half-life and renally cleared active metabolites. As a result, it is recommended that glyburide be avoided in high risk patients, such as the elderly and those with renal or hepatic impairment. Long-acting first generation sulfonylureas are also associated with increased risk of hypoglycemia. Some evidence suggests that the incidence of hypoglycemia is lower with glimepiride compared to glyburide, but similar to other sulfonylureas; however, further studies are needed. The symptoms of hypoglycemia include tachycardia, sweating, palpitations, tremor, headache, confusion, visual disturbances, irritability, personality changes, seizures or coma. When severe, hypoglycemia can lead to permanent neurological deficit or death. In one study, 10% of patients with severe hypoglycemia died and 9% had permanent sequelae. See also hypoglycemia, page 185.</td>
</tr>
<tr>
<td>weight gain</td>
<td>Weight gain and increased appetite are common with sulfonylureas. For example, in UKPDS 33, at 10 years, patients assigned sulfonylureas gained approximately 2–3 kg more than patients assigned to conventional therapy.</td>
</tr>
</tbody>
</table>

Note: Table continued on next page
Table 10. Adverse effects associated with sulfonylureas (continued).

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI effects</strong></td>
<td>Gastrointestinal complaints (e.g. nausea, diarrhea, heartburn, anorexia and metallic taste) occur in 1–3% of patients receiving sulfonylureas. These effects are usually mild, dose-related, and less troublesome when these drugs are taken with meals.</td>
</tr>
<tr>
<td><strong>dermatologic reactions</strong></td>
<td>Rash is an infrequent adverse effect of sulfonylureas. Erythema multiforme, exfoliative dermatitis and photosensitivity have been rarely reported. Allergic reactions may occur, particularly in patients with a history of allergy to sulfonamides. See contraindications and precautions, page 48.</td>
</tr>
<tr>
<td><strong>hepatic effects</strong></td>
<td>Hepatotoxicity has been rarely reported with sulfonylureas. Liver enzyme alterations can affect 0.5% of patients.</td>
</tr>
<tr>
<td><strong>hematologic changes</strong></td>
<td>Hematological adverse effects have been rarely reported and include thrombocytopenia, agranulocytosis, aplastic anemia and hemolytic anemia.</td>
</tr>
<tr>
<td><strong>visual disturbances</strong></td>
<td>Transient visual disturbances may occur at the start of therapy. This is thought to result from the change in blood glucose levels.</td>
</tr>
<tr>
<td><strong>hyponatremia</strong></td>
<td>The occurrence of hyponatremia in sulfonylurea treated patients has been almost entirely associated with chlorpropamide, although there have been a few reports implicating tolbutamide. Elderly patients and those treated with diuretics appear to be most at risk.</td>
</tr>
</tbody>
</table>

GI = gastrointestinal
### Drug interactions

**Table 11. Potential drug interactions associated with sulfonylureas.**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>other antihyperglycemic agents</strong></td>
<td>The hypoglycemic risk may be increased when sulfonylureas are combined with other antihyperglycemic agents.</td>
</tr>
<tr>
<td><strong>other drugs with risk of hypoglycemia</strong></td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hypoglycemia when used in combination with antihyperglycemic agents (see Appendix 1, page 195).</td>
</tr>
<tr>
<td><strong>drugs with risk of hyperglycemia</strong></td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hyperglycemia. When used in combination with antihyperglycemic agents vigilant monitoring of blood glucose concentrations may be needed (see Appendix 2, page 197).</td>
</tr>
<tr>
<td><strong>inhibitors of CYP2C9 (e.g. cimetidine, sulfonamide antibiotics, NSAIDs, fluoxetine, fluvoxamine, amiodarone, fluconazole, miconazole)</strong></td>
<td>These drugs may theoretically increase hypoglycemic effects of sulfonylureas, all of which appear to be metabolized, at least in part, by CYP2C9. Monitor effects on blood glucose concentrations.</td>
</tr>
<tr>
<td><strong>drugs which are highly protein bound (e.g. salicylates, NSAIDs, sulfonamides)</strong></td>
<td>Sulfonylureas may compete for protein binding sites with other highly protein bound drugs resulting in higher concentrations of unbound drug in the plasma. Monitor for increased effects of either drug. An interaction is not expected with low dose aspirin therapy (i.e. antiplatelet doses).</td>
</tr>
<tr>
<td><strong>alcohol</strong></td>
<td>Alcohol increases hypoglycemic effects and masks hypoglycemic warning symptoms. It may also cause a disulfiram-like reaction — this has been seen particularly with chlorpropamide, but can occur in about 5% of patients receiving tolbutamide. It is rare with other sulfonylureas. Patients should be advised to only drink alcohol in moderation and accompanied by food. One small study in elderly patients with diabetes suggested that even low dose alcohol (approximately one to two standard drinks) could predispose to sulfonylurea induced hypoglycemia.</td>
</tr>
</tbody>
</table>

CYP2C9 = cytochrome P450 2C9; NSAIDs = non-steroidal anti-inflammatory drugs

Note: Table continued on next page
Table 11. Potential drug interactions associated with sulfonylureas (continued)

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
</table>
| charcoal         | Activated charcoal can reduce bioavailability of sulfonylureas. Avoid concurrent use or separate doses as much as possible.  
78                |
| cholestyramine   | Cholestyramine may impair intestinal absorption of sulfonylureas resulting in reduced hypoglycemic effects. Give the sulfonylurea at least one hour before cholestyramine.  
78                |
| ciprofloxacin    | Isolated reports have described hypoglycemia when glyburide has been combined with ciprofloxacin. Monitor blood glucose levels and adjust dose as needed if combination is necessary.  
129, 142          |
| cyclosporine     | Cyclosporine concentrations (and hence toxicity) may be increased by sulfonylureas. Monitor cyclosporine concentrations and adjust dose as necessary.  
129, 143          
Cyclosporine may increase the hypoglycemic effect of sulfonylureas. Monitor blood glucose levels and adjust dose as necessary. |
| ketoconazole     | Ketoconazole has been shown to increase the hypoglycemic effects of tolbutamide.  
140                |
| rifampin         | Rifampin may induce the metabolism of sulfonylureas, resulting in reduced hypoglycemic effects. Monitor blood glucose levels and adjust dose as necessary.  
78                |
METFORMIN

Glucophage®, Glucophage XR®

Mechanism of action

Antihyperglycemic effects

Metformin has no effect on pancreatic insulin secretion and is not effective in the absence of insulin.\[^{144-146}\] It enhances the sensitivity of both hepatic and, to a lesser degree, peripheral tissues to insulin.\[^{109}\] Proposed mechanisms for these effects include decreased intestinal absorption of glucose, increased uptake of glucose from the blood into the tissues (i.e. skeletal muscle and fat), decreased glucose production in the liver (i.e. gluconeogenesis), and decreased insulin requirements for glucose disposal.\[^{144-146}\] The reduction in hepatic gluconeogenesis is thought to be the primary mechanism.\[^{108, 114}\]

Metformin therapy generally decreases the FPG level by 60–70 mg/dL and A1C by 1.5–2% in patients with poorly controlled type 2 diabetes.\[^{109}\]

Effects on body weight

Weight gain does not generally occur in patients who receive metformin alone or in combination with other oral antihyperglycemics or insulin. Most studies show modest weight loss of 2–3 kg during the first six months of treatment with metformin as monotherapy.\[^{109}\]

Effects on lipid profile

Metformin has favorable effects on lipid profile. Serum triglycerides have decreased by 50% or more in patients with hypertriglyceridemia, and 10–20% where hypertriglyceridemia is not present.\[^{144}\] Decreases in LDL cholesterol and total cholesterol, and slight elevations in HDL cholesterol have also been observed.\[^{108, 144}\]

Vascular effects

Decreased platelet density and aggregability and increased fibrinolytic activity have been reported with metformin in some studies.\[^{147}\]
**Pharmacokinetics**

Metformin is extensively eliminated by the kidneys through active tubular secretion.\(^{144}\) The plasma elimination half-life ranges from 2–6 hours after oral administration in healthy volunteers.\(^{148}\) Clearance is decreased in patients with renal dysfunction, and renal insufficiency is a significant risk factor for lactic acidosis with metformin.\(^{144, 148, 149}\) See Table 13, page 58. Clearance is also reduced in the elderly.\(^{149}\)

**Efficacy/role in diabetes**

Metformin is generally considered the drug of first choice in overweight patients with type 2 diabetes, (except where it is contraindicated, see page 56) who are unresponsive to lifestyle modification alone. Advantages of metformin include favorable effects on lipid profile and body weight, and a low risk of hypoglycemia.\(^{108}\) The main disadvantage of metformin is the risk of lactic acidosis which precludes its use in at risk patients.

In UKPDS 34, metformin was found to have favorable effects on macrovascular end points in overweight patients with type 2 diabetes.\(^{85}\) For further information see UKPDS 34, page 38.

The benefit of metformin in patients with type 2 diabetes using surrogate end points has been assessed in many trials. A 1999 meta-analysis\(^{150}\) included nine trials which compared metformin with placebo and ten which compared metformin with sulfonylureas. Metformin decreased fasting blood glucose levels and A1C significantly more than placebo and to a similar degree to sulfonylureas. Body weight was significantly lowered with metformin compared to sulfonylureas.\(^{150}\) Clinical trials have also found comparable effects on glycemic control between metformin and acarbose,\(^{93, 151}\) insulin,\(^{152}\) and repaglinide.\(^{153}\)

Most metformin studies have involved overweight patients with type 2 diabetes. However, short-term studies have found that metformin also improves glycemic control in non-overweight patients with type 2 diabetes. Hence, its use need not be restricted to obese patients.\(^{154}\)

Metformin has been useful in combination with sulfonylureas,\(^{92, 93, 155, 156}\) alpha-glucosidase inhibitors,\(^{157-159}\) meglitinides,\(^{153, 160}\) thiazolidinediones,\(^{126, 161, 162}\) and insulin.\(^{94, 163-167}\) For further information on combination therapy, see combination antihyperglycemic therapy, page 41.

For further information concerning the treatment of hyperglycemia, see antihyperglycemics in the management of type 2 diabetes, page 37.
Role in other disorders

Metformin is currently only approved for the treatment of type 2 diabetes. However, it has been suggested to have a potential role in the following indications.

- **Polycystic ovary syndrome (PCOS):** PCOS is a diagnosis made in 5–10% of women between late adolescence and menopause. Patients may present with oligomenorrhoea or amenorrhoea, anovulation or infertility, hirsutism or acne. Women with PCOS have an increased risk of CVD, and by the age of 40 years up to 40% will have type 2 diabetes or IGT. PCOS is associated with insulin resistance, with consequent hyperinsulinemia and (frequently) dyslipidemia and obesity. A number of small clinical trials have found that metformin can reduce parameters such as insulin resistance, serum androgens, luteinizing hormone and weight, and improve fertility and fibrinolysis in both obese and lean women with PCOS. However, not all studies have demonstrated beneficial effects. Larger randomized controlled studies are needed.

- **The Metabolic Syndrome:** Metformin has been suggested as a potential treatment for the Metabolic Syndrome in order to prevent type 2 diabetes, and to reduce cardiovascular morbidity and mortality. The efficacy of metformin in the prevention of type 2 diabetes was investigated in the DPPRG study in patients with IGT. The DPPRG study concluded that both metformin and lifestyle modification are highly effective at preventing or delaying type 2 diabetes. Studies assessing cardiovascular outcomes with metformin in patients without type 2 diabetes are currently lacking. For further information about this disorder, see the Metabolic Syndrome, page 2.

Dose and administration

Table 12, page 56 outlines dosage recommendations for metformin in type 2 diabetes.
Table 12. Dosing schedule for metformin in type 2 diabetes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand names</th>
<th>Preparations</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin</td>
<td>Glucophage®, Glucophage XR®</td>
<td>Tablet 500 mg, 850 mg, 1000 mg XR 500 mg</td>
<td>Initially 500 mg twice daily or 850 mg once daily. Increase by 500 mg weekly or 850 mg every 2 weeks according to response. Maximum recommended daily dose is 2250 mg (XR is 2000 mg).</td>
</tr>
</tbody>
</table>

**Important considerations**

- Metformin should be taken with, or at the end of, a meal in order to minimize gastrointestinal adverse effects.\(^{183}\) Initiating therapy with a low dose and slowly titrating the dose can also improve tolerance.
- The full therapeutic effect of metformin may be delayed for up to two weeks.\(^{148}\)

**Contraindications and precautions**

Due to the risk of lactic acidosis, metformin is contraindicated in the following settings.\(^{183}\)

- impaired renal function;\(^*\)
- severe hepatic disease;\(^{184}\)
- acute congestive heart failure;\(^{184-186}\)
- acute MI;\(^{185}\)
- respiratory insufficiency, pulmonary embolism or other conditions associated with tissue hypoxia;\(^{184}\)
- pancreatitis;\(^{187}\)
- severe dehydration;\(^{188}\)
- acute or chronic alcoholism;\(^{183}\)
- septicemia,\(^{184, 185}\)
- patients undergoing surgery or receiving parenteral iodinated radiograph contrast media (see page 60);\(^{145}\)
- presence of acute or chronic metabolic acidosis;\(^{108}\) and
- patients with known hypersensitivity to metformin\(^{144}\) or a history of lactic acidosis,\(^{184, 189}\)

\(^*\) The degree of renal impairment at which metformin should no longer be used is SrCr > 1.5 mg/dL (males) and > 1.4mg/dL (females), or with a creatinine clearance < 60mL/min.\(^{183, 190}\)
Creatinine clearance can be estimated by using the Cockcroft-Gault equation, as follows.

\[
\text{Creatinine clearance (mL/min)} = \frac{\left[140 - \text{age (years)}\right] \times \text{weight (kg)}}{72 \times \text{Serum creatinine (mg/dL)}}
\]

** Ideal body weight should be used for overweight patients.

*Note:* Multiply result by 0.85 for females.

Metformin is inappropriate for patients with type 1 diabetes, diabetic coma, ketoacidosis, severe infection, trauma or other conditions where it is unlikely to control the hyperglycemia; insulin should be administered in such situations.

Caution is advisable when metformin is used in anovulatory premenopausal women with insulin resistance (e.g. patients with PCOS), as ovulation may resume, with subsequent risk of pregnancy unless contraceptive measures are initiated.

**Monitoring recommendations**

- Monitor renal function at baseline and at least annually.\(^{183}\)
- Monitor hematologic parameters (e.g. hemoglobin) at baseline and at least annually.\(^{68}\) Monitor vitamin B\(_{12}\) levels every 2–3 years in patients predisposed to vitamin B\(_{12}\) deficiency\(^{68}\) (see Table 13, page 58).
- For information about monitoring glycemic control, see monitoring and goals in type 2 diabetes, page 8.
### Adverse effects

Table 13. Adverse effects associated with metformin.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>gastrointestinal effects</td>
<td>Gastrointestinal adverse effects (including diarrhea, nausea, abdominal pain, anorexia and metallic taste) are common, occurring in up to 30% of patients. Most of these effects are dose related and transient, and can be minimized by administration with meals and gradual dose escalation. These adverse effects are most often noted during initiation of therapy but case reports describe gastrointestinal disturbances 1.5–2 years after therapy was begun. However, it should be noted that late onset gastrointestinal symptoms may signal the onset of lactic acidosis.</td>
</tr>
<tr>
<td>decreased vitamin B₁₂ absorption</td>
<td>Impaired gastrointestinal absorption of vitamin B₁₂ has been noted in 10–30% of patients prescribed long-term metformin therapy. It is usually not clinically significant, and can be reversed by calcium supplementation as shown in one study. Only rare reports describe megaloblastic anemia. Hematologic parameters should be evaluated at baseline and at least annually during metformin therapy. Monitor vitamin B₁₂ levels every 2–3 years in patients predisposed to vitamin B₁₂ deficiency (e.g. those with an inadequate absorption or intake of vitamin B₁₂ or calcium) and consider periodic parenteral vitamin B₁₂ supplementation in this group.</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>Hypoglycemia is uncommon in patients receiving metformin as monotherapy; however, it may occur when metformin is used concomitantly with an oral sulfonylurea, meglitinides or insulin; when caloric intake is deficient; or when strenuous exercise is not accompanied by food intake.</td>
</tr>
<tr>
<td>Rash</td>
<td>Dermatological reactions reported include erythema, photosensitivity and hypersensitivity. Rare isolated case reports have described hepatic adverse events possibly associated with metformin including hepatitis and jaundice.</td>
</tr>
</tbody>
</table>

Note: Table continued on next page
Table 13. Adverse effects associated with metformin (continued).

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactic acidosis</td>
<td>Lactic acidosis is the most serious adverse effect of metformin, but is rare (incidence 0.03 cases per 1000 patient years). It is fatal in about 50% of cases when it does occur. (Note: This is a similar fatality rate to sulfonylurea induced hypoglycemia.) Metformin may cause lactic acidosis by altering the normal production and clearance of lactate. Lactic acidosis is characterized by elevated blood lactate concentration, decreased blood pH (&lt; 7.35), electrolyte disturbances with an increased anion gap and an increased lactate/pyruvate ratio. Most reported cases of lactic acidosis have occurred in patients with contraindications to the drug (see contraindications, page 56). The most commonly overlooked contraindication has been renal insufficiency. In addition, a number of cases of metformin induced lactic acidosis occurred when metformin was initiated in a patient with normal renal function, but was not discontinued when renal impairment developed. Abnormal renal or hepatic function, cardiac insufficiency, and elderly age are risk factors for the development of lactic acidosis. Impaired renal function reduces metformin clearance, impaired liver function reduces lactate clearance, and impaired cardiac function increases lactate production. When lactic acidosis occurs, it is difficult to discern whether it is due to the severe underlying medical disorder or to metformin therapy. Lactic acidosis often has a subtle onset and early symptoms include anorexia, nausea, vomiting, abdominal pain, cramps, malaise, weight loss, respiratory distress and increased somnolence. Patients should be instructed to notify their clinician immediately if these symptoms occur. Associated hypothermia, hypotension and bradycardias, with more marked acidosis, may also occur. If lactic acidosis is suspected, metformin should be stopped immediately and the patient hospitalized. Dialysis is an option for the treatment of metformin induced lactic acidosis and correlates to a 64% survival rate in cases currently reported in the literature.</td>
</tr>
</tbody>
</table>
**Drug interactions**

The risk for drug interactions is low with metformin due to the lack of hepatic metabolism and the low or absent protein binding.\(^{148}\) Table 14 below outlines selected drug interactions associated with metformin.

**Table 14. Selected drug interactions associated with metformin.**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol</td>
<td>The combination of metformin and alcohol can increase blood lactate levels. Acute alcohol intoxication can directly lead to lactic acidosis, and chronic alcohol abuse, with resultant liver damage and vitamin B1 deficiency, may predispose to development of lactic acidosis in metformin treated individuals.(^{185}) Patients should be advised not to consume excessive amounts of alcohol, either acutely or chronically,(^{68}) and to limit consumption to 1–2 standard drinks per day.(^{140})</td>
</tr>
<tr>
<td>sulfonylureas, insulin or meglitinides</td>
<td>Hypoglycemic risk may be increased if metformin is combined with sulfonylureas, insulin(^{148}) or meglitinides.(^{140, 153})</td>
</tr>
<tr>
<td>alpha-glucosidase inhibitors</td>
<td>Metformin absorption may be delayed — clinical significance unclear.(^{203}) Gastrointestinal adverse effects may be additive when combining alpha-glucosidase inhibitors and metformin.(^{159, 204})</td>
</tr>
<tr>
<td>cimetidine</td>
<td>Cimetidine competitively inhibits renal tubular secretion of metformin.(^{145, 148}) This theoretically may increase the risk of lactic acidosis.(^{140}) Monitor the patient and adjust dose as necessary.(^{148}) Consider use of an alternative H(_2)-antagonist.</td>
</tr>
<tr>
<td>iodinated radiograph contrast media</td>
<td>Radiographic iodinated contrast media can temporarily impair renal function,(^{148}) increasing the risk of lactic acidosis with metformin. The manufacturer suggests that in patients in whom radiological studies involving use of iodinated contrast materials are planned, metformin should be discontinued at the time of, or prior to, the procedure, held for 48 hours after the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.(^{183})</td>
</tr>
</tbody>
</table>

Note: Table continued on next page
Table 14. Selected drug interactions associated with metformin (continued).

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>other drugs which may cause renal impairment</td>
<td>Drugs which can impair renal function may increase the risk of lactic acidosis with metformin. For example, a number of case reports have described metformin associated lactic acidosis with concurrent NSAID therapy, which is expected to be due to NSAID induced renal dysfunction. Caution is advised in patients at risk of NSAID induced renal impairment, such as the elderly. Such caution should also be extended to the COX-2 inhibitors. Caution is also advised with ACE inhibitors and ARBs, as they have a potential risk of precipitating renal failure in high risk groups (e.g. elderly age, renally impaired, bilateral renal artery stenosis, hypovolemia and concurrent NSAID or COX-2 inhibitor use). Close monitoring of renal function is warranted, particularly when ACE inhibitors or ARBs are being initiated.</td>
</tr>
<tr>
<td>drugs with a risk of hyperglycemia</td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hyperglycemia. When used in combination with antihyperglycemic agents vigilant monitoring of blood glucose concentrations may be needed. See Appendix 2, page 197.</td>
</tr>
</tbody>
</table>

NSAID = non-steroidal anti-inflammatory drug; COX-2 inhibitor= cyclo-oxygenase-2 inhibitor; ACE = angiotensin converting enzyme; ARBs = angiotensin II receptor antagonists
ALPHA-GLUCOSIDASE INHIBITORS

acarbose (Precose®), miglitol (Glyset®)

Mechanism of action

Antihyperglycemic effects

Acarbose and miglitol primarily target postprandial hyperglycemia.\textsuperscript{108, 206} They are reversible competitive inhibitors of alpha-glucosidase enzymes in the brush border of the small intestine.\textsuperscript{204, 206, 207} Alpha-glucosidase enzymes break down dietary carbohydrates, such as starch and sucrose, into the monosaccharide glucose.\textsuperscript{207} Alpha-glucosidase inhibitors reduce the rate of glucose production and absorption, which results in a more even distribution of glucose absorption throughout the small and large intestine. This results in a decrease in the sharp, postprandial blood glucose peak that normally occurs after meals.\textsuperscript{206-208} Acarbose does not affect the absorption of orally administered glucose, lactose or simple sugars, such as fructose.\textsuperscript{203, 204} Miglitol has minimal inhibitory activity against lactase, but at recommended doses this is considered insignificant.\textsuperscript{206}

Acarbose and miglitol decrease FPG concentrations to a small extent (10–20%),\textsuperscript{108, 208} but less than with other antihyperglycemic agents. A1C concentrations are generally decreased by approximately 0.5–1.0%.\textsuperscript{108, 203, 207-210} Postprandial plasma glucose levels are reduced by 20–50%.\textsuperscript{108, 208}

Effects on body weight

Body weight does not change significantly in patients taking alpha-glucosidase inhibitors.\textsuperscript{134, 204, 208, 210} Some studies have documented slight weight loss,\textsuperscript{134, 208} however, significant weight loss has not occurred, and is unlikely, because they are simply delaying (i.e. not blocking) absorption of carbohydrates.\textsuperscript{206-208}

Effects on lipid profile

Postprandial triglyceride levels are reduced by acarbose and miglitol.\textsuperscript{208, 211} Total cholesterol may be slightly reduced by acarbose.\textsuperscript{203}
Pharmacokinetics

Following oral administration of acarbose, only 1–2% of the unchanged drug is absorbed.\textsuperscript{207} About half of the drug is excreted unchanged in the feces.\textsuperscript{207} The remainder is degraded either by digestive enzymes in the gastrointestinal tract and/or by natural flora of the gut. Systemically absorbed acarbose is excreted renally.\textsuperscript{207}

Miglitol is completely absorbed at a dose of 25 mg, but with doses > 50 mg saturation of absorption is evident. Miglitol is excreted as unchanged drug in the urine (95%).\textsuperscript{206, 208}

Efficacy/role in diabetes

Acarbose may be used as monotherapy or in combination with sulfonylureas, metformin, and insulin. Miglitol is indicated as monotherapy and in combination with sulfonylurea.\textsuperscript{206} As monotherapy, these drugs reduce FPG concentrations and A1C to a lesser degree than sulfonylureas and metformin, so they may be less preferable in patients with marked fasting hyperglycemia. They are most suited as monotherapy in patients in whom the primary lack of glycemic control stems from high postprandial glucose peaks.\textsuperscript{203, 206} Alpha-glucosidase inhibitors have the benefit of a lack of weight gain and hypoglycemia, but the disadvantage of a high incidence of gastrointestinal adverse effects, and the need for frequent daily dosing.

To date there have been no large controlled studies assessing the effect of acarbose or miglitol on diabetic related morbidity and mortality.

Clinical trials have assessed the benefit of acarbose in type 2 diabetes using surrogate end points. Alpha-glucosidase inhibitors have been found to improve glycemic control, compared to placebo, in type 2 diabetes.\textsuperscript{118, 120, 208, 210, 212-215} Another trial found acarbose reduced the risk of progression to diabetes by 25% in patients with impaired glucose tolerance.\textsuperscript{216} Clinical trials have also found acarbose and metformin to be equally efficacious in patients already on sulfonylureas.\textsuperscript{93, 151} Acarbose was less effective at reducing A1C than tolbutamide in one comparison study,\textsuperscript{119} but equal in efficacy to glyburide in another.\textsuperscript{217} Acarbose and miglitol have been useful in combination with sulfonylureas,\textsuperscript{117-121, 208, 210} metformin\textsuperscript{118, 120, 157-159} and insulin.\textsuperscript{118, 120, 208, 210, 218, 219}

For further information on combination therapy, see combination antihyperglycemic therapy, page 41.
For further information concerning the treatment of hyperglycemia, see antihyperglycemics in the management of type 2 diabetes, page 37.

**Role in other disorders**

Alpha-glucosidase inhibitors are currently only approved for use in patients with type 2 diabetes. Other proposed (but not approved) indications for acarbose include IGT, reactive hypoglycemia, Dumping Syndrome and hypertriglyceridemia. Controlled studies are either limited or lacking for these indications; hence, further trials are needed before acarbose or miglitol can be routinely recommended for these indications.

**Dose and administration**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Preparations</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>acarbose</td>
<td>Precose®</td>
<td>Tablet 25 mg, 50 mg, 100 mg</td>
<td>Initially 25 mg 3 times daily (some may require 25 mg once daily). May be increased after 4–8 weeks according to response and tolerance to 50 mg 3 times daily. Maximum daily dose is &lt; 60 kg: 50 mg 3 times daily &gt; 60 kg: 100 mg 3 times daily.</td>
</tr>
<tr>
<td>miglitol</td>
<td>Glyset®</td>
<td>Tablet 25 mg, 50 mg, 100 mg</td>
<td>Initially 25 mg 3 times daily (some may require 25 mg once daily). May be increased after 4–8 weeks to maximum dose of 100 mg 3 times daily.</td>
</tr>
</tbody>
</table>

**Important considerations**

- Acarbose and miglitol MUST be taken immediately before meals or with the first few mouthfuls of food for proper action.
- It is important to start therapy at a low dose and increase it very gradually to minimize gastrointestinal adverse effects.
- Patients receiving acarbose or miglitol should maintain a diet high in complex carbohydrates and low in simple sugars to help achieve the most benefit and to minimize adverse effects. Alpha-glucosidase inhibitors will have no effect on meals which do not contain carbohydrate.
Contraindications and precautions

Alpha-glucosidase inhibitors are contraindicated in patients with the following conditions:

- inflammatory bowel disease;\(^{203, 204, 206, 224}\)
- partial intestinal obstruction (or predisposition);\(^{203, 204, 206, 224}\)
- gastrointestinal disorders associated with malabsorption;\(^{203, 204, 206, 224}\)
- conditions aggravated by formation of intestinal gas (e.g. hernias);\(^{203, 204, 206, 224}\)
- severe renal impairment;\(^{203, 204, 206, 224}\)
- lactation;\(^{203, 204, 206, 224}\)
- age < 18 years;\(^{203, 204, 206, 208, 224}\) or
- hypersensitivity to the drug.\(^{203, 204, 206, 224}\)

Alpha-glucosidase inhibitors are inappropriate for patients with type 1 diabetes, diabetic coma, ketoacidosis, severe infection, trauma or other conditions where it is unlikely to control the hyperglycemia; insulin should be administered in such situations.

Monitoring recommendations

- Monitor plasma transaminase concentrations with acarbose every 3 months for the first year of therapy, periodically thereafter;\(^{224}\) decrease dosage if transaminases are elevated; stop treatment if elevations persist.\(^{224}\)
- For information about monitoring glycemic control, see monitoring and goals in type 2 diabetes, page 8.
### Adverse effects

Table 16. Adverse effects associated with alpha-glucosidase inhibitors.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>gastrointestinal</td>
<td>Gastrointestinal effects including flatulence, diarrhea and abdominal pain are very common, occurring in approximately two thirds of patients. These effects relate to increased intestinal gas formation from fermentation of unabsorbed carbohydrates in the colon. Gastrointestinal tolerability usually improves after 4–8 weeks, probably due to redistribution of carbohydrate digesting enzymes in the small and large intestines. Gastrointestinal effects are reduced by initiation with low doses and gradual dose titration, and are increased by sucrose consumption. They are unlikely to be alleviated with antacids. In a large postmarketing trial, approximately 40% of patients discontinued acarbose, with the reason being adverse effects (mainly gastrointestinal) in over half of these cases. There have been isolated case reports of ileus in Japanese patients, possibly associated with acarbose treatment.</td>
</tr>
<tr>
<td>hepatic effects</td>
<td>Acarbose has been associated with elevated transaminase levels, particularly with doses above 100 mg three times a day. If increased transaminases are noted, a dose reduction or withdrawal of therapy may be indicated. In most cases, patients have been asymptomatic and the elevations in transaminases have been reversible upon acarbose discontinuation. A number of case reports have described acarbose associated hepatotoxicity, but this is considered a rare adverse event.</td>
</tr>
<tr>
<td>anemia</td>
<td>An increased incidence of anemia has been noted with acarbose and miglitol, but the incidence is less than 1% and not usually clinically significant. It may be due to decreased iron absorption from the gut.</td>
</tr>
<tr>
<td>dermatologic effects</td>
<td>Rash and erythema multiforme have been reported rarely.</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>Alpha-glucosidase inhibitors do not induce hypoglycemia as monotherapy, but if prescribed in combination with other antihyperglycemic drugs, the risk is increased.</td>
</tr>
</tbody>
</table>
### Drug interactions

**Table 17. Selected drug interactions associated with alpha-glucosidase inhibitors.**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sulfonylureas, meglitinides and insulin</strong></td>
<td>Hypoglycemic risk is increased.¹⁴⁰, ²⁰⁶, ²⁰⁷, ²²⁴, ²³⁴. Treat hypoglycemia with glucose and not sucrose as its absorption may be delayed by alpha-glucosidase inhibitors.¹⁴⁰, ²⁰⁶, ²³⁴</td>
</tr>
<tr>
<td><strong>metformin</strong></td>
<td>Metformin absorption may be delayed — clinical significance unclear.²⁰³, ²⁰⁶. Gastrointestinal adverse effects may be additive when combining acarbose or miglitol and metformin.¹⁵⁹, ²⁰⁴</td>
</tr>
<tr>
<td><strong>digoxin</strong></td>
<td>Digoxin levels may be reduced in some patients.²⁰⁶, ²³⁵, ²³⁶. This appears to result from decreased absorption of digoxin.²⁰⁶, ²³⁵, ²³⁷. Consider monitoring digoxin levels.¹⁴⁰</td>
</tr>
<tr>
<td><strong>charcoal, digestive enzymes</strong></td>
<td>Acarbose and miglitol effects may be decreased by charcoal and digestive enzymes. Avoid concurrent use.¹⁴⁰, ²⁰⁶, ²³⁴</td>
</tr>
<tr>
<td><strong>cholestyramine</strong></td>
<td>Acarbose effects may be enhanced by cholestyramine.¹⁴⁰. Acarbose dose may need to be reduced.</td>
</tr>
<tr>
<td><strong>drugs with a risk of hyperglycemia</strong></td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hyperglycemia. When used in combination with antihyperglycemic agents vigilant monitoring of blood glucose concentrations may be needed. See Appendix 2, page 197.</td>
</tr>
<tr>
<td><strong>warfarin</strong></td>
<td>Isolated case reports describe either increased or decreased INR when acarbose was used in patients stabilized on warfarin. One small study found no interaction.¹⁴⁰. Monitor INR following initiation or discontinuation of acarbose therapy.¹⁴⁰, ²³⁴</td>
</tr>
<tr>
<td><strong>sodium valproate</strong></td>
<td>An isolated case report found a fall in sodium valproate levels when acarbose was added. Be alert for any evidence of reduced anticonvulsant effects if using this combination.¹⁴⁰</td>
</tr>
<tr>
<td><strong>propranolol</strong></td>
<td>Propranolol bioavailability may be decreased with miglitol as much as 40%.²⁰⁶. May need to increase propranolol dose based on response.</td>
</tr>
</tbody>
</table>

INR = International normalized ratio
MEGLITINIDES

repaglinide (Prandin®), nateglinide (Starlix®)

Mechanism of action

Antihyperglycemic effects

Meglitinides are non-sulfonylurea insulin secretagogue agents. Like the sulfonylureas, meglitinides stimulate the release of insulin from pancreatic β cells by closing the adenosine triphosphate (ATP) dependent potassium channels. This is mediated through a different binding site to sulfonylureas on the β cell.

Meglitinides are taken with every meal and lead to a rapid but brief release of insulin to reduce postprandial plasma glucose levels. This is associated with concomitant decreases in A1C, which is less than that of sulfonylureas. FPG levels are also reduced.

Meglitinides have a more rapid onset of action and a shorter half-life than sulfonylureas. As a result, they may achieve a greater decrease in postprandial plasma glucose levels than sulfonylureas. Meglitinides also have the advantage of a decreased risk of hypoglycemia as a result of missed meals (providing the dose of the meglitinide is omitted if a meal is missed). Hence, they may be particularly valuable in patients with irregular meal patterns.

Effects on body weight

Meglitinides are associated with body weight gain; however, less than is seen with sulfonylureas. In drug-naïve patients treated with meglitinides, body weight has been increased by about 1–3%.

Effects on lipid profile

Meglitinides have no significant effect on plasma lipid levels.

Pharmacokinetics

Meglitinides are rapidly absorbed from the gastrointestinal tract. Plasma levels begin to rise within 15 minutes following oral administration, with peak plasma concentrations occurring within 30–40 minutes. The mean half-life is approximately one hour. Repaglinide is extensively metabolized in the liver, predominantly by cytochrome P450 3A4.
(CYP3A4) to three inactive metabolites. Excretion is principally by the biliary route with only 6% of the drug being renally cleared. Nateglinide is metabolized in the liver by CYP2C9 (70%) and CYP3A4 (30%). Excretion is primarily renal (83%).

**Efficacy/role in diabetes**

Meglitinides may be considered as monotherapy or in combination with other antihyperglycemic agents. They have an advantage over sulfonylureas in patients with irregular meal patterns. Disadvantages of meglitinides include the need for frequent daily dosing (dosed with each meal), and the risk of hypoglycemia and weight gain. Meglitinides particularly target postprandial glucose levels so they may be valuable in patients where this is the primary defect. As meglitinides are not sulfonamides, they may also be considered as an alternative to a sulfonylurea in patients with a history of sulfonamide hypersensitivity reactions.

Controlled studies assessing the effect of meglitinides on diabetic related morbidity and mortality are currently lacking.

Clinical trials have assessed the benefit of meglitinides in type 2 diabetes using surrogate end points. Placebo-controlled studies have demonstrated the ability of meglitinides to improve glycemic control. Comparison trials have found repaglinide to be equally effective as glyburide and metformin, and at least as effective as glipizide and troglitazone.

Trials have demonstrated efficacy of meglitinides in combination with metformin and the combination of meglitinides and troglitazone to be effective. Repaglinide has also successfully been combined with bedtime intermediate insulin. Studies in combination with sulfonylureas are lacking so it is not known whether it can enhance insulin secretion in sulfonylurea treated patients. One small study with nateglinide found the combination of no benefit.

For further information on combination therapy, see combination antihyperglycemic therapy, page 41.

For further information concerning the treatment of hyperglycemia, see antihyperglycemics in the management of type 2 diabetes, page 37.
Role in other disorders

Meglitinides are currently only approved for the treatment of type 2 diabetes.68, 185

Dose and administration

Table 18. Dosing schedule for meglitinides in type 2 diabetes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Preparations</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>nateglinide</td>
<td>Starlix®</td>
<td>Tablet 60 mg, 120 mg</td>
<td>Recommended dose is 120 mg three times daily. Patients close to their A1C goal may start at 60 mg three times daily.185, 190</td>
</tr>
<tr>
<td>repaglinide</td>
<td>Prandin®</td>
<td>Tablet 0.5 mg, 1 mg, 2 mg</td>
<td>Initially 0.5 mg three times daily immediately before main meals. Increase every 1–2 weeks according to blood glucose control up to 4 mg four times daily. Maximum recommended daily dose is 16 mg.190</td>
</tr>
</tbody>
</table>

* An initial dose up to 1 mg three times daily can be considered in patients being transferred directly from other oral antihyperglycemic agents.190

Important considerations

- Meglitinides should be taken immediately before meals for proper action and to minimize the risk of hypoglycemia.
- If a meal is missed, the meglitinide dose should be omitted to minimize the risk of hypoglycemia. If a meal is added, a dose of the meglitinide should be added.103, 185, 238
- Patients started on a meglitinide need to be educated about the identification, treatment and prevention of hypoglycemic episodes. For further information see hypoglycemia, page 185.
- Titrate the dose carefully in renal or hepatic impairment and in patients above 75 years of age.185, 190, 240
- Meglitinides have a lower risk of hypoglycemia than sulfonylureas.90
Contraindications and precautions

Meglitinides are contraindicated in the following situations: \(^{185, 190}\)
- age < 12 years;
- pregnancy and lactation; or
- known hypersensitivity to the drug.

Meglitinides are inappropriate for patients with type 1 diabetes, diabetic coma, ketoacidosis, severe infection, trauma or other conditions where it is unlikely to control the hyperglycemia; insulin should be administered in such situations. Insulin should be used in pregnancy.

Meglitinides are predominantly metabolized in the liver. Clearance is significantly reduced in patients with hepatic impairment; hence, caution is needed in this patient group. \(^{109, 185}\) They appear to be safe and well tolerated in patients with renal impairment. However, careful dose titration is advisable in patients with severe renal impairment, as clearance appears to be reduced in this patient group. \(^{185, 254}\)

Caution is recommended in patients at high risk of hypoglycemia. See Table 19, page 72.

Monitoring recommendations
- For information about monitoring glycemic control, see monitoring and goals in type 2 diabetes, page 8.
**Adverse effects**

Table 19. Adverse effects associated with meglitinides.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypoglycemia</td>
<td>Hypoglycemia is the most frequent and serious adverse effect of meglitinides. Risk factors include hepatic dysfunction, advanced age, debility, malnourished state, adrenal insufficiency, pituitary insufficiency, concurrent ( \beta )-blocker therapy, severe or prolonged exercise, and concurrent therapy with more than one antihyperglycemic agent.(^{185,238}) The incidence of hypoglycemia overall appears to be slightly lower with meglitinides than sulfonylureas. The incidence of severe hypoglycemia appears to be lower with meglitinides than sulfonylureas.(^{185,240,255,256}) Because of their rapid onset of action, hypoglycemia may result if a dose is taken and a meal is delayed or omitted.(^{103,160,185,240}) The risk of symptomatic hypoglycemia as a result of missed meals appears to be less with meglitinides administered preprandially (if the dose is omitted when a meal is missed) than with glyburide once or twice a day.(^{103,160,185,240}) For further information see hypoglycemia, page 185.</td>
</tr>
<tr>
<td>weight gain</td>
<td>Meglitinides are associated with body weight gain. In drug-naive patients treated with meglitinides, body weight has increased by about 1–3%.(^{109,185,238})</td>
</tr>
<tr>
<td>gastrointestinal effects</td>
<td>Nausea, vomiting, abdominal pain, diarrhea and constipation are common adverse effects, but occurred to a similar degree as with placebo in clinical studies.(^{68,190,257})</td>
</tr>
<tr>
<td>visual disturbances</td>
<td>Infrequent. Changes in blood glucose levels have been known to result in transient visual disturbances, especially at the initiation of treatment.(^{190,240,257})</td>
</tr>
<tr>
<td>dermatological effects</td>
<td>Rash is considered an infrequent adverse effect of repaglinide.(^{190})</td>
</tr>
<tr>
<td>hepatic effects</td>
<td>Increases in liver enzymes occur infrequently with repaglinide.(^{190})</td>
</tr>
</tbody>
</table>
**Drug interactions**

Table 20. Selected drug interactions associated with meglitinides.

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>inhibitors of CYP3A4 and CYP2C9 (e.g. ketoconazole, fluconazole, itraconazole, erythromycin, fluoxetine clarithromycin, diltiazem nefazodone, fluvoxamine)</td>
<td>Plasma concentrations of meglitinides may be increased (and hence hypoglycemic risk increased) by inhibitors of CYP3A4 and CYP2C9. Monitor blood glucose concentrations and warn patients about the risk of hypoglycemia if coadministration with CYP3A4 and CYP2C9 inhibitors is essential.</td>
</tr>
<tr>
<td>other antihyperglycemic agents</td>
<td>Hypoglycemic risk is increased.</td>
</tr>
<tr>
<td>inducers of CYP3A4 and CYP2C9 (e.g. rifampin, carbamazepine, phenytoin, St John’s wort)</td>
<td>May decrease plasma concentrations of meglitinides. In a study in nine healthy volunteers, rifampin decreased the plasma concentrations and the hypoglycemic effects of repaglinide. Monitor blood glucose concentrations closely and adjust the meglitinide dose as necessary if coadministration is essential.</td>
</tr>
<tr>
<td>drugs with a risk of hyperglycemia</td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hyperglycemia. When used in combination with antihyperglycemic agents vigilant monitoring of blood glucose concentrations may be needed (see Appendix 2, page 197).</td>
</tr>
<tr>
<td>other drugs with risk of hypoglycemia</td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hypoglycemia when used in combination with antihyperglycemic agents (see Appendix 1, page 195).</td>
</tr>
<tr>
<td>alcohol</td>
<td>Alcohol may intensify and prolong the hypoglycemic effects of repaglinide.</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450
**THIAZOLIDINEDIONES**

*rosiglitazone (Avandia®, pioglitazone (Actos®)*

**Mechanism of action**

**Antihyperglycemic effects**

Rosiglitazone and pioglitazone are insulin sensitizing agents that heighten the response to insulin in adipose tissue, skeletal muscle and the liver, without stimulating insulin secretion.²⁵⁹, ²⁶⁰ The insulin sensitizing effects are thought to result from binding to and activating the peroxisome proliferator-activated receptor gamma (PPAR-γ). PPAR-γ is found in insulin dependent glucose requiring tissues, and is involved in the regulation of genes controlling glucose homeostasis and lipid metabolism.²⁶⁰, ²⁶¹ PPAR-γ activation results in a reduction in hepatic glucose production, and increased insulin dependent glucose uptake in adipose and skeletal tissues.²⁵⁹ The main site of action for thiazolidinediones appears to be adipose tissue.²⁶²

In patients with type 2 diabetes, rosiglitazone and pioglitazone have been found to decrease FPG levels, A1C (by 1–1.5%), serum insulin and circulating free fatty acids.²⁶⁰, ²⁶³-²⁶⁵ The onset of action is slow, with some effects noted within 1–2 weeks,²⁶⁶ but full effects may not be evident for 6–12 weeks.

**Effects on body weight**

Significant weight gain has been reported with the thiazolidinediones.²⁶³, ²⁶⁷ In clinical trials, dose-dependent increases in body weight have been in the order of 0.7–3.5 kg²⁵⁹ and 0.5–2.8 kg²⁶³ with rosiglitazone and pioglitazone, respectively. The cause is unclear but may be related to increased fluid retention, degree of non-compliance with dietary restrictions, or increases in subcutaneous, not visceral fat.²⁵⁹
**Effects on lipid profile**

Thiazolidinediones profoundly affect lipid metabolism.\(^{262}\)

Rosiglitazone can increase LDL cholesterol levels up to 18.6\%.\(^{259}\) This has been observed in the first 1–2 months of therapy then gradually approach baseline values over 6–12 months. HDL cholesterol levels have increased in proportion to LDL cholesterol concentrations (18\%) resulting in an unchanged LDL cholesterol/HDL cholesterol ratio.\(^{259, 268}\) Effects on triglyceride levels have been variable and usually insignificant.\(^{109, 259, 269}\)

Beneficial effects on lipid profiles have been seen with pioglitazone monotherapy,\(^{263}\) including significant increases in HDL cholesterol levels (up to 13\%) and significant reductions in triglycerides (up to 28\%). These were associated with little or no change in total and LDL cholesterol levels.\(^{263, 270}\)

Pioglitazone has partial effects at PPAR-\(\alpha\) as well as effects at PPAR-\(\gamma\), whereas rosiglitazone is a pure PPAR-\(\gamma\) agonist. This may explain the differing effects on triglyceride levels.\(^{108}\)

**Pharmacokinetics**

**Rosiglitazone**

Rosiglitazone is extensively metabolized in the liver primarily by CYP2C8, with minor contributions from CYP2C9.\(^{259, 261, 271}\) The metabolites lack clinically significant effects.\(^{259, 261}\) The elimination half-life is approximately 3–4 hours.\(^{259, 261}\)

**Pioglitazone**

Pioglitazone is extensively metabolized in the liver principally by CYP2C8 and CYP3A4, with involvement of several other isoforms including CYP2C9 and CYP1A1/2.\(^{260, 272}\) Three of the six metabolites are active.\(^{270}\) The serum half-life of unchanged pioglitazone is 3–7 hours and for its total active metabolites it is 16–23 hours.\(^{270}\)
Efficacy/role in diabetes

Rosiglitazone and pioglitazone are approved for type 2 diabetes as monotherapy and in combination with sulfonylureas or metformin to improve glycemic control.\textsuperscript{268, 270} Pioglitazone, in lower doses, is also approved for use in combination with insulin.\textsuperscript{270} These agents have the advantage of a low risk of hypoglycemia and benefits on lipid profile. Disadvantages include the risk of weight gain and the need for monitoring of LFTs.

Controlled studies assessing the effect of rosiglitazone and pioglitazone on diabetic related morbidity and mortality are currently lacking.

Clinical trials have assessed the benefit of rosiglitazone and pioglitazone in type 2 diabetes using surrogate end points. Placebo-controlled studies have demonstrated their ability to improve glycemic control.\textsuperscript{273-280} A small open-label trial found similar efficacy between pioglitazone and rosiglitazone at improving glycemic control.\textsuperscript{265} Trials comparing rosiglitazone and pioglitazone with other antihyperglycemic agents are limited.

Studies have demonstrated efficacy of combining metformin and rosiglitazone\textsuperscript{161} or pioglitazone.\textsuperscript{162} Even though thiazolidinediones and metformin are insulin sensitizing agents, their mechanisms of action are different so that their effects can be additive. Metformin has most of its action in the liver and the thiazolidinediones have most action in the periphery.

Data suggest combining rosiglitazone or pioglitazone with a sulfonylurea can also be effective,\textsuperscript{123-126} although the risk of excessive weight gain should be considered.\textsuperscript{108} A number of studies suggest potential benefit when thiazolidinediones are used in combination with insulin,\textsuperscript{95-99} but the risk of edema appears to be increased with such combinations and is related to the dosage of thiazolidinediones.\textsuperscript{95}

For further information on combination therapy, see combination antihyperglycemic therapy, page 41.

For further information concerning the treatment of hyperglycemia, see antihyperglycemics in the management of type 2 diabetes, page 37.
Role in other disorders

Rosiglitazone and pioglitazone are currently only approved for the treatment of type 2 diabetes. However, they have been suggested to have a potential role in the following indications.

- **Polycystic ovary syndrome (PCOS):** PCOS is a diagnosis made in 5–10% of women between late adolescence and menopause. Patients may present with oligomenorrhoea or amenorrhea, anovulation or infertility, hirsutism or acne. Women with PCOS have an increased risk of CVD, and by the age of 40 years up to 40% will have type 2 diabetes or IGT. PCOS is associated with insulin resistance, with consequent hyperinsulinemia and (frequently) dyslipidemia and obesity. Some patients with insulin resistance and anovulation may ovulate while receiving thiazolidinediones. Hence, these agents may be useful as adjuvant therapy for anovulation in selected patients. A number of small trials have found benefit of troglitazone in this condition, but studies with rosiglitazone and pioglitazone are currently lacking.

- **The Metabolic Syndrome.** One small study found troglitazone improved insulin sensitivity in obese patients without diabetes. An additional study found troglitazone decreased insulin resistance and improved glucose tolerance in non-diabetic obese subjects with either impaired or normal glucose tolerance. As a result it has been proposed that troglitazone may be useful in prevention of type 2 diabetes. The Troglitazone in Prevention of Diabetes (TRIPOD) trial found troglitazone significantly decreased the incidence of type 2 diabetes in young Hispanic women with a history of gestational diabetes. As well as improving insulin sensitivity, the thiazolidinediones may benefit other components of the Metabolic Syndrome. For example, they can lead to a reduction in circulating triglyceride levels (particularly pioglitazone), increases in HDL cholesterol levels and decreases in blood pressure (shown with troglitazone and rosiglitazone). Controlled clinical studies are needed to determine whether the thiazolidinediones are effective in prevention of type 2 diabetes and cardiovascular complications in patients with the Metabolic Syndrome. For further information see the Metabolic Syndrome, page 2.
Doses and administration

Table 21, below outlines dosage recommendations for the thiazolidinediones in the treatment of type 2 diabetes.

Table 21. Dosing schedules for the thiazolidinediones in type 2 diabetes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Preparations</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>rosiglitazone</td>
<td>Avandia®</td>
<td>Tablet 2 mg, 4 mg, 8 mg</td>
<td>Initially 4 mg/day in one or two divided doses. Increase to 8 mg/day (in one or two divided doses) after 8–12 weeks if necessary.</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>Actos®</td>
<td>Tablet 15 mg, 30 mg, 45 mg</td>
<td>Initially 15 mg or 30 mg once daily. Increase to 45 mg once daily after 4 weeks if necessary. Maximum recommended daily dose is 45 mg.</td>
</tr>
</tbody>
</table>

Important considerations

- Rosiglitazone and pioglitazone can be taken with or without food.
- Dose reduction is not necessary in renal impairment.263, 264
- Rosiglitazone is generally more effective when taken in divided doses rather than as a single dose.259, 292
- The full effects of these drugs may not be evident for 6–12 weeks.

Contraindications and precautions

Rosiglitazone and pioglitazone are not recommended in patients with the following conditions.268, 270

- Known hypersensitivity to the drug.
- New York Heart Association (NYHA) Class III or IV heart failure.
- Moderate to severe liver impairment, and where ALT > 2.5 times the upper limit of normal at the start of treatment.

Caution is required in the following situations.

- Patients with edema or heart failure, due to the risk of fluid retention.
- Anovulatory premenopausal women with insulin resistance (e.g. patients with PCOS), as ovulation may resume, with subsequent risk of pregnancy unless contraceptive measures are initiated.68, 259
The thiazolidinediones are inappropriate for patients with type 1 diabetes, diabetic coma, ketoacidosis, severe infection, trauma or other conditions where they are unlikely to control the hyperglycemia; insulin should be administered in such situations. Insulin should be used in pregnancy.

**Monitoring recommendations**

- For rosiglitazone and pioglitazone, it is recommended that liver function be monitored at baseline, every two months for the first year, and periodically thereafter. More frequent monitoring is recommended in patients with mild hepatic impairment (ALT 1–2.5 times the upper limit of normal).

- Patients should be advised to report their signs/symptoms of hepatic dysfunction (e.g. unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine). The drug should be discontinued if ALT increases to three times the upper limit of normal during therapy and remains elevated, or if jaundice develops. Note that in the three reports describing either hepatocellular injury or hepatic failure with rosiglitazone, the onset was within 2–3 weeks of drug initiation. See Table 22, page 80.

- For information about monitoring glycemic control, see monitoring and goals in type 2 diabetes, page 8.
### Adverse effects

#### Table 22. Adverse effects associated with thiazolidinediones.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>weight gain</td>
<td>Significant weight gain has been reported with this drug class. In clinical trials, dose-dependent increases in body weight have been in the order of 0.7–3.5 kg and 0.5–2.8 kg with rosiglitazone and pioglitazone, respectively. The cause is unclear but may be related to increased fluid retention, degree of compliance with dietary restrictions, or changes in fat distribution.</td>
</tr>
<tr>
<td>edema</td>
<td>Fluid retention, blood plasma volume expansion and edema are a class effect of the thiazolidinediones. The reported incidence of edema is 3–5%. The median change in plasma volume is 1.8 mL/kg. The incidence of edema is dose related and appears highest when these drugs are combined with insulin. Caution is needed in patients with pre-existing edema or heart failure.</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>Hypoglycemia occurs infrequently with rosiglitazone and pioglitazone when used as monotherapy, but it may occur when the drugs are used in combination with sulfonylureas, repaglinide or insulin.</td>
</tr>
<tr>
<td>elevated creatinine phosphokinase</td>
<td>This has been noted in some patients in clinical trials with pioglitazone, with elevations to more than 10 times the upper limit of normal reported in seven patients. The drug was not withdrawn in any of these patients and all elevations resolved without incident.</td>
</tr>
<tr>
<td>decreased hemoglobin and hematocrit</td>
<td>In clinical trials of rosiglitazone and pioglitazone, mean hemoglobin values have declined. For example, mean decreases with rosiglitazone were $\leq 1.0$ g/dL and $\leq 3.3%$ for hemoglobin and hematocrit, respectively. These changes have generally been in the first 1–2 months of therapy and have remained relatively stable, and have not been a cause for discontinuation in clinical trials. It is thought that these changes reflect increased plasma volume rather than any serious hematologic adverse effects, as the patients were not truly anemic.</td>
</tr>
</tbody>
</table>

Note: Table continued on next page
Table 22. Adverse effects associated with thiazolidinediones (continued).

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>hepatic effects</td>
<td>Because of reports of rare but sometimes lethal hepatic toxicity, troglitazone (Rezulin®) was voluntarily withdrawn from the market in the United States in 1999. The incidence of hepatic injury with rosiglitazone and pioglitazone appears to be less than that seen with troglitazone. In clinical trials, for example, the incidence of ALT elevation $\geq$ three times the upper limit of normal was 0.25% with rosiglitazone, 0.26% with pioglitazone and 0.25% with placebo (compared with 1.9% with troglitazone). Isolated published case reports have described elevation of alkaline phosphatase levels, hepatocellular injury and hepatic failure possibly attributable to rosiglitazone. Note that in the three reports describing either hepatocellular injury or hepatic failure, the onset was within 2–3 weeks of rosiglitazone initiation. There are two published case reports describing hepatocellular injury 6–7 months after initiation of pioglitazone. Further information is required to determine the risk of hepatic adverse effects with rosiglitazone and pioglitazone. Until such time, regular monitoring of LFTs is recommended (see monitoring recommendations, page 79). It is recommended that the drugs be discontinued if LFTs increases to three times the upper limit of normal and remains elevated, or if jaundice develops.</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; LFT = liver function test

**Drug interactions**

Clinically relevant pharmacokinetic drug interactions have not been observed with rosiglitazone or pioglitazone to date in the form of clinical trials or case reports. A pharmacodynamic interaction is possible if rosiglitazone or pioglitazone are combined with other antihyperglycemic agents. Table 23 page 82, outlines drug interactions that could theoretically be associated with rosiglitazone and pioglitazone.
Table 23. Potential drug interactions associated with thiazolidinediones.

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>insulin, sulfonylureas, meglitinides</td>
<td>Rosiglitazone and pioglitazone may increase the risk of hypoglycemia.(^{259, 260, 267, 270, 301}) Risk of edema is increased if these drugs are combined with insulin.(^{95, 260})</td>
</tr>
<tr>
<td>inhibitors of CYP2C8 (e.g. omeprazole)</td>
<td>Rosiglitazone is primarily metabolized by, and pioglitazone is metabolized in part by, CYP2C8. Hence, in theory, inhibitors of this enzyme may increase the thiazolidinedione concentrations and effects.(^{259}) Monitor effects.</td>
</tr>
<tr>
<td>inducers of CYP2C8 (e.g. phenobarbitol, primidone)</td>
<td>Rosiglitazone is primarily metabolized by, and pioglitazone is metabolized in part by, CYP2C8. Hence, in theory, inducers of this enzyme may reduce the thiazolidinedione concentrations and effects.(^{259}) Monitor effects.</td>
</tr>
<tr>
<td>substrates of CYP2C8 (e.g. paclitaxel)</td>
<td>Rosiglitazone causes moderate inhibition of this enzyme. In theory, it may increase concentrations and effects of drugs metabolized by this enzyme. Few drugs are known substrates of CYP2C8 making this risk of drug interactions small.(^{271})</td>
</tr>
<tr>
<td>inhibitors of CYP3A4 (e.g. ketoconazole, fluconazole, nefazadone, itraconazole, diltiazem, erythromycin, clarithromycin, fluvoxamine, fluoxetine, diltiazem)</td>
<td>Pioglitazone is metabolized in part by CYP3A4. Hence, in theory, inhibitors of this enzyme may increase pioglitazone concentrations and effects.(^{272}) Monitor effects.</td>
</tr>
<tr>
<td>inducers of CYP3A4 (e.g. rifampin, phenytoin, carbamazepine, St John’s wort)</td>
<td>Pioglitazone is metabolized in part by CYP3A4. Hence, in theory, inducers of this enzyme may decrease pioglitazone concentrations and effects.(^{272}) Monitor effects.</td>
</tr>
<tr>
<td>drugs with a risk of hyperglycemia</td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hyperglycemia. When used in combination with antihyperglycemic agents vigilant monitoring of blood glucose concentrations may be needed. See Appendix 2, page 197.</td>
</tr>
</tbody>
</table>

CYP2C8 = cytochrome P450 2C8; CYP3A4 = cytochrome P450 3A4
### Table 24. Comparative information for the oral antihyperglycemic agents.

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Sulfonylureas</th>
<th>Metformin</th>
<th>Glitazones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Stimulate insulin release to reduce glycemia over 24 hour period</td>
<td>Improves insulin sensitivity (hepatic &gt; periphery)</td>
<td>Improve insulin sensitivity (periphery &gt; hepatic)</td>
</tr>
<tr>
<td><strong>A1C</strong></td>
<td>↓ 1.5–2.0%</td>
<td>↓ 1.5–2.0%</td>
<td>↓ 1–1.5%</td>
</tr>
<tr>
<td><strong>Body weight</strong></td>
<td>↑↑</td>
<td>0/↓ (2–3 kg)</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td>0</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>0</td>
<td>↓</td>
<td>0/↑ (rosiglitazone) 0/↓ (pioglitazone)</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td>↑/↓</td>
<td>↑ (slightly)</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>TG</strong></td>
<td>↓ (modest)</td>
<td>↓↓</td>
<td>0 (rosiglitazone) ↓↓ (pioglitazone)</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>↑↑</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>Mainly hepatic (and involving CYP2C9) (some renal clearance for glyburide and glimepiride)</td>
<td>Renal</td>
<td>Hepatic (rosiglitazone mainly CYP2C8; pioglitazone mainly CYP2C8 and CYP3A4)</td>
</tr>
<tr>
<td><strong>Common adverse effects</strong></td>
<td>Hypoglycemia, weight gain</td>
<td>Gastrointestinal (30%)</td>
<td>Fluid retention, edema, weight gain</td>
</tr>
<tr>
<td><strong>Important risks</strong></td>
<td>Use glyburide with caution in patients at high risk of hypoglycemia (i.e. elderly and those with renal or hepatic impairment).</td>
<td>Lactic acidosis — avoid in patients with renal impairment. Caution in other high risk groups.</td>
<td>Troglitazone removed from market because of hepatic adverse effects. Isolated case reports with rosiglitazone and pioglitazone. Need to monitor LFTs.</td>
</tr>
</tbody>
</table>

↑↑ = marked increase; ↓↓ = marked decrease; ↑ = increase; ↓ = decrease; 0 = no change;
LDL = low density lipoprotein; HDL = high density lipoprotein; CYP = cytochrome P450; TGs = triglycerides; LFT = liver function test

Note: Table continued on next page
Table 24. Comparative information for the oral antihyperglycemic agents (continued).

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Alpha-glucosidase Inhibitors</th>
<th>Meglitinides</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Improves postprandial hyperglycemia by delaying absorption of glucose after meals</td>
<td>Stimulates insulin release - taken with meals to reduce postprandial hyperglycemia</td>
</tr>
<tr>
<td><strong>A1C</strong></td>
<td>↓ 0.5–1.0%</td>
<td>↓ 0.5–1.5%</td>
</tr>
<tr>
<td><strong>Body weight</strong></td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td>↓ (slightly)</td>
<td>0</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TG</strong></td>
<td>0/↓ (postprandial TGs ↓)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>0</td>
<td>↑*</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>Mainly fecal (very little systemic absorption)</td>
<td>Hepatic (mainly by CYP3A4)</td>
</tr>
<tr>
<td><strong>Common adverse effects</strong></td>
<td>Gastrointestinal (60–70%)</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td><strong>Important risks</strong></td>
<td>Reports of hepatic adverse events — need to monitor LFTs.</td>
<td></td>
</tr>
</tbody>
</table>

↑↑ = marked increase; ↓↓ = marked decrease; ↑ = increase; ↓ = decrease; 0 = no change; LDL = low density lipoprotein; HDL = high density lipoprotein; CYP = cytochrome P450; TGs = triglycerides; LFT = liver function test

* The risk of symptomatic hypoglycemia as a result of missed meals appears less with the meglitinides administered preprandially (and hence missing the dose if a meal is missed) than with sulfonylureas administered once or twice a day.
INSULIN

Mechanism of action

Antihyperglycemic effects

Insulin, a hormone secreted by the β cells of the pancreas, plays a key role in regulating carbohydrate, protein and fat metabolism. The main stimulus for its secretion is glucose, although many other factors including amino acids, catecholamines, cortisol, glucagon and growth hormone are involved in its regulation. The secretion of insulin is not constant and peaks occur in response to the intake of food.

The major effects of insulin on carbohydrate homeostasis follow its binding to specific cell surface receptors on insulin sensitive tissues, notably the liver, muscles and adipose tissue. It inhibits hepatic glucose production and enhances peripheral glucose disposal thereby reducing blood glucose concentration. Exogenous insulin elicits all the pharmacological responses usually produced by endogenous insulin.

Effects on body weight

Weight gain is common with insulin therapy. For example, in UKPDS 33, after 10 years, patients assigned insulin gained 4 kg more than those assigned conventional therapy. This exceeded the weight gain observed with sulfonylureas.

The reason for weight gain with insulin is unclear. Mechanisms proposed include reduction in glucosuria (hence urinary calorie loss is reduced), increased appetite and accumulation of adipose tissue. Weight gain with insulin is closely related to the mean day-long plasma insulin level and daily insulin dose.

Effects on lipid profile

Improved glycemic control with insulin may result in beneficial effects on lipid profile.

Pharmacokinetics

Table 25, page 86 compares the onset and duration of action for the various forms of insulin which are currently available.
### Table 25. Comparative information for insulins.

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Insulin type</th>
<th>Onset (hours)</th>
<th>Peak (hours)</th>
<th>Duration (hours)</th>
<th>Can be mixed with</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting</strong></td>
<td>Insulin lispro</td>
<td>0.25–0.5</td>
<td>0.5–2.5</td>
<td>3–6.5</td>
<td>U, NPH</td>
</tr>
<tr>
<td></td>
<td>Insulin aspart</td>
<td>0.17–0.33</td>
<td>1–3</td>
<td>3–5</td>
<td>NPH</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td>Insulin (R)</td>
<td>0.5–1</td>
<td>1–5</td>
<td>6–10</td>
<td>All</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>Insulin zinc (Lente)</td>
<td>1–3</td>
<td>6–14</td>
<td>16–24+</td>
<td>Regular (R)</td>
</tr>
<tr>
<td></td>
<td>Isophane insulin (NPH)</td>
<td>1–2</td>
<td>6–14</td>
<td>16–24+</td>
<td>Regular (R)</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td>Insulin glargine</td>
<td>1.1</td>
<td>2–20</td>
<td>24</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Insulin human zinc extended (Ultralente)</td>
<td>4–6</td>
<td>8–20</td>
<td>12–20</td>
<td>Regular (R)</td>
</tr>
<tr>
<td><strong>Mixed Insulins</strong></td>
<td>75/25 (NPL/Lispro)</td>
<td>0.15–0.25</td>
<td>1–12</td>
<td>18–24</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>70/30 or 50/50 (NPH/R)</td>
<td>0.5–1</td>
<td>2–12</td>
<td>18–24</td>
<td>None</td>
</tr>
</tbody>
</table>

Adapted from the AHFS 2004, Facts and Comparisons and Drug Information Handbook.68, 78, 190

Insulin is fairly rapidly absorbed from subcutaneous tissue following injection, and although the half-life of unmodified insulin in blood is very short (minutes), the duration of action of most preparations is considerably longer due to their formulation.302 The rate of absorption from different sites may vary depending on local blood flow, with absorption being faster from the abdomen than the arm, buttock or thigh.302 Insulin is absorbed more rapidly following intramuscular administration than when given subcutaneously.68, 302

Insulin lispro is an insulin analogue obtained by recombinant DNA technology.68 It is essentially identical to human regular insulin except that the amino acids, proline at β28 and lysine at β29, in the β chain of insulin, are transposed.108 As a result, it is more rapidly absorbed and has a more rapid onset of action.68 It has been shown to improve postprandial hyperglycemia in both type 1 and 2 diabetes to a greater extent than regular insulin.108, 305-307 It has been claimed to reduce the frequency of
hypoglycemia compared to short-acting insulin, but results of studies have been conflicting.\textsuperscript{305, 308-310} This type of insulin is most useful in patients using multiple daily insulin injections,\textsuperscript{108} and appears to have the greatest role in type 1 diabetes.

Insulin aspart is another rapid-acting insulin analogue, created by replacing proline at position $\beta_{28}$ with aspartic acid.\textsuperscript{305, 311} Studies show it also has favorable effects on postprandial hyperglycemia, and the advantage of being able to administer the insulin injection immediately before a meal.\textsuperscript{108, 311} Its pharmacokinetics are similar to that of insulin lispro.\textsuperscript{305}

Intermediate and long-acting insulins have a prolonged duration of action resulting from either complexing insulin with a protein (e.g. protamine) or modifying particle size (e.g. insulin zinc suspensions).\textsuperscript{68} Mixed insulins combine a short or ultrashort-acting insulin in varying proportions (20–50\%) with an intermediate-acting insulin.\textsuperscript{68}

**Efficacy/role in diabetes**

Insulin is indicated in type 2 diabetes when weight reduction, dietary modification, and/or oral antihyperglycemics have failed to maintain satisfactory blood glucose control. Insulin is also indicated in otherwise stable patients with type 2 diabetes in the presence of major surgery, fever, severe trauma, infections, serious renal or hepatic dysfunction, hyperthyroidism or other endocrine dysfunction, or pregnancy.\textsuperscript{68}

In UKPDS 33, intensive treatment with insulin had favorable effects on microvascular end points in patients with type 2 diabetes.\textsuperscript{84} For further information see UKPDS 33, page 37.

When oral therapy has failed to control glycemia, it is generally recommended that the oral agents are continued with insulin, but insulin can be given as the sole pharmacotherapy.\textsuperscript{312} The combination of insulin and metformin,\textsuperscript{94, 163-167} or insulin and a thiazolidinedione\textsuperscript{96-99} can be particularly useful, although the risk of edema is increased with the latter combination.

While intuitively there would seem to be little benefit from combining insulin with sulfonylureas, studies have demonstrated that this combination can result in a smaller daily insulin dose and modestly improve glycemic control.\textsuperscript{99, 127} The most widely used approach in combining insulin and sulfonylureas is termed *BIDS* therapy (*bedtime insulin daytime sulfonylurea*).\textsuperscript{98}
Insulin has also been useful in combination with alpha-glucosidase inhibitors, and the meglitinides.

For further information on combination therapy, see combination antihyperglycemic therapy, page 41.

For further information concerning the treatment of hyperglycemia, see antihyperglycemics in the management of type 2 diabetes, page 37.

**Doses and administration**

The following five tables describe the various insulin preparations available.

**Table 26. Rapid-acting insulins.**

<table>
<thead>
<tr>
<th>Type/origin</th>
<th>Brand names</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin lispro</td>
<td>Humalog®</td>
<td>10 mL vial 5 x 1.5 mL and 3 mL cartridges (for use in HumaPen® or B-D Pen®)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 x 3 mL disposable pen</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>NovoLog®</td>
<td>10 mL vial 5 x 3 mL PenFill® cartridge (for use in NovoPen® and Novolin Pen®)</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>Apidra®</td>
<td>10 mL vial</td>
</tr>
</tbody>
</table>

* Rapid-acting insulins should be given immediately before meals

**Table 27. Short-acting insulins.**

<table>
<thead>
<tr>
<th>Type/origin</th>
<th>Brand names</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Humulin R®</td>
<td>10 mL vial</td>
</tr>
<tr>
<td></td>
<td>Novolin R®</td>
<td>10 mL vial 5 x 1.5 mL and 3 mL cartridges (for use in NovoPen® and Novolin Pen®)</td>
</tr>
<tr>
<td>Purified pork</td>
<td>Iletin II®</td>
<td>10 mL vial</td>
</tr>
</tbody>
</table>

* Short-acting insulins should be given 30 minutes before meals.
Table 28. Intermediate-acting insulins.

<table>
<thead>
<tr>
<th>Type/origin</th>
<th>Brand names</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human isophane</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin N®</td>
<td>10 mL vial</td>
<td>5 x 3 mL cartridges (for use in HumaPen® or B-D Pen®)</td>
</tr>
<tr>
<td>Novolin N®</td>
<td>10 mL vial</td>
<td>5 x 1.5 mL and 3 mL cartridges (for use in NovoPen® and Novolin Pen®) 5 x 1.5 mL disposable prefilled syringe</td>
</tr>
<tr>
<td><strong>Human lente</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin L®</td>
<td>10 mL vial</td>
<td></td>
</tr>
<tr>
<td>Novolin L®</td>
<td>10 mL vial</td>
<td></td>
</tr>
<tr>
<td><strong>Purified pork</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH Iletin II®</td>
<td>10 mL vial</td>
<td></td>
</tr>
<tr>
<td>Lente Iletin II®</td>
<td>10 mL vial</td>
<td></td>
</tr>
</tbody>
</table>

* Intermediate-acting insulins are used in the morning or evening (given with short-acting insulin in the same syringe before the evening meal or in a separate injection just before bed).78

† Intermediate-acting insulin vials and cartridges should be gently rotated in hands before use to allow resuspension.78

Table 29. Intermediate-acting insulins, pre-mixed.

<table>
<thead>
<tr>
<th>Type/origin</th>
<th>Brand names</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin lispro protamine suspension (75%) +</strong></td>
<td>Humalog Mix 75/25®</td>
<td>10 mL vial 5 x 3 mL cartridge (for use in HumaPen® or B-D Pen®)</td>
</tr>
<tr>
<td><strong>insulin lispro (25%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin aspart protamine suspension (70%) and</strong></td>
<td>NovoLog Mix 70/30®</td>
<td>3 mL cartridge (for use in FlexPen®) 3 mL prefilled syringe</td>
</tr>
<tr>
<td><strong>insulin aspart (30%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin isophane (70%) +</strong></td>
<td>Humulin 70/30®</td>
<td>10 mL vial 5 x 3 mL cartridges (for use in HumaPen® or B-D Pen®)</td>
</tr>
<tr>
<td><strong>insulin regular (30%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin isophane (50%) +</strong></td>
<td>Humulin 50/50®</td>
<td>10 mL vial 5 x 1.5 mL and 3 mL cartridges (for use in NovoPen® and Novolin Pen®) 5 x 1.5 mL prefilled syringes</td>
</tr>
<tr>
<td><strong>insulin regular (50%)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pre-mixed insulins should be followed by a meal within approximately 30 minutes of administration. The exception is Humalog 75/25® and NovoLog Mix 70/30® which should be administered immediately before meals.

† Intermediate-acting insulin vials and cartridges should be gently rotated in hands before use to allow resuspension.78
Table 30. Long-acting insulins.

<table>
<thead>
<tr>
<th>Type/origin</th>
<th>Brand names(^*)</th>
<th>Preparation(^†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human ultralente</td>
<td>Humulin U(^®)</td>
<td>10 mL vial</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus(^®)</td>
<td>10 mL vial</td>
</tr>
</tbody>
</table>

\(^*\) Long-acting insulins are used in the morning or evening (given with short-acting insulin in the same syringe before the evening meal or in a separate injection just before bed).\(^78\)

\(^†\) Long-acting insulin vials should be gently rotated in hands before use to allow resuspension.\(^78\)

**Important considerations**

- Insulin dosage and regimen should be determined for each person, depending on individual treatment end points, and adjusted according to blood glucose monitoring.\(^68\)

- Insulin can be combined with oral antihyperglycemic agents in type 2 diabetes.\(^94, 127, 312, 316\) A common combination is insulin and metformin.\(^312\) For example, in one study, combining evening intermediate-acting insulin with daytime metformin was more effective at achieving glycemic control and associated with less hypoglycemic episodes than twice daily intermediate insulin. In addition, this combination was not associated with the weight gain seen with twice daily insulin.\(^94\)

- Patients commencing insulin need to be educated about the identification, treatment and prevention of hypoglycemic episodes. For further information see hypoglycemia, page 185.

- Subcutaneous injections may be given in the abdomen (fastest rate of absorption), or less commonly in the thighs, upper arms or buttocks. Injection site should be rotated in the same general area to avoid lipodystrophy.\(^68\) The abdomen is generally the preferred site. Absorption can be variable when exercising following injection in the extremities.

- The use of insulin in the elderly is feasible but the dosage schedule and delivery device should be as simple as possible.\(^312\)

- Rapid and short-acting insulins are soluble insulins (clear solution) and are the only type that can be given intravenously.

- When mixing insulins, the short-acting insulin (clear) should be drawn up into the syringe first to avoid contamination with the long-acting insulin (cloudy).\(^78\)
• Insulin not in use should be stored at 2–8°C (36–46°F) and protected from light. It should not be frozen. Storage of an insulin preparation at up to 30°C (86°F) is acceptable for up to one month.
• Discomfort of injection can be minimized by keeping insulin in use at room temperature.

Contraindications and precautions
• Insulin should not be administered in the presence of hypoglycemia.68
• Insoluble insulin preparations (suspensions) must not be given intravenously.68

Increased insulin doses are usually necessary during infection, emotional stress, accidental or surgical trauma, and the latter two trimesters of pregnancy. Decreased insulin doses are usually necessary in patients with impaired renal or liver function.302

Monitoring recommendations
• For information about monitoring glycemic control, see monitoring and goals in type 2 diabetes, page 8.

Drug interactions

Table 31, below outlines selected drug interactions associated with insulin.

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral antihyperglycemics</td>
<td>Hypoglycemic risk may be increased if insulin is combined with oral antihyperglycemic agents.</td>
</tr>
<tr>
<td>other drugs with a risk of hypoglycemia</td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hypoglycemia when used in combination with antihyperglycemic agents (see Appendix 1, page 195).</td>
</tr>
<tr>
<td>drugs with a risk of hyperglycemia</td>
<td>Many drugs affect blood glucose concentrations and may increase the risk of hyperglycemia. When used in combination with antihyperglycemic agents vigilant monitoring of blood glucose concentrations may be needed (see Appendix 2, page 197).</td>
</tr>
</tbody>
</table>
### Adverse effects

Table 32. Adverse effects associated with insulin.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>hypoglycemia</strong></td>
<td>Hypoglycemia is the most frequent and serious adverse effect of insulin.(^{76, 190, 302, 317}) It can occur with excessive dose, delayed meals, insufficient food and increased physical activity. Symptoms of hypoglycemia resulting from increased sympathetic activity include hunger, pallor, sweating, palpitations, anxiety and tremulousness. Other symptoms include headache, visual disturbances, slurred speech, paraesthesia of the mouth and fingers, alterations in behavior, and impaired mental or intellectual ability. If untreated, hypoglycemia may lead to convulsions and coma. Some patients, especially the elderly or those with tightly controlled diabetes or long standing diabetes, may not experience the typical early warning symptoms of a hypoglycemic episode. There have been reports of hypoglycemia, sometimes with decreased warning symptoms in patients changing from bovine to human insulin.(^{68, 302}) Repeated hypoglycemia also appears to reduce the awareness of hypoglycemic symptoms.(^{68}) In UKPDS 33, the mean proportion of patients per year with one or more major hypoglycemic episodes while taking their assigned treatment was 2.3% for insulin versus 0.1% for diet, and the corresponding rates for any hypoglycemic episode were 36.5% versus 1.2%.(^{84}) Moves toward more intensive insulin therapy, in order to reduce the development of diabetic complications, increases the risk of hypoglycemic episodes.(^{302}) For further information see hypoglycemia, page 185.</td>
</tr>
<tr>
<td><strong>weight gain</strong></td>
<td>Weight gain is common with insulin therapy.(^{109, 303, 304}) In UKPDS 33, after 10 years, patients assigned insulin gained 4 kg more than those assigned conventional therapy. This exceeded the weight gain observed with sulfonylureas.(^{84}) The reason for weight gain with insulin is unclear. Mechanisms proposed include reduction in glucosuria (hence urinary calorie loss is reduced), increased appetite and accumulation of adipose tissue.(^{303}) Weight gain with insulin is closely related to the mean day-long plasma insulin level and daily insulin dose.(^{109})</td>
</tr>
</tbody>
</table>

Note: Table continued on next page
<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>lipoatrophy and lipohypertrophy</td>
<td>Insulin, administered subcutaneously, may cause either lipoatrophy or lipohypertrophy. Lipoatrophy appears to occur less frequently with purified insulins than with conventional insulins. Direct injection of purified insulin into the outside edge of the atrophied area may result in improvement or complete disappearance of the atrophy in some patients. Lipohypertrophy is usually associated with repeated injections at the same site and may usually be overcome by rotating the site of injection. Rotating injection sites within one anatomical region (e.g. rotating injections systematically in the abdominal area) rather than selecting a different anatomical region is recommended to decrease day to day variability in insulin absorption.</td>
</tr>
<tr>
<td>blurred vision</td>
<td>Transient blurred vision may occur in patients with diabetes given insulin. This appears to be related to the change in blood glucose concentrations.</td>
</tr>
<tr>
<td>hypersensitivity</td>
<td>Insulin may occasionally cause local or systemic hypersensitivity. Local reactions include erythema, pruritus, swelling, heat and burning at the injection site, with or without painful sensations. These may occur immediately or after some hours. In 95% of cases the local reactions disappear spontaneously. A switch to less immunogenic, highly purified insulins (or lispro) is necessary if the reaction persists. Generalized hypersensitivity may produce urticaria, angioedema, and very rarely anaphylactic reactions. If continued therapy with insulin is essential, hyposensitisation procedures may need to be performed. Hypersensitivity reactions are less frequent with purified than conventional insulins. Hypersensitivity reactions to insulin preparations may be caused not only by the insulin itself, but also by other components of the formulation such as zinc or protamine.</td>
</tr>
<tr>
<td>edema</td>
<td>Severe acute edema is a rare adverse effect of insulin treatment, occurring most often at the initiation of therapy. Possible mechanisms are sodium retention resulting from a direct action of insulin on the renal tubule or an effect of insulin on vascular permeability. The edema usually responds to a decrease in insulin dose.</td>
</tr>
</tbody>
</table>
REDUCING CARDIOVASCULAR RISK IN TYPE 2 DIABETES

HYPERTENSION

The prevalence of hypertension is 1.5–2 times greater in patients with type 2 diabetes compared to patients without diabetes.\textsuperscript{10} Approximately 40–50\% of patients with diabetes are hypertensive compared to 20\% of patients without diabetes.\textsuperscript{318}

Hypertension is a well recognized risk factor for both microvascular and macrovascular disease in type 2 diabetes.\textsuperscript{319} For further information see diabetic complications — microvascular, page 146; and diabetic complications — macrovascular, page 172.

Risk stratification

Blood pressure on its own is an incomplete predictor of cardiovascular risk. Risks and benefits of treatment are predicted more accurately by taking into account the other main cardiovascular risk factors, such as age, gender, smoking, lipid profile and family history of CVD.\textsuperscript{10} Importantly, diabetes is a major cardiovascular risk factor on its own and the presence of hypertension therefore significantly escalates this risk. The process of combining a patient’s individual risk factors to estimate their level of cardiovascular risk is termed risk stratification. The risk stratification process can be useful in making treatment decisions in newly diagnosed patients with mild hypertension and a variety of risk factors.\textsuperscript{10, 26} It is also useful for patient education about the benefits of lifestyle changes and to aid with ongoing treatment compliance.

A number of risk stratification charts and programs have been developed. Table 33, page 95 lists internet addresses for some of the cardiovascular risk assessment tools currently available and key hypertension guidelines.
**Table 33. Cardiovascular risk assessment tools and hypertension guidelines.**

| National Heart, Lung, and Blood Institute | National Cholesterol Education Panel Cardiovascular Risk Calculator
| American Heart Association | Risk Calculator for cardiovascular disease |
| World Health Organization | WHO-International Society of Hypertension Guidelines for the Management of Hypertension 1999 |
| [http://www.who.int/ncd/cvd/ht_guide.html](http://www.who.int/ncd/cvd/ht_guide.html) |
| Podock S, McCormack V, *et al* | A risk score for cardiovascular disease |
| [http://www.riskscore.org.uk](http://www.riskscore.org.uk) |
| British guidelines | Joint British Societies Coronary Risk Prediction Chart |
| [http://www.hyp.ac.uk/bhs/risktables.html](http://www.hyp.ac.uk/bhs/risktables.html) |
| Cardiac Risk Assessor Computer Program | [http://www.hyp.ac.uk/bhs/risk.xls](http://www.hyp.ac.uk/bhs/risk.xls) |
| The National Heart Foundation of New Zealand | New Zealand Risk Calculator Chart |
| The Oxford Center for Diabetes, Endocrinology, and Metabolism | The United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine |

**The evidence**

The most important outcome study assessing the efficacy of lowering blood pressure in patients with diabetes is UKPDS 38, which is outlined on page 96. This study demonstrates the importance of addressing hypertension in patients with diabetes. When compared with the results of UKPDS 33, it appears that tight blood pressure control is more effective than intensive glycemic control in protecting against macrovascular disease in patients with type 2 diabetes and hypertension. Lowering blood pressure also appears to be an important strategy in reducing the risk of microvascular complications. The benefit of lowering blood pressure in patients with diabetes has also been observed in a number of other large
outcome trials, including the Hypertension Optimal Treatment (HOT) study which is described briefly on page 96.

**UKPDS 38**

UKPDS 38 included 1148 hypertensive patients with newly diagnosed type 2 diabetes who had been recruited to the UKPDS. Patients were randomized to tight blood pressure control (with aim of blood pressure $< 150/85$ mmHg) with either captopril or atenolol as the main treatment, or to less tight blood pressure control (with aim of blood pressure $< 180/105$ mmHg) avoiding treatment with an angiotensin converting enzyme (ACE) inhibitor or β-blocker. In the tight control group captopril was started at 25 mg twice daily and increased to 50 mg twice daily, and atenolol was initiated at 50 mg daily and increased to 100 mg daily, if required. Other antihypertensives could be added if the control criteria were not met in the group assigned to tight control despite maximum allocated treatment, or in the group assigned to less tight control without drug treatment. The suggested sequence was furosemide, slow release nifedipine, methyldopa and prazosin.

The study end points were the same as for UKPDS 33 (see page 37). Mean blood pressure in patients over nine years of follow up was 144/82 mmHg in patients assigned to tight control compared with 154/87 mmHg in those assigned to less tight control. Compared to patients in the less tight control group, patients allocated to tight blood pressure control had a significant 24% reduction in the risk of developing any end point related to diabetes, 32% reduction in the risk of deaths related to diabetes, 44% reduction in the risk of stroke, 34% reduction in the risk of macrovascular diseases combined, 56% reduction in the risk of heart failure, and a 37% reduction in the risk of microvascular disease.

The authors calculated that approximately six patients need to be treated for 10 years to prevent one patient developing any complication, and 15 patients need to be treated for 10 years to prevent one death from a cause related to diabetes.

**Hypertension Optimal Treatment (HOT) study**

The HOT study, which included 18,790 patients with hypertension, aimed to assess optimal target diastolic blood pressure. Patients were randomly assigned to three different target diastolic blood pressures ($\leq 90$ mmHg, $\leq 85$ mmHg or $\leq 80$ mmHg) with felodipine being the baseline therapy. In
the subset of 1501 patients with diabetes at baseline, major cardiovascular events were halved and stroke was reduced by about 30% in the ≤ 80 mmHg group compared to the ≤ 90 mmHg group. Cardiovascular mortality was also significantly lower in the ≤ 80 mmHg group compared to each of the other target groups.322

Evidence for individual drug classes

There have been large outcome studies which have demonstrated benefit in patients with type 2 diabetes for low dose thiazide diuretics,320 ACE inhibitors,319, 323, 324 angiotensin II receptor antagonists (ARBs),325 β-blockers319, 323 and calcium channel blockers (CCBs).321, 322

However, when considering outcome evidence, the following studies are worth noting.

UKPDS 39

UKPDS 39 aimed to determine whether tight blood pressure control with captopril or atenolol provided a specific advantage or disadvantage in preventing the macrovascular and microvascular complications of type 2 diabetes. The conditions for the study were as mentioned in UKPDS 38 (see page 96). The study found no benefit of either drug over the other. The two drugs were equally effective in reducing blood pressure as well as reducing macrovascular and microvascular complications of diabetes. Since no major difference between the two drugs was found, the authors stated that blood pressure reduction in itself may be more important than the type of treatment used.323

The Heart Outcomes Prevention Evaluation (HOPE) study

The HOPE study was a randomized controlled study involving 9297 patients who were at least 55 years old and had a history of coronary artery disease, stroke, PVD or diabetes, plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL cholesterol levels, cigarette smoking or documented microalbuminuria). A total of 4645 patients were randomized to receive 10 mg ramipril once per day and 4652 were randomized to receive matching placebo. Approximately 47% of patients had hypertension at baseline and 38% had diabetes. Patients could be receiving aspirin, lipid lowering agents, and antihypertensives other than ACE inhibitors at baseline, and these were able to be continued throughout the study. The mean blood pressure at entry was 139/79 mmHg in both groups.326
At the end of the study, the mean blood pressure was 136/76 mmHg in the ramipril group and 139/77 mmHg in the placebo group. After a follow up period of 4.5 years, 14% of the ramipril group reached the primary end point (composite of MI, stroke or death from cardiovascular causes) compared with 17.8% of the placebo group (relative risk (RR) = 0.78). Compared with placebo, ramipril significantly reduced the rates of death from cardiovascular causes (6.1% vs 8.1%, RR = 0.74); MI (9.9% vs 12.3%, RR = 0.80); stroke (3.4% vs 4.9%, RR = 0.68); and death from any cause (10.4% vs 12.2%, RR = 0.84). Significant reductions in the risk of revascularization procedures, cardiac arrest, heart failure and complications related to diabetes were also noted in the ramipril group. The authors concluded that only a small part of the benefit could be attributed to a reduction in blood pressure with ramipril.

A total of 3577 of the patients included in the HOPE study had diabetes. When the results were analyzed separately in these patients, it was found that ramipril significantly lowered the risk of the primary end point by 25%, MI by 22%, stroke by 33%, cardiovascular death by 37%, total mortality by 24%, revascularization by 17% and overt nephropathy by 24% compared with placebo. The benefits were similar in those who were hypertensive or normotensive at baseline, and the risk of the primary outcome was still reduced by 25% when adjustments were made for the changes in systolic and diastolic blood pressure. The authors calculated that 15 high risk patients with diabetes would have to be treated with ramipril for a median of 4.5 years to prevent one individual from having a MI, stroke, cardiovascular death, admission to hospital for heart failure, a revascularization procedure, development of overt nephropathy, laser therapy for retinopathy or renal dialysis.

It has been suggested that the benefits of ramipril may be due largely to a protective effect of ACE inhibitors on the arterial wall.

**Effects of Low Dose Ramipril on Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes and Raised Excretion of Urinary Albumin (The DIABHYCAR Study)**

The DIABHYCAR study was a randomized, double-blind, placebo-controlled trial involving 4937 type 2 diabetic patients with elevated urinary albumin excretion (>20 mg/l) and serum creatinine concentrations of 150 µmol/l or less. Exclusion criteria comprised treatment with insulin, an ACE inhibitor, or an angiotensin II receptor blocker, documented CHF, MI in the past three months, UTI, or previous intolerance to ACE inhibitors.
There was no statistically significant difference in blood pressure between groups at randomization. Patients were randomized either to treatment with ramipril 1.25 mg daily or placebo, and followed for a median of 4 years.³²⁸

At the end of the study, the mean systolic and diastolic blood pressures were reduced by 1.54 and 0.30 mm hg, respectively, in the ramipril group. This reduction, although small, was found to be significant.³²⁸ Despite the reduction in blood pressure and a trend toward reduction of urinary albumin excretion, there was no significant reduction of the composite primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, non-fatal heart failure, or end stage renal failure) or individual primary endpoints in the ramipril group.³²⁸

In light of the results from the HOPE study, which involved a 10 mg daily dose of ramipril, the authors of the DIABHYCAR study suggested that the cardiovascular and renal protective effects of ramipril may be dose dependent.³²⁸ Therefore, they concluded that intensive blockade of the renin-angiotensin system may be required to improve cardiovascular and renal outcomes in diabetic patients.³²⁸

**Losartan Intervention for Endpoint Reduction (LIFE) Trial**

The LIFE trial was a randomized parallel group trial involving 9193 previously treated or untreated hypertensive patients aged 55 to 80 with electrocardiographic (ECG) evidence of left ventricular hypertrophy (LVH). A total of 4605 were assigned losartan 50 mg daily and 4588 were assigned atenolol 50 mg daily, each titrated to 100 mg daily to reach the goal blood pressure of 140/90 mmHg. Using a titration schedule, hydrochlorothiazide 12.5 mg to 25 mg could be added as well as other antihypertensives, excluding ACE Inhibitors, ARBs, and β-blockers, if blood pressure remained persistently high during follow-up. Approximately 13% of patients had diabetes. Patients could be receiving aspirin, and lipid lowering agents throughout the study. Pre-study blood pressure values ranged between 160–200 mmHg and 95–115 mmHg, systolic and diastolic respectively.³²⁵

At the end of the study, the mean blood pressures were 144/81 mmHg and 145/80 mmHg for losartan and atenolol groups respectively. Blood pressure goal was reached in 48% of losartan group and 45% in the atenolol group. After a mean follow-up of 4.8 years, 11% of the losartan group reached the primary end point (composite of MI, stroke, progressive heart failure, or death from cardiovascular causes) compared with 13% of the atenolol group (relative risk (RR) = 0.87). Compared with atenolol, losartan
significantly reduced the rate for stroke (5% vs. 7%, RR = 0.75); and new onset diabetes (6% vs. 8%, RR = 0.75). LVH regression was reduced more in the losartan group. There was no significant difference between the two groups for fatal or non-fatal MI or cardiovascular mortality. The authors concluded that it is possible that losartan confers benefits beyond reduction in blood pressure and LVH regression.

A total of 1195 of the patients in the LIFE trial had diabetes. When the results were analyzed separately in these patients, it was found that losartan significantly lowered the risk of the primary endpoint by 24%, total mortality by 39%, and cardiovascular mortality by 37% compared to atenolol. There was no statistically significant difference between the two groups for stroke or myocardial infarctions.

The authors suggested that the cardiovascular protective effect of losartan could result from the pronounced blockade of the detrimental effect of angiotensin II.

**Calcium channel blocker (CCB) uncertainty**

Data on the effects of CCBs on cardiovascular outcomes in patients with diabetes have been conflicting. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial and the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) found a greater risk of macrovascular end points in patients with type 2 diabetes with a CCB compared with an ACE inhibitor. These findings, however, were secondary end points and hence require confirmation in additional studies. On the other hand, a number of large outcome trials involving CCBs have found beneficial effects on cardiovascular outcomes when considering those patients with diabetes at baseline in post hoc analyses.

While some investigators would be reluctant to advocate CCBs as a first line treatment for hypertension in patients with diabetes, their use in combination therapies is reasonable given the current evidence.

**Target levels**

In patients with type 2 diabetes, blood pressure should be measured at each clinic visit. Both sitting and standing blood pressure should be assessed, particularly in patients with autonomic neuropathy who are prone to orthostatic hypotension.

The target blood pressure for patients with diabetes and no signs of diabetic nephropathy is < 130/80 mmHg. In patients with diabetic nephropathy
with proteinuria > 1 g per day, the target blood pressure is < 125/75 mmHg.\textsuperscript{10, 26}

**Hypertension management**

**Lifestyle modifications**

Non-pharmacological measures are first line in managing hypertension in the majority of patients and should be continued life long. The lifestyle modifications listed below can lower blood pressure, and more significantly, cardiovascular risk.\textsuperscript{25, 336}

- Smoking cessation (see smoking cessation, page 31).
- Regular physical activity (see exercise in type 2 diabetes, page 28).
- Weight reduction if necessary (see weight loss, page 25).
- Healthy eating (see nutrition in type 2 diabetes, page 19).
- Alcohol intake should be limited to two standard drinks per day or less. By limiting alcohol intake, blood pressure can be substantially reduced in some patients. On average, a reduction of 1 mmHg systolic blood pressure may be seen for each standard drink eliminated per day.\textsuperscript{44}
- Reduced salt intake (see nutrition in type 2 diabetes, page 19).

Dyslipidemia is an additional cardiovascular risk factor and hence should also be addressed.\textsuperscript{27} For further information see dyslipidemia, page 117.

**Pharmacological management**

Thiazide and thiazide-like diuretics, β-blockers, ACE inhibitors, CCBs and ARBs are the main drug classes used in the treatment of hypertension. They do not differ substantially with respect to effect on blood pressure. However, adverse effect profiles and evidence from randomized controlled trials in type 2 diabetes varies.

Drug choice for treatment of hypertension in type 2 diabetes will be influenced by:
- patient’s cardiovascular risk profile;
- presence of clinical CVD or renal disease;
- co-existing conditions which may either favor or limit the use of particular drug classes;
- variation in individual patient responses to drugs from different classes;
- possibility of interactions with other co-prescribed drugs;
- evidence for reduction in macrovascular and microvascular disease in patients with diabetes for individual drugs;
When choosing an antihypertensive class in patients without diabetes, consideration should be given to compelling indications and compelling contraindications. This same approach is also appropriate for patients with type 2 diabetes (see Table 34, page 103).

Importantly, to achieve blood pressure targets, combination therapy will often be required in patients with type 2 diabetes and this need should be anticipated. For example, in the HOT study, 76% of patients assigned to the diastolic blood pressure target of ≤ 80 mmHg required combination therapy. In UKPDS 38, approximately 30% of patients assigned to the tight blood pressure control group required three or more agents to control blood pressure after nine years of treatment.

In light of the results of the HOPE study and the numerous studies regarding the effects on diabetic nephropathy, ACE inhibitors are often advocated as the initial drug group of choice in patients with type 2 diabetes. For patients who experience intolerable cough with ACE inhibitors, an ARB appears appropriate. However, to achieve blood pressure targets, thiazide and thiazide-like diuretics, β-blockers and CCBs are all options to consider in combination regimens.

Table 35, page 105 and Table 36, page 106 outline the preparations currently available for the more common antihypertensive drug classes that are used in the management of hypertension in type 2 diabetes.

**Doses for antihypertensives**

Table 37, page 107, outlines dosage recommendations for the antihypertensives that are more commonly used in patients with type 2 diabetes in the primary care setting.

**Adverse effects and contraindications of antihypertensives**

Table 38, page 109 outlines selected adverse effects and contraindications associated with antihypertensives that are commonly used to treat hypertension in patients with type 2 diabetes in the primary care setting. It is not intended to be an exhaustive list of all reported adverse effects associated with these agents.
**Drug interactions with antihypertensives**

Table 39, page 113 outlines selected drug interactions associated with antihypertensives that are commonly used to treat hypertension in patients with type 2 diabetes in the primary care setting. It is not intended to be an exhaustive list of all potential drug interactions associated with these agents.

**Table 34. Guidelines for selecting drug treatment for hypertension.**

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Compelling indications</th>
<th>Possible indications</th>
<th>Compelling CIs</th>
<th>Possible CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide and thiazide-like diuretics</td>
<td>Elderly patients</td>
<td>Systolic hypertension</td>
<td>Gout</td>
<td>Dyslipidemia*</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td></td>
<td></td>
<td>Sexually active males*</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Angina</td>
<td>After myocardial infarct</td>
<td>Asthma and COPD (with reversible airways)</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>Tachyarrhythmias</td>
<td>Heart block†</td>
<td>Athletes and physically active patients PVD§</td>
</tr>
<tr>
<td>ACE-inhibitor (ACE-I)</td>
<td>Heart failure</td>
<td>Left ventricular dysfunction</td>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>After myocardial infarct</td>
<td>Hyperkalemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bilateral renal artery</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>stenosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>History of angioedema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>with an ACE-I</td>
<td></td>
</tr>
<tr>
<td>ARBs</td>
<td>ACE-I cough</td>
<td>Heart failure</td>
<td>See ACE-I</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Angina</td>
<td>Systolic hypertension</td>
<td>Heart block†¶</td>
<td>Heart failure¶</td>
</tr>
<tr>
<td></td>
<td>PVD proteinuria</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = contraindications; PVD = peripheral vascular disease; COPD = chronic obstructive pulmonary disease; ARB = angiotensin II receptor antagonist

* Very low and low dose thiazide and thiazide-like diuretics are expected to have a minimal and clinically insignificant effect on serum lipid profiles in most patients, and are less likely to cause sexual dysfunction compared with the higher doses once used.

† Grade 2 or 3 atrioventricular block.

‡ Cardioselective β-blockers (e.g. atenolol and metoprolol) and β-blockers with intrinsic sympathomimetic activity (e.g. pindolol) may be expected to have a minimal and clinically insignificant effect on serum lipid profiles in most patients.

§ In patients with severe PVD, β-blockers are not contraindicated although they should be administered with extreme caution. In less severe forms of PVD, β-blockers have little effect on the peripheral circulation. It may be useful to choose a cardioselective β-blocker (e.g.
metoprolol and atenolol) or β-blockers with intrinsic sympathomimetic activity (e.g. pindolol) if a patient complains of cold extremities.  
¶ Verapamil or diltiazem only.

Adapted from World Health Organization-International Society of Hypertension.  

10
Table 35. Single drug antihypertensive preparations.

<table>
<thead>
<tr>
<th>Thiazide and thiazide-like diuretics</th>
<th>β-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazide and thiazide-like diuretics</strong></td>
<td><strong>β-blockers</strong></td>
</tr>
<tr>
<td>chlorthalidone Hygroton®, Thalitone®</td>
<td>atenolol Tenormin®</td>
</tr>
<tr>
<td>chlorothiazide Diuril®, Diurigen®</td>
<td>carvedilol Coreg®</td>
</tr>
<tr>
<td>hydrochlorothiazide Aguazide®, Esidrix®, Ezide®, Hydro-Par®, HydroDIURIL®, Microzide®, Oretic®</td>
<td>labetalol Normodyne®, Trandate®</td>
</tr>
<tr>
<td>indapamide Lozol®</td>
<td>metoprolol Lopressor®, Toprol XL®</td>
</tr>
<tr>
<td></td>
<td>nadolol Corgard®</td>
</tr>
<tr>
<td></td>
<td>propranolol Inderal®, Inderal LA®</td>
</tr>
<tr>
<td></td>
<td>bisoprolol Zebeta®</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-dihydropyridine CCBs</strong></td>
<td><strong>Non-dihydropyridine CCBs</strong></td>
</tr>
<tr>
<td>amlodipine Norvasc®</td>
<td>diltiazem Cardizem®, Cardizem CD®,</td>
</tr>
<tr>
<td>felodipine Plendil®</td>
<td>Cardizem SR®, Cartia XT®</td>
</tr>
<tr>
<td>nifedipine Adalat CC®, Procardia®, Procardia XL®</td>
<td>Dilacor XR®, Diltia XT®, Tiazac®</td>
</tr>
<tr>
<td>nisoldipine Sular®</td>
<td>verapamil Calan®, Calan SR®, Covera-</td>
</tr>
<tr>
<td></td>
<td>HS®, Isoptin®, Isoptin SR®, Verelan®,</td>
</tr>
<tr>
<td></td>
<td>Verelan PM®</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td><strong>ARBs</strong></td>
</tr>
<tr>
<td>benazepril Lotensin®</td>
<td>candesartan Atacand®</td>
</tr>
<tr>
<td>captopril Capoten®</td>
<td>eprosartan Teveten®</td>
</tr>
<tr>
<td>enalapril Vasotec®</td>
<td>irbesartan Avapro®</td>
</tr>
<tr>
<td>fosinopril Monopril®</td>
<td>losartan Cozaar®</td>
</tr>
<tr>
<td>lisinopril Prinivil®, Zestri®</td>
<td>telmisartan Micardis®</td>
</tr>
<tr>
<td>quinapril Accupril®</td>
<td>valsartan Diovan®</td>
</tr>
<tr>
<td>ramipril Altace®</td>
<td>olmesartan Benicar®</td>
</tr>
<tr>
<td>trandolapril Mavik®</td>
<td></td>
</tr>
<tr>
<td>moexipril Univasc®</td>
<td></td>
</tr>
</tbody>
</table>

CCB = calcium channel blocker; ARB = angiotensin II receptor antagonist

Note: This table outlines more commonly used preparations available as of 05 November 2004
Table 36. Combination antihypertensive preparations.

<table>
<thead>
<tr>
<th>ACE-I plus diuretic</th>
<th>ARB plus diuretic</th>
<th>β-blockers plus diuretic</th>
</tr>
</thead>
<tbody>
<tr>
<td>benazepril with HCTZ 65/6.25, 10/12.5, 25/20, 20/12.5 mg&lt;br&gt;Lotensin HCT®</td>
<td>candesartan and HCTZ 16/12.5, 32/12.5 mg&lt;br&gt;Atacand HCT®</td>
<td>atenolol with chlorthalidone 50/25, 100/25 mg&lt;br&gt;Tenoretic®</td>
</tr>
<tr>
<td>captopril with HCTZ 25/15, 50/15, 25/25, 50/25 mg&lt;br&gt;Capozide®</td>
<td>eprosartan and HCTZ 600/12.5, 600/25 mg&lt;br&gt;Teveten HCT®</td>
<td>bisoprolol with HCTZ 2.5/6.25, 5/6.25, 10/6.25 mg&lt;br&gt;Ziac®</td>
</tr>
<tr>
<td>enalapril with HCTZ 5/12.5, 10/25 mg&lt;br&gt;Vaseretic®</td>
<td>irbesartan with HCTZ 150/12.5, 300/12.5 mg&lt;br&gt;Avalide®</td>
<td>metprolol with HCTZ 50/25, 100/25, 100/50 mg&lt;br&gt;Lopressor HCT®</td>
</tr>
<tr>
<td>lisinopril with HCTZ 10/12.5, 20/12.5, 20/25 mg&lt;br&gt;Prinizide®, Zestoretic®</td>
<td>losartan with HCTZ 50/12.5, 100/25 mg&lt;br&gt;Hyzaar®</td>
<td></td>
</tr>
<tr>
<td>moexipril with HCTZ 7.5/12.5, 15/25 mg&lt;br&gt;Uniretic®</td>
<td>olmesartan with HCTZ 20/12.5, 40/12.5, 40/25 mg&lt;br&gt;Benicar HCT®</td>
<td></td>
</tr>
<tr>
<td>quinapril and HCTZ 10/25, 20/12.5, 20/25 mg&lt;br&gt;Accuretic®</td>
<td>telmisartan and HCTZ 40/12.5, 80/12.5 mg&lt;br&gt;Micardis Plus®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>valsartan with HCTZ 80/12.5, 150/12.5 mg&lt;br&gt;Diovan HCT®</td>
<td></td>
</tr>
</tbody>
</table>

Diuretic plus potassium sparing agents

| HCTZ with amiloride 50/5 mg<br>Moduretic® | amlodipine with benazepril 2.5/10, 5/10, 5/20 mg<br>Lotrel® | |
| HCTZ with triamterene 25/37.5 mg<br>Dyazide®, Maxzide-25®, 25/75 mg<br>Maxzide® | enalapril with diltiazem 5/180 mg<br>Teczem® | |
| | enalapril with felodipine 5/2.5, 5/5 mg<br>Lexxel® | |
| | trandolapril with verapamil 1/240, 2/240, 4/240 mg<br>Tarka® | |

HCTZ = hydrochlorothiazide; ACE-I = ACE Inhibitor; ARB = angiotensin II receptor antagonist
Note: These tables outline more commonly used preparations available as of 05 November 2004
Table 37. Doses for antihypertensives in hypertension.

<table>
<thead>
<tr>
<th><strong>Thiazide and thiazide-like diuretics</strong></th>
<th><strong>Calcium channel blockers</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>chlorothiazide</td>
<td>amlodipine</td>
</tr>
<tr>
<td>0.5–2 g daily in 1–2 divided dose</td>
<td>Initially 2.5–5 mg once daily. Maintenance up to 10 mg once daily.</td>
</tr>
<tr>
<td></td>
<td>felodipine</td>
</tr>
<tr>
<td></td>
<td>Initially 2.5–5 mg once daily. Maintenance up to 10 mg once daily.</td>
</tr>
<tr>
<td>hydrochlorothiazide</td>
<td>nifedipine</td>
</tr>
<tr>
<td>12.5 mg to 50 mg once daily</td>
<td>Standard release: Initially 10–20 mg 2–3 times daily. Maintenance 20–30 mg 3–4 times daily. CR: Initially 30 mg once daily. Maintenance 30–120 mg once daily</td>
</tr>
<tr>
<td></td>
<td>verapamil</td>
</tr>
<tr>
<td></td>
<td>SR: Initially 120–180 mg 2–3 times daily. Maintenance up to 480 mg 2–3 times daily. ER: Initially 120–180 mg once daily. Maintenance up to 480 mg daily in 1–2 divided doses.</td>
</tr>
<tr>
<td>chlorothalidone</td>
<td></td>
</tr>
<tr>
<td>25–100 mg once daily</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>chlorthalidone</td>
<td></td>
</tr>
<tr>
<td>25–100 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>indapamide</td>
<td></td>
</tr>
<tr>
<td>1.25 mg to 5 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td></td>
</tr>
<tr>
<td>atenolol</td>
<td></td>
</tr>
<tr>
<td>25–100 mg once daily</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>metoprolol</td>
<td></td>
</tr>
<tr>
<td>Initially 50–100 mg in 1–2 divided doses. Maintenance 100–450 mg once or twice daily.</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>carvedilol</td>
<td></td>
</tr>
<tr>
<td>3.125–6.25 mg twice daily. Maintenance 12.5–25 mg twice daily</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>nadolol</td>
<td></td>
</tr>
<tr>
<td>Initially 40 once daily. Maintenance 40–320 mg once daily.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>labetalol</td>
<td></td>
</tr>
<tr>
<td>Initially 100 mg twice daily. Maintenance 200–400 mg twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>propranolol</td>
<td></td>
</tr>
<tr>
<td>Initially 20–40 mg twice daily or 80 mg SR once daily. Maintenance 120–640 mg daily in 2–3 divided doses or once daily SR.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>bisoprolol</td>
<td></td>
</tr>
<tr>
<td>Initially 2.5–5 mg once daily. Maintenance 5–20 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>diltiazem</td>
<td></td>
</tr>
<tr>
<td>CR: Initially 180–240 mg once daily. Maintenance up to 540 mg once daily. SR: Initially 60–120 mg twice daily. Maintenance up to 360 mg daily in divided doses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>nisoldipine</td>
<td></td>
</tr>
<tr>
<td>Initially 20 mg once daily Increase dose by 10 mg weekly up to a max dose of 60 mg daily Usual maintenance is 20–40 mg once daily</td>
<td></td>
</tr>
</tbody>
</table>

Note: Table continued on next page – see footnotes on next page
### Table 37. Doses for antihypertensives in hypertension (continued)

<table>
<thead>
<tr>
<th>ACE inhibitors‡</th>
<th>Angiotensin II receptor antagonists‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>benazepril‡</strong></td>
<td><strong>candesartan‡</strong></td>
</tr>
<tr>
<td>Initially 10 mg once daily (5 mg once daily‡). Maintenance 20–40 mg daily in 1–2 divided doses.</td>
<td>Initially 8 mg once daily (2 mg once daily‡). Maintenance 8–32 mg once daily.</td>
</tr>
<tr>
<td><strong>lisinopril‡</strong></td>
<td><strong>losartan‡</strong></td>
</tr>
<tr>
<td>Initially 5–10 mg once daily (2.5 mg once daily‡). Maintenance 10–40 mg once daily.</td>
<td>Initially 50 mg once daily (25 mg once daily). Maintenance 50–100 mg daily in 1–2 divided doses</td>
</tr>
<tr>
<td><strong>captopril‡</strong></td>
<td><strong>eprosartan‡</strong></td>
</tr>
<tr>
<td>Initially 12.5–25 mg 2–3 times daily (6.25 mg once daily‡). Maintenance 25–150 mg daily in 2–3 times daily.</td>
<td>Initially 600 mg once daily (400 mg once daily‡). Maintenance 600–800 mg daily in 1–2 divided doses.</td>
</tr>
<tr>
<td><strong>quinapril‡</strong></td>
<td><strong>telmisartan‡</strong></td>
</tr>
<tr>
<td>Initially 10–20 mg once daily (2.5 mg once daily‡). Maintenance 20–80 mg daily in 1–2 divided doses.</td>
<td>Initially 40 mg once daily (20 mg once daily‡). Maintenance 40–80 mg once daily.</td>
</tr>
<tr>
<td><strong>enalapril‡</strong></td>
<td><strong>valsartan</strong></td>
</tr>
<tr>
<td>Initially 5 mg once daily (2.5 mg once daily‡). Maintenance 10–40 mg daily in 1–2 divided doses.</td>
<td>Initially 80 mg once daily. Maintenance 80–320 mg once daily.</td>
</tr>
<tr>
<td><strong>ramipril‡</strong></td>
<td></td>
</tr>
<tr>
<td>Initially 2.5 mg once daily (1.25 mg once daily‡). Maintenance 2.5–20 mg daily in 1–2 divided doses.</td>
<td></td>
</tr>
<tr>
<td><strong>moexipril</strong></td>
<td></td>
</tr>
<tr>
<td>Initially 7.5 mg once daily Maintenance 7.5–30 mg daily in 1–2 divided doses.</td>
<td></td>
</tr>
<tr>
<td><strong>trandolapril‡</strong></td>
<td></td>
</tr>
<tr>
<td>Initially 1 mg once daily (0.5 mg once daily‡). Maintenance 1–8 mg daily in 1–2 divided doses.</td>
<td></td>
</tr>
<tr>
<td><strong>fosinopril‡</strong></td>
<td></td>
</tr>
<tr>
<td>Initially 10 mg once daily (5 mg once daily‡). Maintenance 20–80 mg daily in 1–2 divided doses.</td>
<td></td>
</tr>
<tr>
<td><strong>eprosartan‡</strong></td>
<td></td>
</tr>
<tr>
<td>Initially 600 mg once daily (400 mg once daily‡). Maintenance 600–800 mg daily in 1–2 divided doses.</td>
<td></td>
</tr>
<tr>
<td><strong>irbesartan‡</strong></td>
<td></td>
</tr>
<tr>
<td>Initially 150 mg once daily (75 mg once daily‡). Maintenance 150–300 mg once daily.</td>
<td></td>
</tr>
<tr>
<td><strong>olmesartan</strong></td>
<td></td>
</tr>
<tr>
<td>Initially 20 mg once Maintenance dose is 20–40 mg once daily</td>
<td></td>
</tr>
</tbody>
</table>

SR = sustained release; CR = controlled release

‡ For patients at risk of first dose hypotension or acute renal impairment (see page 112) the initial dose should generally be the dose indicated in the brackets.

Note: Where maintenance doses are indicated, this represents the usual maintenance dose in patients with hypertension and does not necessarily represent the maximum recommended dose according to the approved product information for each preparation.
<table>
<thead>
<tr>
<th>Class</th>
<th>Adverse effects</th>
<th>Contraindications</th>
</tr>
</thead>
</table>
| Thiazide and thiazide-like diuretics | • Common adverse effects include dizziness, weakness, muscle cramps, polyuria, postural hypotension, hyponatremia, hypokalemia, hyperuricemia, hypochloremic alkalosis and hypomagnesemia.  
  • Hyperglycemia, rash, hypercalcemia, blurred vision, impotence and dyslipidemia are infrequent adverse effects. Rare effects include hepatic events, thrombocytopenia and pancreatitis.  
  • All thiazide and thiazide-like diuretics have a sulfonamide group in their structure; therefore, they should not be used in patients who have had a serious allergic reaction to sulfonamides.  
  • It is important to note that the low doses of thiazide and thiazide-like diuretics which are currently recommended in the treatment of hypertension are unlikely to cause adverse effects on lipids, glucose or other electrolytes.  
  In addition, the risk of male sexual dysfunction is low with these doses. Hence, the use of thiazide and thiazide-like diuretics is not considered contraindicated in patients with diabetes. | • anuria  
• severe renal impairment  
• Addison’s disease  
• hepatic pre-coma or coma. Should also be avoided in the presence of gout. |
| β-blockers                      | • Common adverse effects include nausea, diarrhea, bronchospasm, dyspnea, cold extremities, exacerbation of Raynaud’s syndrome, bradycardia, hypotension, postural hypotension (labetalol), heart failure, heart block, fatigue, dizziness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, depression, and alteration of glucose and lipid metabolism (see drug induced hypoglycemia, Appendix 1, page 195). | • reversible airways disease (e.g. asthma, COPD)  
• bradycardia  
• sick sinus syndrome  
• 2nd or 3rd degree atrioventricular block  
• shock (cardiogenic and hypovolemic)  
• severe hypotension. |

Note: Table continued on next page
Table 38. Adverse effects and contraindications of antihypertensives (continued).

<table>
<thead>
<tr>
<th>Class</th>
<th>Adverse effects</th>
<th>Contraindications</th>
</tr>
</thead>
</table>
| Calcium channel blockers     | • Common adverse effects include headache, flushing, dizziness, peripheral edema, nausea, abdominal pain, gastrointestinal reflux, gingival hyperplasia (mainly with nifedipine), bradycardia (diltiazem and verapamil) and constipation (verapamil). 78, 190, 349 | • cardiogenic shock.  
• diltiazem and verapamil are CI in  
  - severe bradycardia  
  - sick sinus syndrome  
• 2nd or 3rd degree heart block (without pacemaker) or hypotension.  
• verapamil is also CI in atrial fibrillation or flutter complicating Wolff-Parkinson-White Syndrome. 190 |
|                              | • Flushing, headache, dizziness and peripheral edema are more common with the dihydropyridine CCBs. 190 |                                                                                  |
| ACE Inhibitors               | • Dry cough is a very common adverse effect. 190, 317  
• Other common adverse effects include hypotension, hyperkalemia, headache, dizziness, fatigue, nausea and renal impairment. The risk of first dose hypotension, acute renal impairment and potassium retention can be reduced by recognizing and minimizing risk factors (see page 112).  
• Less frequent events include skin rash, taste disturbance, hematological disturbances and hepatotoxicity. 78  
Angioedema is a rare, but potentially life threatening, adverse effect of all ACE inhibitors, occurring in 0.1–0.2% of patients treated with an ACE inhibitor. 350  
Importantly, whilst most common the first week of treatment, ACE inhibitor associated angioedema may be delayed for up to several years before it occurs for the first time, 78 and it may recur if the initial episode goes unrecognized. | • pregnancy  
• patients with a history of angioedema associated with previous treatment with an ACE inhibitor  
• aortic stenosis or cardiac outflow tract obstruction  
• bilateral renal artery stenosis. 78  
• hyperkalemia |

Note: Table continued on next page
Table 38. Adverse effects and contraindications of antihypertensives (continued).

<table>
<thead>
<tr>
<th>Class</th>
<th>Adverse effects</th>
<th>Contraindications</th>
</tr>
</thead>
</table>
| ARBs  | • Common adverse effects include dizziness, headache, weakness, fatigue and hyperkalemia. 190, 317  
• Less frequent events include rash, hypotension, renal impairment, taste disturbance, hepatic events and migraine. 190  
The risk of first dose hypotension, acute renal impairment and potassium retention can be reduced by recognizing and minimizing risk factors (see page 112). Cough is less frequent than with ACE-I. 78  
Case series and case reports have described angioedema with ARBs. The incidence appears to be lower than that with ACE inhibitors; however, extreme caution is advised if considering the use of an ARBs in patients with a history of angioedema with ACE-I therapy. 351 | Same as for ACE inhibitors — see above. |
ACE inhibitors and ARBs— reducing the risks of first dose hypotension, acute renal impairment and hyperkalemia

Risk factors
- dehydration or high diuretic dose
- salt depletion
- elderly age
- heart failure
- malignant or renin-dependent hypertension
- aortic stenosis
- renal artery stenosis (especially bilateral renal artery stenosis)
- pre-existing renal impairment
- low pre-treatment blood pressure
- concomitant use of NSAIDs, COX-2 inhibitors, potassium sparing diuretics or potassium supplements
- postural hypotension (moderate to severe autonomic neuropathy)

Minimizing the risks
- Correct dehydration.
- Consider withdrawing, suspending or decreasing the dose of diuretics.
- Relax salt restriction.
- Use short acting agent when possible
- Use a small initial dose of ACE inhibitor or ARBs. See Table 37, page 107 for dosage recommendations for hypertension. Note that in Table 37, the dose indicated in brackets is the recommended starting dose for patients with any of the risk factors outlined above.
- Discontinue NSAID or COX-2 inhibitor therapy when possible.
- Discontinue potassium sparing diuretics and potassium supplements before initiating ACE inhibitors or ARBs.
- Monitor patient carefully. Before initiating therapy with ACE inhibitors or ARBs, measure blood pressure, serum creatinine and electrolytes. These tests should be repeated within one week of starting therapy in patients at risk of complications, and within one month in all other patients.
Table 39. Selected drug interactions associated with antihypertensives.

<table>
<thead>
<tr>
<th>Class</th>
<th>Interacting drugs</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazide and thiazide-like diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Increased risk of first dose hypotension (see page 112).</td>
<td></td>
</tr>
<tr>
<td>calcium, vitamin D, calcitriol</td>
<td>Increased risk of hypercalcemia. Monitor plasma calcium levels.</td>
<td></td>
</tr>
<tr>
<td>digoxin</td>
<td>Hypokalemia induced by thiazide and thiazide-like diuretics may increase the risk of digoxin toxicity. Monitor potassium levels.</td>
<td></td>
</tr>
<tr>
<td>drugs which prolong QT interval (e.g. amiodarone, quinidine, TCAs, phenothiazines)</td>
<td>Hypokalemia induced by thiazide and thiazide-like diuretics may increase the risk of arrhythmia. Use of very low or low doses of thiazide and thiazide-like diuretics minimizes the risk of hypokalemia.</td>
<td></td>
</tr>
<tr>
<td>lithium</td>
<td>Increased serum lithium concentrations with significant risk of toxicity. Lithium levels may increase within 3–10 days. Monitor lithium levels and reduce dose as necessary.</td>
<td></td>
</tr>
<tr>
<td>NSAIDs and COX-2 inhibitors</td>
<td>Reduced antihypertensive and natriuretic effects. Increased risk of renal impairment. Monitor and use very low or low dose thiazide and thiazide-like diuretics only.</td>
<td></td>
</tr>
</tbody>
</table>

Note: Table continued on next page
Table 39. Selected drug interactions associated with antihypertensives (continued).

<table>
<thead>
<tr>
<th>Class</th>
<th>Interacting drugs</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td>amiodarone</td>
<td>Increased risk of bradycardia. Monitor cardiac function.</td>
</tr>
<tr>
<td></td>
<td>antihyperglycemic agents</td>
<td>See drug induced hypoglycemia, Appendix 1, page 195.</td>
</tr>
<tr>
<td></td>
<td>cimetidine</td>
<td>Reduced hepatic metabolism of metoprolol and propranolol which may increase the risk of adverse effects. Avoid combination or reduce dose of β-blocker as required.</td>
</tr>
<tr>
<td></td>
<td>diltiazem, verapamil, negative inotropes (e.g. flecainide, quinidine, procainamide)</td>
<td>Enhanced negative inotropic effects resulting in increased risk of bradycardia and heart block. Monitor cardiac function.</td>
</tr>
<tr>
<td></td>
<td>hepatic enzyme inducers (e.g. phenytoin, rifampin)</td>
<td>Increased metabolism of β-blockers (excluding atenolol and sotalol). Increase dose of β-blocker or use atenolol which is renally cleared.</td>
</tr>
<tr>
<td></td>
<td>NSAIDs and COX-2 inhibitors</td>
<td>Impaired antihypertensive effect. Avoid concurrent use or monitor blood pressure and adjust treatment if necessary.</td>
</tr>
<tr>
<td></td>
<td>SSRIs (especially fluoxetine, paroxetine and sertraline)</td>
<td>Reduced hepatic metabolism of metoprolol and propranolol; therefore, increased risk of adverse effects. Reduce dose of β-blocker or avoid interaction by using atenolol or a less interacting SSRI.</td>
</tr>
</tbody>
</table>

Note: Table continued on next page
Table 39. Selected drug interactions associated with antihypertensives (continued).

<table>
<thead>
<tr>
<th>Class</th>
<th>Interacting drugs</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium channel blockers</strong>*</td>
<td>antiarrhythmic agents (e.g. amiodarone, quinidine, mexiletine)</td>
<td>Increased risk of heart failure, bradycardia and proarrhythmic effects with diltiazem and verapamil. Monitor cardiac function if combined use is essential.</td>
</tr>
<tr>
<td></td>
<td>β-blockers</td>
<td>Increased risk of bradycardia and heart block with diltiazem and verapamil. Plasma concentrations of metoprolol and propranolol may be increased by diltiazem and verapamil. Avoid combined use, but if essential monitor cardiac function.</td>
</tr>
<tr>
<td></td>
<td>carbamazepine</td>
<td>Induces metabolism of all CCBs leading to reduced plasma concentrations and effects of the CCB. Diltiazem and verapamil may inhibit metabolism of carbamazepine leading to increased plasma concentrations and adverse effects of carbamazepine. Monitor effects.</td>
</tr>
<tr>
<td></td>
<td>cimetidine</td>
<td>May inhibit metabolism of all CCBs leading to increased plasma concentrations and adverse effects of the CCB. Monitor effects. Consider use of a different H₂-antagonist.</td>
</tr>
<tr>
<td></td>
<td>cyclosporine</td>
<td>Cyclosporine plasma concentrations and toxicity may be increased with diltiazem and verapamil. Monitor cyclosporine concentrations. Such combinations are used deliberately in some settings to reduce dose requirements of cyclosporine. Risk of gingival hyperplasia with nifedipine may be increased. Encourage good dental hygiene.</td>
</tr>
<tr>
<td></td>
<td>digoxin</td>
<td>Increased digoxin plasma concentrations and additive effects on heart rate and conduction with diltiazem and verapamil. Monitor digoxin levels and signs of toxicity.</td>
</tr>
<tr>
<td></td>
<td>grapefruit juice</td>
<td>A normal glass of grapefruit juice may cause a marked increase in bioavailability and hence effects of dihydropyridine CCBs (especially felodipine, and to a lesser extent nifedipine). Advise patients not to dramatically change grapefruit juice consumption and to be as consistent as possible.</td>
</tr>
<tr>
<td></td>
<td>hepatic enzyme inducers (e.g. phenytoin, rifampin)</td>
<td>Increased metabolism of all CCBs leading to a decrease in plasma concentrations and effects of the CCB. Monitor effects.</td>
</tr>
</tbody>
</table>

Note: Table continued on next page
Table 39. Selected drug interactions associated with antihypertensives (continued).

<table>
<thead>
<tr>
<th>Class</th>
<th>Interacting drugs</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium channel blockers (cont.)</strong></td>
<td>statins</td>
<td>Metabolism of statins may be decreased by verapamil and diltiazem which may increase the risk of adverse effects of the statin. Monitor effects and advise patients to report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.</td>
</tr>
<tr>
<td></td>
<td>nefazodone</td>
<td>Nefazodone may inhibit metabolism of all CCBs. Verapamil or diltiazem may reduce metabolism of nefazodone and increase risk of nefazodone adverse effects. Monitor effects.</td>
</tr>
<tr>
<td></td>
<td>SSRIs (fluoxetine, fluvoxamine)</td>
<td>May inhibit metabolism of all CCBs leading to increases in plasma concentrations of CCBs. Monitor effects.</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>antihyperglycemic agents</td>
<td>See drug induced hypoglycemia, Appendix 1, page 195</td>
</tr>
<tr>
<td></td>
<td>diuretics</td>
<td>Increased risk of first dose hypotension when initiating ACE inhibitors (see page 112).</td>
</tr>
<tr>
<td></td>
<td>general anesthetics</td>
<td>Risk of marked hypotension. Monitor blood pressure closely.</td>
</tr>
<tr>
<td></td>
<td>lithium</td>
<td>Lithium excretion may be reduced with increased risk of toxicity. Monitor lithium levels.</td>
</tr>
<tr>
<td></td>
<td>potassium sparing diuretics and potassium supplements</td>
<td>Increased risk of hyperkalemia. Cease prior to commencing ACE inhibitor (see page 112).</td>
</tr>
<tr>
<td></td>
<td>NSAIDs and COX-2 inhibitors</td>
<td>Reduced hypotensive effects, and increased risk of hyperkalemia and renal failure. Avoid combined use if possible (see page 112). If concomitant use is essential, monitor blood pressure, renal function and potassium levels closely.</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td>Same as for ACE inhibitors — see above</td>
<td></td>
</tr>
</tbody>
</table>

---

* Diltiazem and verapamil inhibit cytochrome CYP3A4 and hence could potentially increase blood levels and effects of other drugs metabolized by CYP3A4 (e.g. repaglinide, pioglitazone, sildenafil, sertraline, alprazolam, midazolam, triazolam, and methadone). Blood levels of all CCBs could be increased by other drugs which inhibit CYP3A4 (e.g. azole antifungals, erythromycin and clarithromycin).

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; COX-2 = cyclo-oxygenase-2 inhibitor; SSRI = selective serotonin reuptake inhibitor; CCB = calcium channel blocker

Table adapted from Drug Information Handbook and Facts and Comparisons78, 190
DYSLIPIDEMIA

Dyslipidemia is a major modifiable cardiovascular risk factor, in addition to smoking, hypertension and obesity. Dyslipidemia may also contribute to the effect of the major non-modifiable risk factors (e.g. age, gender and family history).9

The most common pattern of dyslipidemia in type 2 diabetes is elevated triglyceride (TG) levels and decreased high density lipoprotein (HDL) cholesterol levels. The concentration of low density lipoprotein (LDL) cholesterol is usually not significantly different from people without diabetes; however, there is a preponderance of smaller, denser LDL cholesterol particles which may increase the atherogenicity even if the absolute concentration of LDL cholesterol is not significantly increased.27

In the Multiple Risk Factor Intervention Trial (MRFIT), total cholesterol as well as cigarette smoking and blood pressure predicted the development of CVD in both patients with and without diabetes. As shown in Figure 2 below, the shape of the curve relating CVD mortality to cholesterol in patients with diabetes is similar to that in individuals without diabetes. However, for any given level of cholesterol, the incidence of CVD in diabetes is increased 2–4 times.352

Figure 2. The incidence of cardiovascular disease deaths in patients with or without diabetes from the MRFIT study.352
The evidence

In type 2 diabetes, improvement of lipid values occurs with improved glycemic control. However, normalization of lipid levels does not occur. Hence, further intervention with non-pharmacological measures, such as a lipid lowering diet and/or pharmacological measures aimed at the particular lipid abnormality, is required.

Relatively few prospective studies of lipids as predictors of CHD have been reported in patients with type 2 diabetes. Almost all outcome studies of lipid lowering agents have excluded patients with diabetes. Table 40, page 119 provides an overview of the randomized controlled trials examining the influence of lipid lowering therapy on CVD outcomes which have included patients with type 2 diabetes.

Direct interpretation of the results of the Scandinavian Simvastatin Survival Study (4S) and application to the type 2 diabetes population requires consideration. This trial excluded patients with TG levels > 220 mg/dL. As hypertriglyceridemia is common in patients with diabetes, the results of the 4S study may not be generalizable to the usual type 2 diabetes population. The Cholesterol and Recurrent Events (CARE) trial results highlighted the benefits, in terms of reduced CVD events, of lipid lowering in patients with diabetes without grossly elevated LDL cholesterol. Although statistical significance was achieved in these trials, their results are based on post hoc subgroup analyses, and hence should be interpreted with caution.

Based on the results of secondary prevention trials, it appears that a reduction in LDL cholesterol of approximately 38 mg/dL, maintained for 5–6 years, reduces the risk of CVD events by about one quarter to one third in patients with pre-existing CHD, with or without diabetes. However, as type 2 diabetes is now considered a ‘CHD risk equivalent’ (see page 94), focus also needs to be directed to the outcomes of primary prevention trials, which have been limited to date. Several primary prevention outcome trials are currently underway.

Evidence for target lipid levels in type 2 diabetes

In contrast to evidence available for other CVD risk factors, such as hypertension, there is a paucity of information regarding target lipid levels for patients with type 2 diabetes. Even within the general population there is a lack of consensus regarding the optimal lipid levels for patients with and without CHD.
Table 40. Overview of randomized controlled clinical trials evaluating effects of lipid lowering agents in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean baseline lipid (mg/dL)</th>
<th>% LDL reduction</th>
<th>Significant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARE\textsuperscript{357}</td>
<td>Pravastatin 40 mg daily vs placebo. Mean duration 5 years. 586 men and postmenopausal women aged 21–75 years, prior MI</td>
<td>TG: 164 LDL: 136 HDL: 37.6</td>
<td>RR = 0.75* (CHD death, non-fatal MI, CABG and PTCA), p = 0.05, borderline significance. ARR in patients with diabetes vs those without = 2.9%. NNT 12</td>
</tr>
<tr>
<td>LIPID\textsuperscript{359}</td>
<td>Pravastatin 40 mg daily vs placebo. Mean duration 6.1 years. 782 men and women aged 31–75 years, prior MI or unstable angina</td>
<td>NA</td>
<td>RR = 0.84* (CHD death and non-fatal MI), not significant NNT 28</td>
</tr>
<tr>
<td>4S\textsuperscript{355, 356}</td>
<td>Simvastatin 20–40 mg daily vs placebo. Mean duration 5.4 years. 202 men aged 35–70 years, prior MI, or active, stable angina pectoris</td>
<td>TG: 150 LDL: 186 HDL: 43 (excluded patients with TG &gt; 220)</td>
<td>Using guidelines for diagnosis of diabetes post 1997: RR = 0.58 (CHD death and non-fatal MI), p = 0.001 NNT 5</td>
</tr>
<tr>
<td>VA-HIT study\textsuperscript{360}</td>
<td>Gemfibrozil 600 mg twice daily vs placebo. Mean duration 5.1 years. 627 men aged &lt; 74 years, prior MI or angina</td>
<td>TG: 160 LDL: 116 HDL:32</td>
<td>RR = 0.76* (CHD death and non-fatal MI), p = 0.05 NNT 13</td>
</tr>
</tbody>
</table>

NA = data not available; ARR = absolute risk reduction; CARE = Cholesterol and Recurrent Events; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; 4S = Scandinavian Simvastatin Survival Study; VA-HIT = Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trial; RR = relative risk

* Study not powered adequately to detect effects of treatment reliably in subgroups, such as patients with diabetes.

Note: Table continued on next page
Table 40. Overview of randomized controlled clinical trials evaluating effects of lipid lowering agents in patients with type 2 diabetes (continued).

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean baseline lipid (mg/dL)</th>
<th>% LDL reduction</th>
<th>Significant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helsinki Heart Study</td>
<td>TG: 220 LDL: 201 HDL: 41.6</td>
<td>10</td>
<td>RR = 0.32* (CHD death and non-fatal MI), not significant NNT 14</td>
</tr>
<tr>
<td>SENDCAP Study</td>
<td>TG: 184 LDL: 141 HDL: 39</td>
<td>9.6</td>
<td>RR = 0.31 (MI or new ischemic change on electrocardiograph) p = 0.01 NNT 6</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>NA</td>
<td>NA</td>
<td>RR = 0.56* (MI, unstable angina or sudden cardiac death), not significant NNT 27</td>
</tr>
<tr>
<td>CARDS</td>
<td>TG 174 LDL 119 HDL 54</td>
<td>39.5</td>
<td>RR = 0.63 (Fatal and non-fatal MI, unstable angina, coronary revascularizations, fatal and non-fatal stroke) P = 0.001 NNT 27</td>
</tr>
</tbody>
</table>

* Study not powered adequately to detect effects of treatment reliably in subgroups, such as patients with diabetes.

NA = data not available; SENDCAP = St Mary’s, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; RR= relative risk

**Strong Heart Study**

The Strong Heart Study investigated the risk of increasing levels of LDL cholesterol in over 2000 American Indians with type 2 diabetes without pre-existing CHD.\(^{366}\) It found that for every 10 mg/dL increase in LDL cholesterol levels, CVD risk increased by 12%. For every 10 mg/dL
decrease in HDL cholesterol levels, CVD risk increased by 22%. The authors suggested that these results are applicable to the general type 2 diabetes population, as well as to other ethnic groups that have high rates of diabetes, insulin resistance and obesity, such as American Indians. The results also suggest that even when LDL cholesterol levels are within acceptable ranges, further lowering may lead to further reduction in CVD risk, and that management of dyslipidemia in patients with type 2 diabetes should be aggressive.

Similarly, in the UKPDS, it was found that for every 39 mg/dL increase in LDL cholesterol, there was a 1.57 fold increased risk of CVD. For every 3.9 mg/dL increase in HDL cholesterol level, there was a 0.15 fold decrease in risk of CVD.

**Heart Protection Study**

The aim of the Heart Protection Study (HPS) was to assess the effects of lipid lowering drug therapy and antioxidant vitamin supplementation on mortality and major morbidity in a wide range of patients at high risk of CHD. HPS involved 15,454 men and 5082 women, aged between 40 and 80 years, followed for an average of five years. All participants were regarded to be at high risk of CHD death over the next five years due to coronary disease (definite or probable clinical diagnosis of MI, unstable angina, stable angina, percutaneous transluminal angioplasty (PTCA) or CABG), occlusive disease of non-coronary arteries (stroke, transient ischemic attack, peripheral vascular disease), diabetes mellitus or treated hypertension (in men aged 65 years and over). Therefore, HPS is a mixed primary and secondary prevention trial. The average baseline total cholesterol level was 227 mg/dL, LDL cholesterol level 131 mg/dL, HDL cholesterol level 41 mg/dL and TG level 158 mg/dL

Patients were randomized to either simvastatin 40 mg at night or matching placebo, and two vitamin capsules each containing vitamin E 300 mg, vitamin C 125 mg and beta-carotene 10 mg, or matching placebo. The primary outcomes were all-cause mortality, CHD mortality, and all mortality from causes other than CHD for simvastatin versus placebo. For the antioxidant vitamin supplementation, the primary outcome measures were total CHD and fatal CHD.

The major results of HPS were:
- significant ARR in all-cause mortality, major vascular and CHD events, ischemic stroke and non-fatal MI (subgroup analysis not provided);
• significant ARR in vascular events in patients with and without CHD at baseline;
• significant ARR in vascular events in women, the elderly (70–85 years) and those with LDL cholesterol levels < 116 mg/dL at baseline;
• significant ARR in vascular events for patients with diabetes mellitus, cerebrovascular disease or peripheral vascular disease and free from CHD at baseline;
• similar RRR of a vascular event in patients with baseline LDL cholesterol levels < 116 mg/dL compared to those with higher LDL cholesterol levels at baseline; and
• benefits of statin therapy are in addition to other CVD risk reducing drug therapies, such as aspirin, ACE inhibitors or β-blockers.

With respect to the vitamin supplementation, there was evidence that antioxidant vitamins do not prevent deaths, MI, stroke or other vascular disease outcomes.370

The results of HPS with respect to statin therapy have:
• confirmed the National Heart, Lung, and Blood Institute (NHLBI) recommendations of considering treatment with lipid lowering therapy (diet/lifestyle plus drug therapy if needed) in patients at high risk of a CHD event;
• reinforced that any downward movement in plasma lipid levels in high risk patients yields benefit; and
• demonstrated benefit in terms of reduced vascular and coronary events with no evidence of harm when reducing LDL cholesterol levels to an average of 69 mg/dL with statin therapy.

Despite the size and breadth of HPS, many questions regarding statin therapy in the management of dyslipidemia remain unanswered. These include:
• the lowest threshold to which LDL cholesterol levels can be reduced while retaining benefit and not causing harm;
• target lipid levels for all lipoproteins, in particular HDL cholesterol levels and triglyceride levels;
• the effect of statin therapy on all-cause mortality in high risk patients without CHD; and
• the effect of statin therapy on stroke recurrence in patients with cerebrovascular disease (with or without CHD).
Collaborative Atorvastatin Diabetes Study

The aim of the Collaborative Atorvastatin Diabetes Study (CARDS) was to assess the effectiveness of a 10 mg daily dose of atorvastatin in the primary prevention of CVD in patients with type 2 diabetes. CARDS was the first study to examine the effects of statin therapy exclusively in patients with type 2 diabetes. The study was a multicenter, randomized, placebo-controlled study involving 2838 patients between 40–75 years of age with type 2 diabetes and no previous history of CVD (MI, angina, CVA, coronary vascular surgery, or severe PVD). Participants also had to have at least one other risk factor for, or manifestation of, cardiovascular disease such as retinopathy, micro- or macroalbuminuria, cigarette smoking, or history of hypertension. At baseline, all participants were required to have an LDL-cholesterol concentration of 162 mg/dL or less and serum triglycerides of 600 mg/dL or less. The mean baseline total cholesterol level was 207 mg/dL, LDL cholesterol level 119 mg/dL, HDL cholesterol level 54 mg/dL and TG level 174 mg/dL.

A total of 1428 patients were randomized to receive 10 mg atorvastatin once daily and 1410 were randomized to receive matching placebo. The primary endpoint was the first occurrence of the following: acute coronary heart disease event (fatal or non-fatal myocardial infarction including silent infarction, unstable angina, resuscitated cardiac arrest, other acute coronary heart disease death), coronary revascularization procedures, or stroke.

CARDS was terminated two years early, after 3.9 years median follow up, because prespecified termination criteria for efficacy had been met. The results included a significant 37% reduction in the primary endpoint in the atorvastatin group versus placebo. When analyzed separately, risk reductions of 36% in acute coronary heart disease events, 31% in coronary revascularizations, and 48% in the rate of stroke, occurred in the atorvastatin group when compared with placebo (significance levels not provided).

The authors suggested that atorvastatin 10 mg daily is safe and effective in the primary prevention of cardiovascular disease events, including stroke, in patients with type 2 diabetes who do not have elevated cholesterol. The authors also claimed that an individual’s risk factors, in addition to LDL cholesterol, should be considered when making a decision to initiate statin therapy. However, it is important to note that the baseline lipid levels for the patients enrolled in CARDS may not be reflective of the lipid profiles typically seen in patients with type 2 diabetes.
In contrast to HPS and CARDS, two other large scale statin trials involving subgroups with large numbers of type 2 diabetic patients showed no significant difference in outcomes between patients randomized to intervention therapy versus existing therapy or placebo. A discussion of these two trials follows.

**The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial**

The aim of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) was to determine whether pravastatin in comparison to usual care reduces all-cause mortality in older, hypertensive, moderately hypercholesterolemic patients with at least one additional CHD risk factor. ALLHAT-LLT involved 10355 patients including 3638 type 2 diabetics, randomized to pravastatin 40 mg daily or existing therapy. The design was open-label with a mean follow up of 4.8 years. Several important subgroups were represented with a distribution of 49% women, 38% black, 35% diabetic, 23% Hispanic, and 14% with a history of CHD. Mean baseline total cholesterol was 224 mg/dl, LDL cholesterol was 146 mg/dl, HDL cholesterol was 48 mg/dl, and triglycerides were 152 mg/dl.

There were no significant differences in the primary or secondary endpoints of all-cause mortality or coronary event rates, respectively. These outcomes were irrespective of the presence of type 2 diabetes at baseline. The results of this study are somewhat controversial due to evidence from other recent large trials regarding the efficacy and safety of statins as prevention and treatment of atherosclerotic cardiovascular disease. Given the small percentage reduction of total cholesterol (10%) and LDL cholesterol (about 17%), the power of the study to detect statistically significant differences in outcomes measured was inadequate. The reduction in total cholesterol was about half that seen in other long-term, large scale statin trials.

**The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm**

The Anglo Scandinavian Cardiac Outcomes Trial-substudy The Anglo Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) was designed to compare the effects of long-term therapy with a statin vs placebo (both arms having a matched antihypertensive regimen). The primary outcome was the combined endpoint of non-fatal myocardial infarction, silent myocardial infarction, and fatal coronary heart disease.
The study included 10,305 patients, primarily men (81%) with a mean age of 63 years, randomized to atorvastatin 10 mg daily or placebo, with a median follow-up period of 3.3 years. The study was originally designed for a follow-up of 5 years but was terminated early due to a relative risk reduction in the primary endpoint of 36% (p=0.0005). Interestingly, there was no significant difference found in the diabetic subgroup of 2532 patients. The authors suggest that this is due to reduced power resulting from a shortened follow-up period. Additionally, a higher number of patients in the diabetic subgroup of the placebo arm received statin therapy independent of the study.

**Target levels**

Evidence from clinical trials regarding the optimal target lipid concentrations for patients with diabetes are lacking.

The recommended targets for lipid concentrations for patients with diabetes are:

- **Total cholesterol**: ≤ 200 mg/dL
- **Triglycerides**: < 150 mg/dL
- **HDL cholesterol**: > 40 mg/dL (men) > 50 mg/dL (women)
- **LDL cholesterol**: < 100 mg/dL

It is recommended that fasting plasma lipid concentrations be measured at diagnosis of diabetes and annually thereafter. If the lipid profile is abnormal, or if the patient is on or requires lipid lowering therapy or develops overt macrovascular disease, lipid concentrations should be re-evaluated every 3–6 months.

It is important to note that lipid levels decline within 24 hours of an acute MI and may remain low for 2–3 months. For this reason, if a blood sample for measurement of plasma lipids has not been drawn within the first 24 hours of an acute MI, an accurate measurement of plasma lipid levels may not be possible for six weeks.
**Dyslipidemia management**

**Lifestyle interventions**

All pharmacological therapy for dyslipidemia in type 2 diabetes should be combined with lifestyle interventions, including dietary modifications and exercise. For further information see lifestyle interventions in the management of type 2 diabetes, page 17. Weight loss secondary to lifestyle modification may be associated with significant metabolic benefits, such as reduced TGs, elevated HDL cholesterol and an improvement in insulin sensitivity.

The focus of nutritional management of dyslipidemia is fat restriction, and exchange of saturated fats with unsaturated fats, resulting in increased proportions of monounsaturated or polyunsaturated fat of both the omega-3 and omega-6 variety. Such nutritional modifications can result in a 10–15% reduction in plasma cholesterol. Referral to a dietitian is often desirable.

A further reduction of 10% in total cholesterol and 6–15% in LDL cholesterol levels (with minimal change in HDL cholesterol and TGs) may be achieved by an intake of at least 2 g per day of plant sterols. Plant sterols reduce cholesterol absorption from the intestine. They can be conveniently delivered through an intake of 25 g per day of plant sterol enriched margarine (sufficient to spread over 3–4 slices of bread). Such products, however, are not desirable in people with normal cholesterol levels and in pregnant women.

In addition to lifestyle interventions, glycemic control with antihyperglycemic agents can result in improved lipid profile. See Table 24, page 83 for the effect of individual agents.

**Pharmacological treatment**

**Effects of lipid lowering agents**

If improved glycemic control and lifestyle interventions fail to correct the dyslipidemia, therapy with specific lipid lowering agents should be considered. If the dyslipidemia is severe initially, such as high risk patients, drug therapy with a lipid lowering agent may be considered immediately in conjunction with these other measures.

In diabetic dyslipidemia, reduction of excess levels of LDL cholesterol remains a priority as the evidence from clinical trials, although limited,
indicates that gains in terms of reduced risk of CVD events can be achieved. The choice of lipid lowering agent depends on the particular lipid abnormalities that predominate, as outlined in Table 42, page 130. The treatment choices are not specific to patients with type 2 diabetes, and consideration should be given to potential adverse effects and drug interactions associated with each of the agents. The effect of individual agents on various lipoproteins is outlined Table 41 page 129.

Apart from the influence of altered glycemic control and insulin resistance on lipoproteins, genetic factors may also influence the particular dyslipidemic picture. These include familial combined hyperlipidemia and familial hypercholesterolemia, as well genetic defects leading to lipoprotein lipase mutations and remnant removal disease. Treatment of these specific dyslipidemias is beyond the scope of this document. Secondary causes of dyslipidemia should also be considered, such as excess alcohol intake and hypothyroidism.

**Specific lipid lowering agents and combinations in diabetic dyslipidemia**

**Statins**

*Post hoc* analyses of outcome trials indicate that therapy with simvastatin or pravastatin reduces LDL cholesterol levels in patients with type 2 diabetes, and may lead to reduced CVD events. This is likely to be a class effect of the statins.

The doses of statin therapy employed in the aforementioned clinical trials are equivalent to the usual doses recommended for statins. A recent trial, which investigated the effect of aggressive therapy versus standard therapy with atorvastatin in patients with diabetic dyslipidemia and no CHD, found atorvastatin 10 mg and 80 mg daily significantly reduced plasma TG levels, without a significant difference between the two doses. Atorvastatin 80 mg, however, produced a significantly greater decrease in LDL cholesterol levels than atorvastatin 10 mg.

In this trial, the adverse effects reported with the two doses were similar. However, it is important to note that with any statin, as the dose is increased, the likelihood of adverse effects, including serious muscular adverse reactions, increases. Ideally, initiating therapy at a low dose and gradually increasing the dose to attain the desired response is recommended. More than 80% of the lipid lowering effect of statin therapy is achieved with 50% of the maximum dose.
**Statins and fibric acid derivatives**

The combination of statin therapy and fibric acid derivatives is known to increase the risk of rhabdomyolysis. The risk is increased with higher doses of statins. The risk may be lower with fenofibrate than gemfibrozil in combination with statins. Cerivastatin was withdrawn from the US market in August 2001 as a result of a large number of reports of rhabdomyolysis, particularly when it has been used in combination with gemfibrozil.\(^{379}\)

A recent post-marketing observational study of the incidence of rhabdomyolysis with statin and fibrate use in the US concluded that the risk of rhabdomyolysis is low and similar with simvastatin, atorvastatin, and pravastatin. Combined statin-fibrate use increases the risk, particularly in older patients with diabetes. The study confirmed that cerivastatin was associated with a greater risk of rhabdomyolysis. Fibrate therapy was associated with a 5.5-fold increase in relative risk compared with statin monotherapy. An additional 2-fold increase in risk was reported with combined use of a fibrate and statin versus fibrate alone. The relative risk of rhabdomyolysis with combined use of a statin and fibrate was increased 12-fold versus statin monotherapy. When monotherapy with atorvastatin, pravastatin or simvastatin was considered in this study, the number needed to treat per year of therapy to observe one case of rhabdomyolysis was 22,727; however for older patients with diabetes mellitus treated with a statin plus a fibrate, this number reduced to 484.\(^{380}\)

However, in patients with specific lipid abnormalities unresponsive to monotherapy, such as mixed hyperlipidemia, combination therapy may be required and can be undertaken with caution. Patients should be educated about the signs and symptoms of myopathy (e.g. unexplained muscle pain, tenderness or weakness) and encouraged to immediately report any suspected reactions. Then creatinine kinase (CK) should be monitored. For further information see Table 44, page 136 and Table 45, page 139.
<table>
<thead>
<tr>
<th>Drug</th>
<th>LDL</th>
<th>TG</th>
<th>HDL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects of drugs on lipid levels in hypercholesterolemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>statins</td>
<td>↓ 18–55%</td>
<td>↓ 7–30%</td>
<td>↑ 5–15%</td>
<td>Most effective LDL lowering drugs.</td>
</tr>
<tr>
<td>bile acid binding resins</td>
<td>↓ 15–30%</td>
<td>↑ 5%</td>
<td>↑ 3–5%</td>
<td>Useful for isolated hypercholesterolemia. Useful in low dose in combination with a statin. May exacerbate hypertriglyceridemia if TG &gt; 260 mg/dL.</td>
</tr>
<tr>
<td>fibric acid derivatives</td>
<td>↓ 0–25%</td>
<td>↓ 25–50%</td>
<td>↑ 10–35%</td>
<td>Low efficacy for isolated hypercholesterolemia.</td>
</tr>
<tr>
<td>niacin (nicotinic acid)</td>
<td>↓ 15–25%</td>
<td>↓ 25–50%</td>
<td>↑ 15–35%</td>
<td>Use is limited by its adverse effects.</td>
</tr>
<tr>
<td>Selective cholesterol absorption inhibitors (ezetimibe)</td>
<td>↓ 16–17%</td>
<td>↓ 10–11%</td>
<td>↑ 2–4%</td>
<td>Early indications suggest combination therapy with statins improves efficacy versus statin monotherapy.</td>
</tr>
</tbody>
</table>

LDL = low density lipoprotein cholesterol; TG = triglycerides; HDL = high density lipoprotein cholesterol; NA = not available. Adapted from the ATPIII. 
Table 42. Choice of lipid lowering agent depending on nature of dyslipidemia.

<table>
<thead>
<tr>
<th>Dyslipidemia</th>
<th>First line</th>
<th>Second line</th>
<th>Possible combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia (elevated LDL)</td>
<td>statin or bile acid binding resin</td>
<td>nicotinic acid, fibric acid derivative</td>
<td>Statin plus bile acid binding resin (low dose can be more effective than increasing the dose of statin). Bile acid binding resin plus nicotinic acid.</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>fibric acid derivative and glycemic control</td>
<td>statin, fish oil (omega-3 fatty acid), nicotinic acid</td>
<td>Any combination of first and second line therapy.</td>
</tr>
<tr>
<td>Combined hyperlipidemia (elevated LDL and TG)</td>
<td>glycemic control and statin (if elevated LDL predominates) or fibric acid derivative (if elevated TG predominates)</td>
<td>high-dose statin, nicotinic acid</td>
<td>Specialist advice may be required. Adding fish oil to first line therapy may further reduce TG. Addition of bile acid resin to first line therapy may further reduce LDL (care as resins may increase TG). Statin plus fibric acid derivative. *</td>
</tr>
<tr>
<td>Low HDL</td>
<td>non-pharmacological intervention</td>
<td>nicotinic acid or fibric acid derivative</td>
<td>Combination of non-pharmacological agents and one of the second line agents.</td>
</tr>
</tbody>
</table>

LDL = low density lipoprotein cholesterol; TG = triglycerides; HDL = high density lipoprotein cholesterol

* Combination of a statin plus fibric acid derivatives, and a statin plus niacin (nicotinic acid) carries an increased risk of rhabdomyolysis. See Table 44, page 136 and Table 45, page 139.
**Fish oil**

Fish oil supplements containing at least 2 g daily of omega-3 fatty acids may be useful in lowering elevated TG levels. A recent systematic review, which investigated the effects of fish oil supplements in patients with type 2 diabetes, found fish oil significantly lowered TGs and raised LDL cholesterol, with a non-significant effect on HDL cholesterol levels. The LDL cholesterol raising effect was most pronounced with larger doses of fish oil. The TG lowering effect was most marked in patients with hypertriglyceridemia. None of the trials assessed effect on clinical end points, hence routine use cannot be advocated for patients without elevated TG levels resistant to first line therapy. Fish oil therapy may be useful in combination with other lipid lowering therapy in certain dyslipidemic profiles (see Table 42, page 130).

**Niacin (Nicotinic acid)**

Caution is advised when using nicotinic acid with patients with type 2 diabetes because of adverse effects on glycemic control (see Table 44, page 136). In a post hoc analysis, the Arterial Disease Multiple Intervention Trial (ADMIT) investigated the effect of nicotinic acid on lipid levels and glycemic control in 125 patients with diabetes and peripheral artery disease over 48 weeks. Nicotinic acid elevated plasma glucose levels by an average of 7.3 mg/dL, but A1C levels were unchanged. Nicotinic acid did not significantly increase use of either insulin or oral antihyperglycemic agents. Significant elevations in HDL cholesterol levels, and significant decreases in LDL cholesterol and TG levels were seen with nicotinic acid. Glycemic control, however, should be carefully monitored in patients with diabetes when initiating nicotinic acid, with gradual upward dose titration of nicotinic acid and dose modification of therapy for glycemic control, if required. Further investigation is required to ensure that the potential adverse effect on glycemic control does not offset the potential benefit of reduced CVD risk that has been observed with nicotinic acid in patients without diabetes.

**Zetia (ezetimibe)**

Ezetimibe represents a new class of drugs available to treat dyslipidemias termed selective cholesterol absorption inhibitors. Ezetimibe acts locally at the brush border of the small intestine to inhibit the absorption of cholesterol. This leads to a decrease in hepatic cholesterol stores and an overall reduction in serum cholesterol levels.
Evidence regarding cardiovascular outcomes of ezetimibe therapy in the treatment of dyslipidemia is lacking. Ezetimibe has been shown to complement the beneficial effects of statins and has an indication for combination therapy of primary hypercholesterolemia and homozygous familial hypercholesterolemia.\textsuperscript{386} The use of ezetimibe as monotherapy should be in addition to a standard cholesterol-lowering diet. The initial and maintenance dose of ezetimibe is 10 mg per day.\textsuperscript{386}

**Doses for lipid lowering agents**

Table 43, page 133 outlines dosage recommendations and preparations available for the lipid lowering agents that are commonly used to treat dyslipidemia in patients with type 2 diabetes in the primary care setting.

**Adverse effects and contraindications of lipid lowering agents**

Table 44, page 136 outlines selected adverse effects and contraindications associated with the lipid lowering agents that are commonly used to treat dyslipidemia in patients with type 2 diabetes in the primary care setting. It is not intended to be an exhaustive list of all reported adverse effects with these agents.

**Drug interactions with lipid lowering agents**

Table 45, page 139 outlines selected drug interactions associated with lipid lowering agents that are commonly used to treat dyslipidemia in patients with diabetes in the primary care setting. It is not intended to be an exhaustive list of all potential drug interactions with these agents.
### Table 43. Preparations and doses for lipid lowering agents.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Preparations</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG CoA reductase inhibitors (statins)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| atorvastatin     | Tablets 10 mg, 20 mg, 40 mg, 80 mg | Initially 10–20 mg once daily, increase after 4 weeks if necessary. Usual range is 10–80 mg once daily. 
| Lipitor®         |                                   |                                                                                                                                 |
| fluvastatin      | Capsules 20 mg, 40 mg             | Initially 20 mg once daily in the evening with or after food. Increase after 4 weeks if necessary. Usual range is 20–40 mg once daily. Maximum dose is 40 mg twice daily or 80 mg tablet once daily. |
| Lescol®,         | Tablet 80 mg XL                   |                                                                                                                                 |
| Lescol XL®       |                                   |                                                                                                                                 |
| lovastatin       | Tablets 10 mg, 20 mg, 40 mg       | Initially 20 mg once daily at bedtime. Increase after 4 weeks if necessary. Usual range is 10–80 mg in 1–2 divided doses. Extended release dosing range is 20–60 mg once daily. |
| Mevacor®,        | Tablets ER 10 mg, 20 mg, 40 mg, 60 mg |                                                                                                                                 |
| Altocor ER®      |                                   |                                                                                                                                 |
| pravastatin      | Tablets 10 mg, 20 mg, 40 mg, 80 mg | Initially 10–20 mg once daily at bedtime (10 mg in renal impairment and elderly). Increase after four weeks if necessary. Usual range is 10–80 mg once daily. |
| Pravachol®       |                                   |                                                                                                                                 |
| simvastatin      | Tablets 5 mg, 10 mg, 20 mg, 40 mg, 80 mg | Initially 10–20 mg once daily in the evening. Increase after 4 weeks if necessary. Maximum dose is 80 mg once daily. |
| Zocor®           |                                   |                                                                                                                                 |
| rosvastatin      | Tablets 5 mg, 10 mg, 20 mg, 40 mg | Initially 5–10 mg once daily. Increase after 4 weeks if necessary. Usual range is 10–20 mg once daily. Maximum dose is 40 mg once daily. |
| Crestor®         |                                   |                                                                                                                                 |
| **Fibric Acid Derivatives**                                                                                                            |
| fenofibrate      | Tablets 54 mg, 160 mg             | Recommended dose is 54–160 mg once daily. |
| Tricor®          |                                   |                                                                                                                                 |
| gemfibrozil       | Tablets 600 mg                    | Recommended dose is 600 mg twice daily half an hour before food. maximum dose is 600 mg twice daily half an hour before food. If gastrointestinal adverse effects occur, it can be taken with food. |
| Lopid®           |                                   |                                                                                                                                 |

Note: Table continued on next page
### Table 43. Preparations and doses for lipid lowering agents (continued).

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Preparations</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bile acid binding resins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholestyramine</td>
<td>Packets 4 g</td>
<td>Initially 4 g twice daily, increasing to maintenance dose over 2–4 weeks. Usual range is 8–16 g daily in 1–2 divided doses. Maximum dose is 24 g daily in 2–3 divided doses. In combination with other lipid lowering drugs, give 4 g once or twice daily.</td>
</tr>
<tr>
<td>Questran Lite®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questran®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lo CHOLEST®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalite®</td>
<td></td>
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</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>colestipol</td>
<td>Packets 5 g Tablet 1 g</td>
<td>Initially 5–10 g granules or 2–16 g tablets daily in 1–2 divided doses, increasing gradually at 1–2 month intervals. Usual range is 10–30 g daily in 2–3 divided doses. In combination treatment with other lipid lowering drugs, give 5 g once or twice daily.</td>
</tr>
<tr>
<td>Colestid®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>colesevelam</td>
<td>Tablet 625 mg</td>
<td>Usual dose is 3 tablets twice daily with meals or 6 tablets once daily.</td>
</tr>
<tr>
<td>Welchol®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Selective cholesterol absorption inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ezetimibe</td>
<td>Tablets 10 mg</td>
<td>Initial and maintenance dose is 10 mg once daily. Max dose is 10 mg once daily.</td>
</tr>
<tr>
<td>Zetia®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>niacin (nicotinic acid)†</td>
<td>Tablets 250 mg, 500 mg ER 500 mg, 750 mg, 1000 mg</td>
<td>Initially 250 mg once daily, increasing by 250 mg every 4 days to maintenance dose of 3 g daily in three divided doses. ER initially 500 mg at bedtime. Increase dose every 4 weeks by 500 mg to maximum of 2000 mg daily at bedtime.</td>
</tr>
<tr>
<td>Niacor®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niaspan®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>omega-3 fatty acids</td>
<td>Capsules 1000 mg, 1200 mg</td>
<td>Recommended dose is 5–20 g daily in divided doses.</td>
</tr>
<tr>
<td>e.g. Max EPA®, Promega®, EPA capsules®, Sea-Omega®</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mix dose with water, juice or highly fluid foods. For cholestyramine, the gritty texture can be reduced by mixing the dose and standing it in the refrigerator for at least four hours or overnight. Refer to the approved product information for further details about administration of these products.
† Minimize adverse effects by increasing the dose gradually and by dividing doses, and administering with antacids or food. Reduce or prevent flushing by taking aspirin 325 mg 30 minutes before nicotinic acid. Tolerance develops to flushing, but may be lost if the patient misses three or more doses.

Note: Table continued on next page
Table 43. Preparations and doses for lipid lowering agents (continued).

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Preparations</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin ER/lovastatin</td>
<td>Tablets: 500/20 mg, 750/20 mg, 1000/20 mg</td>
<td>Can switch from stable dosage of niacin. In patients stabilized on lovastatin, titrate to response using niacin ER and then switch to niacin ER/lovastatin combination.</td>
</tr>
<tr>
<td>Advicor®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ezetimibe/simvastatin</td>
<td>Tablets: 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg</td>
<td>Recommended starting dose is 10/20 mg/day taken as a single dose in the evening with or without food. Individualize dose according to goals of therapy, baseline LDL-C level and patient response.</td>
</tr>
<tr>
<td>Vytorin®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aspirin/pravastatin</td>
<td>Tablets: 81/20 mg, 81/40 mg, 81/80 mg, 325/20 mg, 325/40 mg, 325/80 mg</td>
<td>Recommended daily dose is 40 mg pravastatin with either 81 mg or 325 mg of aspirin. Should be taken with full glass of water due to aspirin component, unless patient is fluid restricted.</td>
</tr>
<tr>
<td>Pravidgard PAC®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amlodipine/atorvastatin</td>
<td>Tablets: 5/10 mg, 5/20 mg, 5/40 mg, 5/80 mg, 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg</td>
<td>Individualize therapy. May be substituted based on its individually titrated components. Maximum dose of amlodipine component is 10 mg once daily. Maximum dose of atorvastatin component is 80 mg/day.</td>
</tr>
</tbody>
</table>
Table 44. Adverse effects and contraindications of lipid lowering agents.

<table>
<thead>
<tr>
<th>Class</th>
<th>Adverse effects</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>statins</td>
<td>Statins are generally well tolerated and associated with low rates of withdrawal due to adverse effects in clinical trials. Common adverse effects include mild transient gastrointestinal symptoms, headache, insomnia, dizziness and myalgia. While myalgia is a common muscle adverse effect, myopathy and rhabdomyolysis have also been reported, but are rare. Myopathy is defined as an increase in creatinine kinase (CK) activity (to greater than 10 times the upper limit of normal) in conjunction with symptoms of muscle pain, weakness and tenderness. Rhabdomyolysis involves extensive breakdown of skeletal muscle, with the potential for development of acute renal failure. Patients should be advised to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. The statin should be stopped if CK is greater than 10 times the upper limit of normal; or the patient complains of muscle pain and CK levels are greater than 4 times the upper limit of normal. A number of drugs interact with statins to increase the risk of this adverse effect (see Table 45, page 139). A recent post-marketing observational study of the incidence of rhabdomyolysis concluded that the risk of rhabdomyolysis is similar and low with simvastatin, atorvastatin, and pravastatin. Combined statin-fibrate use increases this risk, particularly in older patients with diabetes. The study confirmed that cerivastatin was associated with a greater risk of rhabdomyolysis. Cerivastatin was withdrawn from the US market in 2001. Statins are associated with a small risk of hepatic adverse effects. This is most commonly asymptomatic (and usually transient) elevations in serum levels of transaminases in about 1–2% of patients. Rare cases of hepatotoxicity have occurred. Hepatic adverse effects have been reported with all statins, and there is currently no evidence of a significant difference between individual agents with regard to this risk. It is recommended that liver function be monitored before starting a statin, with repeat levels at three months and then at six month intervals thereafter. The drug should be stopped if transaminase concentrations are persistently elevated to more than three times the upper limit of normal.</td>
<td>pregnancy(^{190}) patients with active liver disease(^{387}) previous hypersensitivity to this drug class</td>
</tr>
</tbody>
</table>

Note: Table continued on next page – see footnotes at end of table
### Table 44. Adverse effects and contraindications of lipid lowering agents (continued).

<table>
<thead>
<tr>
<th>Class</th>
<th>Adverse effects</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bile acid binding resins</strong></td>
<td>Common adverse effects include constipation, abdominal pain, dyspepsia, flatulence, nausea, vomiting, (less than constipation) and anorexia. These effects are dose-related and can be minimized by starting with a low dose and increasing the dose gradually. Less frequently, there are reports of rash, increases in TG levels and decreased absorption of fat soluble vitamins. There is a risk of increased bleeding due to decreased vitamin K absorption. It is advised that supplements of vitamins A and D and folic acid are considered for patients taking high doses of resins over a long period of time.</td>
<td>patients with a history of hypersensitivity to the product in complete biliary obstruction use Questran Lite® with caution in patients with phenylketonuria</td>
</tr>
<tr>
<td><strong>fibric acid derivatives</strong></td>
<td>Common adverse effects include dyspepsia, abdominal pain, dry mouth, headache and myalgia. Less frequent events include photosensitivity, gallstones, myopathy, rhabdomyolysis, sexual dysfunction, hepatic effects and blood dyscrasias. It is recommended that full blood count and liver function be monitored before initiation and during treatment. Bioavailability is optimal if the drug is taken half an hour before food, but gastrointestinal tolerance can be improved by administration with meals. Patients should be advised to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. The risk is greatest when fibric acid derivatives are used in combination with a statin (see page 128).</td>
<td>primary biliary cirrhosis gallstones or gallbladder disease severe renal or hepatic impairment</td>
</tr>
</tbody>
</table>

Note: Table continued on the next page – see footnotes at end of table
Table 44. Adverse effects and contraindications of lipid lowering agents (continued).

<table>
<thead>
<tr>
<th>Class</th>
<th>Adverse effects</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>niacin</strong>  (nicotinic acid)</td>
<td>Facial and neck flushing and pruritus occur in most patients. Tolerance develops to this and it can be reduced or prevented by taking aspirin 325 mg 30 minutes before the dose. Hypotension, dyspepsia, diarrhea, nausea, vomiting and hyperpigmentation are also common. Less frequent effects include skin reactions, hepatic effects, myopathy, blurred vision, hyperglycemia and hyperuricemia. Care is needed when using nicotinic acid in patients with gout, CHD and peptic ulcer disease as these conditions may be exacerbated by nicotinic acid. Care is needed in patients with diabetes due to the risk of hyperglycemia (see Appendix 2, page 197).</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>Selective cholesterol</td>
<td>Common adverse effects include abdominal pain, diarrhea, arthralgia, back pain, coughing pharyngitis, sinusitis, fatigue, and viral infection. The frequency of less common adverse effects was comparable to placebo. When used in combination with statins, all adverse effects and contraindications relating to statins apply (see Table 44, page 136). Adverse effects associated with combination therapy were comparable to placebo.</td>
<td>hypersensitivity to any component of ezetimibe tablets</td>
</tr>
<tr>
<td>absorption inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = contraindication; TG = triglyceride; MI = myocardial infarction; CHD = coronary heart disease
Table 45. Selected drug interactions associated with lipid lowering agents.

<table>
<thead>
<tr>
<th>Class</th>
<th>Interacting drugs</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>bile acid binding resins</td>
<td>May reduce absorption of statins. Give the statin at least one hour before, or four hours after, the bile acid binding resin.</td>
</tr>
<tr>
<td></td>
<td>cyclosporine</td>
<td>Increased risk of myopathy or rhabdomyolysis. If concomitant use is necessary, monitor CK and advise patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. In addition, isolated reports describe elevated cyclosporine levels; therefore, monitoring cyclosporine levels is advised.</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 inhibitors* (e.g. diltiazem, clarithromycin, erythromycin, azole antifungals, nefazodone, fluvoxamine, fluoxetine, grapefruit juice)</td>
<td>May decrease hepatic metabolism of some statins, increasing the risk of adverse effects. If concomitant use is necessary, monitor CK and advise patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. For interacting antimicrobials, it may be appropriate to stop the statin temporarily, for the duration of antimicrobial treatment.</td>
</tr>
<tr>
<td></td>
<td>fibric acid derivatives</td>
<td>Increased risk of myopathy or rhabdomyolysis. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.</td>
</tr>
<tr>
<td></td>
<td>niacin (nicotinic acid)</td>
<td>Increased risk of myopathy or rhabdomyolysis. If concomitant use is necessary, advise patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.</td>
</tr>
<tr>
<td></td>
<td>warfarin</td>
<td>Increased anticoagulant effect (less risk with pravastatin and atorvastatin). Monitor INR when initiating or ceasing treatment with a statin.</td>
</tr>
</tbody>
</table>

* The risk of these interactions may vary depending on the particular statin. The risk may be greatest with simvastatin which is predominantly metabolized by CYP3A4. Atorvastatin is also primarily metabolized by CYP3A4. Pravastatin is approximately 50% renally cleared, with the remainder cleared by the biliary route and biotransformation — CYP3A4 plays only a minor role in its metabolism. Fluvastatin is metabolized predominantly by CYP2C9.

CK = creatinine kinase; INR = international normalized ratio; CYP = cytochrome P450

Note: Table continued on next page.
Table 45. Selected drug interactions associated with lipid lowering agents (continued).

<table>
<thead>
<tr>
<th>Class</th>
<th>Interacting drugs</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>bile acid binding resins</td>
<td>Digoxin</td>
<td>Absorption of digoxin may be reduced. Separate administration and monitor effects.</td>
</tr>
<tr>
<td></td>
<td>Thyroxine</td>
<td>Absorption of thyroxine may be reduced. Separate administration and monitor effects.</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Anticoagulant effect may be increased or decreased. Separate administration by at least three hours and monitor INR.</td>
</tr>
<tr>
<td>Others</td>
<td>Bile acid binding resins may bind many drugs in the intestine. For example, in addition to the above drugs, this interaction has been demonstrated with amiodarone, glipizide and some TCAs. To reduce the potential for such interactions, administer other drugs at least one hour before, or 4–6 hours after, the resin.</td>
<td></td>
</tr>
<tr>
<td>fibric acid derivatives</td>
<td>Antacids</td>
<td>One small study found absorption of gemfibrozil to be significantly reduced by antacids. The authors suggested that gemfibrozil be administered 1–2 hours before antacids.</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>Increased risk of myopathy or rhabdomyolysis. In addition, patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Anticoagulant effect may be increased. Monitor INR closely and anticipate the need to reduce the warfarin dose.</td>
</tr>
<tr>
<td>niacin (nicotinic acid)</td>
<td>antihypertensives</td>
<td>May potentiate hypotensive effects.</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>Increased risk of myopathy or rhabdomyolysis. If concomitant use is necessary, monitor CK and advise patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.</td>
</tr>
</tbody>
</table>

Note: Table continued on next page

CK = creatinine kinase; INR = international normalized ratio; TCA = tricyclic antidepressant
Adapted from Facts and Comparisons and Drug Information Handbook.78, 190
ASPIRIN THERAPY

Diabetes is associated with a 2–4 fold increase in the risk of CHD.\textsuperscript{388, 389, 390} Patients with diabetes without manifestations of CHD have been shown to have the same risk of future coronary events as patients without diabetes who have established CHD.\textsuperscript{388}

Meta-analyses of large trials in patients with diabetes support the view that low dose aspirin should be prescribed as a secondary prevention strategy, if no contraindications exist.\textsuperscript{390, 391}

The role for aspirin as primary prevention in diabetes is not as clear. The United States Physicians’ Health Study, a large primary prevention trial, compared low dose aspirin (325 mg every other day) with placebo in 22,701 male physicians. Among 533 people with diabetes, MI was significantly reduced after five years from 10.1% (placebo) to 4.0% (aspirin).\textsuperscript{392}

The HOT study compared aspirin 75 mg/day with placebo in 18,790 patients (1501 with diabetes) with hypertension who were randomized to one of three target blood pressure groups. Overall, aspirin reduced major cardiovascular events by 15% and all MIs by 36%, with relative benefit similar between patients with or without diabetes. The authors concluded that aspirin could prevent 1.5 (2.5 in patients with diabetes) MIs per 1000 patients treated for one year.\textsuperscript{322} One concern is that the number of clinically significant bleeding episodes caused by aspirin was similar to the number of cardiovascular events prevented in this study, suggesting a narrow margin between benefit and harm. However, given the higher number of absolute events prevented in patients with diabetes, the margin would be expected to be less narrow in this group.

Recommendations

The American Diabetes Association recommends aspirin therapy as a secondary prevention strategy in patients with diabetes who have evidence of large vessel disease.\textsuperscript{389} This includes patients with a history of MI, vascular bypass procedure, stroke, transient ischemic attack (TIA), PVD, claudication and/or angina.\textsuperscript{389}
They also suggest that aspirin therapy is considered as a primary prevention strategy in high risk patients with diabetes. This includes patients with:

- a family history of CHD;
- cigarette smoking;
- hypertension;
- obesity (≥ 120% desirable weight) — BMI > 27.3 kg/m² in women and BMI > 27.8 kg/m² in men;
- albuminuria (micro or macro);
- dyslipidemia; or
- age > 30 years.

**Adverse effects and contraindications**

Aspirin can increase the number of gastrointestinal bleeds and possibly hemorrhagic strokes. In the HOT study, the incidence of fatal bleeds was similar between aspirin and placebo but major and minor non-fatal bleeds were more frequent among aspirin recipients.

Aspirin is considered to be contraindicated in patients with active peptic ulceration; allergy and anaphylactic reactions to NSAIDs, including aspirin; hemophilia or other bleeding disorders; and active liver disease. In patients who are intolerant of aspirin, clopidogrel or ticlopidine may be considered. For further information see page 183.

**Dose and administration**

The recommended antiplatelet aspirin dose is 81–325 mg daily, taken with food to reduce gastric irritation.

**Summary**

Aspirin is recommended for all patients with type 2 diabetes and established CVD unless specific contraindications exist. For primary prevention, there are no definitive guidelines on when to commence aspirin therapy in patients with diabetes. However, patients with type 2 diabetes, even at diagnosis, would typically be at significant cardiovascular risk, justifying consideration for aspirin therapy commencement. However, the benefits of aspirin need to be weighed against the risk of adverse events in each individual patient.
Evidence for the impact of multiple concurrent interventions addressing the risk factors for cardiovascular disease in people with type 2 diabetes has been limited. A recent study (STENO-2) has addressed this issue.

The aim of the Multifactorial Intervention and Cardiovascular Disease in Patients with type 2 diabetes (known as the STENO-2 study) was to assess the effects of an intense, long-term, goal-oriented, multifactorial intervention on micro- and macro-vascular outcomes in patients with type 2 diabetes.393

The study assessed 160 patients with type 2 diabetes and microalbuminuria, a strong risk factor for micro- and macro-vascular complications. Patients averaged 55 years of age and were randomized to either conventional or intensive treatment over 7.8 years. Targeted risk factors for CVD included hypertension, hyperlipidemia, hyperglycemia, smoking, and sedentary lifestyle.393

Conventional treatment was in accordance with generally accepted guidelines in use during the course of the trial.393 All patients were treated with statins, and fibrates were used in cases of isolated hypertriglyceridemia.393 Hyperglycemia was treated with metformin in obese patients and with glipizide in non-obese patients. Combination oral therapy was used if needed to achieve predetermined goals for glycemic control, and a night-time insulin was added if required.393 All patients with known ischemic cardiovascular disease were given aspirin. By the end of the study, all patients in the intensive group were receiving aspirin therapy.393

Intensive therapy included additional therapy as follows:

- Exercise comprising 30 minutes of light to moderate exercise, 3 to 5 times per week
- Fat intake restricted to 30% or less of total daily intake with saturated fatty acid intake comprising 10% or less of total daily intake
- Smoking cessation classes offered
- Vitamin and mineral supplements
- ACE-I or ARB to control hypertension and reduce urinary albumin excretion
• Other antihypertensive agents if needed to reach predetermined BP goals
• More stringent glycosylated hemoglobin goal
• Aspirin therapy

Primary endpoint was a composite of:
• Death from CV causes
• Nonfatal MI
• Nonfatal stroke
• Revascularization procedures
• Amputation secondary to ischemia
• Vascular surgery secondary to peripheral vascular disease

Secondary endpoints included the incidence of:
• Nephropathy (urinary albumin excretion > 300 mg /day)
• Neuropathy (autonomic or peripheral)
• Retinopathy

Results for biochemical markers of CV risk factors, at 7.8 years of follow-up, are shown below in Table 46.394

| Table 46. Overview of direct and surrogate markers of CV risk factors. |
|-----------------------------|-----------------------------|-----------------------------|
| Marker                      | Conventional therapy        | Intensive therapy           |
| HbA1c (%)                   | 9.0                         | 7.9                         |
| Systolic BP (mmHg)          | 146                         | 131                         |
| Diastolic BP (mmHg)         | 78                          | 73                          |
| Total cholesterol (mg/dL)   | 218                         | 151                         |
| LDL (mg/dL)                 | 128                         | 81                          |
| Triglycerides (mg/dL)       | 267                         | 151                         |
| Urinary albumin             | 126                         | 26                          |
The major results and conclusions of the Steno-2 study in terms of macro- and micro-vascular outcomes were:

- **A 50% relative risk reduction in the composite primary endpoint (i.e. cardiovascular disease).**
- **A 60% relative risk reduction in the composite secondary endpoint (i.e. microvascular complications: nephropathy, neuropathy, and retinopathy).**
- **STENO-2 provides the first prospective, primary prevention trial targeting multiple interventions addressing multiple risk factors.**
- **The results suggest that long-term, intensive interventions targeting the multiple risk factors for CVD, reduce the risk of both micro- and macro-vascular complications of diabetes.**
- **The positive findings of this trial provide further evidence that early, intensive treatment is pivotal in reducing complications in high risk patients with type 2 diabetes.**
DIABETIC COMPLICATIONS — MICROVASCULAR

DIABETIC NEUROPATHY

General information

Diabetic neuropathy is a common complication of diabetes, with high morbidity and mortality. It is the most common form of neuropathy in the developed countries of the world, accounts for more admissions to hospital than all other diabetic complications combined, and is responsible for 50–75% of non-traumatic amputations.395

Diabetic neuropathy is not a single entity with a single characteristic presentation. Depending on which nerves are affected and the degree of impairment, the patient with diabetic neuropathy may present with a wide variety of signs and symptoms associated with different syndromes.396 For example, diabetic neuropathy predisposes patients to plantar ulcers, which may become infected and possibly progress to cellulitis, osteomyelitis and gangrene. Neuropathy may also manifest with ophthalmologic symptoms, gastrointestinal disturbances, cardiovascular abnormalities and sexual dysfunction, in addition to the more familiar neurological complaints of pain, sensory loss and weakness.396

Although multiple factors are involved in the pathogenesis of diabetic neuropathy, the key factors appear to be metabolic disturbance caused by poor glycemic control and vascular disease.397

Peripheral nerve function should be checked at least yearly in the patient with diabetes and should include a quantitative somatosensory threshold test, using the Semmes-Weinstein 5.07 (10 g) monofilament. The presence of PVD should also be assessed (see page 180) as well as joint mobility, gait and balance.31 For further information about monitoring patients for neuropathy and its complications, see foot examination, page 13 and foot care, page 154.

Classification

Different types of clinical syndromes of diabetic neuropathy have been summarized and are outlined briefly in Table 47, page 147.397
147

Table 47. Clinical syndromes of diabetic neuropathy.

<table>
<thead>
<tr>
<th>Symmetric neuropathies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic sensory neuropathy</strong></td>
<td>Most common presentation of diabetic neuropathy. Involves hypoesthesia, dysesthesia or pain affecting peripheries (first the feet, later the hands). Loss of sensation in classic ‘stocking and glove’ distribution. Symptoms are worse at night. Peripheral autonomic and motor fibers may also be affected, with loss of sweating and atrophy of the small muscles of the foot.</td>
</tr>
<tr>
<td><strong>Acute painful neuropathy</strong></td>
<td>Can cause sudden onset lower leg and/or thigh pain, with loss of power and muscle wasting. Usually improves with better diabetic control.</td>
</tr>
<tr>
<td><strong>Diffuse motor neuropathy</strong></td>
<td>Mainly affects elderly with type 2 diabetes. Results in severe, progressive muscle weakness and wasting.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Asymmetric neuropathies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic amyotrophy</strong></td>
<td>Similar to acute painful neuropathy, but usually unilateral.</td>
</tr>
<tr>
<td><strong>Pressure neuropathy</strong></td>
<td>Occurs in nerves made vulnerable by diabetes. Most commonly, pressure on median nerve at the wrist causes carpal tunnel syndrome or pressure on the peroneal nerve at the knee causes foot drop.</td>
</tr>
<tr>
<td><strong>Vascular neuropathies</strong></td>
<td>Cranial nerves are commonly affected. Usually nerves and nerve roots recover with time.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autonomic neuropathies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>This is a serious and often overlooked component of diabetic neuropathy. Clinical problems include loss of warning signs of hypoglycemia or effects on the following systems: urogenital system (e.g. impotence, bladder dysfunction, vaginal dryness), gastrointestinal tract (e.g. gastric stasis, diarrhea, constipation) and the cardiovascular system (e.g. orthostatic hypotension, loss of cardiac pain, ‘silent’ ischemia or infarction). The treatment of symptoms of autonomic neuropathy are variable and depend on individual circumstances, and will not be discussed further in this review.</td>
<td></td>
</tr>
</tbody>
</table>

Prevention

**Glycemic control**

Good glycemic control is thought to be important for both the prevention and treatment of diabetic neuropathy. There is evidence from outcome trials demonstrating that tight glycemic control can prevent the development of diabetic neuropathy in patients with type 1 diabetes. Evidence for prevention in type 2 diabetes is less conclusive. For example, in the UKPDS, intensive treatment did not significantly decrease the risk of
amputation or death from PVD, although numbers of these events were small. For the surrogate end points of neuropathy, the only significant benefit noted was less patients with biothesiometer readings greater than 25 V after 15 years of treatment.84

**Others**

Other preventive measures which have been suggested include the control of other potential risk factors, such as alcohol, cigarette smoking, hypertension and dyslipidemia.401 Recently, the microvascular complications analysis of Steno-2 investigated the progression of neuropathy in patients with type 2 diabetes and microalbuminuria (discussed in more detail on page 170). A significant 68% reduction in the rate of progression of autonomic neuropathy was found in the intensive multifactorial treatment group versus the conventional multifactorial treatment group.402 However, intensive treatment did not seem to have an effect on progression of peripheral neuropathy. Therefore, intensive multifactorial intervention in patients with type 2 diabetes and microalbuminuria may slow the progression of autonomic neuropathy.402

**Investigational therapies**

A number of therapies have been investigated for both prevention and treatment of diabetic neuropathy, but cannot yet be recommended for routine use. Some of these have attempted to improve the underlying pathophysiological abnormalities contributing to diabetic neuropathy.403 The most publicized are the aldose reductase inhibitors. One theory for the etiology of diabetic peripheral neuropathy is that excess glucose accumulation results in conversion of glucose to sorbitol in nerve cells by aldose reductase. Accumulated sorbitol is toxic to nerve cells.404 Aldose reductase inhibitors, which address this deficit, have been the subject of numerous trials but results have been disappointing overall, and the potential future role for this class of drugs is currently unclear.403 Aldose reductase inhibitors are not currently available for use in the United States, although tolrestat is undergoing clinical trials.405
Treatment of diabetic neuropathic pain

There is no one therapy that is of benefit to all patients with chronic painful diabetic neuropathy. Patients should be offered the available therapies in a stepwise fashion. Referral to a pain clinic should be considered for patients when pain management is not optimal. Options which can be considered for the treatment of painful diabetic neuropathy are outlined in Table 48, page 150.
Table 48. Treatment options for painful diabetic neuropathy.

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>glycemic control</strong></td>
<td>Good glycemic control has been suggested to be of benefit in the prevention and treatment of neuropathy. See page 147 for further information.</td>
</tr>
<tr>
<td><strong>non-pharmacologic measures</strong></td>
<td>There are a number of non-drug options which may be of benefit to some patients. For example, use of bed cradles to remove pressure at night,(^{397}) transcutaneous nerve stimulation(^{395, 403}) and wrapping the symptomatic limb in plastic (Opsite(^\text{TM}))(^{406}) may help to relieve pain in some patients. Psychologists may be able to teach patients techniques to help cope with pain, and physiotherapists can demonstrate exercise programs that are good for general well being and for pain management.(^{407}) Other non-pharmacological therapies that have been tried with limited success include sympathectomy, spinal cord blockade, electrical spinal cord stimulation(^{408}) and percutaneous electrical nerve stimulation.(^{409})</td>
</tr>
<tr>
<td><strong>topical therapies</strong></td>
<td>Topical capsaicin, the active ingredient in hot peppers, has been used in the treatment of painful diabetic neuropathy. A meta-analysis of four controlled trials found that capsaicin cream gave more pain relief to patients with diabetic neuropathy than placebo. The authors noted that true blinding in these studies is difficult because of the irritant effects of capsaicin after application to the skin. This may mean that much of capsaicin's effectiveness could be attributable to placebo effects.(^{408, 410, 411}) A controlled comparison study in 235 patients found capsaicin cream to be equally effective as amitriptyline in the treatment of painful diabetic neuropathy of the feet.(^{412}) Capsaicin (various brands) is available over-the-counter from pharmacies. The recommended dose is the 0.075% cream applied three to four times a day to skin over the painful areas.(^{78})</td>
</tr>
<tr>
<td><strong>complementary medicines</strong></td>
<td>Vitamins B(_1), B(_6) and E may benefit some patients, although controlled trials are lacking.(^{413, 414}) Evening primrose oil was associated with an improvement in diabetic neuropathy in animal studies and a small human trial.(^{415, 416})</td>
</tr>
</tbody>
</table>

Note: Table continued on next page
Table 48. Treatment options for painful diabetic neuropathy (continued).

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>analgesics</strong></td>
<td>Simple analgesics such as acetaminophen or aspirin could be effective in mild cases; however, good evidence for efficacy is lacking. NSAIDs may assist some patients. NSAIDs and COX-2 inhibitors should be used judiciously in patients with diabetes, particularly those with renal impairment and/or those taking metformin, due to the risk of acute renal failure. Use in patients taking ACE inhibitors or ARBs also requires caution. Narcotic analgesics should generally be avoided because of their high potential for abuse, and the high incidence of constipation, which may exacerbate features of autonomic neuropathy. Tramadol was found to be effective in treating diabetic neuropathic pain in one six week randomized controlled study in 131 patients. Benefit was also noted in a follow up six month open study involving 117 of these patients.</td>
</tr>
<tr>
<td><strong>tricyclic antidepressants</strong></td>
<td>TCAs are often the initial form of treatment for painful diabetic neuropathy. Clinical trials with TCAs for diabetic neuropathy are currently limited in size and duration. Two systematic reviews, which assessed the efficacy of antidepressants in diabetic neuropathic pain, found TCAs to be effective. For example, one review found the number needed to treat (NNT) to achieve at least 50% pain relief was 3.5 with low to mid range doses of TCAs. Amitriptyline is the most studied TCA for this indication. Small trials have also shown imipramine and desipramine to be superior to placebo. While randomized controlled trials with nortriptyline are lacking, it is commonly used for neuropathic pain. Nortriptyline has less sedative and anticholinergic effects than amitriptyline, so it may be more favorable in elderly patients. Doses of TCAs for pain reduction tend to be lower than that needed for depression and time to onset is more rapid. It is generally recommended that initial doses of TCAs are low (10–25 mg at night) and that the dose be increased gradually according to benefit and tolerance. Caution is warranted because adverse effects of TCAs may be especially problematic in the patient with diabetes. For example, patients with autonomic neuropathy may be particularly susceptible to orthostatic hypotension and anticholinergic effects.</td>
</tr>
</tbody>
</table>

NSAID = non-steroidal anti-inflammatory drug; COX-2 = cyclo-oxygenase-2 inhibitor; TCA = tricyclic antidepressant; SSRI = Selective serotonin reuptake inhibitor; NNT = number needed to treat

Note: Table continued on next page
Table 48. Treatment options for painful diabetic neuropathy (continued).

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>other antidepressants</strong></td>
<td>A systematic review found SSRIs not significantly better than placebo.(^{422}) Comparative trials with TCAs are too few in number and size to make a definitive statement, but the trend is for less efficacy with SSRIs. Further well controlled trials are needed to determine the role of SSRIs in this condition. Duloxetine is a new antidepressant approved by the FDA and is the first drug which has an indication for the treatment of diabetic neuropathic pain.(^{386}) Large scale clinical trials evaluating the efficacy of duloxetine in this role are lacking. Venlafaxine has been effective in painful diabetic neuropathy in case reports and small case series.(^{405, 424-426}) Controlled trials are needed.</td>
</tr>
<tr>
<td><strong>anticonvulsants</strong></td>
<td>A systematic review, which included three trials with anticonvulsants (321 patients), found the NNT for at least 50% pain relief in diabetic neuropathy was 2.7.(^{422}) These trials involved carbamazepine, phenytoin and gabapentin. Randomized controlled trials evaluating the efficacy of carbamazepine and phenytoin are limited, and were published in the 1960s and 1970s. Carbamazepine was beneficial in one study but results with phenytoin have been conflicting.(^{403, 427}) An initial dose of carbamazepine of 100 mg once or twice daily has been suggested, with dose increases dependent on efficacy and tolerance.(^{408, 428}) Complete blood picture needs to be monitored when using carbamazepine.(^{429}) There has also been interest in the use of gabapentin to treat painful diabetic neuropathy. Three randomized controlled studies have been conducted. The largest study, which included 165 patients randomized to gabapentin (up to 3600 mg per day) or placebo for eight weeks, found that gabapentin was efficacious for treatment of pain and sleep interference and had positive effects on mood and quality of life.(^{430}) These results were supported by a second smaller study,(^{431}) but the third study (which used a smaller dose of gabapentin (900 mg per day)) found minimal efficacy.(^{426}) Two small studies have compared the efficacy of gabapentin with amitriptyline. The first found both drugs produced pain relief to a similar degree.(^{432}) The second, which was an open study, concluded that gabapentin was more effective and better tolerated than amitriptyline.(^{433}) Larger controlled comparison studies are clearly needed before conclusions can be made. Newer agents such as lamotrigine and zonisamide are under investigation for use in various neuropathic pain syndromes as well.(^{429})</td>
</tr>
</tbody>
</table>

NSAID = non-steroidal anti-inflammatory drug; COX-2 = cyclo-oxygenase-2 inhibitor; TCA = tricyclic antidepressant; SSRI = Selective serotonin reuptake inhibitor; NNT = number needed to treat

Note: Table continued on next page
Table 48. Treatment options for painful diabetic neuropathy (continued).

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>mexiletine</td>
<td>Controlled trials have evaluated the efficacy of mexiletine in the treatment of painful diabetic neuropathy, with variable success being reported. Further well controlled trials are needed. Some evidence suggests that mexiletine may benefit specific types of pain, with one study finding that patients with stabbing or burning pain, heat sensations or formication benefited most from mexiletine. The initial dose of mexiletine should be low and titration done slowly to minimize gastrointestinal intolerance.</td>
</tr>
<tr>
<td>investigational therapies</td>
<td>Other agents which have been investigated for treatment of painful diabetic neuropathy include dextromethorphan, clonidine, and calcitonin. Further studies are needed before these therapies can be routinely recommended.</td>
</tr>
</tbody>
</table>

**Foot care**

The presence of diabetic neuropathy significantly increases the risk of foot ulcerations and infections which may lead to amputations. It is possible to reduce amputation rates by 50–85% with strategies which include prevention, patient and staff education, multidisciplinary treatment of foot ulcers and close monitoring.

Diabetic neuropathy predisposes to foot problems by a number of mechanisms including: changes in foot structure due to myopathy and clawing of the feet leading to development of pressure points; loss of sweating resulting in drying and cracking of the skin which increases vulnerability to trauma; and loss of pain and temperature sensation allowing minor problems to progress to disasters.

The risk of foot ulcers or amputations is increased in patients who have had diabetes for ≥ 10 years, are male, have poor glycemic control, or have cardiovascular, retinal or renal complications.

Education about footwear, foot care and foot surveillance is a major part of the management of diabetic neuropathy. The feet of patients with diabetes should be examined regularly to detect early lesions. Patients should be advised to wear footwear that avoids pressure, and skin moisturizers should be advocated to keep the skin supple. Table 49, page 155 outlines guidelines for patients for foot care.
In addition to those factors outlined in Table 49, page 155, patients should be advised not to use chemical agents or plasters to remove corns and calluses. Corns and calluses should only be treated by a health care provider.  

All patients with diabetes should be examined at diagnosis and at least once a year to identify high risk foot conditions. Patients with demonstrated high risk foot conditions should be examined more often (every 1–6 months) preferably by a podiatrist. Risk factors include the presence of sensory neuropathy, foot deformities, bony prominences, signs of peripheral ischemia, and/or previous ulcer or amputation. Patients with neuropathy should have a visual inspection of their feet at every visit.

Foot examination by a health professional should include assessment of foot structure and biomechanics, neuropathy, vascular status, ulcerations and evidence of infection.

**Table 49. Guidelines for foot management.**

<table>
<thead>
<tr>
<th>Routine Foot Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Wash feet each day with mild soap.</td>
</tr>
<tr>
<td>• Do not soak.</td>
</tr>
<tr>
<td>• Dry between toes.</td>
</tr>
<tr>
<td>• Inspect feet daily. If needed use a mirror for the soles. If vision is poor, ask someone else to check each day. Report any changes, especially injury, color changes, or discharge to the doctor or podiatrist.</td>
</tr>
<tr>
<td>• Nails should be cut straight across with clippers.</td>
</tr>
<tr>
<td>• Shoes should never be ‘broken in’; they should fit from the start. Buy them in the afternoon when the feet are slightly swollen.</td>
</tr>
<tr>
<td>• Check inside shoes before wearing them.</td>
</tr>
</tbody>
</table>

The management of diabetic foot infections/ulcers is beyond the scope of this review.
**DIABETIC RETINOPATHY**

**Incidence**

Up to 21% of patients with type 2 diabetes have retinopathy at diagnosis. It is thought to be the most common cause of new vision loss among adults aged 20–74 years. Greater than 60% of patients with type 2 diabetes will develop some form of retinopathy after 20 years.\(^30\)

With early detection and adequate treatment, the onset of diabetic retinopathy can be prevented or delayed in a large percentage of diabetic patients.\(^30\)

**Pathogenesis**

Diabetes causes damage to the retinal vascular endothelium leading to diabetic retinopathy.\(^439\) The progression of retinopathy is generally orderly, advancing from mild non-proliferative abnormalities, characterized by increased vascular permeability; to moderate and severe non-proliferative diabetic retinopathy, characterized by vascular closure; to proliferative diabetic retinopathy, characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous.\(^30\)

Vision loss due to diabetic retinopathy results from several mechanisms.\(^30\)

- Central vision may be impaired by macular edema or capillary non-perfusion.
- The new blood vessels of proliferative diabetic retinopathy and contraction of the accompanying fibrous tissue can distort the retina and lead to tractional retinal detachment, producing severe and often irreversible vision loss.
- The new blood vessels may bleed, adding the further complication of pre-retinal or vitreous hemorrhage.

Patients with diabetes are also at increased risk of developing cataracts.\(^36\) In addition, diabetes may significantly worsen the visual outcome after cataract surgery.\(^440\)

Special population groups are at increased risk for developing retinopathy. African Americans develop retinopathy 40–50% more frequently and Hispanic Americans have twice the risk of retinopathy than non-Hispanic whites.\(^441\)
Prevention and treatment

The key to reducing retinopathy is early detection and early intervention. When diabetic retinopathy is properly detected and treated, the majority of severe vision loss (bilateral blindness) can be prevented.

The development and progression of retinopathy may be reduced through intensive diabetes lifestyle management (including smoking cessation) to achieve optimal glycemic, blood pressure and lipid control.

Glycemic control

Evidence from outcome studies suggests that good glycemic control can reduce the onset and progression of diabetic retinopathy in patients with both type 1 and type 2 diabetes. For example, in UKPDS 33, intensive blood glucose control (with a sulfonylurea or insulin) was associated with a significant 25% risk reduction in microvascular end points compared with conventional treatment. Most of this was attributed to fewer cases of retinal photocoagulation. For further information see UKPDS 33, page 37.

Blood pressure control

Evidence shows that good blood pressure control can reduce the development and progression of diabetic retinopathy. For example, in UKPDS 38, tight blood pressure control was associated with a significant 35% reduction in the risk of retinal photocoagulation. The tight blood pressure control group also had a significant 34% reduction in the risk of retinopathy progression and a 47% reduced risk of deterioration in visual acuity.

It is currently unclear whether any particular antihypertensive agents would be more advantageous than others. UKPDS 39 reported that captopril and atenolol did not differ in regard to the above benefit on retinopathy development and progression. However, it has been hypothesized that ACE inhibitors may have beneficial effects, independent of blood pressure lowering, on retinopathy progression. While preliminary data provide some support, further controlled studies are needed before conclusions can be drawn.

For further information on UKPDS 38 and 39, see pages 96 and 97, respectively.
**Lipid control**

Limited data suggest that lowering elevated lipids in patients with diabetes may help stabilize retinal status and possibly visual acuity.\(^{439}\) Since patients with diabetes are also at high risk of cardiovascular complications, adequate treatment of dyslipidemia is paramount.

**Multifactorial Intervention**

In the microvascular complications analysis of Steno-2 (discussed in more detail on page 170), progression of retinopathy was examined as a secondary endpoint in patients with type 2 diabetes and microalbuminuria. A significant 55% reduction in progression of retinopathy was found in the intensive multifactorial treatment group versus the conventional multifactorial treatment group.\(^{445}\) Therefore, intensive multifactorial intervention in patients with type 2 diabetes and microalbuminuria may slow progression to retinopathy.

**Laser photocoagulation therapy**

Timely laser photocoagulation therapy can prevent severe visual loss in the vast majority of patients with vision-threatening retinopathy. Laser therapy is used to reduce loss of vision in patients with severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy and/or macular edema.\(^{30}\)

Controlled clinical trials show that photocoagulation is a satisfactory treatment for retinopathy if the condition is detected before irreversible changes have taken place.\(^{446}\) Patients need to be advised that laser therapy is usually not able to restore vision that has already been damaged by diabetic retinopathy.\(^{30}\)

**Vitrectomy**

If the vessels have already bled into the vitreous and that blood does not absorb spontaneously with time, then a vitrectomy may be required. In this operation, the vitreous with hemorrhage is removed through a small scleral incision and is replaced with a clear balanced salt solution, which allows light to pass through the eye and form a clear image on the retina.\(^{447}\)
**Medications**

No medication, other than in the context of improving glycemic, blood pressure, and lipid control, has been shown conclusively to influence the development or progression of diabetic retinopathy. Aspirin is safe for use in patients with diabetic retinopathy but it confers no benefits for retinopathy.\(^{30}\)

**Screening**

Although laser photocoagulation can prevent severe visual loss in the majority of patients with vision-threatening diabetic retinopathy, it will not restore vision that has already been damaged.\(^{30}\) As diabetic retinopathy is often asymptomatic early in the course of the disease, screening is vital in order to prevent visual loss.\(^{448}\)

A dilated and comprehensive eye examination by an optometrist or ophthalmologist should be completed at the time of diagnosis and then annually. Once diabetic retinopathy is detected, more frequent examinations will be required. Risk factors for development of diabetic retinopathy include gross proteinuria and poor glycemic control.\(^{30}\)

Patients need to be educated that diabetic retinopathy can begin without causing any change in vision initially, and that the optimal time to treat it is before any damage to vision has occurred.\(^{439}\) Hence, ongoing screening is crucial.
DIABETIC NEPHROPATHY

General information

Diabetes has become the most common single cause of end-stage renal disease (ESRD) in the United States. The incidence of ESRD due to diabetes is increasing, probably because of the increasing incidence of type 2 diabetes, and more patients are now living long enough to progress to ESRD due to improved prevention and treatment of cardiovascular complications. These patients are now being accepted into ESRD programs where formerly they had been excluded.37

About 20–30% of patients with type 2 diabetes develop evidence of diabetic nephropathy. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels of albumin in the urine (≥ 30 mg/day and < 300 mg/day), referred to as microalbuminuria. Patients with microalbuminuria are referred to as having incipient nephropathy. Without specific interventions, 20–40% of patients with type 2 diabetes and microalbuminuria progress to overt nephropathy (≥ 300 mg/day of albumin in the urine). By 20 years after the onset of overt nephropathy, about 20% will have progressed to ESRD.37

As well as being the earliest manifestation of nephropathy, microalbuminuria is a marker of greatly increased cardiovascular morbidity and mortality in patients with diabetes.37, 38, 449-451 Thus, the finding of microalbuminuria is an indication for screening for possible vascular disease and aggressive intervention to reduce all cardiovascular risk factors (e.g. treating hypertension and dyslipidemia, cessation of cigarette smoking and increasing exercise).37

Screening

In type 2 diabetes, the incidence of albuminuria at the time of diagnosis of diabetes ranges from 3–30%.38 Therefore, a test for microalbuminuria should be performed at diagnosis.37

A quick screen for microalbuminuria can be conducted in the clinical setting with reagent tablets or dipsticks specific for microalbumin. These methods have acceptable sensitivity (95%) and specificity (93%) when performed by trained personnel, and can provide a useful snapshot of albumin present in the urine.39 However, these methods assess urinary
albumin by concentration rather than by excretion rate, and they do not correct for creatinine. A diagnosis of microalbuminuria cannot be established with these methods, and all positive tests from reagent strips or tablets should be confirmed by the more specific methods described below.

A diagnosis of microalbuminuria can be established by one of three methods:

- measurement of albumin to creatinine ratio in a random spot collection, preferably using the first void or morning collection of urine;
- timed collection, such as over four hours or overnight; or
- 24-hour collection with creatinine, allowing simultaneous measurement of creatinine clearance.

The analysis of a spot sample for the albumin-to-creatinine ratio is the preferred method in the office setting and is strongly encouraged.

If the test for microalbumin is positive, it should be repeated twice during the next 6 months. **If two of the three tests are positive for microalbuminuria, treatment should be considered.** If the test for microalbuminuria is negative, re-screening should occur on an annual basis.

For more information about detection of microalbuminuria, see monitoring and goals in type 2 diabetes - urinalysis, page 14.

**Risk factors**

A number of factors have been suggested to predispose patients with type 2 diabetes to diabetic nephropathy, including genetic predisposition, hyperglycemia, duration of diabetes, elevated cholesterol levels, advanced age, hypertension and smoking.

There are also special population groups that are at an increased risk for developing ESRD. African Americans experience ESRD at least four times more frequently and American Indians six times more frequently than non-Hispanic whites.

**Reducing onset and progression of nephropathy**

The most important factors to reduce onset and progression of nephropathy in type 2 diabetes appear to be good glycemic control, meticulous blood pressure control, cessation of cigarette smoking and treatment of dyslipidemia.
**Glycemic control**

Outcome evidence has demonstrated that the quality of glycemic control affects the risk of nephropathy in patients with type 1 diabetes.\textsuperscript{399, 442, 443}

The evidence in type 2 diabetes is less robust. For example, UKPDS 33 did not find intensive glycemic control to significantly improve the risk of renal failure or death from renal disease, although the number of these events was small. However, for the surrogate end points demonstrating progression of albuminuria, intensive treatment was significantly better than conventional treatment (for some measurements at some time intervals). For example, the authors state that there was a 67% risk reduction in the proportion of patients who had a two-fold increase in plasma creatinine. The authors state that there was a 67% risk reduction in the proportion of patients who had a two-fold increase in plasma creatinine.\textsuperscript{84} For further information about UKPDS 33, see page 37.

**Blood pressure control**

Many studies in patients with type 1 diabetes have demonstrated the benefit of good blood pressure control on the rate of progression of renal disease.\textsuperscript{458-460} Less extensive evidence suggests this is also likely to be the case in type 2 diabetes. For example, in UKPDS 38, there was no significant benefit from tight blood pressure control compared to less tight control for the end points of renal failure or death from renal failure, although the number of these events was small. By six years, tight blood pressure control was associated with a significant 29% reduction in the risk of having a urinary albumin concentration of \( \geq 50 \) mg/L, and a non-significant 39% reduction in the risk for proteinuria \( \geq 300 \) mg/L. However, these were surrogate end points and the risk reduction for both measures at nine years was not statistically significant.\textsuperscript{319} For further information about UKPDS 38, see page 96.

Of additional interest is whether specific antihypertensive agents are more effective than others in reducing the onset and progression of diabetic nephropathy. The antihypertensives studied the most in this regard are the ACE inhibitors, CCBs and ARBs.

**ACE inhibitors**

ACE inhibitors have long been advocated as the drug class of first choice in the treatment of hypertension in patients with diabetes, particularly in the presence of microalbuminuria or overt nephropathy. This is because it has been thought that ACE inhibitors have advantages over other antihypertensives with respect to renal protective effects, by actions independent of lowering blood pressure.
One of the first studies to suggest that ACE inhibitors are able to slow progression of diabetic nephropathy, independent of their blood pressure lowering ability, was a study by Lewis et al in 1993. This study included 409 patients, with or without hypertension with type 1 diabetes and overt diabetic nephropathy, randomized to captopril or placebo. The placebo group could receive non-ACE inhibitor antihypertensives to achieve target blood pressures. Captopril was associated with a 48% reduction in the risk of the primary end point of doubling of serum creatinine and a 50% reduction in the risk of the combined end point of death, dialysis and transplantation. However, blood pressure was slightly lower in the captopril group than in the control group at baseline and throughout the study, which may be relevant in terms of outcomes noted.

A Cochrane review included 11 randomized controlled trials (≥ one year in duration) involving normotensive patients with type 1 or type 2 diabetes with microalbuminuria or overt albuminuria, being treated with placebo or an ACE inhibitor. Meta-analysis revealed that treatment with an ACE inhibitor resulted in a significant reduction in albumin excretion rate in both type 1 and type 2 diabetes compared with control patients. However, pooled end-of-study mean blood pressures for the treated group were significantly lower than for the control group. Hence, it is not possible to be certain that the reduction of albumin excretion rate is due to a separate renal effect.

The microalbuminuria, cardiovascular, and renal outcomes HOPE substudy (MICRO-HOPE), which evaluated data from the patients with diabetes who were included in the HOPE study (discussed in more detail on page 97), found that after 4.5 years, ramipril significantly lowered the risk of overt nephropathy by 24%. A lower blood pressure was again achieved in the ramipril group than the placebo group, which may be responsible in part for this observation.

The DIABHYCAR study examined the effect of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised urinary albumin excretion. The study was a randomized, double-blind, placebo-controlled trial, using 1.25 mg ramipril, with a median follow up of 4 years (discussed in more detail on page 98.) Despite a small but significant reduction in both BP and urinary albumin excretion, there were no significant differences in cardiovascular or renal outcomes. The results suggest that the cardiovascular and renal benefits of ramipril reported elsewhere (see the HOPE study on page 97) may be dose dependent.
A more recent study, the multicenter double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)\textsuperscript{464}, evaluated whether ACE inhibitors and non-dihydropyridine calcium channel blockers, alone or in combination, prevented microalbuminuria in hypertensive patients with type 2 diabetes and normal urinary albumin excretion. 1204 patients were randomly assigned to receive treatment with trandolapril alone, verapamil alone, trandolapril plus verapamil, or placebo. The primary end point consisted of development of persistent microalbuminuria (defined as overnight albumin excretion $\geq 20\mu g/\text{min on two consecutive visits}$). After a median follow-up of 3.6 years, the primary outcome was reached in 5.7% of patients receiving trandolapril plus verapamil, 6.0% of patients receiving trandolapril alone, 11.9% of patients receiving verapamil, and 10.0% of patients receiving placebo. When adjusted for baseline characteristics and compared to placebo, trandolapril as well as trandolapril plus verapamil significantly delayed the onset of microalbuminuria. There was no significant reduction in the onset of microalbuminuria with verapamil when compared to placebo.\textsuperscript{464}

Furthermore, in a comparison between subjects who received an ACE inhibitor, alone or in any combination, compared with those who received a calcium channel blocker, alone or in any combination, results showed that there was a significant reduction in the progression to microalbuminuria in the ACE inhibitor group versus those who did not take an ACE inhibitor. However, no effect on progression to microalbuminuria was seen in those taking a calcium channel blocker compared to those who did not. Based on these results, the use of an ACE inhibitor appeared to significantly delay the onset of microalbuminuria, while use of a calcium channel blocker did not have any such effect. In addition, when compared to placebo, trandolapril alone significantly delayed the onset of microalbuminuria while verapamil alone did not significantly delay the onset of microalbuminuria. It should be noted that a comparison of average trough blood pressures between the groups showed a significant decrease in systolic and diastolic blood pressure in the trandolapril alone group and the trandolapril plus verapamil group versus placebo. There was no significant difference in a comparison between the verapamil alone and placebo groups with regard to trough blood pressures. A comparison for significance with regard to change in blood pressure between the trandolapril alone group and the verapamil alone group was not provided.\textsuperscript{464}

The authors concluded that the reduced incidence of microalbuminuria seen in the patients taking trandolapril plus verapamil and patients taking
trandolapril alone is evidence that the onset of microalbuminuria can be delayed in patients with type 2 diabetes.\textsuperscript{464}

In conclusion, numerous studies provide evidence that ACE inhibitors can slow the progression of diabetic nephropathy in patients with diabetes. ACE inhibitors are often stated to be more advantageous than other antihypertensives because of independent renoprotective effects. However, this is still somewhat controversial,\textsuperscript{465} particularly when considering the results of UKPDS 39 (discussed in more detail on page 97).\textsuperscript{323} In this study, there was no difference in the incidence of aggregate microvascular end points and surrogate measures of nephropathy between captopril and atenolol.\textsuperscript{323}

**Calcium channel blockers**

In the ABCD trial, moderate to intensive blood pressure control appeared to stabilize renal function in patients with type 2 diabetes without overt albuminuria over a five year period. There were no significant differences between nisoldipine and enalapril in this regard.\textsuperscript{466} However, the nisoldipine group had a higher incidence of MIs than the enalapril group in this study.\textsuperscript{331}

Other trials assessing the effects of CCBs on diabetic nephropathy have had inconsistent results. For example, a number of studies suggest dihydropyridine CCBs to be less effective than ACE inhibitors,\textsuperscript{464, 467-472} while others report equal effects.\textsuperscript{473-477} A non-dihydropyridine CCB was equally effective as ACE inhibitors in one small trial.\textsuperscript{478} The recent Irbesartan Type II Diabetic Nephropathy Trial (IDNT) (see page 165) found amlodipine to be less effective than irbesartan in slowing the progression of overt nephropathy to ESRD.\textsuperscript{479}

Given the ongoing uncertainty regarding cardiovascular outcomes in patients with diabetes, CCBs are not generally indicated as first line therapy for hypertension. However, they may be useful as part of combination regimens. For further information on the use of CCBs in the treatment of hypertension in patients with diabetes, see calcium channel blocker uncertainty, page 99.

**Angiotensin II receptor antagonists**

Outcomes studies involving ARBs in patients with type 2 diabetes have recently been published.

The Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT) included 1715 hypertensive patients with nephropathy due to type 2 diabetes. After a mean
follow up of 2.6 years, the risk of the primary end point (composite of
doubling of serum creatinine levels, ESRD or death from any cause) was
significantly reduced by 23% with irbesartan 300 mg daily compared with
amlodipine 10 mg daily, and 20% compared with placebo. In this study the
mean blood pressure was significantly higher in the placebo group than the
two treatment groups but it did not differ between irbesartan and
amlodipine.  

The Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive
Patients (IRMA 2) study included 590 patients with hypertension, type 2
diabetes and microalbuminuria. After two years, 5.2% of patients receiving
irbesartan 300 mg daily progressed to diabetic nephropathy compared to
14.9% of the placebo recipients. The authors stated the effects were
independent of blood pressure lowering.

A substudy of IRMA 2 involving 133 hypertensive type 2 diabetic patients
has recently been published. The primary endpoints were mean arterial
blood pressure (MABP), overnight urinary albumin excretion rate (UAR),
and glomerular filtration rate, following a one month washout period as
compared to baseline values. In summary, the placebo group returned to
baseline for all endpoints measured, the irbesartan treated groups
approached baseline with respect to GFR, MABP increased significantly,
and UAR was significantly reduced in the high dose irbesartan group.

These findings support the argument that irbesartan provides additional
renoprotection beyond blood pressure lowering (and decreased GFR). The
authors suggest that therapy with higher doses confer long-term
renoprotection secondary to increased suppression of the effects of
angiotensin II. Although beneficial effects were only measured for 4
weeks following removal of irbesartan, the evidence strongly refutes the
argument that reduction of albumin excretion seen with angiotensin
receptor blocker therapy is solely related to decreases in GFR.

The Reduction in End points in Non-Insulin Dependent Diabetes Mellitus
with the Angiotensin II Antagonist Losartan (RENAAL) study included
1513 patients with type 2 diabetes and nephropathy. It found that losartan
significantly reduced the risk of the primary end point (composite of
doubling of serum creatinine, ESRD or death) by 16% compared to
placebo. For progression to ESRD alone, losartan significantly reduced the
risk by 28% compared to placebo.

Several short-term studies of interest have been published regarding ARBs
and their effect on microalbuminuria in normotensive and hypertensive
patients with type 2 diabetes.
The Microalbuminuria Reduction with Valsartan (MARVAL) study included 332 patients with type 2 diabetes and microalbuminuria, with or without hypertension. After a 24 week active control comparison, a significant reduction in urine albumin excretion rate occurred in the valsartan 80 mg daily group versus the amlodipine 5 mg daily group. Blood pressure reductions remained similar between the two groups throughout the study period. The effect of valsartan on albumin excretion rate occurred irrespective of baseline hypertensive status and the authors concluded that this effect was independent of valsartan’s blood pressure lowering effects. In addition, a greater number of patients receiving valsartan reversed to normoalbuminuria compared with those receiving amlodipine.

One recent study examined the effects of losartan on urinary albumin excretion rate in 147 normotensive patients with type 2 diabetes and microalbuminuria. In multiple outpatient clinics in the Netherlands, 74 patients received losartan and 73 patients received matching placebo for 10 weeks. This study involved a screening and washout period. The dose of losartan was increased from 50 mg daily to 100 mg daily after a five week titration period. Results of the study showed a significant reduction in the adjusted mean difference in albumin excretion rate between the losartan and placebo groups at both 5 weeks and 10 weeks. The authors suggested that the reduction in albumin excretion rate occurred independently from losartan’s blood pressure lowering effects.

Another recent study looked at the effect of irbesartan on the excretion of microalbumin and on blood pressure in hypertensive and normotensive patients with type 2 diabetes. The study included 64 hypertensive and 60 normotensive male patients with microalbuminuria and type 2 diabetes. Each group was further divided into an irbesartan or placebo group and effects on blood pressure and microalbuminuria measured during a 60 day time period and then crossed over for an additional 60 days. Results of the study showed a significant reduction in microalbuminuria in both the hypertensive and normotensive groups over placebo. The hypertensive group had a significant reduction in blood pressure over placebo while the normotensive group did not.

**Dual Blockade of the Renin-Angiotensin System**

Combination therapy with ACE inhibitors and ARBs to achieve dual blockade of the renin-angiotensin system in patients with type 2 diabetes and nephropathy is an emerging practice. It is thought that therapy with an ACE inhibitor and an ARB may result in more complete inhibition of the renin-angiotensin system than either agent used alone. Therefore, in
patients with type 2 diabetes and microalbuminuria, dual blockade of the renin-angiotensin system may confer potential additional benefits in terms of blood pressure and renoprotection compared to monotherapy.

Studies investigating dual blockade of the renin-angiotensin system by ACE inhibitors and ARBs in patients with diabetes are limited. However, a recent literature review by Wade and Gleason included five short-term randomized, double-blind trials totaling approximately 300 patients with type 1 or type 2 diabetes with microalbuminuria or overt nephropathy. The authors concluded that dual blockade with an ACE inhibitor and an ARB in diabetic nephropathy is generally safe and will provide an additional 11-43\% reduction in albuminuria versus monotherapy. Dual blockade provided statistically significant reductions in microalbuminuria, and also produced reductions in blood pressure, although the reductions in blood pressure were not always significant when compared to monotherapy.

There is insufficient evidence from well-designed trials regarding the utility of dual blockade at this time, especially in regards to long-term clinical outcomes. In addition, it is difficult to determine whether the additional benefits of these two drug classes result purely from dual blockade, or if these effects are a result of an additional decrease in blood pressure. Therefore, dual blockade should be considered on an individual patient basis and serum creatinine and potassium should be closely monitored if therapy with this combination is chosen.

Cardiovascular and renal outcome studies involving dual blockade with ACE inhibitors and ARBs, and a comparison of this therapy with other antihypertensives, are lacking.

**Comparing the Renoprotective Effects of ACE inhibitors and ARBs**

Outcome studies comparing the renoprotective effects of ACE inhibitors and ARBs in type 2 diabetes are limited.

The Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study, was a prospective, head-to-head comparison between ACE inhibitors and ARBs in patients with type 2 diabetes and nephropathy. DETAIL included 250 patients randomized to receive either telmisartan 80 mg daily or enalapril 20 mg daily following a dose titration. After five years, there was no significant difference in the primary endpoint (change in glomerular filtration rate between the baseline value and last available value during the treatment period) between the two treatment groups. Adjusted for body-surface area, the changes in GFR were a decrease of 17.9 ml/min in the telmisartan group and a decrease of 14.9 ml/min in the enalapril group.
There was also no significant difference between the change in serum creatinine level and percentage change in urinary albumin excretion rate from baseline between the two groups. The authors concluded that telmisartan and enalapril are equivalent in terms of long-term renoprotective effects, although they do acknowledge that the high drop out rate in both groups (approximately 33%) and concomitant medication use by participants may have influenced some of the study outcomes.488

**Conclusion**

Tight blood pressure control appears to be important in reducing the onset and progression of diabetic nephropathy. ACE inhibitors have been the most widely studied drug class for this indication and are often advocated as first choice for treating hypertension in patients with diabetes, particularly in the presence of microalbuminuria or overt nephropathy. Benefit has also been documented for normotensive patients with microalbuminuria. Recent data for the ARBs is also favorable and they are now recommended in the treatment of albuminuria/nephropathy in type 2 diabetes.37 Some evidence supports the hypothesis that these drug classes have renal protective effects independent of their blood pressure lowering ability; however, further studies are needed, particularly to compare ACE inhibitors with ARBs. Importantly, the need for combination antihypertensive treatment in patients with diabetes is common. Renoprotection through inhibition of the renin-angiotensin system may also be dose-dependent.328, 489 Therefore, individual dose titration to achieve optimal antiproteinuric effect could be more important than initial choice between an ACE inhibitor or an ARB.489 Note that the blood pressure target in patients with type 2 diabetes and proteinuria exceeding 1 g/day is < 125/75 mmHg. For further information see hypertension, page 94.

**Smoking cessation**

Patients with type 2 diabetes who smoke have a greater risk of microalbuminuria than patients who do not smoke, and their rate of progression to ESRD is about twice as rapid.453, 456 Cessation of cigarette smoking appears to be important in preventing the onset and progression of diabetic nephropathy.452 For further information about smoking cessation, see page 31.

**Treatment of dyslipidemia**

Preliminary evidence suggests that treatment of dyslipidemia may slow the rate of decline of renal function in patients with type 2 diabetes.37, 454 Since
this group is also at high risk of cardiovascular complications, adequate treatment of dyslipidemia is paramount. For further information see dyslipidemia, page 117.

**Multifactorial Intervention in Patients with T2D and Microalbuminuria**

The microvascular analysis of Steno-2 investigated the effects of an intensive multifactorial treatment compared with a conventional multifactorial treatment on the progression and development of microvascular complications in patients with type 2 diabetes and microalbuminuria (defined as an albumin excretion rate of 30-300 mg/day). Intensive treatment included a stepwise implementation of behavior modification and pharmacological therapy targeting hyperglycemia, hypertension, dyslipidemia and microalbuminuria. Intensive treatment targeted achieving goals of current practice guidelines. Steno-2 is discussed in more detail on page 143.

The primary endpoint in the microalbuminuria analysis of Steno-2 was progression to overt nephropathy, defined as an albumin excretion rate of >300 mg/day. After a median follow up of 3.8 years, there was a significant 73% relative risk reduction in the development of nephropathy in the intensive treatment group versus the standard treatment group. The authors concluded that intensive multifactorial treatment slowed the progression to overt nephropathy in patients with type 2 diabetes and microalbuminuria. The authors also suggested that the increased use of ACE inhibitors in the intensive treatment group may have been responsible for most of the reduction in urinary albumin excretion rate seen in the intensive group versus the conventional treatment. It should also be noted that the reduction in GFR was similar between the two groups, although a difference in GFR may have been masked due to improved glycemic control and ACE inhibitor use (known to decrease GFR) in both groups.

**Others**

A Cochrane review, which examined whether protein restriction can be of benefit in patients with diabetic nephropathy, found that overall a protein restricted diet (0.3–0.8 g/kg per day) does appear to slow the progression of diabetic nephropathy towards renal failure. However, the optimum level of protein restriction is unclear. The authors suggest a pragmatic approach would be to reduce high protein intake to perhaps a maximum of 1 g/kg/day, or to 0.8 g/kg/day in those patients prepared to comply with that. It has been suggested that further restriction to 0.6 g/kg/day may be helpful
once the glomerular filtration rate (GFR) begins to fall. A dietitian should be involved in meal planning for all patients on protein-restricted diets. It is important to note that all of the trials were in patients with type 1 diabetes. It remains to be seen if a lower protein intake would slow the progression of nephropathy affecting patients with type 2 diabetes.\textsuperscript{37,490}

Other treatment modalities, such as phosphate lowering, may have benefits in selected patients.\textsuperscript{37,490}
DIABETIC COMPLICATIONS — MACROVASCULAR

CORONARY HEART DISEASE

**Background**

Type 2 diabetes is associated with a 2–4 fold increased risk of CHD, and the prognosis of clinical CHD is worse in patients with diabetes compared to patients without diabetes. CHD accounts for up to 70% of the observed mortality in patients with type 2 diabetes.

It has been shown that, even without prior MI, patients with diabetes have the same level of cardiovascular risk as patients without diabetes having sustained an MI.

Patients with type 2 diabetes often have more advanced CHD at the time of diagnosis than patients without diabetes. One explanation for this is that patients with type 2 diabetes more often experience silent or asymptomatic ischemia, probably as a result of autonomic neuropathy.

**Risk factors**

Diabetes is an independent risk factor for increased morbidity and mortality due to CHD. Other risk factors include:

- dyslipidemia;
- hypertension;
- poor glycemic control;
- elderly age;
- family history of CHD;
- cigarette smoking;
- lack of exercise; and
- albuminuria (micro or macro).
Prevention

Lifestyle modification

Non-pharmacological measures, such as smoking cessation, weight loss and increased physical activity, are important measures to reduce the risk of CHD in patients with diabetes. Appropriate nutrition is also important. See lifestyle interventions in the management of type 2 diabetes, page 17.

Lipid lowering therapy

Clinical trials in patients without diabetes have established that lowering cholesterol levels can reduce the incidence of new CHD as well as delaying the progression of established disease. Studies specifically investigating the effects of lipid lowering therapy on the development of CHD in patients with diabetes are limited, although a number of such trials are currently underway.

Results from CARDS (see page 123 for additional information) recently found that atorvastatin, as compared to placebo, was associated with a 36% reduction in acute coronary events and a 31% reduction in coronary revascularization events in patients with type 2 diabetes. In addition, when unstable angina was excluded from the definition of non-surgical acute coronary events, there was a 33% risk reduction in the incidence of acute coronary heart disease events in the atorvastatin group versus placebo. The results of CARDS also showed a reduction in the incidence of coronary heart disease events plus revascularization with atorvastatin as compared to placebo.

A number of clinical trials have included small numbers of patients with type 2 diabetes. For example, subgroup analysis of the 4S study indicated that in patients with diabetes and hypercholesterolemia, normal triglycerides and established CHD, lowering LDL cholesterol with simvastatin was associated with a marked reduction of major CHD and any atherosclerotic events. Similarly, in the CARE study pravastatin significantly reduced the risk of coronary events by 25% in patients with diabetes, average cholesterol levels and history of MI, during a five year follow up period. The absolute risk reduction was higher in patients with diabetes than in those without. In the Helsinki Heart Study, gemfibrozil was associated with a reduction in CHD in patients with diabetes without prior CHD (but this was not statistically significant). In the VA-HIT study, gemfibrozil was associated with a 24% decrease in the combined end point of death due
to CHD, non-fatal MI and stroke in patients with type 2 diabetes, low HDL cholesterol and CHD. In the LIPID trial, pravastatin reduced the composite end point of CHD related death and MI by 19% (not statistically significant) in a subgroup of patients with diabetes who had a history of MI or unstable angina with a broad range of initial cholesterol levels.

Therefore, treatment of dyslipidemia in patients with diabetes is recommended to reduce the risk of CHD. For further information see dyslipidemia, page 117.

**Blood pressure control**

Evidence clearly shows that managing hypertension in patients with type 2 diabetes is able to reduce the risk of macrovascular end points including CHD. For example, in UKPDS 38, compared to patients in the less tight blood pressure control group, patients allocated to tight blood pressure control had a significant reduction in the risk of developing any end point related to diabetes, deaths related to diabetes, macrovascular diseases combined and heart failure. The reduction in risk of MI was not statistically significant. For further information see UKPDS 38, page 96.

Whether there are differences in antihypertensive drug classes with respect to their ability to reduce the risk of CHD is currently unclear. Benefit has been demonstrated, in patients with diabetes, with low dose thiazides, β-blockers, ACE inhibitors and ARBs. The effect of CCBs on the risk of CHD is uncertain with some studies finding negative effects and others finding positive effects. See page 99 for further explanation.

Comparison studies had previously not proven superiority of one class over another. For example, in UKPDS 39, captopril and atenolol were similarly effective at reducing the risk of macrovascular disease, including MI in patients with type 2 diabetes. For further information see UKPDS 39, page 97. More recently in LIFE, losartan reduced the risk of macrovascular disease, excluding MI and stroke, compared to atenolol in patients with type 2 diabetes. For further information see LIFE, page 99.

Reduction in the risk of MI, revascularization, and the combined end point of MI, stroke or cardiovascular death, was demonstrated with ramipril in patients with diabetes plus at least one other cardiovascular risk factor, who took part in the HOPE study. Importantly, almost half of these patients were not hypertensive at baseline, suggesting that ACE inhibitors may be
exerting benefit through mechanisms other than just blood pressure lowering.\textsuperscript{327, 505} For further information see the HOPE study, page 97.

**Blood glucose control**

The impact of intensive blood glucose control on the risk of CHD in type 2 diabetes is unclear. In UKPDS 33 & 34, intensive blood glucose control with sulfonylureas or insulin was not associated with a significant reduction in the incidence of diabetes related deaths, all-cause mortality or macrovascular complications. However, there was a borderline significant 16\% risk reduction for MI in the intensive versus conventional group and the incidence of microvascular complications was significantly reduced.\textsuperscript{84} Metformin therapy in overweight patients significantly reduced the risk of any diabetes related end point, diabetes related death, all-cause mortality and MI.\textsuperscript{85} For further information see UKPDS 33, page 37, and UKPDS 34, page 38.

**Antiplatelet therapy**

Aspirin is recommended for all patients with type 2 diabetes with established CVD unless specific contraindications exist. Aspirin therapy should also be considered as primary prevention in patients with diabetes due to their high cardiovascular risk.\textsuperscript{506} For further information see page 141.

**Treatment**

The treatment of CHD events in patients with type 2 diabetes is beyond the scope of this document and will not be discussed further.

Following an MI, studies have demonstrated that both β-blockers and ACE inhibitors are associated with reduced morbidity and mortality in patients with diabetes.\textsuperscript{492, 506}
STROKE

Background

Patients with type 2 diabetes are at a 2–4 fold increased risk of stroke compared to patients without diabetes. The strokes are often more severe in patients with diabetes and are associated with a higher mortality rate. Furthermore, patients with diabetes are more likely to have a stroke at presentation without warning TIAs than patients without diabetes.

In the non-diabetic population, a stroke results from ischemic cerebral infarction in 80% of cases and cerebral hemorrhage in 20% of cases. In patients with diabetes, hemorrhagic stroke is less prevalent and ischemic stroke is more prevalent than in patients without diabetes.

Cerebral atherosclerosis is the leading cause of ischemic stroke in patients with diabetes.

Risk factors

Diabetes is an independent risk factor for stroke. Other risk factors include:

- elderly age;
- hypertension;
- cigarette smoking;
- atrial fibrillation;
- history of CVD, particularly previous stroke;
- poor glycemic control;
- duration of diabetes;
- dyslipidemia;
- clinical proteinuria;
- hyperuricemia; and
- hyperhomocysteinemia.

Prevention

Lifestyle modification

Body weight reduction, salt intake reduction, appropriate nutrition and exercise have all been shown to lower blood pressure in hypertensive
patients; hence, these measures should be encouraged in an attempt to reduce the risk of stroke and other diabetes related complications. Moderation of alcohol intake also appears to be important in the prevention of stroke, and smoking cessation should be encouraged. See lifestyle interventions in the management of type 2 diabetes.

**Blood pressure control**

Hypertension appears to be the most important modifiable risk factor for stroke in patients with or without diabetes, with elevated diastolic and systolic blood pressure both being important.

Treatment of hypertension with antihypertensives, in patients with or without diabetes, has reduced the risk of stroke in large outcome trials. For example, in UKPDS 38, tight blood pressure control significantly reduced the risk of fatal and non-fatal stroke by 44% compared with less tight blood pressure control in type 2 diabetes. For further information see UKPDS 38.

Whether antihypertensive drug classes differ in their ability to reduce the risk of stroke is unclear. Benefit has been demonstrated, in patients with or without diabetes, with low dose thiazides, β-blockers, ACE inhibitors, ARBs, and CCBs. Comparison studies have not proven superiority of one class over another. For example, in UKPDS 39, captopril and atenolol were similarly effective at reducing the risk of stroke in type 2 diabetes. For further information about UKPDS 39, see page 97. More recently in LIFE, there was no significant difference between losartan and atenolol for stroke risk reduction in type 2 diabetes.

Ramipril was associated with a reduction in stroke risk in patients with diabetes in the HOPE study. Importantly, almost half of these patients were not hypertensive at baseline, suggesting that ACE inhibitors may be exerting benefit through mechanisms other than just blood pressure lowering. For further information see the HOPE study, page 97.

For further information on managing hypertension in patients with diabetes, see hypertension.

**Blood glucose control**

The impact of intensive blood glucose control on the risk of stroke in patients with type 2 diabetes is unclear. In UKPDS 33, intensive blood glucose control with sulfonylureas or insulin was not associated with a
reduction in the incidence of stroke. In UKPDS 34, metformin therapy had a significantly greater effect on reducing stroke risk than sulfonylureas or insulin in overweight patients, but did not significantly lower stroke risk when compared with conventional treatment.

However, good glycemic control has been shown to reduce microvascular complications, and metformin has been shown to reduce diabetes related morbidity and mortality in overweight patients. For further information see UKPDS 33, page 37 and UKPDS 34, page 38.

Lipid lowering therapy

There is limited data concerning the efficacy of lipid lowering therapy on the risk of stroke. The LIPID study found that pravastatin moderately reduced the risk of stroke in patients with previous MI or unstable angina. There was a non-significant trend for this effect in patients with diabetes. The Heart Protection Study found that simvastatin in high risk patients reduced the risk for stroke, although subgroup analysis for type 2 diabetes was not available. More recently, the results of CARDS showed a 48% relative reduction in the rate of stroke with atorvastatin versus placebo in patients with type 2 diabetes without elevated LDL cholesterol. For further information on the results of CARDS see page 123.

Despite the lack of data concerning lipid lowering therapy and stroke risk reduction in patients with type 2 diabetes, treatment of dyslipidemia is recommended because of the overall impact on cardiovascular mortality. For further information see page 117.

Antiplatelet therapy

Aspirin therapy should be considered in patients with diabetes due to their high cardiovascular risk. For further information see page 141.

Anticoagulants

Patients with atrial fibrillation who are at high risk of stroke benefit from anticoagulation with warfarin. Antiplatelet agents are less effective than warfarin but have a lower bleeding risk, and are a reasonable alternative if warfarin is contraindicated. People defined as high risk include patients with a previous TIA or stroke, or a history of rheumatic vascular disease, CHD, congestive heart failure and/or impaired left ventricular function or echocardiography; and people aged 75 years and over with hypertension, diabetes, or both.
Treatment

The treatment of stroke is beyond the scope of this document. However, when faced with a patient with diabetes with a suspected cerebral event, it is important to rule out hypoglycemia as a non-vascular cause of a neurological disorder with sudden onset.\textsuperscript{511} Hyperosmolar non-ketotic coma, which is induced by hyperglycemia, is also associated with focal neurological signs and could be mistaken for a stroke.\textsuperscript{514}
PERIPHERAL VASCULAR DISEASE

Background

PVD is typically characterized by a gradual reduction in blood flow to one or more limbs secondary to atherosclerosis. The legs are the most common site affected, particularly in patients with type 2 diabetes.

The most common clinical manifestation of PVD is intermittent claudication, which is defined as pain, ache, cramp, numbness or sense of fatigue in the muscles. It occurs during exercise, but is relieved with rest. Patients with intermittent claudication often have marked impairment in exercise performance and overall functional capacity, and typically report great difficulty in walking short distances, even at a slow speed.

In most patients, intermittent claudication is associated with a relatively benign natural course. For example, in the general population after 5–10 years, the conditions of about 70–80% of patients remain unchanged or improved. Approximately 20–30% have progression of symptoms and require intervention, and < 10% require amputation. However, importantly, PVD is associated with an increased risk of coronary and cerebrovascular events. For example, people with severe or symptomatic large vessel PVD have been shown to have a 15 times increased risk of mortality due to CVD and CHD than those without large vessel PVD.

Other clinical manifestations of PVD include acute and chronic critical limb ischemia, in which limb viability is threatened. Acute critical limb ischemia is a vascular emergency and most patients with chronic critical limb ischemia require surgical intervention. The management of critical leg ischemia is considered beyond the scope of this document and will not be discussed any further.

The prevalence of PVD is increased in patients with diabetes compared to the general population, and the disease is often more severe. Patients with PVD and diabetes have a higher incidence of severe coronary artery and cerebrovascular disease, and a higher (mostly cardiac) mortality rate compared with people with PVD without diabetes. In addition to the increased risk of cardiovascular mortality, the risk of foot ulceration and amputation is increased in patients with diabetes and PVD.
Screening

Screening for PVD in patients with type 2 diabetes is important to minimize complications resulting from diabetic feet and macrovascular disease. Annual assessment, which includes asking the patient about rest pain and intermittent claudication, and checking peripheral pulses, is recommended.\(^{543}\)

Physical examination in patients with PVD may reveal absent distal pulses, arterial bruits, skin and hair changes on the affected limb, or edema.\(^{536}\) Confirmation of vascular obstruction is usually determined by using Doppler ankle pressures.\(^{536}\)

Risk factors

Diabetes and cigarette smoking are the two major risk factors for PVD.\(^{502, 536, 540, 545, 547, 548}\) Other important risk factors include:

- older age;\(^{540, 544, 545, 549, 550}\)
- dyslipidemia;\(^{536, 540, 544, 545, 549, 550}\)
- hypertension;\(^{536, 540, 544, 545, 549}\)
- duration of diabetes;\(^{541, 549}\)
- albuminuria;\(^{551}\) and
- hyperhomocysteinemia.\(^{525, 552}\)

Prevention and treatment

CHD is the cause of death in about 75% of patients presenting with PVD. Assessment and treatment of coexistent CHD and aggressive risk factor modification are essential aspects of management and may determine the outcome for these patients.\(^{542}\)

In addition to risk factor modification, antiplatelet therapies and strategies for symptomatic relief may be necessary.\(^{540, 553}\)

Smoking cessation

Cigarette smoking is one of the most important risk factors, and as such, it is a prime target for intervention.\(^{545}\) Smoking cessation has been shown to slow the progression to critical leg ischemia, and reduce the risk of MI and death from vascular causes in patients with PVD.\(^{536, 540}\) For further information see smoking cessation, page 31.
Exercise

The primary non-pharmacological treatment for claudication is a formal exercise training program. Exercise therapy has been found to significantly improve maximal walking time in patients with intermittent claudication. Current evidence suggests a regimen of walking three times weekly to near-maximal pain provides the best improvement. Exercise training must be maintained on a regular basis or the benefits will be lost.

In addition to supervised exercise training, which usually involves walking, other forms of exercise like bicycle riding and swimming provide overall cardiovascular and psychological benefit, and often are tolerated better than walking.

Foot care

Attention to appropriate foot care is vital for patients with diabetes, particularly in the presence of PVD and/or peripheral neuropathy. For further information see foot care, page 154.

Blood glucose control

The impact of intensive blood glucose control on PVD in patients with type 2 diabetes is unclear. In UKPDS 33 & 34, intensive blood glucose control with sulfonylureas, insulin or metformin was not associated with a decreased risk of amputation or death from PVD; however, the numbers of these events were small. However, good glycemic control has been shown to reduce the risk of microvascular complications, and metformin has been shown to reduce the risk of diabetes related morbidity and mortality in overweight patients. For further information see UKPDS 33, page 37 and UKPDS 34, page 38.

Blood pressure control

In UKPDS 38, tight blood pressure control was not associated with a significant reduction in the risk of amputation or death from PVD, although the numbers of these events were small. However, tight blood pressure control in patients with type 2 diabetes did result in reduction in the risk of death related to diabetes and reductions in incidences of many diabetes complications. For further information see UKPDS 38, page 96.

β-blockers have traditionally been considered relatively contraindicated in PVD. However, a meta-analysis concluded that β-blockers do not adversely affect walking capacity or symptoms of intermittent claudication in patients.
with mild to moderate PVD. Caution is advocated in severe PVD. Metoprolol, atenolol or pindolol are generally the preferred agents.

In the HOPE study, approximately 44% of patients had evidence of PVD at baseline. In the entire study, the primary end point of death from vascular causes, non-fatal MI or stroke, occurred in 17.8% of the placebo group, as compared with 14.0% of the ramipril group. The benefit was also demonstrated when considering only those patients with PVD. For further information see the HOPE study, page 97.

**Lipid lowering therapy**

There is limited data concerning the efficacy of lipid lowering therapy on progression of PVD. However, treatment of dyslipidemia is recommended in patients with PVD because of the overall impact on cardiovascular mortality. For further information see page 117.

**Antiplatelet therapy**

Antiplatelet agents have a well established role in treatment of PVD, with the long-term benefit of reducing cardiovascular morbidity and mortality. Aspirin therapy has been shown to reduce the progression of PVD, as well as reduce cardiovascular morbidity and mortality in the long-term. Low dose aspirin should be considered in all patients with PVD to reduce the incidence of MI and stroke in this high risk group.

Ticlopidine (Ticlid®) has been shown to improve symptoms of PVD and to reduce the risk of fatal and non-fatal cardiovascular events. Ticlopidine may be considered in patients allergic to aspirin, but it has the disadvantage of a risk of neutropenia.

Clopidogrel (Plavix®) may also be considered if aspirin is ineffective and/or inappropriate. Clopidogrel 75 mg once daily was compared with aspirin 325 mg once daily in 19,185 patients in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study; a randomized controlled trial in patients with recent ischemic stroke, MI or symptomatic PVD. After a follow up of 1–3 years, the annual risk of ischemic stroke, MI or vascular death was 5.32% in patients taking clopidogrel compared to 5.83% in patients taking aspirin, representing a statistically significant relative risk reduction of 8.7% in favor of clopidogrel.
**Intermittent claudication therapy**

Pentoxifylline (Trental®) improves abnormal erythrocyte deformability, reduces blood viscosity, and decreases platelet reactivity and plasma hypercoagulability.\(^5\) Trials which have evaluated pentoxifylline for intermittent claudication have had conflicting results, with some showing an improvement in walking distances and others showing no consistent benefit.\(^5\)

Pentoxifylline may have a role in patients with markedly reduced walking distances who are unresponsive to, or cannot engage in, exercise therapy. For such patients, even a small increase in claudication walking distance may allow activities that were previously impossible.\(^5\) The recommended dose is 400 mg orally three times daily.\(^7\)

Cilostazol (Pletal®) a type III phosphodiesterase inhibitor with antiplatelet and vasodilating properties,\(^5\) has been found to improve both pain-free and maximal treadmill walking distance and quality of life.\(^5\) Cilostazol may be used in patients with intermittent claudication, with understanding that it may take up to 12 weeks of therapy before symptomatic relief occurs.\(^6\)

**Vasodilators**

Conventional vasodilator therapies have generally not been helpful in managing symptomatic PVD.\(^5\)

**Surgical interventions**

Percutaneous catheter-based techniques have an important role in the treatment of PVD.\(^6\) Surgical correction of peripheral vascular defects is an option for many patients in whom less invasive procedures are not adequate.\(^6\)
HYPOGLYCEMIA

Hypoglycemia is the most frequent and serious adverse effect of sulfonylureas, meglitinides and insulin. In UKPDS 33, hypoglycemic episodes were significantly more common with intensive therapy compared with conventional therapy, with minor episodes reported in 20–30% of patients annually. Insulin was associated with the highest incidence of all hypoglycemic episodes, with an annual incidence of major hypoglycemic events of 2.3%. It is therefore important that patients with diabetes be educated about the prevention, recognition and treatment of hypoglycemia. For further information see UKPDS 33, page 37; Table 10, page 49; Table 19, page 72; Table 32, page 92.

Blood glucose monitoring and education are invaluable for the prevention and recognition of hypoglycemia. More frequent blood glucose monitoring enables patients to determine when they are most likely to become hypoglycemic. Monitoring is useful before undertaking an activity that may cause hypoglycemia (e.g. exercise) or when hypoglycemia could lead to problems (e.g. while driving). Blood glucose monitoring also enables patients to learn ways of detecting hypoglycemia.

Risk factors

Patients with type 1 diabetes appear to be at greater risk for developing hypoglycemia than patients with type 2 diabetes. The major risk factors for hypoglycemia include:

- personal: erratic lifestyle, living or sleeping alone;
- medical: liver or kidney dysfunction, hypothyroidism or hypoadrenalism; and
- medication: see drug induced hypoglycemia, Appendix 1, page 195.

Other factors which increase the risk of hypoglycemia are:

- an inappropriately high dose of insulin or an insulin secretagogue (i.e. a drug that induces insulin secretion);
- forgotten or delayed meals (especially with rapid-acting insulins or insulin secretagogues); and
- unaccustomed or unplanned exercise.
Elderly people are at special risk of hypoglycemia. The risk of hypoglycemia is also increased when antihyperglycemic agents are used in combination.

**Signs and symptoms**

Hypoglycemia can occur at any time of the day or night, and may occur with all insulins or insulin secretagogues. There are two groups of symptoms of hypoglycemia.

- Symptoms mediated by the sympathetic nervous system. These include sweating, tremor, tachycardia, anxiety, hunger, paraesthesias and palpitations.
- Symptoms due to dysfunction of the CNS (i.e. neuroglycopenia). These include dizziness, headache, clouding of vision, blunted mental acuity, loss of fine motor skill, confusion, abnormal behavior, convulsions and loss of consciousness.

During the waking hours, the usual symptoms of hypoglycemia are those mediated by the sympathetic nervous system. Symptoms of hypoglycemia which occur during the night or early morning hours while the patient is asleep include night sweats, unpleasant dreams/nightmares and early morning headache.

If patients do not develop, note or act upon the warning symptoms of hypoglycemia, and if the normal counter-regulatory responses to hypoglycemia are impaired, these patients are at risk of dangerous hypoglycemia and even death.

**Management**

An episode of hypoglycemia requires urgent treatment. This includes short-term measures to reverse the hypoglycemia, initiating measures to prevent subsequent episodes, and identifying the probable cause of the episode. It is important that the patient be re-educated about hypoglycemia after an episode. It may be necessary to alter the patient’s nutritional habits, exercise plan and/or drug treatment.

**Mild to moderate hypoglycemia**

If the patient is conscious and co-operative, the initial treatment should be with oral glucose or sucrose, in the form of a readily available sugar source (e.g. orange juice, regular soda, two glucose tablets). This should be followed by a longer acting carbohydrate (e.g. sandwich, dried fruit) to
prevent recurrent hypoglycemia. Glucose, and not sucrose, is recommended for patients treated with alpha-glucosidase inhibitors because of delayed absorption of sucrose.\textsuperscript{68}

**Severe hypoglycemia**

**Glucagon**

If the patient is unconscious or unable to take oral foods or fluids, glucagon may be administered. Glucagon is commonly used to treat hypoglycemia outside of the hospital setting, and hence, patients at risk of hypoglycemia should carry glucagon with them. In addition, their family, friends and work colleagues should be familiar with the identification of hypoglycemia and its treatment, including the administration of glucagon.\textsuperscript{548, 566}

For adults and children weighing over 20 kg, give glucagon 1 mg subcutaneously, intramuscularly or intravenously. For children less than 20 kg, give glucagon 0.5 mg subcutaneously or intramuscularly, followed by oral feeding when conscious.\textsuperscript{548}

The unconscious patient should wake usually within 10–20 minutes after glucagon administration. After an episode of hypoglycemia, it is important to follow resuscitation with ongoing monitoring and carbohydrate input. However, caution must be used to not overtreat.\textsuperscript{68, 548, 566}

**Glucose**

If glucagon is not available, or if there is no response within 10–15 minutes, it is recommended that intravenous glucose be administered (into an antecubital vein if possible as superficial thrombophlebitis often occurs with injection into hand veins).\textsuperscript{566}

In adults, give 50–100 mL of 50% glucose injection intravenously, through a securely positioned catheter. Follow this with a continuous infusion of 10% glucose.\textsuperscript{569}

In children, give 10% glucose intravenously at a rate of 2–5 mg/kg/minute until the patient is fully conscious. The 10% glucose injection is recommended in children as excessive use of 50% glucose injection has caused deaths in children due to hyperosmolality. It is important that blood glucose be rechecked as continued glucose boluses may render a young child hyperosmolar, with the risk of cerebral edema.\textsuperscript{569}

After an episode of hypoglycemia, it is important to follow resuscitation with ongoing monitoring and carbohydrate input.\textsuperscript{569}
Driving licenses

Current evidence does not clearly indicate a higher risk of motor vehicle accidents for people with diabetes (even those taking insulin) than for drivers without diabetes.\textsuperscript{570} Despite this evidence, limitations to driving licenses may apply to some patients with diabetes because of frequent or severe hypoglycemia (and also reduced visual acuity and visual fields). Mild hypoglycemic symptoms, such as sweating or tremor, are not as significant as more severe episodes which affect consciousness, level of alertness and motor skills.
SPECIAL PATIENT GROUPS

AFRICAN AMERICANS, HISPANIC AMERICANS, ASIAN AMERICANS AND AMERICAN INDIANS

Prevalence

Diabetes represents a major threat to the health of the African-American, Hispanic American, Asian American and American Indian communities.\textsuperscript{441, 571}

The prevalence of diabetes in these special patient groups is 2–4 times higher than in non-Hispanic whites of similar age. This is likely to continue to rise in the future as more people are exposed for longer periods to the adverse environments that have precipitated high rates in some of these communities.\textsuperscript{441, 571}

Type 2 diabetes is the predominant form of diabetes in these populations. The incidence of type 1 diabetes is similar to, or lower than, the incidence in non-Hispanic whites.\textsuperscript{441, 571} A high prevalence of risk factors for type 2 diabetes and CVD in the children and adolescents of these populations living in westernizing communities has been found.\textsuperscript{441, 571}

The high prevalence of diabetes in these populations has been attributed to lifestyle risk factors as well as genetic susceptibility. The prevalence of overweight and obesity in African Americans, Hispanic Americans and American Indians appears to exceed the level in white Americans. This is related to the degree of westernization, together with inappropriate diet and low physical activity. This high prevalence clearly is a major contributor to the high rates of both diabetes and CVD. There is also a theory of the ‘thrifty gene.’ Years ago, this gene enabled Africans, Asians, and American Indians to survive during ‘feast and famine’ by using energy more efficiently when food was scarce. This gene may now place these groups at greater risk for obesity and type 2 diabetes.\textsuperscript{441, 571}

Complications

Microvascular complications

African Americans experience ESRD at least four times that of non-Hispanic whites, and have a 40–50\% higher frequency of retinopathy. Hispanic Americans have twice the risk of retinopathy than non-Hispanic
whites. American Indians experience ESRD six times more frequently than non-Hispanic whites.

**Macrovascular disease**

All heart-related deaths from 1975–1984 in Pima Indians occurred in those with diabetes. African Americans, Asian Americans and Hispanic Americans also tend to have higher levels of other cardiovascular risk factors, such as hypertension, hypertriglyceridemia and central obesity, than the non-Hispanic white populations.

**Prevention**

Nutritional modification and physical activity should be encouraged for the prevention of diabetes in all these special populations and strategies to achieve this should commence at an early age. The avoidance of weight gain in young people is particularly important.

**Screening**

Testing may be considered at an earlier age in these high risk groups; clinical judgement is advised.

**Management**

Randomized controlled trials involving treatment of diabetes in these special populations are lacking.

Management of diabetes in these populations, like the wider population, should involve lifestyle interventions and, where necessary, medication to manage hyperglycemia, hypertension and dyslipidemia. A health care team approach including access to podiatry, advice on nutrition, early detection and treatment of infections, and the regular monitoring of renal function, eye disease, PVD and CVD is essential.

The usual range of drugs for the management of type 2 diabetes in non-Hispanic whites are used in these populations.
The American Diabetes Association recommends testing for type 2 diabetes in children ≥10 years of age who are overweight (BMI > 85th percentile for age and sex; weight for height > 85th percentile or weight > 120% of ideal for height) and have at least two other risk factors. Risk factors include:

- having a family history of type 2 diabetes in first or second degree relatives;
- belonging to certain race or ethnic groups; and
- having signs or conditions associated with insulin resistance (e.g. acanthosis nigricans, hypertension, dyslipidemia or PCOS).

These individuals should be tested every two years from 10 years of age or onset of puberty by FPG or an OGTT.

CHILDREN AND ADOLESCENTS

Until recently, most children with diabetes mellitus had type 1 diabetes. However, increasingly, type 2 diabetes is being reported in children from the United States and Australia. Type 2 diabetes is an important precursor to future morbidity from cardiovascular and renal disease, and early recognition and appropriate treatment may delay the onset of complications.

Prevalence

The prevalence of type 2 diabetes in children and adolescents appears to be increasing, coincident with the rapid increase in obesity. Type 2 diabetes in childhood now accounts for 8–50% of new cases of diabetes in children in some pediatric diabetes clinics in the United States, and outnumbers the new cases of type 1 diabetes diagnosed annually in Japanese children. These trends coincide with the rising prevalence of obesity and physical inactivity world wide.

One study found the number of new cases of diabetes in children diagnosed as type 2 went from 2% to 4% from 1982–1992, and to 16% by 1994.

Screening

Only children at substantial risk for the presence or the development of type 2 diabetes should be screened. The American Diabetes Association issued a consensus statement on type 2 diabetes in children as shown below.
Management

Patients who are not ill at diagnosis can be managed initially with nutrition therapy and exercise. Referral to a dietitian may be necessary as lifestyle changes are an invaluable component of treatment. Individualized plans need to be based on assessment of food preferences, timing and location of meals and snacks, food preparation, and willingness to change behaviors.\textsuperscript{577}

The use of very low calorie or high protein diets as well as other fad diets is not recommended. Quick fix weight loss programs are unsafe for children and rarely result in long-term weight control. In addition, they do not promote long-term healthy eating behavior. Weight loss programs with the best results have been those combining exercise and dietary components, along with behavior modification.\textsuperscript{577}

Antihyperglycemic agents may be needed to treat some children with type 2 diabetes. Metformin, sulfonylureas, repaglinide and insulin have been used as monotherapy and in combinations.\textsuperscript{576} Consideration should also be given to the treatment of hypertension and dyslipidemia, and to monitoring for complications.

Prevention

Primary prevention efforts can be directed to high risk individuals and to the overall population of children. Lifestyle interventions should be promoted in all children at high risk for the development of type 2 diabetes.

These should focus on:

- weight management (encouraging healthy eating habits, and decreasing high calorie, high fat food choices);
- increasing daily physical activity (at least 30 minutes of physical activity daily and participation in sports);
- limiting sedentary time spent watching television and playing computer and video games;
- decreasing the frequency of snacking (promoting more healthy snacks when snacking occurs); and
- limiting intake of soft drinks.

Specific recommendations need to be individualized to the family and social situation, and include safety considerations. Encouraging healthy eating habits by the entire family is important. Involvement of family members can provide positive reinforcement and make overall family health a higher priority.\textsuperscript{577}
COMPLEMENTARY MEDICINES IN TYPE 2 DIABETES

Chromium is a complementary medicine which is used by some patients in an attempt to improve diabetes control, as discussed below. Complementary medications may also be taken for painful peripheral neuropathy, as described briefly in Table 48, page 150. It is recognized that many other complementary medicines may be used by patients with diabetes. For questions about complementary medicines not covered in this document, please call your local DATIS office.

CHROMIUM

Chromium is one of the more controversial complementary medicine products that is used by some patients with diabetes. Chromium is an essential trace element that can occur in several oxidative states. The most commonly occurring forms are hexavalent (VI) and trivalent (III) chromium. Hexavalent chromium is used for dyes, leather tanning and chrome plating. Trivalent chromium occurs naturally in food and is believed to be required for normal metabolic function.\(^\text{578}\) The mechanism by which trivalent chromium participates in carbohydrate metabolism is complex and not clearly established. Theories range from a direct interaction of chromium with insulin to a role of chromium in the regulation of insulin receptors.\(^\text{579}\)

The frequency of actual chromium deficiency in patients with diabetes is unknown and is thought to be rare. Although severe chromium deficiency can lead to glucose intolerance,\(^\text{580}\) and inadequate dietary intake has been implicated in several metabolic abnormalities,\(^\text{581}\) its role in the pathogenesis of diabetes does not appear to be significant.\(^\text{579}\) It is possible that chromium supplementation may improve insulin action only in patients with frank chromium deficiency.\(^\text{579}\) Although chromium levels in blood, urine and hair can be assessed, none of these levels accurately reflect body chromium stores.\(^\text{582}\) Currently no reliable method exists to evaluate chromium deficiency.\(^\text{579}\)

Studies examining the results of chromium supplementation in people with diabetes have been varied and the results are inconclusive.\(^\text{580, 582-585}\) Many of the studies involved small patient numbers and were uncontrolled. One double-blind placebo-controlled study involved 180 non-obese Chinese patients with diabetes. The patients were divided into three groups: a
placebo group and two groups taking different dosages of chromium supplements (i.e. 100 micrograms twice daily or 500 micrograms twice daily). Patients continued their usual medications and diet. At two months, the group receiving 500 micrograms of chromium twice daily experienced significant improvements in A1C compared with the placebo group. After four months, subjects in both treatment groups had improved glucose control compared with the placebo group. However, in this study, there was no investigation of chromium status and the subjects were not considered to be overweight. Therefore, the results may not be accurately extrapolated to Western diabetic populations.582

The mean American dietary intake of chromium is 60 micrograms per day, and the current recommended dietary intake of chromium is 100 micrograms per day.586 Good dietary sources of chromium include brewer’s yeast, liver, potatoes with skin, beef, fresh vegetables, fruits, whole grains and cheese.134, 581

Little information is available regarding the toxicity of trivalent chromium. Due to the lack of information on the accumulation of chromium, the long-term supplementation of high doses should be approached very cautiously. Two cases of renal failure were attributed to ingestion of excessive doses of trivalent chromium in women with no history of renal dysfunction.578, 587 Concerns about possible chromosomal damage from long-term high dose chromium have been raised. Hexavalent chromium, the form of chromium used in industries, is a known carcinogen. Currently, no carcinogenic activity has been ascribed to the trivalent chromium used as a medicinal supplement. However, some investigators continue to express concerns about excessive doses of supplemental chromium and believe that all forms of chromium should be considered human carcinogens.581

**Conclusion**

Although some human studies show positive effects, more randomized controlled studies are needed to assess the efficacy and toxicity of chromium before it can be recommended as a supplement to improve glycemic control.
APPENDIX 1

DRUG INDUCED HYPOGLYCEMIA

Table 50, below outlines some of the non-antihyperglycemic drugs which have been associated with hypoglycemia. These reports may have involved patients with or without diabetes. Explanatory notes are included for those drugs more commonly encountered in general practice where there have been several case reports, clinical studies or controversy assessing the association. Care is warranted when initiating drugs which have been associated with hypoglycemia to patients with diabetes receiving insulin or oral antihyperglycemic agents.

Table 50. Drugs associated with hypoglycemia.

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Explanatory notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol</td>
<td>Acute alcohol consumption can make the signs of hypoglycemia less clear and can cause delayed hypoglycemia. Alcohol is the most common cause of disabling hypoglycemia in the United States. It can occur in healthy children, occasional drinkers and chronic alcoholics. Alcohol induces hypoglycemia by direct interference with gluconeogenesis. Patients with diabetes receiving antihyperglycemic medications are at risk of hypoglycemia with the ingestion of even moderate amounts of alcohol, particularly in the absence of food.</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Patients with diabetes using insulin may have a prolonged or delayed recovery response to hypoglycemia while on β-blockers, but very severe hypoglycemia and/or coma is rare. The risk is greatest with propranolol and least with cardio-selective β-blockers (e.g. atenolol and metoprolol). Some signs of hypoglycemia may be blunted by β-blockers, such as tachycardia and tremors, but other signs like hunger, irritability and nausea may be unaffected and sweating may even be increased. Patients with diabetes taking sulfonylureas rarely seem to have serious hypoglycemic episodes caused by β-blockers. β-blockers are not contraindicated in patients with diabetes.</td>
</tr>
<tr>
<td>aspirin (high doses only) and salicylates</td>
<td>It is well established that in high doses (i.e. doses used to treat rheumatoid arthritis) aspirin and the salicylates can have hypoglycemic effects. Excessive and unwanted hypoglycemia is unlikely with small to moderate analgesic or antiplatelet doses.</td>
</tr>
</tbody>
</table>

* This is not an exhaustive list of all drugs which have been associated with hypoglycemia — a number of other drugs have been associated with hypoglycemia in isolated case reports.

Note: Table continued on next page
Table 50. Drugs associated with hypoglycemia (continued).

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Explanatory notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>The risk of hypoglycemia may be increased when ACE inhibitors are used in patients with diabetes taking insulin, sulfonylureas or meglitinides. However, concurrent use need not be avoided but it would be prudent to warn patients commencing such a combination to be vigilant for signs and symptoms of hypoglycemia. This interaction has been the subject of considerable debate and conflicting studies. The mechanism is unclear but increased glucose utilization and insulin sensitivity have been suggested.</td>
</tr>
<tr>
<td>sulfonamides</td>
<td>As well as the potential for pharmacokinetic drug interactions between sulfonamides and sulfonylureas, the sulfonamides have sometimes induced hypoglycemia in the absence of conventional antihyperglycemic agents.</td>
</tr>
<tr>
<td>quinine</td>
<td>Patients with malaria who are treated with quinine may develop severe and life-threatening hypoglycemia. A few reports of hypoglycemia have also occurred in patients taking quinine for leg cramps.</td>
</tr>
<tr>
<td>clonidine</td>
<td>Clonidine may suppress the signs and symptoms of hypoglycemia (particularly tachycardia, palpitations and sweating) in patients with diabetes.</td>
</tr>
<tr>
<td>others</td>
<td>An association between hypoglycemia and the following drugs has also been noted: anabolic steroids, disopyramide, chloroquine, irreversible monoamine oxidase inhibitors, quinidine and pentamidine.</td>
</tr>
</tbody>
</table>

* This is not an exhaustive list of all drugs which have been associated with hypoglycemia — a number of other drugs have been associated with hypoglycemia in isolated case reports.
Table 51, page 197 outlines some of the drugs which have been associated with hyperglycemia. These reports may have involved patients with or without diabetes. Explanatory notes are included for those drugs more commonly encountered in general practice where there have been several case reports, clinical studies or controversy assessing the association. More vigilant monitoring of blood glucose is warranted when initiating drugs which have been associated with hyperglycemia in patients with diabetes.

### Table 51. Drugs associated with hyperglycemia.

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Explanatory notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>corticosteroids</td>
<td>Corticosteroids have long been known to increase blood glucose levels. The use is associated with the risk of hyperglycemia in patients without known diabetes and worsened glycemic control in patients with diabetes. The risk is greatest for systemic corticosteroids and is dose related. Corticosteroids increase gluconeogenesis and decrease glucose tolerance and sensitivity to insulin. In patients with diabetes or IGT, the diabetogenic effects of corticosteroids can be prolonged and hyperosmolar non-ketotic coma has been reported. The need for adjustments in antihyperglycemic medications should be anticipated.</td>
</tr>
<tr>
<td>thiazide and thiazide-like diuretics</td>
<td>By raising blood glucose levels, the thiazide and thiazide-like diuretics can reduce the effects of antihyperglycemic agents and impair control of diabetes. This effect is dose related, and has mainly been observed in patients using the more traditional doses of thiazide and thiazide-like diuretics. The low doses of thiazide and thiazide-like diuretics currently recommended for the treatment of hypertension are unlikely to cause adverse effects on glucose or lipid levels. Thiazide and thiazide-like diuretics are therefore not contraindicated in patients with diabetes. Additional monitoring of blood glucose levels around initiation of treatment is warranted. Impaired glucose tolerance is relatively rare with loop diuretics.</td>
</tr>
<tr>
<td>oral contraceptives</td>
<td>The effects of sex hormones on carbohydrate metabolism is complex and controversial. Low dose combined oral contraceptives are associated with only a small elevation in the risk of IGT. The minor changes in glucose metabolism are not generally of clinical importance, with no overall increase in the incidence of diabetes for ever users compared to never users. Some patients with diabetes may experience a deterioration in glucose tolerance.</td>
</tr>
</tbody>
</table>

Note: Table continued on next page – see footnote on next page
Table 51. Drugs associated with hyperglycemia (continued).

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Explanatory notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>antipsychotics</td>
<td>Chlorpromazine has been associated with hyperglycemia, particularly in daily doses of 100 mg or more, where the incidence appears to be about 25%. There are reports of hyperglycemia and development of diabetes with atypical antipsychotics, including clozapine, olanzapine, and quetiapine. The relationship between antipsychotic medication and development of diabetes is not well understood. It appears that changes in glucose homeostasis may be a risk with both typical and atypical antipsychotics. Some evidence also suggests that people with schizophrenia may be at increased risk for type 2 diabetes, which may be related to antipsychotic medication but also to poorer overall physical health, less healthy lifestyles and poorer health care. (Antipsychotics are associated with substantial weight gain which may be one contributing factor to this risk.)</td>
</tr>
<tr>
<td>phenytoin</td>
<td>Hyperglycemia has been reported with phenytoin. However, most of these reports have involved overdosage or long-term high dose treatment.</td>
</tr>
<tr>
<td>sympathomimetics</td>
<td>Hyperglycemia has been reported occasionally with sympathomimetics, such as adrenaline, ephedrine, pseudoephedrine, phenylephrine, terbutaline and albuterol (particularly intravenous administration or high nebulised doses in children).</td>
</tr>
<tr>
<td>niacin (nicotinic acid)</td>
<td>Niacin interferes with the metabolism of carbohydrates. Hyperglycemia has been described with nicotinic acid but is considered an infrequent adverse effect. Caution is needed if using niacin in patients with diabetes. For further information see nicotinic acid, page 131.</td>
</tr>
<tr>
<td>lithium</td>
<td>Information regarding the relation of lithium to glucose tolerance has been controversial, and both diabetogenic and antidiabetic effects have been documented.</td>
</tr>
<tr>
<td>sugar containing pharmaceuticals</td>
<td>Some products contain significant amounts of sugar. Patients with diabetes should be warned.</td>
</tr>
<tr>
<td>glucosamine</td>
<td>Animal studies have shown glucosamine to increase insulin resistance and reduce the rate of glucose uptake into skeletal muscle by 50%. No alteration of glucose homeostasis has been observed in human trials to date, but larger studies of a longer duration are required before conclusions can be made. Caution in patients with diabetes is therefore currently warranted.</td>
</tr>
<tr>
<td>others</td>
<td>An association between hyperglycemia and the following drugs has also been noted: danazol, protease inhibitors, megestrol, l-asparaginase, diazoxide and pentamidine.</td>
</tr>
</tbody>
</table>

* This is not an exhaustive list of all drugs which have been associated with hyperglycemia — a number of other drugs have been associated with hyperglycemia in isolated case reports.
APPENDIX 3

ORLISTAT

Xenical®

Mechanism of action

Orlistat is an antiobesity agent that inhibits dietary fat absorption. It is a potent and slowly reversible inhibitor of gastric and pancreatic lipases. This action prevents these enzymes from hydrolyzing dietary fat (in the form of triglycerides) into absorbable free fatty acids and monoglycerols. Undigested triglycerides are eliminated by the fecal route. Orlistat 120 mg taken three times a day inhibits dietary fat absorption by about 30% thereby contributing to caloric deficit. In addition to its pharmacological effects, orlistat use may lead to weight loss as a result of aversion conditioning due to avoidance of foods high in fat.

Orlistat also appears to reduce total cholesterol and LDL cholesterol levels to a greater extent than expected for the degree of weight loss.

Pharmacokinetics

Orlistat is < 1% absorbed from the gastrointestinal tract. However, all of orlistat’s pharmacological actions are believed to be exerted in the gastrointestinal tract. Metabolism is thought to mainly occur within the gastrointestinal wall. The two major metabolites appear to be inactive. Orlistat is excreted almost completely by the fecal route.

Role of orlistat

Overall goals for weight management should emphasize nutritional therapy, physical activity, behavioral therapy and, when indicated, pharmacotherapy. For further information see weight loss in type 2 diabetes, page 25.

Orlistat is approved for the treatment of obese patients with a BMI ≥ 30 kg/m², and overweight patients with a BMI ≥ 27 kg/m² in the presence of other risk factors (such as diabetes mellitus, hypertension and dyslipidemia), in conjunction with a reduced calorie diet.

Orlistat has been demonstrated, in 1–2 year randomized controlled studies, to assist with weight loss when prescribed in conjunction with a hypocaloric diet (with approximately 30% of energy as fat) in obese patients without
diabetes. In addition, it has been effective in reducing weight regain when prescribed with a weight maintenance diet.\textsuperscript{636-638, 642-644}

One published randomized controlled study addressed the efficacy of orlistat in 391 obese patients with type 2 diabetes who were clinically stable on sulfonylureas were randomized to orlistat or placebo in conjunction with a mildly hypocaloric diet. After one year, the orlistat group lost more weight than the placebo group (6.2\% versus 4.3\%), had significantly greater improvements in A1C and FPG, and were more often able to reduce their dose of, or discontinue, the sulfonylurea therapy. These improvements appear to be related purely to the amount of weight lost. Lipid profile improved more with orlistat than placebo, with greater falls in total and LDL cholesterol and triglycerides. These effects appear to be in part related specifically to the actions of orlistat.\textsuperscript{639}

Results of two additional one year studies in patients with type 2 diabetes were recently published. The first, which assessed efficacy of orlistat in overweight or obese patients with metformin treated type 2 diabetes, found greater weight loss with orlistat compared to placebo, and significantly greater improvements in glycemic control, blood pressure and lipid profile.\textsuperscript{645} The second, which assessed efficacy of orlistat in overweight insulin treated patients with type 2 diabetes, found greater weight loss with orlistat, greater improvements in glycemic control and lipid profile, and the ability to reduce insulin dose.\textsuperscript{646} As in other orlistat trials, patients received mildly reduced calorie diets in both the orlistat and placebo groups.\textsuperscript{647}

Further published studies are needed in patients with diabetes. Studies of orlistat in patients taking other non-sulfonylurea agents are particularly needed. Whether adverse gastrointestinal effects will be increased if orlistat is taken in conjunction with metformin or acarbose (both of which have a high incidence of gastrointestinal effects) remains to be established. One author suggests that preliminary trial data and clinical experience in patients taking metformin does not show an excess of gastrointestinal adverse effects when combined with orlistat.\textsuperscript{648}

Gastrointestinal adverse effects are common with orlistat and can result in a need for therapy discontinuation. Safety and efficacy of long-term orlistat therapy (beyond two years) has not been assessed.

Orlistat should only be considered in patients with diabetes when lifestyle factors (e.g. diet, exercise, behavior modification) have been adequately explored. These measures need to continue to be addressed if orlistat therapy is initiated.
Dose and administration

Table 52. Dosing schedule for orlistat.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Preparation</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>orlistat</td>
<td>Xenical®</td>
<td>Capsule 120 mg</td>
<td>One capsule with each main meal. Maximum of three doses per day.</td>
</tr>
</tbody>
</table>

Important considerations

- Orlistat should be taken with a meal (or up to one hour after a meal). If a meal is missed or contains no fat, the dose may be omitted.
- Patients taking orlistat should consume a reduced calorie, nutritionally balanced diet. This diet should contain approximately 30% of calories from fat. The intake of fat, carbohydrate and protein should be evenly distributed over three meals.
- Orlistat may reduce the absorption of some fat soluble vitamins and β-carotene. As a result, patients should take a multivitamin containing fat soluble vitamins to ensure adequate nutrition. The supplement should be taken at least two hours before or after the administration of orlistat, such as at bedtime.
- Doses above 120 mg three times daily have not been shown to provide additional benefit.
- For information regarding patient support programs for weight loss please call your local DATIS office.

Contraindications and precautions

Orlistat is contraindicated in patients with:
- hypersensitivity to orlistat;
- pancreatic enzyme deficiency or chronic pancreatitis;
- major gastrointestinal surgery;
- chronic malabsorption syndrome; or
- cholestasis.

Patients with type 2 diabetes using orlistat and achieving weight reduction may experience improved glycemic control, possibly necessitating a dosage reduction of oral antihyperglycemic medications or insulin.
## Adverse effects

Table 53, below outlines adverse effects associated with orlistat. It should be noted that safety of orlistat beyond two years has not been assessed.634

Table 53. Adverse effects associated with orlistat.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Features and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>gastrointestinal adverse effects</td>
<td>Gastrointestinal adverse effects are common and can decrease patients' quality of life, adversely impact socialization and contribute to treatment failure.634 Frequently reported events include oily spotting, gas with discharge, fecal urgency, fatty/oily stool, oily discharge, increased defecation and fecal incontinence.634, 635 Most adverse gastrointestinal events are mild and transient, beginning early in treatment, with 50% lasting no more than one week.634, 650 Occasionally, these adverse effects may continue over a six month period or longer.68 Gastrointestinal adverse effects may increase when orlistat is consumed with a high fat diet (&gt; 30% total daily calories from fat). The daily fat intake should be evenly distributed between three main meals. If orlistat is taken with any meal high in fat content, the gastrointestinal adverse effects may increase.</td>
</tr>
<tr>
<td>decreased absorption of fat soluble vitamins</td>
<td>During clinical studies, decreases in levels of some fat soluble vitamins have been noted.634, 635, 639 This is most notable with vitamins D and E and β-carotene.635, 650 A multivitamin supplement (which contains fat soluble vitamins) is therefore recommended during orlistat therapy.635, 641, 649 It should be taken at least two hours before or after the administration of orlistat, such as at bedtime.</td>
</tr>
<tr>
<td>hypersensitivity</td>
<td>Hypersensitivity reactions including urticaria, angioedema and anaphylaxis have been reported rarely.650</td>
</tr>
<tr>
<td>hypertension</td>
<td>Isolated rare case reports have described hypertension possibly associated with orlistat administration.651, 652 Causality has been debated.653, 654</td>
</tr>
<tr>
<td>others</td>
<td>One isolated case report describes depression, possibly associated with orlistat, in a patient with a history of bipolar disorder.655 Another case report described subacute hepatic failure requiring liver transplantation.656</td>
</tr>
</tbody>
</table>
**Drug interactions**

**Table 54. Selected drug interactions associated with orlistat.**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
</table>
| **cyclosporine** | Case reports have described reduced cyclosporine levels with orlistat coadministration.  
Orlistat impairs the absorption of lipophilic molecules by inhibition of pancreatic lipase in the gastrointestinal tract, and hence may reduce absorption of cyclosporine which is highly lipophilic.  
It has been suggested that the conventional non-emulsified preparation of cyclosporine (e.g. Sandimmune®) has a greater risk of interaction with orlistat than the emulsified preparation (e.g. Neoral®); however, reports of interactions have involved both preparations.  
If combined use is essential, consider use of the emulsified cyclosporine preparation, with close monitoring of cyclosporine levels and adjustment of dose as necessary.  
Instructing patients to take the cyclosporine at least two hours before or after orlistat may help to minimize the risk of interaction. |
| **fat soluble vitamins** | During clinical studies, decreases in levels of some fat soluble vitamins have been noted.  
In addition, absorption of supplementary doses of vitamins E and A and β-carotene is reduced with concomitant orlistat administration. Vitamin supplements (containing fat soluble vitamins) should be taken at least two hours before or after the dose of orlistat, such as at bedtime. |
| **antihyperglycemics** | Patients with type 2 diabetes using orlistat and achieving weight reduction may experience improved glycemic control, possibly necessitating a dosage reduction of oral antihyperglycemic medications or insulin. |
| **pravastatin** | One small study found pravastatin levels increased by approximately 30% when used in conjunction with orlistat.  
Consider monitoring CK levels and advising patients to report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. |
| **warfarin** | Small trials have failed to demonstrate an interaction.  
However, vitamin K levels may decline in patients taking orlistat. Therefore, patients stabilized on warfarin should be monitored closely for changes in INR when orlistat is prescribed. |

CK = creatinine kinase; INR = international normalized ratio
SIBUTRAMINE
Meridia®

Mechanism of action
Sibutramine is an agent indicated for the treatment of obesity which acts by norepinephrine, serotonin, and dopamine reuptake inhibition. The predominant pharmacological actions are exerted primarily by sibutramine’s active metabolites, M₁ and M₂. Neither the parent compound nor its metabolites act via release of monoamines. The primary therapeutic effect is due to enhanced satiety and an increased metabolic rate.

Beneficial changes in serum lipids, similar to those seen in non-pharmacologically assisted weight loss, have been noted with sibutramine induced weight loss. Reductions in serum uric acid levels have been observed as well.

Pharmacokinetics
Sibutramine is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver to form the active metabolites, M₁ and M₂. An average of at least 77% of a single oral dose is absorbed. Distribution is rapid and extensive with the highest concentrations found in the liver and kidneys. Sibutramine and its metabolites are extensively protein bound, in vitro.

Metabolism of sibutramine is principally in the liver by cytochrome P450 3A4 to the active metabolites, M₁ and M₂.

Role of sibutramine
Sibutramine is approved for the management of obesity, including weight loss and maintenance, in conjunction with a reduced calorie diet. It is recommended for obese patients with an initial BMI of ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors such as diabetes, hypertension and/or dyslipidemia.

Sibutramine induced weight loss has been demonstrated when compared to placebo in several double-blind, placebo-controlled obesity trials with study
durations of 12–52 weeks. Weight loss occurred in a dose-related manner with doses ranging from 5–20 mg per day.\textsuperscript{78, 663}

Comparison of sibutramine, orlistat and metformin was undertaken in a randomized, prospective clinical trial conducted over a 6 month time period. A total of 150 women with BMI > 30 kg/m\textsuperscript{2} were studied. Patients with endocrine diseases other than type 2 diabetes, uncontrolled hypertension, secondary hypertension, renal or hepatic insufficiency, gastrointestinal disease, autoimmune disease, ischemic heart disease, glaucoma, dysrhythmia, lactation/pregnancy, psychosis, or on drugs with central nervous system effects, cathartics, thyroid supplements, or diuretics, were excluded from the study. Patients were randomized to one of the following three groups: sibutramine 10 mg twice daily, orlistat 120 mg three times a day, or metformin 850 mg twice daily. While this study did not specifically address obesity in type 2 diabetes, there were patients within each group who met the American Diabetes Association criteria for diagnosis. At the end of the study period, the sibutramine, orlistat, and metformin groups all showed a significant reduction in BMI, waist circumference, fasting and postprandial blood glucose levels, and insulin resistance. In addition, reduction in total cholesterol, LDL, VLDL, and triglycerides as well as uric acid levels, pulse rate and blood pressure were observed. The greatest reduction in body weight was seen in the sibutramine group.

Several studies have looked at the effects of sibutramine in the treatment of obese patients with type 2 diabetes.\textsuperscript{665-667}

A study conducted in the United Kingdom looked at the effect of sibutramine in conjunction with a reduced-calorie diet on weight loss and diabetic control in patients with a BMI > 26 kg/m\textsuperscript{2} and \(\leq\) 35 kg/m\textsuperscript{2} and type 2 diabetes. This was a randomized, placebo-controlled, double-blind, parallel-group study conducted over 12 weeks. The study included men and women, ages 30–65 years old with a BMI in the range noted above and a diagnosis of type 2 diabetes of at least 6 months duration. Fasting blood glucose levels had to fall between 127 mg/dL and 218 mg/dL on 3 occasions in the month preceding the start of the study. Patients with type 1 diabetes, obesity of endocrine origin (other than diabetes), or supine diastolic blood pressure of > 100 mm Hg were excluded from the study. Patients were given sibutramine 15 mg/day or placebo and all patients followed a customized, reduced calorie diet 500 kcal/day less than the individual’s estimated energy needs. Outcome measurements included change in body weight, blood glucose levels (fasting and postprandial),
insulin levels, and A1C levels. Three patients in the sibutramine group and two patients in the placebo group discontinued the study due to mild to moderate adverse effects. At the end of the study, weight loss was significantly greater in the sibutramine group than in the placebo group (2.4 kg vs. 0.1 kg) with more patients in the sibutramine group losing greater than 5% of their baseline body weight (19% vs. 0%). Glycemic control was improved in the sibutramine group with reductions observed in fasting glucose and A1C levels.\textsuperscript{665}

The efficacy of sibutramine in female patients who were obese, had poorly controlled type 2 diabetes (A1C > 8%), and were taking maximum doses of hypoglycemic agents (sulfonylureas and/or metformin) was studied in a double-blind, randomized, placebo-controlled trial conducted in Turkey. A total of 60 women were randomly assigned to one of two study groups. The treatment group received sibutramine 10 mg twice a day and the control group received placebo twice a day. Both groups were given a prescribed diet and continued on their antihyperglycemic medications. Patients were excluded from the study if they had type 1 diabetes, obesity of endocrine origin (other than diabetes), uncontrolled hypertension, glaucoma, were pregnant, or taking beta-blockers, MAOIs, or any drug that might affect appetite or body weight. One patient developed hypertension during the study period and was excluded from the sibutramine group. At the end of the 6 month study period, the sibutramine group showed a significantly greater reduction in body weight, fasting plasma glucose and A1C levels than the placebo group.\textsuperscript{666}

A multicenter study conducted in Europe evaluated the efficacy of sibutramine on weight loss in type 2 diabetics on concurrent sulfonylurea therapy. This was a 6 month study of 134 male and female patients age 25–70 years with stable (though not optimal) glycemic control on sulfonylurea therapy and a BMI > 27 kg/m\textsuperscript{2}. Patients were randomized into either treatment or placebo groups. Both groups were placed on calorie restricted diets and given either sibutramine 15 mg/day or placebo. Progressive weight loss was observed in both groups with patients in the sibutramine group losing twice as much weight as the placebo group. A greater percentage of patients in the sibutramine group lost > 5% of their body weight than those in the placebo group (49% vs. 29%). There was a significant reduction in A1C levels in sibutramine-treated patients who lost > 10% of their baseline body weight.\textsuperscript{667}

Safety and efficacy of long-term sibutramine (greater than 2 years) has not been assessed at this time.\textsuperscript{78, 663}
Sibutramine should only be considered in patients with diabetes when lifestyle factors (e.g. diet, exercise, behavior modification) have been adequately explored. When these measures alone have proven to be ineffective for adequate weight reduction, addition of sibutramine appears to be a favorable option for short-term weight loss therapy in appropriately selected patients.

**Dose and administration**

**Table 55. Dosing schedule for sibutramine.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Preparation</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>sibutramine</td>
<td>Meridia®</td>
<td>Capsule 5, 10, 15 mg</td>
<td>Initial starting dose is 10 mg daily with or without food. Dose may be titrated after 4 weeks to a maximum dose of 15 mg per day.</td>
</tr>
</tbody>
</table>

**Important considerations**

- Primary pulmonary hypertension (PPH): No cases of PPH have been reported with sibutramine.

- Blood pressure and heart rate: sibutramine may substantially increase blood pressure and/or heart rate in some patients. Regular monitoring of blood pressure and pulse is required during treatment with sibutramine. Use caution when prescribing other agents that may increase blood pressure or heart rate (e.g. decongestants; cough, cold or allergy preparations containing ephedrine or pseudoephedrine). Should not be used in patients with concomitant cardiovascular disease.

- Monoamine oxidase inhibitors (MAOIs): Do not use concurrently. There should be a 2-week interval between stopping one drug (MAOI or sibutramine) and starting the other (MAOI or sibutramine).

- Serotonin syndrome: do not administer with other serotonergic agents such as agents for migraine therapy, certain opioids, lithium, tryptophan or other serotonin reuptake inhibitors. See Table 57, page 209 for specific drug interactions.

- Glaucoma: may cause mydriasis, use with caution in narrow-angle glaucoma.
- Renal/hepatic impairment: Sibutramine has not been studied in patients with severe renal or hepatic dysfunction. Use with caution in these conditions and elderly patients who may also have diminished renal and hepatic dysfunction.
- Seizures: Seizures have been reported rarely with sibutramine. Use with caution in patients with a history of seizure disorder.
- Pregnancy: Category C--Not recommended for use in pregnant women.
- Lactation: Excretion into breast milk is unknown, therefore use is not recommended in breast-feeding women.
- Children: Safety and efficacy in children under 16 years of age has not been established.

Contraindications and precautions

Sibutramine is contraindicated in the following:78, 663
- Patients receiving monoamine oxidase inhibitors (MAOIs);
- Patients with hypersensitivity to sibutramine or any of the inactive ingredients of Meridia®;
- Patients who have anorexia nervosa;
- Patients taking other centrally acting appetite suppressant drugs.

Patients with type 2 diabetes using sibutramine and achieving weight reduction may experience improved glycemic control,665, 667 possibly necessitating a dosage reduction of oral antihyperglycemic medications or insulin.

Adverse effects

Table 56, below outlines adverse effects associated with sibutramine. It should be noted that safety of sibutramine beyond two years has not been established.78, 663

Table 56. Adverse effects associated with sibutramine.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>most common</td>
<td>Headache, dry mouth, anorexia, insomnia, constipation</td>
</tr>
<tr>
<td>less common</td>
<td>Hypertension, tachycardia, migraine, rhinitis, pharyngitis, arthralgia</td>
</tr>
</tbody>
</table>
**Drug interactions**

Table 57 below outlines selected drug interactions associated with sibutramine.\(^{78,663}\)

**Table 57. Selected drug interactions associated with sibutramine.**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect and management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>monoamine oxidase inhibitors</td>
<td>Contraindication. Do not administer concurrently. Allow 2 week wash-out period before and after each drug.</td>
</tr>
<tr>
<td>sumatriptan, dihydroergotamine, dextromethorphan, meperidine, pentazocine, fentanyl, lithium, tryptophan, other serotonin reuptake inhibitors (SSRIs)</td>
<td>Potential for serotonin syndrome. Do not administer concurrently.</td>
</tr>
<tr>
<td>drugs that may increase blood pressure or heart rate (e.g. decongestants such as pseudoephedrine, ephedrine)</td>
<td>Use with caution.</td>
</tr>
<tr>
<td>ketaconazole, cimetidine, erythromycin</td>
<td>May see a small increase in the AUC of sibutramine. Unlikely to be of clinical significance.</td>
</tr>
</tbody>
</table>
GLOSSARY OF TERMS

A1C    Hemoglobin A1c
ABCD    Appropriate Blood Pressure Control in Diabetes
ACE inhibitor    Angiotensin converting enzyme inhibitor
ACE-I    Angiotensin converting enzyme inhibitor
ARB    Angiotensin II receptor antagonist
ADA    American Diabetes Association
ADMIT    Arterial Disease Multiple Intervention Trial
ALLHAT-LLT    Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ASCOT-LLA    Anglo Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm
ATP    Adenosine triphosphate
ATP III    Adult Treatment Panel III Report—National Cholesterol Education Program
AUC    Area under the curve
AusDiab    Australian Diabetes, Obesity and Lifestyle Study
BENEDICT    Bergamo Nephrologic Diabetes Complications Trial
BIDS    Bedtime Insulin Daytime Sulfonylurea
BMI    Body mass index
CAPRIE    Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CARDS    Collaborative Atorvastatin Diabetes Study
CARE    Cholesterol and Recurrent Events
CCB    Calcium channel blocker
CHD    Coronary heart disease
CHF    Congestive heart failure
CK    Creatinine kinase
CNS    Central nervous system
COPD    Chronic obstructive pulmonary disease
COX-2 inhibitor    Cyclo-oxygenase-2 inhibitor
CVA    Cerebrovascular accident
CVD    Cardiovascular disease
CYP    Cytochrome P450
DETAIL  The Diabetics Exposed to Telmisartan and Enalapril Study

DIABHYCAR  Effects of Low Dose Ramipril on Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes and Raised Excretion of Urinary Albumin

DPPRG  Diabetes Prevention Program Research Group

EASD  European Association for the Study of Diabetes

ESRD  End stage renal disease

FACET  Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial

FDPS  Finnish Diabetes Prevention Study

FPG  Fasting plasma glucose

GDM  Gestational diabetes mellitus

GFR  Glomerular filtration rate

GI  Gastrointestinal

HbA1c  Glycated hemoglobin

HDL  High density lipoprotein

HOPE  Heart Outcomes Prevention Evaluation

HOT  Hypertension Optimal Treatment

HPS  Heart Protection Study

IDF  International Diabetes Federation

IDNT  Irbesartan Type II Diabetic Nephropathy Trial

IFG  Impaired fasting glucose

IGT  Impaired glucose tolerance

INR  International normalized ratio

IRMA 2  Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients

JNC VI  The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure.

LIFE  Losartan Intervention for Endpoint Reduction

LIPID  Long-Term Intervention with Pravastatin in Ischemic Disease

LDL  Low density lipoprotein

LFT  Liver function test

LVH  Left ventricular hypertrophy
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP</td>
<td>Mean arterial blood pressure</td>
</tr>
<tr>
<td>MAOI</td>
<td>Monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MARVAL</td>
<td>Microalbuminuria Reduction with Valsartan Trial</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MICRO-HOPE</td>
<td>Microalbuminuria, cardiovascular, and renal outcomes</td>
</tr>
<tr>
<td>MNT</td>
<td>Medical nutrition therapy</td>
</tr>
<tr>
<td>MRFIT</td>
<td>Multiple Risk Factor Intervention Trial</td>
</tr>
<tr>
<td>NCEP</td>
<td>National Cholesterol Education Panel</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart, Lung and Blood Institute</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NRT</td>
<td>Nicotine replacement therapy</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
</tr>
<tr>
<td>PCOS</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>PPAR</td>
<td>Peroxisome proliferator-activated receptor</td>
</tr>
<tr>
<td>PVD</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>RENAAL</td>
<td>Reduction in End points in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SMBG</td>
<td>Self monitoring of blood glucose</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>STENO-2</td>
<td>Intensified Multifactorial Intervention and Cardiovascular Outcomes in Type 2 Diabetes</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressant</td>
</tr>
<tr>
<td>TGs</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>UAR</td>
<td>Urinary albumin excretion rate</td>
</tr>
<tr>
<td>UGDP</td>
<td>University Group Diabetes Program</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>VA-HIT</td>
<td>Veterans Affairs High-density lipoprotein cholesterol Intervention Trial</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very low density lipoprotein</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WHO-ISH</td>
<td>World Health Organization-International Society of Hypertension</td>
</tr>
<tr>
<td>4S</td>
<td>Scandinavian Simvastatin Survival Study</td>
</tr>
</tbody>
</table>
USEFUL WEB SITES

American Diabetes Association
Provides general information for patients on diabetes and has a section for health professionals. Health professionals can access the American Diabetes Association Clinical Practice Recommendations 2003 which can be downloaded free of charge.
http://www.diabetes.org

National Institute of Diabetes and Digestive and Kidney Diseases
Provides access to various diabetic publications (both consumer and health professional) online which can be downloaded free of charge.

Diabetes UK
Provides patient information about diabetes and information for health professionals, such as United Kingdom diabetes care guidelines.
http://www.diabetes.org.uk

Doctors Guide: Diabetes
Provides medical news and up to date articles covering diabetes related topics.

Joslin Diabetes Center
Affiliated with Harvard Medical School. Provides diabetes news and information for patients and health care providers.
http://www.joslin.org
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