
中国糖尿病综合管理项目

China Initiative for Diabetes Excellence

# Module 5:
# Macrovascular Complications Associated with Diabetes

**International Diabetes Center and Mayo Clinic**
**World Health Organization Collaborating Center for Diabetes Education, Translation and Computer Technology**

**China Diabetes Society**

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# Module 5:
# Macrovascular Complications Associated with Diabetes

**Author:**

**Professor Roger S. Mazze**
Consultant, International Diabetes Center

**Contributing Authors:**

**Professor Richard Bergenstal**
Executive Director, International Diabetes Center

**Professor John Miles**
Co-Director of Translational Research, WHO Collaborating Center, International Diabetes Center and Mayo Clinic

**Professor Lu Juming**
Chief Physician and Professor, Department of Endocrinology, Chinese PLA General Hospital
Vice President, China Diabetes Society
Chairman, Endocrinology Society, Chinese PLA Medical Association

**Professor Xu Zhangrong**
Professor, Chief Physician, and Director of Diabetes Center, 306th Hospital of PLA
Member of Experts Committee of Chronic Diseases Prevention and Control, Health Ministry of China
Committee Member, Chinese Endocrine Society
Committee Member, Chinese Diabetes Society (CDS) and Chairman, Foot and Peripheral Vascular Group of CDS
Deputy Chairman, Endocrine Society of PLA
Member, International Working Group on the Diabetic Foot

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International Diabetes Center
3800 Park Nicollet Boulevard
Minneapolis, Minnesota 55416
1-888-825-6315
www.InternationalDiabetesCenter.com

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# Module 5: Macrovascular Complications Associated with Diabetes

Diabetes is associated with a wide range of microvascular and macrovascular complications. Understanding the pathophysiology of all of these complications, as well as the optimal approach to their management and treatment, are critical for reducing morbidity and mortality in an already high-risk patient population. This module discusses the macrovascular complications associated with diabetes. Module 6 will cover microvascular complications.

While significant attention focuses on the microvascular complications associated with diabetes (e.g., nephropathy, neuropathy, and retinopathy), cardiovascular disease (CVD) remains at the forefront of conditions to be prevented, detected, and treated. CVD accounts for at least 68% of mortality in those with diabetes or metabolic syndrome.[1] Clinical and epidemiological studies have demonstrated a clear association between diabetes and CVD.[2–5] The World Health Organization estimates that from 2005 to 2015, China will suffer an economic loss of 557.7 billion US dollars as a result of diabetes and associated cardiovascular complications.[6] The China Diabetes Society reports that, for hospitalized patients with type 2 diabetes in "3A" (highest-ranking) hospitals, 34.2% have hypertension and 17.1% have cardiovascular disease.[7] According to the China Heart Survey, the prevalence of abnormal blood glucose is 80% higher in Chinese patients with coronary artery disease (CAD) than it is in Westerners with CAD.[8]

## Diabetes and the risk of cardiovascular disease

The early introduction of treatment to achieve near normal glycemic control is essential to reducing long-term microvascular and macrovascular diabetes complications, as long as it is done safely.[9] Research has demonstrated that hyperglycemia and excessive glycemic variability can cause endothelial dysfunction.[10,11] Maintaining near normal blood glucose levels early on protects the vascular cells from damage. This phenomenon is known as "metabolic memory" or legacy effect and will likely involve epigenetic changes.[12] Vascular damage caused by high levels of glucose for extended periods of time cannot easily be reversed when normalization subsequently occurs. Faced with deteriorating glycemic control, metabolic memory cannot be relied upon indefinitely ("metabolic amnesia").

The Framingham Heart Study showed that men and women with diabetes have a 2.4 times and 5.1 times greater risk of CVD, respectively, when compared with individuals without diabetes.[13] Subsequent studies have confirmed that, in the presence of diabetes, women have a greater risk of CVD than men. This finding is not completely understood. Results from the Strong Heart Study support the hypothesis that diabetes in women has a greater negative impact on such CVD risk factors as hypertension and elevated cholesterol than in men.[14] Moreover, individuals with diabetes have significantly lower survival rates after myocardial infarction than age- and sex-matched individuals without diabetes.[15] In addition to the established risk factors for CVD (e.g., family history, diabetes, hypertension, dyslipidemia, smoking, obesity, ethnicity), other diabetes-related risk factors must be considered.

Several studies have shown that poor glycemic is associated with increased CVD risk.[16,17] In the San Antonio Heart Study, individuals with type 2 diabetes were placed into quartiles on the basis of fasting plasma glucose levels. A more than fourfold increase in both CVD mortality and mortality from all causes was found in the quartile with the highest fasting plasma glucose when compared with the quartile with the lowest fasting plasma glucose.[18] The UK Prospective Diabetes Study (UKPDS) demonstrated a 16% reduction (P = 0.052) in risk for myocardial infarction in a cohort that maintained good glycemic control (hemoglobin A1c ($HbA_{1c}$) of 7.0%) compared with a cohort that had average glycemic control ($HbA_{1c}$ of 7.9%).[19]

While growing evidence supports improved glycemic control in the prevention of microvascular disease, large, long-term studies have demonstrated that intensive glucose control (target $HbA_{1c}$ less than 6%) in type 2 patients with existing CVD or at high risk for CVD (e.g., older age; long-term, inadequate blood pressure and lipid control) has no significant CVD benefit—and may possibly be detrimental. In 2008, the results of two trials—Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[20] and the Veterans Affairs Diabetes Trial (VADT)[21]—demonstrated no significant reduction in CVD outcomes in patients at high risk. The intensive-glucose treatment arm of a third study, Action to Control Cardiovascular Risk in Diabetes (ACCORD),[22] was terminated early because of findings of increased mortality in the intensive glycemic group (target $HbA_{1c}$ <6%) compared with the standard treatment group (target $HbA_{1c}$ <7–7.9%). Based on the results of ACCORD, ADVANCE, and VADT, the American Diabetes Association (ADA) recommends, as a "reasonable goal," an $HbA_{1c}$ of less than 7% in nonpregnant adults with diabetes, noting that this target value "has been shown to reduce microvascular and neuropathic complications of diabetes and, if implemented soon after the diagnosis of diabetes, is associated with long-

term reduction in macrovascular disease."[23] Tighter glycemic control is recommended for patients with a short duration of diabetes and no hypoglycemia, and less stringent goals can be applied for patients with severe hypoglycemia, advanced microvascular and/or macrovascular complications, or a limited life expectancy.[23] The ADA and European Association for the Study of Diabetes (EASD) published a position statement on patient-centered approach to care that recognized the importance of individualizing glycemic targets using clinically important elements to guide decision making (see Figure 1).[24]

Research also demonstrates that tight glycemic control has long-term cardiovascular benefits. As a follow-up to the 6.5-year Diabetes Control and Complications Trial (DCCT), investigators from the Epidemiology of Diabetes Interventions and Complications (EDIC) study assessed type 1 diabetes patients (participants in the DCCT) for CVD from 1993 until 2005—an additional

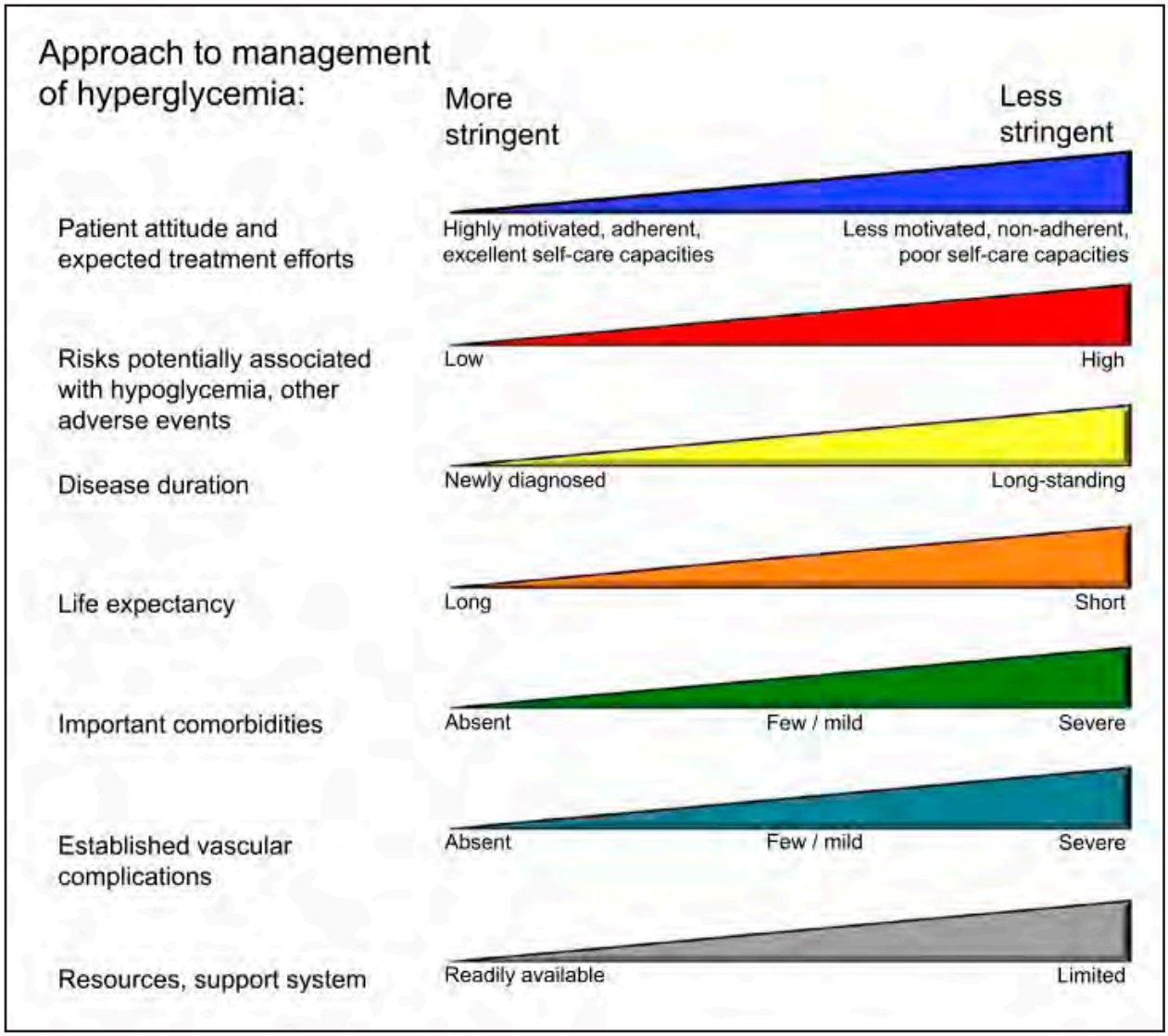



**Figure 1. Approach to management of hyperglycemia.**

Source: Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Apr 19. [Epub ahead of print]. Reprinted with permission.

10-plus years beyond the DCCT. They found that the decrease in $HbA_{1c}$ values during the DCCT was "significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease."[25] Intensive treatment reduced the risk of any CVD event by 42% and reduced the risk of nonfatal myocardial infarction, stroke, or death from CVD by 57%. Such results reflect those of the UKPDS, which randomly assigned patients to intensive glucose control immediately after diagnosis of type 2 diabetes. After receiving intensive glucose therapy for 10 years, the treatment group was followed for an additional 10 years without intervention. After a total of 20 years, study results showed that long-term intensive glycemic control prevents myocardial infarction and decreases all-cause mortality.[26]

A key study, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial,[27] examined the effects of insulin glargine (a long-acting insulin analogue) on CVD end points. The study comprised 12,537 subjects with either prediabetes (12% of study subjects comprising impaired fasting glucose and/or impaired glucose tolerance) or early type 2 diabetes (88% of study subjects) within 5 years of diagnosis with high CVD risk. At trial completion (6.2 years follow-up), 84% of the glargine group were still taking insulin. $HbA_{1c}$ in the insulin glargine group was lower at 6.2% compared with 6.5% in the standard group (baseline 6.4%). Fasting plasma glucose was reduced from 6.9 mmol/L (124 mg/dL) at baseline to 5.3 mmol/L (95 mg/dL) in the glargine group and to 6.8 mmol/L (123 mg/dL) in the standard group at study end. This important study demonstrated that near-normal glycemic control could be maintained over 6 to 7 years with a low-risk of hypoglycemia and minimal weight gain. Despite a very high-risk CVD study population (i.e. ~60% CVD at baseline), no difference in CVD outcomes was found between the glargine and standard therapy group (HR, 1.02; 95% CI, 0.94-1.11; P=0.63). It appears that exogenous insulin per se has no adverse effect on CVD events.

The studies imply that early intensive glycemic control can have macrovascular benefits compared with delayed initiation of intensive glycemic control. This in part may be related to the presence or absence of existing CVD in these study populations. The prevalence of baseline CVD in the various study groups varied from ~5% in the UKPDS; 30-40% in ACCORD, ADVANCE, and VADT; and ~60% in ORIGIN. If baseline CVD is not evident (e.g., UKPDS), intensive glycemic control can improve CVD outcomes after many years (i.e., >16-18 years). In comparison, if baseline CVD (or high risk for CVD) is present in persons with type 2 diabetes, then it is unlikely that intensive glycemic control alone will derive benefits once CVD is present. The VADT observed that macrovascular benefit was mainly derived by those subjects with duration of diabetes <12 years. A series of meta-analyses of intensive glycemic control supported these findings on the benefit of reduced incidence of myocardial infarction.[28,29]

The results from ORIGIN and other intensive glycemic control studies in subjects with type 2 diabetes who have either pre-existing or no CVD demonstrate that exogenous insulin per se does not cause or aggravate CVD (i.e., has neutral CVD effects). Glucose reduction is a relatively weak risk factor in isolation and takes many years to show benefit. Therefore, a multifactorial approach is strongly recommended for this population.

The risk of CVD increases with age in all individuals. Duration of diabetes is an independent risk factor. The Pittsburgh Epidemiology of Diabetes Complications Study demonstrated an association between the number of individuals with type 1 diabetes who died as a result of CVD and the duration of their disease.[30] Similar studies are difficult to conduct for type 2 diabetes because the duration of the disease is less certain;

many people have the disease for a number of years before diagnosis. Finally, the concomitant development of diabetic kidney disease and heart disease must not be overlooked. Microalbuminuria has been shown to be a predictor of, or marker for, CVD in individuals with diabetes.[31]

## Role of inflammation in macrovascular disease

The role of inflammation in the development of CVD is an area of intense basic and clinical research.[32,33] Inflammation of the endothelium and atherosclerotic plaque is thought to occur through the deposition of oxidized low-density lipoprotein (LDL) in the arterial wall. The LDL deposition triggers a proinflammatory response through the depletion of nitric oxide and concomitant activation of numerous cytokine signaling pathways. Cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α induce the release of C-reactive protein (CRP) by the liver. CRP is a nonspecific marker of inflammation in the body that is positively correlated with body mass index (BMI) and insulin resistance. The nonspecificity is a drawback because several conditions unrelated to increased risk of CVD may increase the level of CRP, including bacterial and/or viral infection, arthritis, and cancer. However, since it is currently not clinically feasible to directly measure inflammation in the vascular wall, indirect measures such as CRP have been used clinically to reflect vascular inflammation.

The clinical value of routine collection of CRP levels (and other markers of inflammation such as IL-6) in patients with or without classic risk factors for CVD is currently debated. Those in favor of routine monitoring of CRP levels point to recent large prospective studies such as the Women's Health Study that show CRP is superior to LDL as a predictor of cardiovascular events.[34] Other studies clearly show that patients with increasing number and severity of cardiovascular-related clinical syndromes (i.e., angina, myocardial infarction) have elevated CRP levels. Those in favor of routine CRP determinations would also point out that the new highly sensitive methodologies to measure CRP have made the test more readily available and accurate, especially in the subclinical range of 1–5 μg/mL. Detractors would argue that there are currently no clearly defined CRP criteria associated with a therapeutic intervention. Because of a lack in specificity and the high cost of the test, they argue against measuring CRP levels.

Despite the debate, a number of studies have identified well-established therapies that reduce CRP levels. LDL reduction, daily aspirin therapy, insulin sensitizers (thiazolidinediones), angiotensin-converting enzyme (ACE) inhibitors, and fibrates have all been shown to reduce CRP levels. Researchers have demonstrated that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) possess anti-inflammatory properties independent of LDL lowering.[35] As reported in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, in 18,000 individuals without hyperlipidemia but with increased high-sensitivity CRP levels, rosuvastatin (20 mg daily) reduced LDL cholesterol by 50%, reduced CRP levels by 37%, and was effective in reducing the incidence of major cardiovascular events over a period of 1.9 years.[36] Based primarily on the results of the JUPITER study, the US Food and Drug Administration (FDA) has expanded the labeling of rosuvastatin to include primary CVD prevention in men over 50 years and women over age 60 with CRP level >2.0 mg/dL.

The debate over whether to routinely monitor CRP levels continues. The International Diabetes Center does not recommend routine CRP determinations for all patients because of the absence of a clearly defined CRP target. Individuals with diabetes and/or metabolic syndrome are already at increased cardiovascular risk; thus aggressive management of lipids and hypertension should already be undertaken. In 2003, the American Heart Association (AHA) recommended that CRP testing be conducted in patients at moderate risk for CVD to determine whether more intensive treatment is

warranted.[37] More recently, the American College on Preventive Medicine published recommendations against routine screening of CRP, reserving testing for individuals with intermediate (10-20%) CVD risk to determine if intensification of therapy (e.g. add or increase statin dose) is warranted.[38] However, while CRP is a marker of general inflammation, Lp-$PLA_2$ (an emerging CVD biomarker) appears to specifically indicate vascular inflammation and is not influenced by obesity.[39]

## Prevention of cardiovascular disease in diabetes: importance of a multifactorial approach

The China Diabetes Society (CDS) believes that prevention of macrovascular complications of diabetes requires a comprehensive assessment and control of risk factors of cardiovascular diseases.[7] The CDS notes that after diagnosis of diabetes, risk factors for cardiovascular diseases should be assessed at least once a year. This evaluation should include present and previous history of cardiovascular disease, age, abdominal obesity, conventional cardiovascular risk factors (e.g., smoking, dyslipidemia, and family history), renal damage (i.e., increased urinary albumin excretion), and atrial fibrillation.

In addition to annual screenings, management of hyperglycemia, hypertension, and dyslipidemia is critical for the primary and secondary prevention of CVD in diabetes. Figure 2 presents the CDS's standard clinical screening and decision-making path for lipid-lowering, antihypertensive, and antiplatelet therapy. Although this may appear daunting, the impact of metabolic control on reducing the morbidity and mortality caused by CVD is significant. For example, in the Steno-2 study, two groups of patients with type 2 diabetes and microalbuminuria (a strong predictor of future cardiovascular events) were studied for approximately 8 years.[40] One group of 80 patients was intensively treated with goals of $HbA_{1c}$ <6.5%, blood pressure <130/80 mmHg, total cholesterol <4.5 mmol/L (175 mg/dL), and triglycerides <1.7 mmol/L (150 mg/dL). The second group was randomized to conventional treatment for hyperglycemia, hypertension, and dyslipidemia. The net result was a 50% relative risk reduction and 20% absolute risk reduction of cardiovascular events in the intensively treated group. These results were corroborated by the UKPDS,[41] which demonstrated statistically significant reductions in microvascular complications, cardiovascular events, strokes, and diabetes-related mortality in the cohort with tight blood pressure control.

For patients with existing CVD or with a particularly high CVD risk, intensive treatment to normal—including control of blood glucose and blood pressure—may not provide added benefit in terms of slowing progression of end-stage organ disease. Larger studies, such as ACCORD, investigated whether aggressively addressing hypertension and hyperlipidemia can benefit patients with diabetes who are at risk for CVD. In one part of the ACCORD study, more than 4,700 patients with type 2 diabetes received intensive blood pressure therapy (targeting systolic blood pressure <120 mmHg) or standard therapy (targeting systolic blood pressure <140 mmHg). After more than 4.5 years of follow-up and mean systolic blood pressure of 119.3 and 133.5 mmHg in the intensive and standard therapy groups, respectively, researchers found that intensive blood pressure treatment yielded no reduction in the rates of major cardiovascular events.[33] However, intensive blood pressure control did reduce stroke risk, with annual rate of stroke 0.32% and 0.53% in the intensive and standard care groups, respectively (HR 0.59; 95% CI 0.39-0.89).[42] Similar results were seen when the group investigated the effects of combination lipid therapy—a statin plus a fibrate—in those patients with type 2 diabetes who were at risk for CVD and already receiving statin monotherapy. More than 5,500 patients were randomly assigned either to continue statin-only treatment (simvastatin plus placebo) or to receive combination therapy of statin plus fenofibrate. Results showed that the combination therapy did not reduce the rate of cardiovascular deaths.[43]

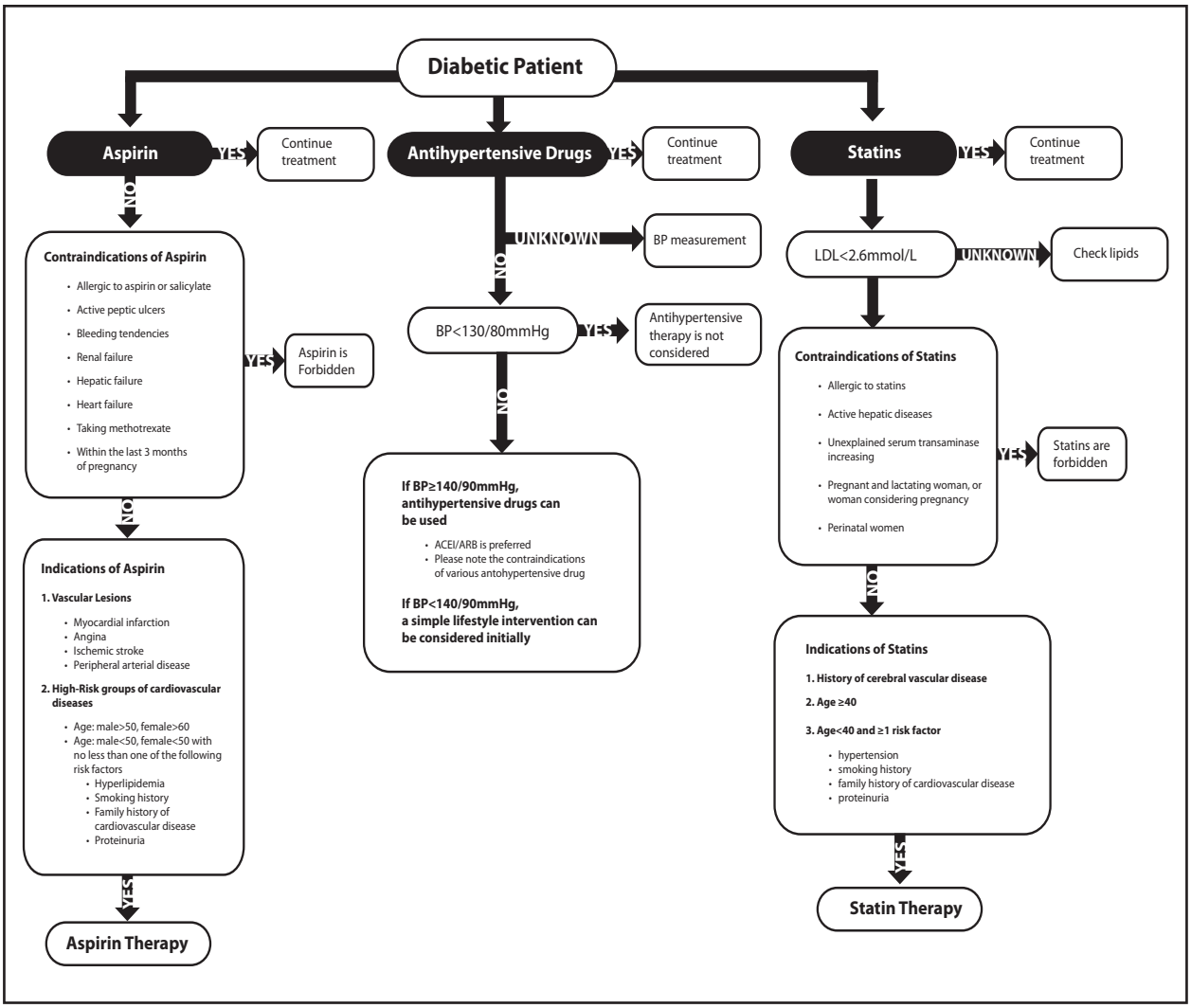



**Figure 2. CDS's standard treatment of type 2 diabetes: screening and clinical decision-making path of lipid-lowering, antihypertensive, and anti-platelet therapy**

The results from ORIGIN and other intensive glycemic control studies in subjects with type 2 diabetes suggest that glucose reduction is a relatively weak risk factor in isolation and takes many years to show benefit. Therefore, a multifactorial approach is strongly recommended for this population.

## Insulin resistance, dyslipidemia, hypertension, and cardiovascular disease

The pathway from insulin resistance to development of CVD occurs through such intermediaries as dyslipidemia, elevated blood pressure, inelastic arteries, inflammatory disease, and coagulation abnormalities. Obesity and hyperglycemia worsen and most probably accelerate these conditions. While the precise mechanism is subject to disagreement, the epidemiologic data combined with the experimental data suggest that the mechanisms are multifactorial. For example, it is known that obese individuals have endothelial dysfunction characterized by deactivation of the nitric oxide pathway. This is accompanied by a stiffening of vessel walls, which increases intra-arterial pressure. This is further compromised by hyperglycemia, which often interferes with normal endothelial function.

### Hypertension

A 2007-08 analysis of a representative population of 46,239 Chinese adults age 20 and older estimates that 30.09% of Chinese males and 24.79% of Chinese females have hypertension.[8] While this estimate is similar to others compiled in 2002, the rates within the older study included only adults older than age 35.[44,45] One can therefore surmise that the prevalence of hypertension, as with all cardiovascular disease risk factors in China, is increasing.

Most researchers who gather prevalence data on hypertension in China define the condition as (1) an average measurement of ≥140/90 mmHg, assessed through two consecutive measurements obtained 30 minutes apart or (2) a previous diagnosis of hypertension.[8] While it remains unclear how a decrease in hypertension rates would affect the prevalence estimates of cardiovascular disease, data from Western populations indicate that lowering blood pressure readings to a level below or even at 140/90 mmHg confers proportional decreases in the risk of cardiovascular disease.[46-48] While no formal hypertension management programs appear to be in place in China currently, experts who have compiled prevalence estimates for hypertension advocate for formalized programs that involve both risk assessment and prevention strategies.[8]

For the most part, the etiology of essential hypertension is poorly understood, yet its association with CVD has been known for decades. Studies have shown a statistically significant relationship between hypertension and the risk of stroke, myocardial infarction, and renal disease. Initially, the discovery of a link between hypertension and cardiovascular morbidity and mortality predated the discovery of antihypertensive drugs. Therefore, most studies compared hypertensive with normotensive age- and sex-matched subjects. These studies showed that survival was significantly more likely in those who were normotensive.[49] With the development of drug therapies, studies could be conducted on whether treatment of hypertensive patients would result in improved survival. Researchers found found that a reduction in blood pressure to near-normal levels (<130/80 mmHg for diabetes) significantly reduced the risk of life-threatening CVD.[49] Hypertension can be linked to two specific states: congestive heart failure and left ventricular hypertrophy. Hypertension also directly affects the arterial vasculature expressed as macrovascular disease, with specific emphasis on the coronary arteries.

The development of hypertension in type 1 diabetes differs from that developed in type 2 diabetes. Blood pressure is usually normal at diagnosis and throughout the initial 7 to 15 years of type 1 diabetes. Hypertension often occurs concomitantly with the onset of diabetic kidney disease. In contrast, blood

pressure is often elevated at the time of diagnosis of type 2 diabetes and is associated with underlying insulin resistance, obesity, nephropathy (often because of delayed diagnosis), and age. Many individuals with type 2 diabetes have isolated systolic hypertension, which may be a direct reflection of macrovascular disease progression. Individuals with type 2 diabetes and hypertension have three factors of clinical importance:

- Reduced exercise ability
- Abnormalities in ventricular filling
- Abnormalities in contractile reserve.

## Dyslipidemia

Dyslipidemia is a significant, modifiable risk factor for cardiovascular disease patients living in Asia. Although mean total cholesterol levels have decreased in Europe, North America, and Australia over the past three decades, the rates have increased in Asia.[50,51] One study indicates that 31.5% of the general Chinese population age 20 years and older—308 million people—have borderline high or high total cholesterol and that 20.4%—196 million—have borderline high, high or very high LDL cholesterol.[50]

Dyslipidemia is a general term encompassing different abnormalities in lipid levels. Hyperlipidemia is defined as elevated levels of total cholesterol, triglyceride, and LDL. Other states of dyslipidemia are characterized by reduced levels of high-density lipoprotein (HDL) and may be found in combination with elevated levels of total cholesterol, triglyceride, and LDL.

Most researchers investigating dyslipidemia in Asia classify the condition according to the Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults:[52]

- Total cholesterol 5.2 mmol/L (200 mg/dL) or greater
- LDL cholesterol 2.6 mmol/L (100 mg/dL) or greater
- Triglyceride level 1.7 mmol/L (150 mg/dL) or greater
- HDL cholesterol 1.1 mmol/L (40 mg/dL) or less in men and 1.3 mmol/L (50 mg/dL) or less in women.

While the goal would be to improve total cholesterol, LDL, and HDL to the point that measurements would no longer lie within these parameters, clinical trials have demonstrated that a 10% difference in serum cholesterol led to a decreased coronary heart disease risk of nearly 15%.[53] Unfortunately, studies have found that the number of people in China who are aware of or being treated for their dyslipidemia is lower than in the United States.[50,54] Programs implemented to address this issue should ideally include both individual and population-based, nationally focused interventions.[50,52,55]

The relationship between dyslipidemia and atherosclerotic disease is through the formation of fatty deposits (plaque) in arterial walls, resulting in diminished circulation. Thus, it is not surprising that as with hypertension, the risk of CVD shows an exponential relationship with increasing serum cholesterol.[56] Commonly associated with both hypertension and type 2 diabetes, dyslipidemia (specifically, hyperlipidemia) contributes to rapid progression of the complications found with both conditions. Type 2 diabetes and dyslipidemia may result in accelerated peripheral vascular disease combined with coronary artery disease and cerebrovascular disease. Generally, a much smaller proportion of individuals with type 1 diabetes has dyslipidemia.

# Detection and treatment of hyperglycemia, hypertension, and dyslipidemia

The clinical manifestations of insulin resistance, diabetes, hypertension, or dyslipidemia can be elusive. It is unlikely that patients will recognize persistent hyperglycemia, hypertension, or dyslipidemia, since their overt symptoms are also associated with aging. Furthermore, it is unlikely that patients will have only one of these disorders. Therefore, whenever any one of these conditions is found, the recommendation is to screen for the others. For example, the risk of hypertension or dyslipidemia in the presence of pre-existing type 2 diabetes may reach 80%. Both hypertension and dyslipidemia are well-established risk factors for type 2 diabetes. As with diabetes, the risk of hypertension and dyslipidemia increases with age, family history, impaired glucose homeostasis (prediabetes), and obesity.

The detection and treatment of these disorders is divided into three areas: (1) tests undertaken in a laboratory to make the diagnosis, (2) steps necessary to monitor the condition or the abnormality (such as self-monitoring of blood pressure), and (3) appropriate treatment for the current disorder.

Prevention of diabetes, hypertension, and dyslipidemia is the optimal goal. Primary prevention of type 2 diabetes, hypertension, and dyslipidemia should focus on modest weight reduction, regular physical activity, and smoking cessation. Secondary prevention should focus on early detection and rapid interventions to prevent the complications associated with these disorders. Tertiary prevention aims at a reduction in the progression of complications through normalization of blood glucose, lipids, and blood pressure.

*Note: While hypertension is predominant in type 2 diabetes and insulin resistance, it is also found in type 1 diabetes, often as an early sign of underlying kidney disease.*

## Obesity: a reliable clinical manifestation of hypertension and dyslipidemia

As mentioned earlier, careful surveillance, with recognition of key risk groups, is the best method to detect hypertension and dyslipidemia. When these two diseases occur in the same individual, being overweight or obese is often the most common clinical manifestation.

Obesity has become a global epidemic affecting both industrialized and developing countries. According to data obtained from 2007-2008, China's prevalence rate for overweight and obesity is 36.7% in males and 29.8% in females.[8] In 1992, the combined prevalence was only 14.6%.[57] These estimates were compiled using World Health Organization standards, in which obesity is defined as body mass index (BMI) $\geq$30 kg/m$^2$ and overweight is defined as BMI 25-30 kg/m$^2$.[58] However, the criteria for overweight and obesity in China is $\geq$25 kg/m$^2$, per CDS,[7] so this estimate may actually be much higher. Because the distribution of fat in the body is an important factor in the development of cardiovascular disease, researchers in China have assessed the impact of abdominal obesity on the risk of cardiovascular disease—specifically, carotid intima-media thickness. One study, published in 2011, found that in Chinese men age 34-66 years, visceral fat area accumulation $\geq$80 cm$^2$ was associated with significantly higher carotid intima-media thickness, regardless of study participants' BMI classification.[59]

Currently, there appears to be a paucity of programs at the national level addressing overweight and obesity in China. Researchers studying these trends note that the most effective strategies will be those that involve (1) health and nutrition education programs, developed with the support of local and

central governments, public health professionals and the media; (2) interventions tailored to younger age groups (school-aged children), (3) regulatory policies designed to increase consumption of healthier foods in China, and (4) reallocation of resources to improve health care systems' ability to respond to the increase in obesity-related chronic diseases.[57]

## Metabolic syndrome as a CVD risk factor in China

Metabolic syndrome refers to a clustering of established (i.e., "traditional") and emerging (i.e.,"nontraditional") cardiovascular disease (CVD) risk factors within a single individual. Both the established risk factors, such as obesity, diabetes, dyslipidemia, and hypertension, microalbuminuria, and emerging risk factors are closely related to central obesity—especially intra-abdominal adiposity, which is also known as visceral obesity.[60] Emerging risk factors include dysfunction of inflammation, coagulation, platelets, fibrinolysis, lipoproteins, endothelium, and miscellaneous biological processes. Individuals may develop these factors in different orders, at different severities, and at different ages. The underlying pathophysiology of metabolic syndrome is believed related to central obesity and insulin resistance. Metabolic syndrome directly contributes to the occurrence of atherosclerotic CVD and also increases the risk of type 2 diabetes.

At present, there is no universal definition for metabolic syndrome.[61] Internationally, the criteria for metabolic syndrome rely on such sources as the World Health Organization, the third report of the US National Cholesterol Education Platform for Adult Education Unit (NCEP-ATP III 2005) and the International Diabetes Foundation. More recently, several of these and other organizations agreed on a harmonized definition.[62] In China, the definition of metabolic syndrome seems to be evolving. According to the China Diabetes Society,[7] a patient in China meets the diagnostic criteria of metabolic syndrome if she or he has three or more of the following:

(1) Overweight and/or obese: BMI ≥25kg/$m^2$
(2) Hyperglycemia: FPG ≥6.1 mmol / L (110 mg/dl) and/or 2hPG ≥7.8 mmol / L (140 mg/dl), and/or has been diagnosed with diabetes and treated.
(3) Hypertension: BP ≥140/90 mmHg and/or has been diagnosed with hypertension and treated.
(4) Dyslipidemia: fasting plasma TG ≥1.7 mmol / L (150 mg/dl), and/or fasting HDL-C <0.9 mmol / L (35 mg/dl) (male) or <1.0 mmol / L (39 mg/dl ) (female)

The prevalence of metabolic syndrome varies regionally. According to the CDS, in Shanghai, Beijing, Wuhan and other major cities, the crude prevalence rate of metabolic syndrome is 14% to 16%, and the standardized prevalence rate is 9% to 12%, showing a trend that the North is higher than the South, and urban is higher than rural areas as a whole. In addition, prevalence rates increased with age and differed according to gender: Before age 65, the prevalence of metabolic syndrome is higher in men than women. After age 65, the prevalence is higher in women than men.

To account for ethnic variations in the characterization of metabolic disturbance, in 2007, the Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (JCDCG) proposed a new definition of metabolic syndrome in Chinese populations. According to this new definition, metabolic syndrome was defined as (1) abdominal obesity (waist circumference >90 cm for men and >85 cm for women) (2) serum triglycerides ≥1.7 mmol/L, (3) HDL cholesterol <1.04 mmol/L for both men and women, (4) blood pressure ≥130/85 mmHg or known treatment for hypertension, and (5) fasting plasma glucose (FPG) ≥6.1 mmol/L and/or 2-hour plasma glucose ≥7.8 mmol/L and/or diagnosed diabetes mellitus and receiving therapy.[63] According to this definition, researchers have found that an estimated 26.1% of Chinese men and 23.0% of Chinese women have metabolic syndrome. The investigators further determined that metabolic syndrome was also associated with an increased risk of cardiovascular disease risk in women, but not men.[64]

The CDS has recommended that prevention and treatment of metabolic syndrome involve both lifestyle modifications (increasing physical activity levels, dietary modification to reduce caloric intake, smoking cessation, and moderation in alcohol intake) and pharmacotherapy to control blood glucose, hypertension, dyslipidemia, and obesity. Literature reviews yield little information regarding whether China has formalized programs in place to prevent and/or manage metabolic syndrome. However, given the high prevalence estimates of metabolic syndrome in Chinese populations, and given the significant morbidity burden associated with the individual factors defining this syndrome (e.g., hypertension, obesity, dyslipidemia, glucose abnormalities), it stands to reason that any effort to address metabolic syndrome as a whole would result in reduced cardiovascular disease risk in China.

## Practice guidelines: hypertension and dyslipidemia

The standards of care for hypertension and dyslipidemia for individuals with diabetes and/or metabolic syndrome differ from those found in people without diabetes. These standards are summarized in this section and in Table 1.

| | |
|---|---|
| **Diagnosis** | |
| Hypertension | Systolic BP ≥130 mmHg on 2 occasions and/or diastolic BP ≥80 mmHg on 2 occasions |
| Dyslipidemia | LDL ≥2.6mmol/L (100mg/dL); HDL ≤1.0 mmol/L (40 mg/dL); TRI ≥1.7 mmol/L (150 mg/dL) |
| **Symptoms** | *Common (classic):* none<br>*Occasional (subtle):* blurred vision, fatigue, headache |
| **Risk factors** | • Overweight; BMI >25 kg/m$^2$ (particularly waist-to-hip ratio >1.0)<br>• Duration of diabetes<br>• Family history of hypertension or dyslipidemia<br>• Nephropathy<br>• Smoking |
| **Treatment options** | |
| Hypertension | • Medical nutrition and activity therapy<br>• Lifestyle modifications<br>• Medications (ACE inhibitor, ARB, diuretics, calcium channel blockers, β-blockers, α-blockers, or direct renin inhibitor) |
| Dyslipidemia | • Medical nutrition and activity therapy alone<br>• Lifestyle modifications<br>• Pharmacological agents<br>1. Statins<br>2. Fibric acid<br>3. Bile acid sequestrants<br>4. Niacin<br>5. Omega-3 fatty acid supplementation |
| **Targets** | |
| Hypertension | • In-office BP <140/80 mmHg*<br>• SMBP <125/75 mmHg |
| Dyslipidemia | • LDL >2.6 mmol/L (100 mg/dL)<br>• 30–40% reduction in LDL regardless of baseline<br>• HDL >1.0 mmol/L (40 mg/dL) men, >1.3 mmol/L (50 mg/dL) women<br>• TRI <1.7 mmol/L (150 mg/dL)<br>*Note* Consider target LDL <3.9 mmol/L for those with evidence of CVD |
| **Monitoring** | SMBP and SMBG recommended daily while adjusting therapy |
| **Follow-up** | |
| Monthly | Office visit while adjusting therapy (weekly phone contact may be necessary); SMBP data |
| Every 3 months | Evaluate weight or BMI; medications; blood pressure; fasting lipid profile; urinalysis; smoking cessation counseling; aspirin therapy if appropriate; SMBP data |
| Yearly (in addition to 3–4 month visit) | Annual comprehensive physical examination; monitor serum creatinine and ALT if taking statin |

ACE, angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin II receptor blocker; BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SMBP, self-monitored blood pressure; SMBG, self-monitored blood glucose; TRI, triglycerides.

* Lower systolic targets (such as <130 mmHg) may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.

Table 1. Hypertension and dyslipidemia practice guidelines. ACE, angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin II receptor blocker; BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SMBP, self-monitored blood pressure; SMBG, self-monitored blood glucose; TRI, triglycerides.

# Management of hypertension

## Diagnosis of hypertension

Current standards for diagnosis of hypertension in individuals with diabetes and/or metabolic syndrome are more stringent than those for the general population because of the high risk of macrovascular and microvascular disease associated with these disorders. Mean systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥80 mmHg on two occasions is considered diagnostic for hypertension in individuals with diabetes. Repeated measures of blood pressure in the office may be supplemented by at-home self-monitored blood pressure (SMBP). While previously used to detect white coat hypertension, SMBP has been shown to detect hypertension among patients believed to have normal blood pressure when blood pressure measurement is based only on the office visit.[65] Although home blood pressure monitors are readily available and have proven reliable and accurate, they are seldom used in practice. Several studies confirm that there is a great disparity between office measurement of blood pressure and SMBP.[65-67] In one study, while office blood pressure classified 80% of the subjects as having uncontrolled hypertension, SMBP identified 97% of the subjects with uncontrolled hypertension. A second study reclassified 23% of the stage 1 hypertensive patients as having "white coat hypertension" and 23% of those with controlled hypertension as having uncontrolled hypertension.[68] Perhaps the most important finding is that, among those with controlled hypertension (office blood pressure <130/80 mmHg), up to 93% would have been reclassified as having uncontrolled hypertension if SMBP had been used in place of office blood pressure determinations.

These data are especially significant in light of findings that elevated blood pressure is linked to increased left ventricular hypertrophy (an early indicator of underlying CVD) as well as declining renal function.[69-71] One study concluded that "the use of SMBP provides an exceptional vantage point from which clinicians are able to obtain important clinical data not uniformly available during routine office visits."[49]

Blood pressure should be measured after 5 minutes of rest with the patient in a seated position. It is important to use the same method each time so that the results are comparable. If the systolic pressure is 140 mmHg or greater and/or the diastolic is 80 mmHg or greater, repeat the measure in the same position, with a resting interval of at least 2 minutes. If the values are between 140/80 and 180/100 mmHg, repeat the measure twice more within the next 2 weeks. If the values are >180/100 mmHg at any time, the patient is considered severely hypertensive and should be given a complete medical evaluation and pharmacological treatment should be initiated immediately. If the values remain between 140/80 and 180/100 mmHg on the first and subsequent visits, therapy should be initiated. Although not a requirement for diagnosis, consider using SMBP for all patients to confirm in-office measurements. Two weeks of home monitoring, with four tests each day at various times, should provide sufficient data to corroborate or refute office blood pressure measurement. Research has shown that many patients with diabetes considered by office blood pressure measurement to have controlled hypertension, when measured by SMBP are found to have uncontrolled hypertension.[65] If there is a substantial discrepancy between office blood pressure and SMBP, consider 24-hour ambulatory blood pressure monitoring.

The systolic definition of hypertension was recently changed from <130 mmHg to <140 mmHg.[23] The primary data for the modified recommendation was derived from a meta-analysis published in

2012 by McBrien et al.[72] The analysis demonstrated that the use of intensive blood pressure targets in patients with type 2 diabetes was associated with a small reduction in the risk for stroke compared with standard targets. However, there was no evidence for decreased mortality or myocardial infarction, and in many cases, the lower targets were associated with an increased risk for hypotension and other adverse events.

In the section discussing the new blood pressure guidelines, the 2013 ADA standards state that the revised recommendation for systolic blood pressure "is not meant to downplay the importance of treating hypertension in patients with diabetes or to imply that lower targets than <140 mmHg are generally inappropriate."[23]

Increasingly, 24-hour ABPM has been employed as a tool to improve diabetes patients' control of their blood pressure. Studies have demonstrated that, in comparison with in-clinic blood pressure assessments, ABPM can offer certain advantages, including the absence of white-coat blood pressure effects, higher reproducibility, and greater awareness of blood-pressure variability that may have clinical relevance to patients with diabetes (e.g., lack of nocturnal fall in blood pressure or an increase in overnight blood pressure), which may be a marker for cardiovascular dysregulation, renal damage, or other defects.[73]

## Clinical manifestations of hypertension

The majority of patients with hypertension have no symptoms. Occasionally, some patients report headache, dizziness, or blurred vision. However, these symptoms are associated with many diseases and therefore cannot be used as a method of

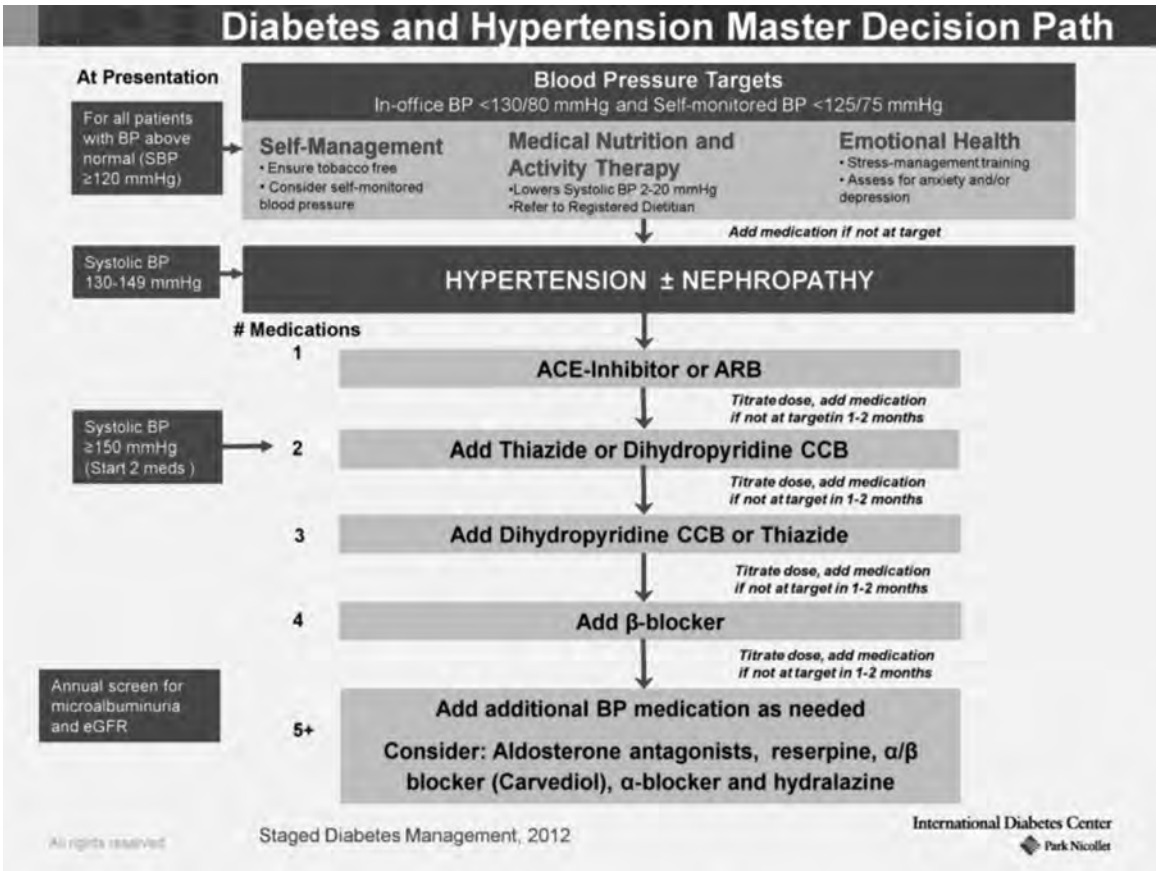


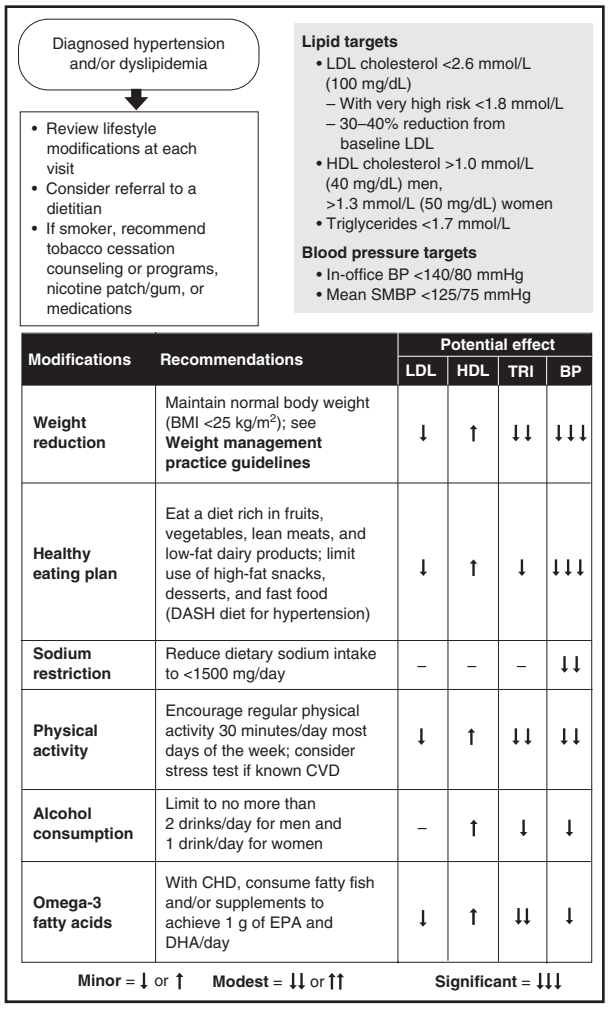

**Figure 3. Diabetes and hypertension Master DecisionPath. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker; SBP, systolic blood pressure.**

monitoring whether hypertension should be suspected. Given current estimates that 50% of all adults are at risk for or already have hypertension, measuring blood pressure at each office visit is a necessity. Particular racial and ethnic groups (e.g., African Americans and Hispanics in the United States) are at significantly higher risk, as are those who are overweight, have hyperglycemia and/or dyslipidemia, have a family history of hypertension, are over 50 years of age, or are smokers. A recent study of cardiovascular risk factors in the Xinjiang region showed the Kazakh, Mongolian ethnic groups had higher levels of hypertension than Uygur and Han groups.[74]

## Determining the *starting* treatment for hypertension

Treatment of hypertension in the individual with diabetes and/or insulin resistance is very important to prevent the development and progression of microvascular and macrovascular disease (see Figure 3). While no data on the effect of hypertension management exist for individuals with metabolic syndrome but without diabetes, there is no reason to believe that the same intensive treatment would be less beneficial in slowing the progression of vascular complications.

Typically, hypertension management begins with alterations in caloric intake and composition, exercise, and changes in lifestyle, especially related to stress (see Figure 4). Specific to dietary changes is the elimination of significant amounts of salt. Recent recommendations from the AHA and ADA call for a very low sodium consumption of less than 1,500 mg/day for all Americans and those with diabetes, respectively.[75] Reducing sodium consumption is best accomplished through a reduction in the use of processed foods in conjunction with a reduction in fats and modest weight reduction. Monitoring blood pressure at home and at work will provide necessary interim data to determine how well these steps are working.




| Modifications | Recommendations | Potential effect | | | |
|---|---|---|---|---|---|
| | | LDL | HDL | TRI | BP |
| **Weight reduction** | Maintain normal body weight (BMI <25 kg/m$^2$); see **Weight management practice guidelines** | ↓ | ↑ | ↓↓ | ↓↓↓ |
| **Healthy eating plan** | Eat a diet rich in fruits, vegetables, lean meats, and low-fat dairy products; limit use of high-fat snacks, desserts, and fast food (DASH diet for hypertension) | ↓ | ↑ | ↓ | ↓↓↓ |
| **Sodium restriction** | Reduce dietary sodium intake to <1500 mg/day | – | – | – | ↓↓ |
| **Physical activity** | Encourage regular physical activity 30 minutes/day most days of the week; consider stress test if known CVD | ↓ | ↑ | ↓↓ | ↓↓ |
| **Alcohol consumption** | Limit to no more than 2 drinks/day for men and 1 drink/day for women | – | ↑ | ↓ | ↓ |
| **Omega-3 fatty acids** | With CHD, consume fatty fish and/or supplements to achieve 1 g of EPA and DHA/day | ↓ | ↑ | ↓↓ | ↓ |

**Minor** = ↓ or ↑ **Modest** = ↓↓ or ↑↑ **Significant** = ↓↓↓

**Figure 4. Lifestyle modifications. BP, blood pressure; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SMBP, self-monitored blood pressure; TRI, triglycerides. Note: ADA is now recommending a very low sodium consumption of less than 1,500 mg/day in persons with diabetes.**

While lifestyle modifications are often the first treatment considered, the means of achieving blood pressure control in individuals with diabetes and/or metabolic syndrome differs from the means used by people without these disorders. If lifestyle-

modification interventions are insufficient to control blood pressure, monodrug therapy consisting of an ACE inhibitor or angiotensin II receptor blocker (ARB) should be considered and are, in fact, recommended as first-line blood pressure medication in patients with diabetes.[23] Studies have shown the presence of a renal protective effect over and above the effect of lowering blood pressure on slowing the progression of diabetic kidney disease.[76-78] In addition, some pharmacological agents used to treat hypertension (thiazides) may aggravate the treatment of diabetes. If one antihypertensive agent is insufficient to control blood pressure, combination therapy should be considered, with the addition of thiazide or a dihydropyridine calcium channel blocker (see Figure 2). Close monitoring of blood glucose after the introduction of antihypertensive medication is recommended. Additional antihypertensive agents should be added (see Figure 2). Many patients with type 2 diabetes require three or more medications to control blood pressure.[41,42]

Currently several types of pharmacologic therapies are available. Choosing the appropriate lifestyle modifications and pharmacologic agent(s) requires careful attention to several factors:

- Severity of hypertension—level of blood pressure, duration of hypertension
- Associated complications—renal (albuminuria), cardiac (congestive heart failure, previous myocardial infarction), retinal
- Presence of obesity—waist/hip ratio >1, BMI >30kg/$m^2$ (in China, the criteria for overweight and obesity is BMI of ≥25 kg/$m^2$, per CDS[7])
- Current composition of diet—sodium intake, fat intake.

Keeping these factors in mind, the choices are initially among:

- Medical nutrition and activity therapy (MNT) or lifestyle—for mild hypertension
- ACE inhibitors
- ARBs
- Diuretics (low-dose thiazides recommended)
- Calcium channel blockers
- β-adrenergic receptor blockers
- α-adrenergic receptor blockers.

*Note: If hypertension and microalbuminuria are present, the therapy of choice is either an ACE inhibitor or an ARB.*

Low-dose thiazide diuretics (12.5–25 mg) are recommended in individuals with diabetes and/or metabolic syndrome to prevent deterioration of blood glucose and lipid levels. They are also especially effective in elderly patients. The results of the 8-year Antihypertensive and Lipid-

## Addressing smoking in China

The importance of addressing tobacco smoking in China cannot be overestimated. China has the highest number of tobacco smokers in the world—close to 300 million. According to the 2007-2008 China National Diabetes and Metabolic Disorders Study, 58.16% of Chinese males and 3.44% of Chinese females are smoking (i.e., one or more cigarettes daily for a year). The investigation also revealed that 45.48% of Chinese men between the ages of 20 and 30 were smoking. The rates prompted the authors to conclude that the "the ability to control the use of tobacco is a critical task for departments of health management or other relevant governmental departments."[8]

As is the case in Western countries, a significant dose-response association exists between pack-years smoked and all-cause mortality. In China, researchers found that of the 673,000 deaths attributable to tobacco in 2005, a total of 146,200 were cardiovascular-related. In 2012, the American Cancer Society and World Lung Foundation released a report indicating that tobacco use kills about 1.2 million people in China and that by 2030, 3.5 million deaths will be attributable to tobacco use.[80] These statistics point to the need for a strong tobacco-control program in China. While it appears that the government is moving forward with such efforts through increased monitoring of tobacco use and dedicated resources for tobacco-control activities within the Chinese CDC, the authors of the aforementioned mortality report have noted that the "government's role in tobacco control is in conflict with the selling of tobacco through its state-owned company and reliance on tobacco revenues."[81,82]

It is difficult to determine the effectiveness of tobacco prevention and cessation programs in China, primarily because the trials evaluating the programs are uncontrolled and poorly designed, especially cessation interventions involving physician counseling and traditional Chinese medicine.[83,84] Future programs require better implementation and methodological quality so that their effectiveness can be evaluated.

Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which enrolled more than 33,000 people with hypertension and at least one other CHD risk factor, demonstrated that the thiazide diuretic chlorthalidone was equal or superior to the calcium channel blocker amlodipine or the ACE inhibitor lisinopril in preventing CHD and heart failure.[79] Approximately 36% of the patients in ALLHAT had type 2 diabetes. Subanalysis of this high-risk group demonstrated that chlorthalidone was superior to lisinopril in most CVD endpoints and equal to lisinopril in terms of preventing development of end-stage renal disease (ESRD). The UKPDS demonstrated that β-blockers are safe and effective in people with type 2 diabetes and should be used with caution in those with a history of severe hypoglycemia.[41]

In most instances, the detection of hypertension when type 1 or type 2 diabetes already exists will not require a change in diabetes therapy.

## Selecting the appropriate therapy for hypertension

Once hypertension has been confirmed, the next step is to determine whether there is underlying kidney disease (Figure 5). If a patient has underlying nephropathy, an ACE inhibitor or ARB therapy should be initiated if there are no contraindications for use. If there is no indication of albuminuria and if the patient has blood pressure between 120/80 and 140/90 mmHg, he or she should be advised on diet and activity changes to reduce blood pressure. In general, however, drug therapy is recommended if blood pressure is greater than 140/90 mmHg.

Initiation of treatment requires a complete history and physical that should take into account the potential for lifestyle modification. The target blood pressure for people with diabetes and/or metabolic syndrome is less than 140/80 mmHg. This may be adjusted for the elderly or in the presence of autonomic neuropathies. Refer patients to a registered dietitian or diabetes educator, if

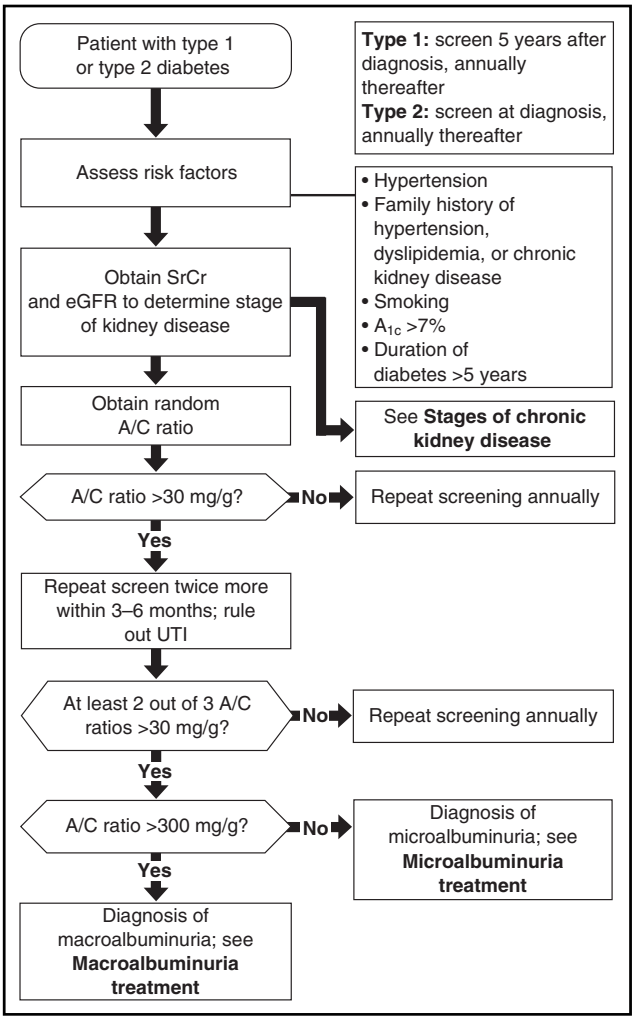



**Figure 5. Screening for kidney disease. A1c, hemoglobin A1c; A/C, albumin-to- creatinine ratio; eGFR, estimated glomerular filtration rate; SrCr, serum creatinine; UTI, urinary tract infection.**

available, to reinforce lifestyle changes. Lifestyle modifications are also recommended for all patients placed on pharmacological therapies for hypertension (see Figure 4).

### Lifestyle modification and medical nutrition and activity therapy

For all individuals with diabetes and hypertension, changes in lifestyle will be necessary. The primary areas of change that lower blood pressure include:

(1) Weight reduction (5–7% body weight)
(2) Increased physical activity (150 minutes/ week)
(3) Healthy eating plan
(4) Sodium restriction
(5) Reduction in alcohol intake
(6) Ensure tobacco-free lifestyle.

Many of these factors are interlinked. Clearly, changes in diet and exercise should be emphasized because the two interventions reduce numerous risk factors at the same time (i.e., hypertension and hyperglycemia).

Do not attempt to change everything at once. Most individuals with diabetes and/or metabolic syndrome achieve their best results when only one or two modifiable lifestyle factors are addressed at a time. Refer patients to a dietitian or diabetes educator (if available) for a food plan that will result in modest weight loss and low sodium intake. Modest weight loss (4 to 5 kg) will not only improve blood pressure but will often improve lipid and glucose levels as well. Alcohol intake and smoking should be addressed. The level of dependence should be assessed and the appropriate therapy offered. With the increased popularity of consuming alcohol for purported cardiovascular benefits, recommend a limit of one alcoholic beverage per day for women and up to two alcoholic beverages per day for men. Alcohol consumption higher than this can increase blood pressure.[85]

The benefits of dietary interventions cannot be overestimated. One plan in particular, known as the Dietary Approaches to Stop Hypertension (DASH) eating pattern, is a low-fat, low-sodium plan that is rich in fruits and vegetables. The DASH diet is effective, with patients following the diet having reduction in systolic blood pressure of 8-14 mmHg that by comparison is similar to addition of an anti-hypertensive medication.[86] Studies demonstrate that the DASH eating plan has statistically significant cardiometabolic and cardiovascular benefit among patients with diabetes.[87]

**Start drug therapy**

In general an ACE inhibitor or ARB should be used as the first-line pharmacological agent in hypertensive patients with diabetes or metabolic syndrome. Contraindications to ACE inhibitors include hyperkalemia, bilateral renal artery stenosis, and potential for drug interactions. Note that patients with impaired renal function (serum creatinine >2.5 mg/dL or 220 μmol/L) require significantly lower doses of ACE inhibitors to provide the same therapeutic response. If there are side effects (such as a cough), switch treatment to an ARB (e.g., losartan, valsartan). If ARBs are not an option, consider calcium channel blockers, low-dose thiazides, α-blockers, or β-blockers.

Initial follow-up should be weekly for 2–3 weeks to determine the reaction to the ACE inhibitor or ARB. If taking an ACE inhibitor, consider switching to an alternative antihypertensive drug if any of the following occur: hyperkalemia (K >5mEq/L), increased creatinine or decreased eGFR, cough, hypotension, rash, or leukopenia.

An interesting study evaluated the timing of antihypertensive therapy. Subjects (>2000) with hypertension were randomly assigned to either take all the hypertension medications in the morning (control group), or take one or more at bedtime (study group). The follow-up period was 5.6 years. During that time, there were significantly fewer events (n=68) in the study group vs. (n=187) in the control group. Events included death, cardiovascular events, cerebral vascular accidents, and others.[88]

**Adjust/maintain treatment**

The adjust treatment phase is marked by the need to reevaluate therapy because the target blood pressure has not been reached. (See Figure 3 for guidelines on the addition/adjustment of therapy.) However, if the therapy has resulted in reaching the target blood pressure, the patient moves into the maintain phase. Continue to monitor the patient

every 3 months. After 6 months to 1 year in the maintain phase, a reduction in antihypertensive drug dose may be considered unless the patient has microalbuminuria.

If the patient has not reached target blood pressure, assess overall adherence to the prescribed regimen. This should address changes in lifestyle as well as following the medication dose and timing. If the patient is adhering to the regimen, increase the dose of the ACE inhibitor or ARB until the maximum dose is reached. If blood pressure is still not controlled, consider adding a second antihypertensive drug from another classification. If significant edema is present, low-dose thiazide diuretics may be added to enhance the antihypertensive properties of the initial drug. If systolic blood pressure is 150 mmHg or greater, start two blood pressure medications. It is common for people with diabetes or metabolic syndrome to be taking three or more different antihypertensive drugs.

Landmark investigations have yielded some interesting findings regarding the selection of additional agents for hypertensive therapy:

- In the ALLHAT, researchers compared three blood pressure medications—amlodipine (a dihydropyridine calcium channel blocker), lisinopril (an ACE inhibitor), and doxazosin (an α-blocker)—with chlorthalidone (a thiazide therapy). In the first two groups, the occurrence of CHD death and nonfatal myocardial infarction was virtually identical. In comparison, study of the alpha-adrenergic blocker was stopped early. Compared with those on the diuretic, those on the alpha adrenergic blocker had substantially more cardiovascular problems, especially hospitalizations for heart failure.[79] Other studies, including the Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial,[89] have demonstrated the benefit of dihydropyridine calcium channel blockers. The ACCOMPLISH study showed the superiority of the dihydropyridine calcium channel blocker amlodipine over hydrochlorothiazide when added to the ACE inhibitor benazepril. A significant absolute risk reduction of 21.7% for cardiovascular events was reported.[90]
- Investigators from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) have recently found that dual blockade of the renin–angiotensin system (RAS)—through use of an ACE inhibitor plus an ARB— has no meaningful clinical benefit for patients with hypertension, proteinuria, heart failure, or CHD as compared with patients on ACE inhibitor or ARB monotherapy. Importantly, the researchers found that dual blockade of the RAS does not reduce the rates of morbidity or death from any cause.[91]
- The ADVANCE trial[20] reported 11,140 high-risk patients with type 2 diabetes showed significant reduction in overall and cardiovascular mortality in the intensive blood pressure arm (mean systolic BP of 135 mmHg) relative to those treated to higher systolic BP levels.
- The ACCORD study[22] found no difference in major cardiovascular outcomes between treating systolic BP to <120 mmHg and treating systolic BP to between 130-139 mmHg. Treating to <120 mmHg resulted in more serious adverse events.

# Management of hyperlipidemia and dyslipidemia

## Diagnosis of hyperlipidemia/ dyslipidemia

Lipid abnormalities are more likely to be found in individuals with type 2 diabetes and/or metabolic syndrome than in people with type 1 diabetes. Nevertheless, the standards are the same. SDM supports the ADA Standards of Medical Care in Diabetes 2012[23] and National Cholesterol Education Program (NCEP) guidelines for the detection of dyslipidemia in the presence of diabetes (Table 1).[52] The diagnosis of dyslipidemia in individuals with diabetes includes one or more of the following:

- Total cholesterol 5.2 mmol/L (200 mg/dL) or greater
- LDL cholesterol 2.6 mmol/L (100 mg/dL) or greater
- Triglyceride level 1.7 mmol/L (150 mg/dL) or greater
- HDL cholesterol 1.1 mmol/L (40 mg/dL) or less in men and 1.3 mmol/L (50 mg/dL) or less in women.

According to the NCEP, diabetes is considered a CHD risk equivalent. Thus, the lipid goals for individuals with diabetes are the same as those for individuals with documented CHD. For example, the goal of therapy for LDL cholesterol is to achieve a level <2.6 mmol/L (100 mg/dL). For individuals with evidence of CVD, an LDL <3.9 mmol/L (70 mg/dL) is recommended. The NCEP has recognized that very low levels of HDL (<1.1 mmol/L [40 mg/dL]) increase the risk of CHD. Conversely, high levels of HDL cholesterol (>1.7 mmol/L [60 mg/dL]) are considered cardioprotective.

*Note: As with hypertension, the targets for people with metabolic syndrome and dyslipidemia should be the same as for those with diabetes. While the evidence for these targets is sparse, there is reason to believe that NCEP recommendations will be equally beneficial for people with metabolic syndrome.*

## Clinical manifestations of hyperlipidemia/dyslipidemia

Generally there are no signs of hyperlipidemia or dyslipidemia that would be readily recognized by the patient. The one exception is lipid deposits in the eye that may be associated with changes in vision. Changes in vision, however, are also associated with hyperglycemia and hypertension and therefore careful evaluation to determine the cause must be carried out. Therefore, it is important to maintain a program of careful surveillance using periodic fasting lipid profile determination, especially in those individuals at highest risk. Once again the combination of type 2 diabetes and/or metabolic syndrome, and obesity with a family history of hyperlipidemia, present the highest risk group in which hyperlipidemia or dyslipidemia may be identified.

## Determining the starting treatment for dyslipidemia

While the discovery of lipid abnormalities in people with hyperglycemia is common, its presentation may be different from that found in patients without diabetes. The key differences are:

- Elevated triglyceride level
- Low HDL cholesterol level
- Small, dense, oxidized LDL cholesterol particles

These differences require that a fractionated lipid profile (total cholesterol, HDL cholesterol, and triglyceride) be carried out. The "calculated" LDL should then be determined if the triglyceride level is not too elevated (e.g. >4.5 mmol/L [400 mg/dL]) (Figure 6). Under these circumstances, a "direct" LDL should be determined.

Non-HDL cholesterol is becoming a more prominent target of lipid management. Non-HDL cholesterol is calculated by subtracting the HDL cholesterol concentration from total cholesterol concentration, providing an estimate of cholesterol contained in all atherogenic particles including LDL cholesterol, Lp(a), very low density lipoprotein (VLDL), and intermediate density lipoprotein (IDL). Non-HDL cholesterol has been shown to be superior to LDL cholesterol in determining cardiovascular risk.[92,93] The ADA and American College of Cardiology Foundation has released a consensus statement on non-HDL cholesterol targeting <3.37 mmol/L (130 mg/dL) for those with diabetes and <2.59 mmol/L (<100 mg/dL) for those with diabetes and known atherosclerotic cardiovascular disease.[94] The National Cholesterol Education Program Adult Treatment Panel IV guidelines that are expected to be released in late 2012 should also provide further guidance on non-HDL targets and treatment recommendations.

As in the case of hypertension, treatment of lipid abnormalities usually will not require a change in diabetes therapy if the patient is maintaining $HbA_{1c}$ within reasonable levels. Poor glycemic control can lead to worsening of dyslipidemia, which should be addressed primarily with improvement in glycemic control. In those patients with type 2 diabetes and/or metabolic syndrome treated by MNT only, some minor alterations in food plan (reduction in saturated fats) may be required with concomitant weight management. The selection of pharmacological agents to combat hyperlipidemia and dyslipidemia raises additional considerations, since some lipid-lowering drugs are known to

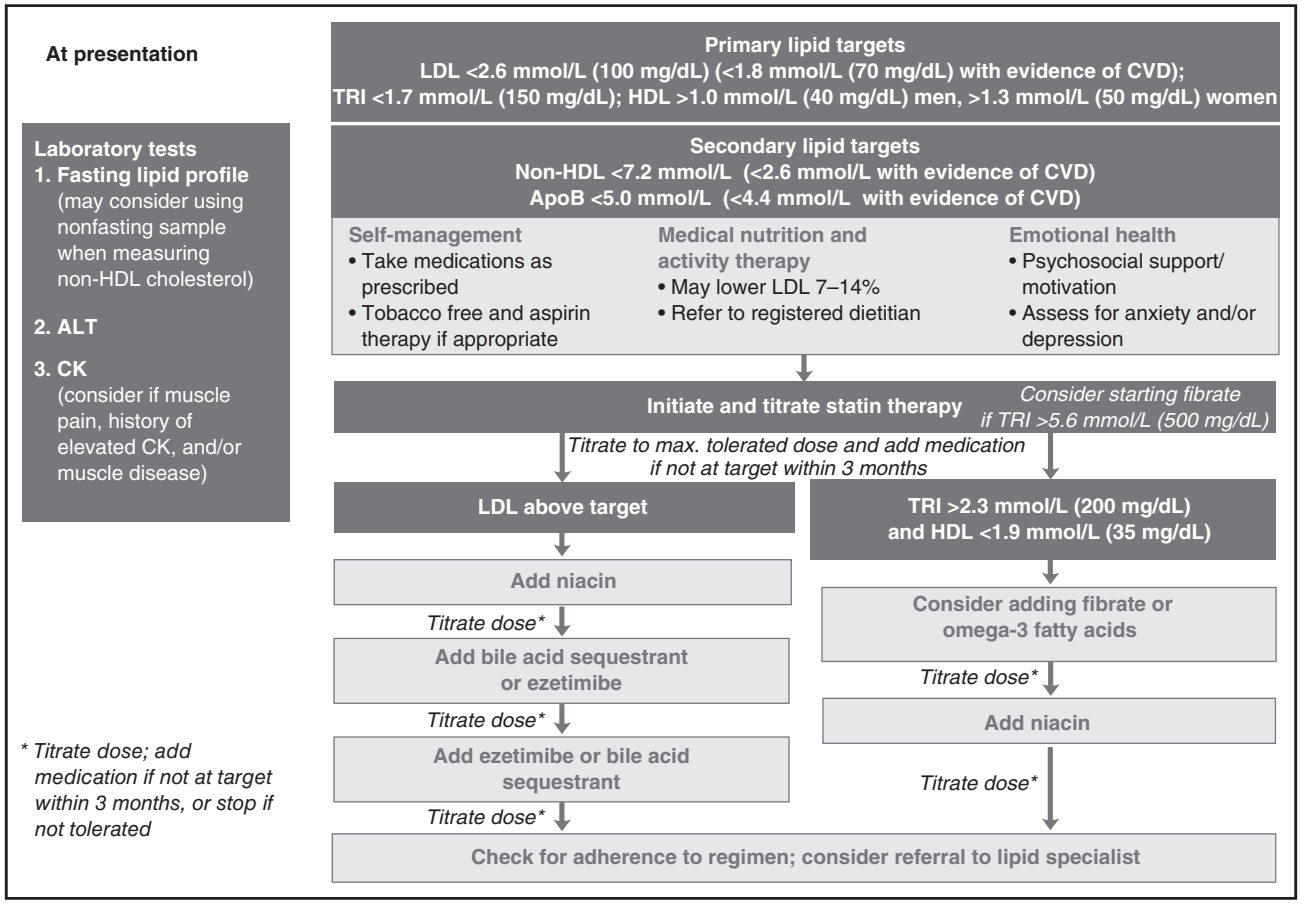



**Figure 6. Diabetes and dyslipidemia Master DecisionPath. Example of diabetes dyslipidemia guideline (local guidelines should be utilized). ALT, alanine transaminase; ApoB, apolipoprotein B; CK, creatine kinase; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TRI, triglycerides.**

aggravate blood glucose control (niacin) and other lower blood glucose (colesevelam)

The current therapies are outlined in Figure 6 and include:

- Lifestyle modification (see also Figure 4)
- HMG-CoA reductase inhibitors (statins)
- Fibrates
- Bile acid sequestrants
- Niacin
- Cholesterol absorption inhibitors
- Omega-3 fatty acids

See Table 2 for dosing guidelines for medications used to treat dyslipidemia.

## Treating hyperglycemia in patients with dyslipidemia

Hyperlipidemia or dyslipidemia in the presence of diabetes and/or metabolic syndrome requires certain precautions. In type 2 diabetes and/or metabolic syndrome, if blood glucose is well controlled by food planning and exercise alone, then no modifications in therapy will be necessary. However, when blood glucose is high and there is hyperlipidemia, lowering blood glucose is important and may require moving to a pharmacological diabetes regimen (e.g., from food plan to oral agent or insulin). Similarly, in type 1 diabetes, if $HbA_{1c}$ is not at target, more intensive blood glucose management is necessary. In terms of priorities, the first step is to determine the severity of the cholesterol level.

## Selecting the appropriate therapy for dyslipidemia

The International Diabetes Center recommends the following strategy to select the appropriate therapy for dyslipidemia, which is consistent with ADA Standards of Medical Care:[23]

| | Start dose (mg/day) | Clinically effective dose (mg/day) |
|---|---|---|
| *Statin* | | |
| Atorvastatin (Lipitor) | 10 | 10–80 |
| Fluvastatin (Lescol) | 20 | 20–80 |
| Lovastatin (Mevacor) | 10–20 | 20–80 |
| Pravastatin (Pravachol) | 10–20 | 10–40 |
| Rosuvastatin (Crestor) | 10 | 10–40 |
| Simvastatin (Zocor) | 10 | 10–80 |
| Amlodipine/atorvastatin (Caduet) | 5/10 | 5/10–10/80 |
| Pitavastatin (Livalo) | 2 | 1-4 |
| *Fibrate* | | |
| Fenofibrate (Fenoglide) | 40–120 | 120 |
| Fenofibrate (Lipofen) | 50–150 | 150 |
| Fenofibrate (Tricor) | 48–145 | 145 |
| Fenofibrate (Triglide) | 50–160 | 160 |
| Fenofibrate, micronized (Antara) | 43–130 | 130 |
| Fenofibrate, micronized (Lofibra) | 67–200 | 200 |
| Fenofibric acid (Trilipix) | 45–135 | 135 |
| Gemfibrozil (Lopid) | 600 mg BID | 600 mg BID |
| *Niacin* | | |
| Nicotinic acid | 1.5 g/day | 3–4.5 g/day |
| Nicotinic acid (Niaspan) | 500 | 1000–2000 |
| *Cholesterol absorption inhibitor* | | |
| Ezetimibe (Zetia) | 10 | 10 |
| Ezetimibe/simvastatin (Vytorin) | 10/10–10/20 | 10/10–10/80 |
| *Bile acid sequestrants* | | |
| Colesevelam (WelChol*) | 3.8 g/day | 3.8–4.4 g/day |
| Cholestyramine | 8 g/day | 16–24 g/day |
| Colestipol (Colestid) | 10 g/day | 20–30 g/day |
| *Omega-3 fatty acids* | | |
| Omega-3 acid ethyl esters (Lovaza) | 4 g/day QD/BID | 4 g/day QD/BID |

**Note** Monitor serum transaminase (AST/ALT) levels before and 8–12 weeks after starting a statin or fibric acid; monitor periodically thereafter; discontinue therapy if AST or ALT >3 times upper limit of normal; see package insert for detailed prescribing information. Trade names are US-based and may be different within other countries. *Also approved for use as a glucose-lowering therapy for type 2 diabetes.

**Table 2. Dyslipidemia start/adjust. Note: Many countries have dose restrictions related to the use of simvastatin when combined with other agents. For example, the FDA has limited the maximum dose of simvastatin to 40 mg unless the patient has been treated for 1 year or greater on a higher dose of 80 mg without experiencing muscle pain.**

- Individuals (1) with diabetes and known CVD or (2) without CVD and age >40 years and who have more than one risk factor should be treated with a statin regardless of baseline lipid levels.

- For those who are <40 years of age and are without overt CVD, a statin is considered with lifestyle if LDL>100 mg/dL or multiple risk factors are present.
- For individuals who do not have overt CVD, the primary goal is an LDL cholesterol <2.6 mmol/L (100 mg/dL).
- Individuals who have overt CVD, an option is to aim for a lower LDL cholesterol goal of <1.8 mmol/L (70 mg/dL), using a high dose of a statin.
- Combination therapy (statins with other lipid-lowering agents) may be considered if targets are not reached on maximally tolerated doses of statins, but the safety of this combination therapy and its effect on CVD outcomes has not been evaluated.

## Lifestyle modification and dietary interventions for dyslipidemia

Significant changes in lifestyle will be necessary for all patients with dyslipidemia. As with hypertension, several areas of change are beneficial: weight reduction, increased physical activity, reduction in excessive alcohol intake, and reduction in dietary saturated fats, trans fats, and cholesterol. Many of these are interlinked. Other changes are also recommended, including increasing intake of omega-3 fatty acids and viscous fiber and plant stanols/sterols. Clearly, alterations in diet and physical activity level are important to emphasize because they have an impact on lipids, hypertension, and hyperglycemia. If available, consider referral to a registered dietitian or diabetes educator to reinforce lifestyle changes and improve likelihood of patients making lifestyle modifications the will improve metabolic control.

### Medical nutrition and activity therapy start treatment

The best results occur when alterations in food and exercise occur over time and are planned. Slow changes in behavior provide both immediate and long-term feedback. As in hypertension management and glycemic control, moderating food intake and increasing activity provide rapid positive feedback, often lowering lipid levels and reducing blood glucose and blood pressure. Replacement of high-calorie and high-fat foods and drinks with lower calorie substitutes is beneficial. If this fails to improve lipids, reduction in food intake is often helpful. A 10 to 20% reduction in meal size will lower total caloric intake by the same amount. If this fails to improve lipid levels, the restriction of food and drink should be attempted. This approach lists those foods that are not acceptable, such as red meat, and those drinks that are not acceptable, such as whole fat milk. The goal should be caloric reduction by between 250 and 500 calories per day, which will result in a 1 to 2 kg (2 to 4 lb) per month weight loss. If physical activity of 30 minutes per day, at least five times per week (i.e., minimum 150 minutes per week), is added, the patient may lose up to an additional 1 kg (2 lb) per month. A reduction in calories should be accompanied by a modification in both fat and sodium intake. Since fat provides more than double the calories of the equivalent quantity of carbohydrate or protein, a further reduction in weight can be realized by replacing fat with carbohydrate and protein.

General recommendations include:

- Fat at less than 30% of total calories
- Saturated fat less than 7% of total calories
- Fat limited to monounsaturated and polyunsaturated (avoid animal and trans fats)
- Meat limited to 170 g (6 ounces) per day (avoid high-fat products)
- Dairy limited to low-fat variety
- Eggs limited to two or three per week
- Breads, whole-grain variety
- Avoid excessive alcohol intake (especially if hypertriglyceridemia).

These recommended changes are for patients on MNT as a solo therapy or as part of the pharmacological therapy.

### Medical nutrition and activity therapy/ adjust/maintain treatment

Improvement in the lipid levels should occur within 3 months of initiation of treatment and continue until normal levels of total cholesterol and LDL cholesterol are reached. Continued modification in diet and increase in activity level should be encouraged to maintain improved lipid levels. If improvement is not occurring, consider evaluation for adherence and introduction of pharmacological therapy. Refer to the dyslipidemia start and adjust DecisionPath to select the appropriate drug therapy and then follow the specific adjust/maintain guide (see Figure 5).

## Treatment with lipid-lowering agents

The choice of drugs is based on the nature of the lipid abnormality, but is usually a statin since the focus of lipid management is bringing the LDL cholesterol into target range.[75] The following classes of medications are commonly used:

- Statins (simvastatin, atorvastatin, lovastatin, pravastatin, fluvastatin, rosuvastatin, pitavastatin) are recommended as first-line therapy—they work by decreasing production of cholesterol by the liver by inhibiting HMG-CoA reductase (the key step in cholesterol synthesis), resulting in lower LDL levels
- Cholesterol absorption inhibitors (ezetimibe)—works in the gastrointestinal tract by blocking the body's absorption of cholesterol found in food
- Bile acid sequestrants (cholestyramine, colestipol, colesevelam)—work by binding to bile acids in the enterohepatic circulation causing an increase of bile acid production from cholesterol taken from LDL particles in the bloodstream
- Fibrates (fenofibrate, gemfibrozil, clofibrate)—work by reducing the levels of triglyceride in the body by increasing lipoprotein lipase expression that breaks down triglyceride-rich particles such as very-low-density lipoprotein (VLDL)
- Nicotinic acid (niacin)—works by reducing apolipoprotein (Apo) B synthesis in the liver, leading to lower LDL and VLDL levels, and increasing ApoA1 synthesis in the liver, leading to increased HDL levels. Niacin has a tendency to modestly raise blood glucose approximately 0.3 to 0.6 mmol/L (5 to 10 mg/dL).

The recommended medication for the treatment of dyslipidemia is a statin because of the sheer number of cardiovascular studies showing the benefit of statin therapy to lower cardiovascular morbidity and mortality. The exception to this is, for triglyceride levels >5.6 mmol/L (500 mg/dL), independent of the LDL level, initiate fibrate therapy to lower the risk of pancreatitis due to very high triglycerides. Baseline alanine transaminase (ALT) and creatine kinase levels should be determined and statin should not be initiated if either is higher than three times the upper limit of normal. Initial patient contact should be weekly for 2 to 3 weeks to determine the reaction to the drug therapy. In particular, patients may report myalgia associated with statin use. Alternative statins may be tried until a statin is found that does not cause muscle pain. Consider referral to a registered dietitian and diabetes educator to reinforce lifestyle changes, if available.

### Adjusting/maintaining drug treatment

At the 3-month visit cholesterol, LDL, HDL, and triglyceride levels are measured to identify any current lipid abnormality. Tables 3, 4, and 5 outline the clinical effectiveness of lipid-lowering therapy. The statin dose should be titrated to maximize LDL-lowering potential. If the therapy has resulted in reaching the target, the patient moves into the maintain phase. Continue to monitor the patient

every 4 to 6 months. If the patient has not reached the target, first determine whether the lipid abnormality is the same as before. If it is the same, assess overall adherence to the prescribed regimen. This should address changes in lifestyle as well as whether the medication dose and timing are followed. Lifestyle changes should be reflected in alteration in diet, activity level, weight, and blood glucose levels. If the patient is on drug therapy and adhering to the regimen, increase the initial drug until the maximum dose is reached. If the maximum dose is reached, consider adding the next drug category. If the first drug has been of some benefit, the second drug is added while the first drug is maintained at the current dose. If the first drug was of no apparent benefit, replace it with the next category drug.

*Note: Should the patient develop a different lipid abnormality or an additional abnormality, follow the change in therapy for dyslipidemia protocol (see Figure 5).*

**Initial lipid abnormality (LDL or HDL)**

If there originally was an elevated LDL, at the 3 month follow-up the patient could have one of the following conditions:

- All lipid levels are normal
- Continued elevated LDL
- LDL improved but now triglyceride is elevated (>2.4 mmol/L [200 mg/dL])
- Both LDL and triglyceride are abnormal
- Low HDL (<1.0 mmol/L [40 mg/dL])

If the LDL abnormality remains the principal concern, the statin should be increased until the maximum dose is reached. At this point, if there is still insufficient improvement, addition of niacin should be considered. While flushing is a concern with niacin it should be emphasized to the patient that the frequency diminishes with repeated consistent dosing. Moreover, consider having patients take aspirin 30–60 minutes before the dose and/or use of extended release niacin. If there is still no improvement, a bile acid sequestrant (e.g., colesevelam which can also improve glucose control) or cholesterol absorption inhibitor (ezetimibe) should be considered. Niacin is often recommended as second-line therapy over ezetimibe because of studies showing lowering of LDL with the addition of ezetimibe to statin therapy without a corresponding additional improvement in cardiovascular biomarkers (e.g., carotid intimal media thickness [CIMT]).[95,96] However, a large randomized control trial involving niacin in combination with statin showed no benefit compared with statin alone.[97] If the LDL is being managed and triglyceride levels are now abnormal, fibrate or omega-3 fatty acids may be added if triglycerides are greater than 2.4 mmol/L (200 mg/dL) and HDL is less than 0.9 mmol/L (35 mg/dL). However, when the ACCORD study group evaluated the effect of a statin (simvastatin) plus fibrate (fenofibrate) against statin monotherapy, the combination therapy did not reduce the rate of cardiovascular events (e.g., nonfatal myocardial infarction, fatal cardiovascular events, a nonfatal stroke) compared with the use of a statin alone. In the event that the therapies are not succeeding, consider referral to a specialist in lipid disorders.

**Initial LDL/triglyceride/HDL abnormality**

If there originally was an elevated LDL and abnormal triglyceride level, at the 3 month follow-up one of the following conditions might be present:

- Continued elevated LDL/triglyceride
- LDL improved but now has elevated triglyceride (>2.4 mmol/L [200 mg/dL]) as well
- Triglyceride level improved, LDL still abnormal
- All values are normal
- HDL <1.0 mmol/L [40 mg/dL]).

Maintain the current therapy when there is improvement. If there is no improvement, continue to adjust the drug until the maximum dose is reached. Change the category of drug if the initial therapy fails.

### Selecting the appropriate therapy for dyslipidemia

Many of the drug therapies and all of the dietary changes benefit more than one of the abnormalities (Tables 3, 4, and 5). MNT for hypertension is identical to that for diabetes or insulin resistance. Further modifications of fat intake due to dyslipidemia would benefit both hyperglycemia and hypertension. A reduction in blood glucose levels to near normal will contribute to improved lipid levels, independent of the type of therapy (medical nutrition, oral agent, or insulin).

## Additional therapeutic options for prevention and treatment of cardiovascular disease

Recently, adjunctive therapies have been introduced for the primary and secondary prevention of CVD in individuals with diabetes (and for people with metabolic syndrome as well). Some of these therapies are highly recommended as part of secondary but not necessarily primary prevention (i.e., aspirin therapy)—on the basis of evidence yielded through peer-reviewed studies—while others are less well investigated and accepted (i.e., folate supplementation). Ultimately, it is up to the provider to weigh the possible benefits and risks before initiating any of these therapies.

| Drug | 10 mg | 20 mg | 40 mg | 80 mg |
|---|---|---|---|---|
| Atorvastatin | ↓↓ | ↓↓↓ | ↓↓↓↓ | ↓↓↓↓ |
| Fluvastatin | – | ↓ | ↓ | ↓↓ |
| Lovastatin | – | ↓ | ↓↓ | ↓↓↓ |
| Pravastatin | ↓ | ↓↓ | ↓↓ | – |
| Rosuvastatin | ↓↓↓ | ↓↓↓↓ | ↓↓↓↓ | – |
| Simvastatin | ↓↓ | ↓↓ | ↓↓↓ | ↓↓↓ |

↓, up to 30%; ↓↓, up to 40%; ↓↓↓, up to 50%; ↓↓↓↓, >50%.
**Note** Statins lower triglycerides 15–25% and increase high-density lipoprotein 5–15%.

**Table 3. Treatment for lowering low-density lipoproteins: low-density lipoprotein-lowering effect of statins. Note: Pitavastatin is also available in some countries.**

| Drug/dose | Triglycerides | High-density lipoprotein | Low-density lipoprotein |
|---|---|---|---|
| Fenofibrate (145 mg/day)† | ↓23–55% | ↑10–20% | ↓10–25%* |
| Gemfibrozil (600 mg BID) | ↓20–31% | ↑6–12% | ↓0–5%* |
| Niacin (2000 mg/day) | ↓20–40% | ↑15–30% | ↓10–20% |

*Treatment of patients with elevated triglycerides as a result of type IV hyperlipidemia may have increased low-density lipoprotein cholesterol.
†Initial dose of 48 mg/dL if mild to moderate renal impairment.

**Table 4. Treatment for lowering low-density lipoproteins: clinical effectiveness of fibrates and niacin**

| Drug/dose | Triglycerides | High-density lipoprotein | Low-density lipoprotein |
|---|---|---|---|
| Colesevelam (3.8 g/day)* | ↑5–10% | ↑3–5% | ↓15–20% |
| Ezetimibe (10 mg/day) | ↓10–15% | ↑1–3% | ↓15–20% |

*Colesevelam is recommended over colestipol and cholestyramine because of improved tolerability and positive effect on lipid panel; colesevelam also has an indication for diabetes (hemoglobin A1c ↓0.5 percentage points).

**Table 5. Treatment for lowering low-density lipoproteins: clinical effectiveness of bile acid sequestrants and cholesterol absorption inhibitors**

### Fish oil therapy

Omega-3 fatty acids that are found in fish oil have been shown to be an effective alternative to fibrates and niacin for treating hypertriglyceridemia. Omega-3 fatty acids reduce triglyceride levels by decreasing the production of VLDL triglycerides in the liver. A meta-analysis of 26 clinical studies demonstrated that fish oil effectively lowers triglyceride levels by up to 30% with no significant change in $HbA_{1c}$.[98] Fatty (nonfarm raised) fish are high in the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The AHA recommends that patients without documented CHD eat fatty fish (lake trout, sea salmon, albacore tuna) at least twice per week because sufficient epidemiological and clinical data exist to support their role in reducing the risk of CVD.[99] It is important to consider that certain fatty fish may have high levels of mercury and other contaminants. In patients with documented CHD, increased consumption of fatty fish and/or supplementation in order to achieve 1 g of EPA and DHA per day is recommended. In patients with isolated hypertriglyceridemia (>2.3–4.5 mmol/L [200 to 400 mg/dL]), further supplementation of EPA and DHA to 2 to 4 g/day may be considered to lower triglyceride levels. In 2009, the US FDA approved the only fish oil-derived agent, prescription-only omega-3 polyunsaturated fatty acids, for treatment of high triglyceride levels (≥5.6 mmol/L [500 mg/dL]). In July 2012, investigators of the ORIGIN trial published results of their study evaluating the effects of omega-3 fatty acids supplements (1 g capsule) on cardiovascular mortality and the rate of cardiovascular events by decreasing risk of cardiac arrhythmias. Compared with placebo, the supplements offered no statistically significant benefit by way of reduced cardiovascular mortality of adverse events.[100]

Thus, currently there is insufficient evidence to support the routine supplementation of omega-3 fatty acids for purported CV benefits in patients with newly diagnosed diabetes with existing CVD or increased CVD risk to reduce risk of cardiac arrhythmias.

### Aspirin therapy

Aspirin blocks the synthesis of thromboxane, a potent vasoconstrictor and stimulator of platelet aggregation. Numerous trials have previously demonstrated the ability of aspirin therapy to offer significant protection from myocardial infarction, stroke, and mortality due to cardiovascular events.[23] However, in recent years, the effectiveness of aspirin in addressing primary prevention of cardiovascular events has become less clear.[101,102] In addition, long-term use of low-dose aspirin carries with it certain health risks, including hemorrhagic stroke and gastrointestinal bleeding.[103]

The American Diabetes Association recommendations for aspirin use are as follows:[23]

- For the primary prevention of heart disease, it is recommended that patients with type 1 or type 2 diabetes aged over 50 years for men and 60 years for women who have one CVD risk factor in addition to diabetes take low-dose aspirin (75–162 mg) daily under the guidance of their primary care provider, unless contraindicated.
- For men younger than 50 years and women younger than 60 years with diabetes and other risk factors, clinical judgment will need to be used when determining the recommendation for aspirin therapy in primary prevention of CVD. These patients may still benefit from daily low-dose aspirin therapy if their 10-year risk score (Framingham) is greater than 5%.[23,104]
- For secondary prevention, people with diabetes and history of CVD are recommended to take daily low-dose aspirin (75 to 162 mg) under the guidance of their primary physician, unless contraindicated.

- Enteric-coated tablets should be used as often as possible to minimize gastrointestinal side effects.

The CDS recommends the following:[7]

- For patients who have diabetes and a 10-year cardiovascular risk of >10%, a conventional small dosage of aspirin should be administered; for patients with diabetes and a 10-year cardiovascular risk of 5%–10%, a small dosage of aspirin should be "considered;" for patients with diabetes with a 10-year cardiovascular risk of <5%, no small dosage of aspirin should be given.

The following are contraindications for aspirin therapy:

- Current anticoagulant or antiplatelet therapy (warfarin, clopidogrel, enoxaparin, heparin)
- Allergy to aspirin or other salicylates or other known aspirin sensitivity (including aspirin-sensitive asthma); both CDS and ADA recommend clopidogrel (75 mg/day) as an appropriate replacement for those who are allergic to aspirin as well as those who have CVD[7,23]
- History of bleeding disorder (e.g., hemophilia) or bleeding tendency (e.g., nose bleeds)
- Active hepatic disease; cirrhosis, hepatitis, ALT levels more than 2.5 times the upper limit of normal
- History of recent major gastrointestinal bleeding (e.g., bleeding ulcer)
- Excessive menstrual bleeding
- Recent major trauma or surgery within 2 months
- Pregnancy or planning pregnancy
- Under age 21

### Hormone replacement therapy

Hormone replacement therapy, which includes estrogen or combined progestin and estrogen, is commonly used to ameliorate conditions associated with menopause (hot flashes, vaginal dryness, and osteoporosis). Several observational clinical studies have shown a strong association between hormone replacement therapy and reduced morbidity and mortality caused by CVD in postmenopausal women. This would appear to be of clinical importance to women with diabetes because they experience a significantly higher rate of CVD than women without the disease. However, in two large randomized clinical trials (Heart and Estrogen/Progestin Replacement Study and Women's Health Initiative) no long-term cardiovascular benefit was demonstrated in subgroup analysis of women in these studies with diabetes.[105,106] Thus, SDM recommends that the decision to initiate hormone replacement therapy for postmenopausal women should not be based on purported protection against CVD and must be weighed against the modest increased risk of endometrial carcinoma and breast cancer found to be associated with long-term estrogen supplementation. Contraindications for hormone replacement therapy include pregnancy, known or suspected breast cancer, known or suspected estrogen-dependent neoplasia, abnormal vaginal bleeding, thrombophlebitis, or thromboembolic disease.

## Nutritional therapies for cardiovascular disease

### Antioxidant supplementation

Vitamins C and E and β-carotene serve as antioxidants in the body by scavenging free radicals that are responsible for catalyzing the oxidation of many cellular components. While the relationship between antioxidant therapy and CHD is not clearly delineated, it is thought to involve

the inhibition of oxidation of LDL cholesterol. Oxidation of LDL cholesterol appears to be required before it can be taken up by macrophages in the arterial wall, leading to atheroma. People with diabetes have enhanced susceptibility to LDL cholesterol oxidation, which may be one of the factors explaining the increased risk of CVD in these individuals. Since large placebo-controlled studies have failed to demonstrate the CVD benefit of high-dose vitamin E,[45] SDM recommends that patients avoid special supplements of vitamin E; rather, a daily multivitamin should be considered.

**Folate supplementation**

Folate and, to a lesser extent, vitamins $B_6$ and $B_{12}$ have been suggested to be effective in preventing CVD because of their ability to lower homocysteine levels. Homocysteine is an amino acid that is formed by the metabolism of methionine in the liver. Folate, vitamin $B_6$, and vitamin $B_{12}$ are critical for the metabolic conversion of homocysteine into other amino acids and have been shown to be effective at reducing homocysteine levels. Elevated homocysteine levels have been shown to be an independent risk factor for coronary artery disease.[107] Currently, SDM does not recommend determining homocysteine levels on a routine basis. Determining homocysteine levels should be considered primarily for patients with established CVD in the absence of other risk factors. If homocysteine levels are elevated (above normal laboratory reference range), folate supplementation of 0.4 to 1 mg per day is recommended. Folate supplementation is not recommended for the prevention of CVD unless elevated homocysteine levels have been documented. Homocysteine levels should be determined after 8 to 12 weeks of folate supplementation to ascertain the effectiveness of therapy.

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