2 CE Credits

Managing Heart-Related Complications in Patients With Diabetes

U.S. Pharmacist Continuing Education

GOAL: *To provide an overview of cardiovascular complications in patients with diabetes mellitus with specific emphasis on the management of these conditions.*

OBJECTIVES: *After completing this activity, participants should be able to:*

1. **Review** *the different cardiovascular conditions commonly encountered in patients with diabetes.*

2. **Discuss** *the metabolic syndrome and its importance in controlling diabetes.*

3. **Discuss** *different methods for controlling diabetes and related heart disease complications.*

4. **Describe** *the available medications dealing with cardiovascular complications in individuals with diabetes.*

Diabetes mellitus (DM) makes up a group of hormonal diseases characterized by alterations in carbohydrate, protein, and lipid metabolism that results in elevated levels of blood glucose. More than 220 million people in the world have DM, and this number is expected to double by 2030.[1] Hyperglycemia that develops is due to either a complete lack of insulin secretion by the pancreas, a reduction in insulin action, or a combination of both. Glucose is taken up by insulin and used as energy by the cells. Insulin is made and secreted by the beta cells of the islets of Langerhans in the pancreas. When insulin does not function properly or is not produced in efficient amounts, glucose remains in the blood, resulting in hyperglycemia or DM, which is characterized by glucose intolerance. The liver, however, continues to make glucose, and additional glucose is secreted into the blood. DM affects virtually all organs in the body, including the macrovascular system (heart) and the microvascular system (eyes, nerves, kidney, and the periodontium in the oral cavity). Cardiovascular complications of diabetes are common and are a leading cause of death in individuals with diabetes. Patients with diabetes with a history of heart disease (e.g., coronary heart disease [CHD]) are at a higher risk for developing cardiovascular events earlier in life than those without heart disease.[2] This article reviews the cardiovascular complications in and management of patients with DM.

Types of Diabetes Mellitus

Diabetes mellitus is classified as type 1 or type 2. Type 1 diabetes mellitus (T1DM) is caused by an absolute insulin deficiency as a result of destruction of pancreatic islet beta cells. Without adequate insulin to allow glucose from the blood to enter cells, the cells starve while glucose accumulates in the blood. The cells do not have glucose as a source of energy, so they begin to break down fat that is available. Free fatty acids accumulate in the blood and are converted into ketones, which may result in ketoacidosis, a potentially life-threatening condition. Diabetic ketoacidosis occurs when there is hyperglycemia (>250 mg/dL) and urinary ketone bodies, resulting in a metabolic acidosis characterized by drowsiness, nausea, sweating, tachycardia, and coma. T1DM is primarily an autoimmune process in which insulin autoantibodies in the body are involved in pancreatic cell destruction. Macrovascular/cardiovascular complications are not prevalent in T1DM.[3]

Type 2 diabetes mellitus (T2DM) is considered to be a type of insulin resistance and is defined as *decreased insulin effectiveness with a reduced sensitivity of the cells to respond to insulin*. Normally, the pancreatic beta cells adjust insulin secretion levels to the feeding or fasting cycle. Endogenous carbohydrates, fats, and proteins are synthesized or degraded at controlled rates. If the caloric intake is greater than the expenditure of calories, nondegraded substrates are stored in the adipose tissue, the body's energy reservoir, and the body weight increases. As the adipose mass increases, insulin receptor numbers on the adipocyte and other cell surfaces including the liver and muscle cells decrease, and the tissues become resistant to the effects of insulin. Insulin must bind with these receptors and become active in bringing glucose into the cell and stimulating glucose metabolism.[2] In T2DM, insulin receptors on the target tissues

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have become insensitive or resistant to insulin. Insulin may bind to the receptor, but there is a defect in both insulin action and secretion, making the insulin ineffective in glucose uptake into the tissues.

When insulin resistance develops, the beta cells are forced to compensate by secreting more insulin, resulting in a condition known as *hyperinsulinemia*. Over time, the beta cells of the pancreas lose their ability to produce insulin in sufficient quantities to overcome insulin resistance. This condition is referred to as *impaired glucose tolerance*, or *prediabetes*. This results in high blood glucose levels, especially after meals, which is called *postprandial hyperglycemia*. The degree of insulin defect is influenced by many factors, including obesity, cigarette smoking, and decreased physical activity. In fact, approximately 80% of patients with T2DM are obese or overweight.[4] Continued insulin resistance and insulin deficiency ultimately will result in T2DM.

Table 1. Predisposing Factors Affecting Both the Development of CVD and DM

- Central obesity (waist circumference >40 inches in men and >35 inches in women)
- Decrease in physical activity (sedentary lifestyle)
- Positive family history of diabetes
- Gender (women have a four- to sixfold increase)
- Advancing age (older than 40 to 45 years of age)
- Hyperglycemia (glucose in the blood)

CVD: cardiovascular disease; DM: diabetes mellitus.
Source: Reference 8.

Epidemiology and Statistics

Cardiovascular disease (CVD) is a major cause of mortality in patients with diabetes, and the prevalence of diabetes is increasing in both developed and undeveloped countries.[5] The prevalence of CVD is as low as 2% to 4% in the population without diabetes to about 55% in adults with diabetes.[5,6] The overall mortality from cardiovascular disease is twice as great in men and four to five times higher in women with diabetes.[5] The presence of diabetes has also been shown to increase the risk of morbidity in patients with CHD.[7]

Risk Factors and Etiology of Heart Complications

There are several important factors that simultaneously influence the development of CVD in patients with DM (**TABLE 1**). These factors exacerbate the major risk factors seen in both DM and CVD, which include dyslipidemia, hypertension, and glucose tolerance. Therefore, it is important to control these predisposing risk factors to prevent both DM and CVD.

Diabetes dramatically increases the risk of microvascular (terminal ends of blood vessels, arterioles, capillaries, and venules) and macrovascular (arteries) complications. Macrovascular/cardiovascular complications often lead to overt CHD, increasing the risk of myocardial infarction, atherosclerotic heart disease, stroke, and peripheral arterial disease. Other cardiovascular complications include heart failure, angina, and hypertension. Obesity and insulin resistance are both strong predictors of CHD risk. Additionally, insulin resistance in the presence of obesity increases the risk of CHD and T2DM.[9]

There is no definite evidence on the cause of these vascular complications. However, a relatively new theory explains that a special enzyme called *poly(ADP ribose) polymerase (PARP)* becomes dysregulated by hyperglycemia, and this enzyme primarily affects systemic inflammation and endothelial cells, including aortic endothelial cells, which are very sensitive to excess blood glucose.[10,11]

Atherosclerotic Dyslipidemia: T1DM and T2DM are independent risk factors for CHD.[12] There are four factors related to atherosclerotic dyslipidemia: elevated low-density lipoproteins (LDLs), very-low-density lipoproteins (VLDLs), decreased levels of high-density lipoproteins (HDLs), and elevated triglycerides. Patients with diabetic dyslipidemia are often insulin resistant and are prone to the development of CHD (atherosclerosis).[12] Of the three lipid factors, elevation of serum LDL cholesterol is considered a major risk factor for atherosclerosis. It seems, however, that the majority of patients with diabetes do not have distinct elevated serum LDL cholesterol, but evidently have high enough levels to support the development of atherosclerosis.[12,13]

LDL serum concentrations have been found to not be significantly different in patients with diabetes than in those without diabetes, except for an increase in the small, dense LDL particles in individuals with diabetes.[13]

Heart Failure: Over 30 years ago, the Framingham Study first identified that patients with diabetes are more prone to develop heart failure (HF) with preserved systolic function due to several factors or comorbidities, including atherosclerosis, long-term hypertension, obesity, sustained hyperglycemia, microvascular disease, and glycosylation of myocardial proteins.[14-17] Some individuals with diabetes and HF also have cardiac risk factors including hypercholesterolemia, obesity, and hypertension.[18] The longer the duration of diabetes, which is more difficult to treat and control than new-onset diabetes, the more likely the patient with diabetes will develop HF.[19] Additionally, mortality increases in

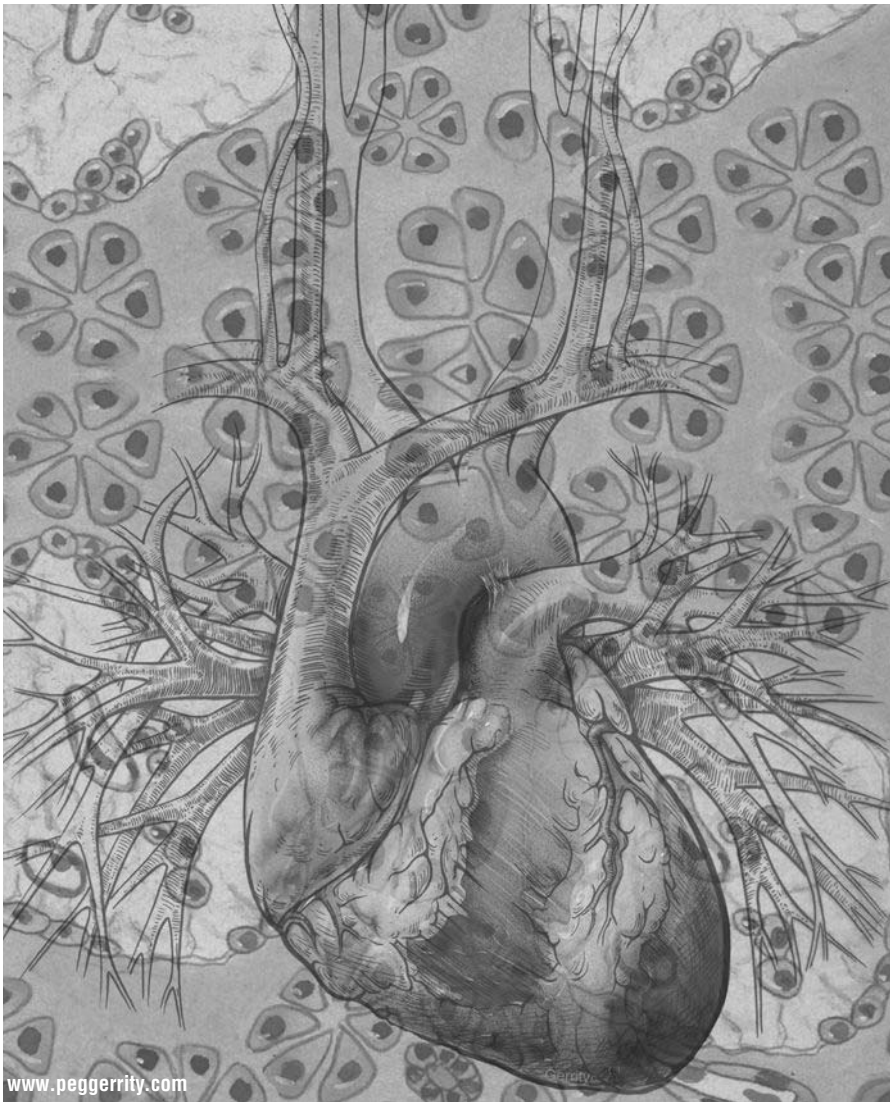

Illustration: © 2012 Peg Gerrity

A heart superimposed over a diseased pancreas, showing hyalinization of pancreatic islets of Langerhans. Patients with diabetes are prone to a host of cardiovascular diseases.

patients with diabetes who develop HF.[20]

Diabetic Cardiomyopathy: Diabetic cardiomyopathy is defined as ventricular dysfunction that occurs in diabetic patients for which a cause cannot be identified. For example, it is not due to CHD or hypertension. It is not commonly diagnosed.[20] However, patients with both diabetes and ischemic heart disease seem to have an increased risk for developing HF or diabetic cardiomyopathy.[12] Possible causes of cardiomyopathy include microangiopathy, myocardial fibrosis, and abnormal myocardial metabolism. Further, cardiomyopathy is more strongly connected with the microvascular rather than the macrovascular complications of diabetes.[15] The presence of a cardiomyopathy alone or associated with other factors may increase the risk of developing HF.[21]

Stroke: Death from stroke in a patient with diabetes is about three times more common than in those without diabetes.[22] About 13% of patients with diabetes who are older than 65 years have had a stroke.[23]

Hypertension: Diabetes and hypertension are often seen in the same patient. Hypertension, in addition to hyperglycemia, dyslipidemia, and smoking, contributes to the development and progression of macrovascular complications in patients with diabetes. Hypertension triples the risk of CAD and may account for up to 75% of all cardiovascular disease complications in patients with diabetes. Increase in systolic blood pressure rather than diastolic pressure is a better predictor for CVD and renal complications.[24] Additionally, hypertension significantly accelerates the progression of diabetic nephropathology, retinopathy, and neuropathy.

Metabolic Syndrome Related to Diabetes Mellitus: Components of the metabolic syndrome include a combination of insulin resistance (glucose intolerance with resultant hyperinsulinemia), central obesity (increase in waist circumference), abnormal lipid profile (increased triglyceride levels, increased LDL cholesterol, decreased HDL cholesterol), high blood pressure, and prothrombotic state.[25] Most individuals with metabolic syndrome will have either prehypertension (systolic 120-139 mmHg or diastolic 80-89 mmHg) or stage 1 hypertension (systolic 140-159 mmHg or diastolic 90-99 mmHg). The insulinemia factor, obesity, and hypertriglyceridemia may be strongly associated with increased development of diabetes.[26] The prothrombotic state is characterized by alterations in blood coagulation (hypercoagulation) or platelet abnormalities that may predispose the patient to intravascular clotting or arterial thrombosis.[27,28] An individual with metabolic syndrome has an increased risk of developing T2DM.[13,26] Abdominal obesity is an underlying cause for the development of atherosclerosis because of the relationship of obesity to hypercholesterolemia, hypertension, and

hyperglycemia.[29] Essentially, obesity and insulin resistance are associated with increased platelet activation or clotting, which can influence the development of thrombotic events in the patient with diabetes.[30]

Obesity leads to fatty cells (or adipocytes that are full), which cause the release of inflammatory cells, damage blood vessels, and contribute to hypertension, dyslipidemia, and insulin resistance—one of the primary clinical features of the syndrome.[12,31,32] The elevated insulin levels seen in insulin resistance can lead to the characteristic metabolic abnormalities seen in patients with T2DM, which further increase the risk of cardiovascular complications. Lipoprotein metabolism is regulated by genetic factors and diet. Metabolic syndrome is a prediabetic condition and is a risk factor for cardiovascular disease that increases with age.[33]

Microalbuminuria: Microalbuminuria is a condition that occurs when albumin, a protein in the blood plasma, passes into the urine. Patients with diabetes are prone to develop microalbuminuria, which is a sign for renal disease and also a risk factor for cardiovascular disease in individuals with and without diabetes.[13]

Insulin Resistance: Insulin resistance (impairment in insulin-mediated glucose disposal) and a defect in insulin secretion are the primary cause of the metabolic problems seen in patients with T2DM. Insulin resistance develops from obesity, decrease in physical activity, and a genetic susceptibility.[12,34] Insulin resistance will usually develop before the onset of diabetes and often is present in prediabetic states and in conjunction with other cardiovascular risk factors such as dyslipidemia, hypertension, and prothrombotic factors.[12,35,36]

Diagnostic Criteria and Evaluation of Glycemic Control

The 2011 American Diabetic Association (ADA) criteria for the diagnosis of diabetes are as follows: hemoglobin A1C ≥ 6.5% OR fasting plasma glucose (FPG) ≥126 mg/dL OR 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT) or a random plasma glucose ≥200 mg/dL. In patients with classic symptoms, hyperglycemia is diagnosed with a random plasma glucose ≥ 200 mg/dL.[37,38] Impaired glucose tolerance detected by OGTT is considered to be a metabolic risk factor for metabolic syndrome.[39] The ADA recommends that either two FPG levels or A1C is appropriate to identify prediabetes and diabetes. Blood glucose testing can be used to screen healthy, asymptomatic individuals as well as to diagnosis diabetes in individuals with symptoms of hyperglycemia such as polyuria, polydypsia, fatigue, blurred vision, and slow healing of infections.

The hemoglobin A1C test (HbA1c) is used to diagnose and monitor glycemic control over approximately 2 to 3 months in the patient with diabetes. According to the ADA, if a patient is 40 or 50 years old, the target A1C is <6%, but if the person is older or is experiencing hypoglycemia, the target A1C would be higher.[38] HbA1c levels show a relationship with the development of diabetic complications.[40]

Management of Cardiovascular Complications of Diabetes

National inpatient hospital costs for diabetes with complications were nearly $3.8 billion in 2001. The risk of hospitalization from cardiovascular disease is two to four times higher for women with diabetes compared to women without diabetes.[41]

It has been suggested that the earlier and more aggressive the treatment of a patient with new-onset T2DM with mild dyslipidemia and hypertension, the lower the risk of a future cardiovascular event compared to treating a patient with long-standing diabetes. This newer, aggressive pharmacologic management targets lipids, blood pressure, blood glucose, and platelets (**TABLE 2**). In addition to drug therapy, lifestyle modifications including weight loss with diet and exercise and smoking cessation are important.[42]

There are several approaches to medical treatment that can prevent cardiovascular complications. Management of cardiovascular complications in patients with diabetes involves both primary prevention (management intended to avoid the development of cardiovascular disease) and secondary prevention (strategies used to diagnosis and treat an existing cardiovascular condition). The control of CVD risk factors is crucial to reducing the risk of developing cardiovascular disease in individuals with DM. This management targets blood pressure and cholesterol control.[44] Primary prevention involves smoking cessation, which is a known risk factor of vascular disease. Modification of lifestyle habits is the mainstay treatment for prevention of CVD and DM; predisposing factors for both DM and CVD must be controlled. Exercise is an effective intervention in patients who are overweight and who are obese. Reducing body weight can improve cardiac risk factors in this population. Improvement in cardiovascular risk factors with regular exercise and dietary changes includes a decrease in blood pressure, cholesterol, triglycerides, and fasting serum glucose levels.[45] Aggressive cardiovascular risk-factor management and prevention of CVD, as well as glycemic control in patients with diabetes, are important in the overall treatment.

Managing Hyperglycemia: A meta-analysis reported an 18% increase in CVD risk for every 1% increase in

Table 2. Management of Cardiovascular Complications in T2DM

Cardiac Condition	Issues	Therapy
Heart failure	According to the 2011 ADA guidelines, there is not a preferred agent. However, beta-blockers may be preferred in patients with diabetes and HF.	BBs combined with ACEIs and ARBs. *ACEIs*: benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril *ARBs*: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Hypertension	The ADA guidelines recommend: • If BP is <130/90, then lifestyle modifications can be used for a maximum of 3 months. If goal is not achieved, add a drug. • If BP is 130-139/80-89, then one drug is used. • If BP is >140/90, then implement 2 drugs.	Combination drug therapy and weight reduction are key to successful management of hypertension in patients who are overweight with metabolic syndrome. Therapy with ACEIs and ARBs is an important part of controlling BP in patients with diabetes. ACEIs have a favorable effect on cardiovascular outcomes in patients with DM. In patients with T2DM, hypertension, and macroalbuminuria, an ARB is strongly recommended.
Dyslipidemia	The 2011 ADA guidelines for hyperlipidemia recommend: a goal of LDL cholesterol <100 mg/dL (<70 mg/dL is also an option when the patient has known CVD). However, elevated LDL is not a primary clinical feature of metabolic syndrome but still needs therapy if elevated. Recommendations for cholesterol-lowering therapy were beneficial for patients with DM even if there was no history of CHD or high cholesterol.	Use of statin drugs (HMG-CoA reductase inhibitors): atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin[a], simvastatin + ezetimibe, lovastatin + niacin, atorvastatin + amiodipine, simvastatin + niacin
Diabetic cardiomyopathy	Control of hypertension and prevention of atherosclerosis with cholesterol-lowering drugs	Use of antihypertensives and statin drugs
Metabolic syndrome[b]	Includes multiple metabolic abnormalities: hypertension, abdominal or central obesity, glucose intolerance (hyperinsulinemia), and abnormal lipid profile. See the individual conditions in the table.	Obesity promotes insulin resistance, so weight control through diet and exercise is important. See above treatments for hypertension and dyslipidemia.

[a] On June 8, 2011, the FDA recommended limiting the highest approved dose (80 mg) of simvastatin because of increased risk of muscle damage.
[b] Metabolic syndrome applies to patients prior to diagnosis of diabetes. If a patient is already diagnosed with diabetes, then metabolic syndrome does not apply since it is assumed the patient with T2DM had metabolic syndrome.
ACEI: angiotensin-converting enzyme inhibitor; ADA: American Diabetes Association; ARB: angiotensin II receptor blocker; BB: beta-blocker; BP: blood pressure; CHD: coronary heart disease; CVD: cardiovascular disease; DM: diabetes melitis; HF: heart failure; HMG CoA: hydroxymethyl glutaryl coenzyme A; LDL: low-density lipoprotein; T2DM: type 2 DM.
Source: References 12, 13, 15, 38, 43.

A1C.[46] Since glycemic control is primarily an intermediary of diabetic microvascular complications, it has been suggested for many years that is important to obtain glycemic control in patients with diabetes. It has been reported that with optimum glycemic control, better control of hypertension and atherosclerosis with cholesterol-lowering drugs can help prevent or stop the progression of diabetic-induced congestive heart failure (CHF).[15] However, the American Heart Association advised that even though hyperglycemia contributes to cardiovascular risk, more treatment is required in addition to controlling glucose in order to reverse or reduce the atherosclerotic process.[7,47,48]

Glycemic control becomes more important in preventing microvascular complications such as retinopathy, nephropathy, and neuropathy.[49] Low blood glucose levels activate the sympathetic nervous system, resulting in increased heart rate, blood pressure, and cardiac output.[50] In 2008, two important clinical trials concluded that intensive glucose lowering was effective in preventing the progression of microvascular complications such as nephropathy, but there was no apparent macrovascular (myocardial infarction and stoke) benefit.[42,51,52] However, according to the ADA, if tight glucose control is started early in the course of the disease, it will also lead to reductions in macrovascular complications.[38] It must be emphasized that although current literature has found that pursuit of very low glucose levels (A1C <6.0%) may not be as beneficial as once thought, failing to control hyperglycemia may considerably increase the possibility of acute metabolic events, chronic complications, and mortality.[53] The American Association of Clinical Endocrinologists (AACE) and the ADA recommend a glycemic target range of an A1C of <6.5% and <7.0%, respectively.[39,54] **TABLE 3** summarizes glucose testing and interpretations.

Managing Insulin Resistance: While there are no drugs that can directly treat the underlying insulin resistance in diabetes, insulin resistance can be reversed through diet (weight reduction) and exercise.

Managing Diabetes and Dyslipidemia: There has long been controversy over when to start lipid-lowering drug therapy. In 2002, the Heart Protection Study (HPS) advised that the use of cholesterol-lowering drugs was beneficial for patients with DM even without a previous history of CHD or high blood cholesterol levels. Good cholesterol levels can help prevent long-term cardiovascular complications of diabetes.[55] Moreover, the CARDS (Collaborative Atorvastatin Diabetes Study) reported that 10 mg of atorvastatin in patients with T2DM with normal lipid levels resulted in a 37% decrease in relative risk for cardiovascular events.[56] However, it has been suggested that the use of statins should not be the first choice for prevention of CHD in patients with diabetes.[12] In its 2001 guidelines, the ADA recommended a statin for any individual who has overt CVD or who is >40 years of age with additional risk factors.[38] The 2011 recommendations from the ADA for hyperlipidemia state a goal of LDL cholesterol <100 mg/dL (optional <70 mg/dL).[38] The Cholesterol Treatment Trialists' Collaborators found that in patients with T2DM there was a 21% reduction in major cardiovascular events for each reduction of 1 mmol/L in LDL cholesterol.[10,38,57]

The three ACCORD (Action to Control Cardiovascular Risk in Diabetes) studies showed significantly higher mortality and no reduction in the rates of cardiovascular outcomes in patients with T2DM who had intensive glycemic control (goal A1C <6%) versus conventional control. There were high A1C values observed despite intensive glycemic control. Additionally, there were no specific target levels for HDL or triglycerides; however, the results showed an increase in HDL cholesterol and a decrease in triglycerides with simvastatin, which was given to all subjects, versus fenofibrate or a placebo.[58] In 2009, the study was stopped because of safety concerns regarding the intensive blood glucose–lowering strategy. The study goal of A1C 6% is very difficult to reach for most patients who have had diabetes for several years, often requiring multiple medications.

Most clinical studies have shown that statin drugs improve insulin sensitivity.[58,59] Adding exercise to the statin drug regimen in patients with diabetes who are obese is safe for these individuals because they are prone to develop insulin resistance.[60] Recently, it has been reported that high-dose (80 mg) satins may increase the risk of new-onset diabetes, and it is recommended that clinicians monitor A1C when treating patients with high-dose statin therapy.[61] More trials are needed to confirm this.

Managing Diabetes and Heart Failure: In a patient with HF and DM, there is no drug preference for treating HF. Besides ACE inhibitors and angiotensin II receptor blockers (ARBs), beta-blockers (BBs) are also preferred since they have morbidity and mortality outcome data in HF.[38]

Managing Diabetes and Hypertension: The goal of hypertension treatment is to return arterial blood pressure to acceptable levels before irreversible damage occurs to the cardiovascular system, as well as other major organ systems. Recommendations from the ADA for appropriate target blood pressure for adults with diabetes is <130/80 mmHg.[38] Hypertension may be difficult to control, especially when associated with obesity, glucose intolerance, and hyperinsulinemia. Each of these factors is also associated with insulin resistance. Besides emphasizing weight reduction to reduce insulin resistance, appropriate drug therapy is sometimes necessary. Often, inappropriate use of diuretics in these patients cause volume overload, which is a common cause of resistant hypertension.[62]

The most recent Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends starting antihypertensive drugs in patients with diabetes the metabolic syndrome with hypertension.[38,63] Angiotensin-converting enzyme (ACE) inhibitors and ARBs are considered as first-line therapy in reducing CVD events in patients with diabetes and hypertension.[5] There is a clear benefit of renoprotection with ARBs in patients with nephropathy due to T2DM. ACE inhibitors have a more favorable effect on cardiovascular outcomes. Most patients with diabetes and hyperten-

Table 3. Fasting/Oral Glucose Tolerance Test Goals Set by the AACE and the ADA

Test	Values	Diagnosis
Fasting plasma glucose 8 to 12 h fasting (mg/dL)	≤99 100-125 ≥126	Normal Impaired fasting glucose Diabetes; confirm with a second test on a different day
Oral glucose tolerance test, 2 h after ingestion of 75-g glucose load (mg/dL)	≤139 140-199 ≥200	Normal Impaired fasting glucose Diabetes; confirm with a second test on a different day

AACE: American Association of Clinical Endocrinologists; ADA: American Diabetes Association. Source: References 38, 39.

sion require a combination of antihypertensive drugs including diuretics, ACE inhibitors, ARBs, BBs, and calcium channel blockers. For patients with diabetes, two drugs are needed if blood pressure exceeds 140/90 mmHg. ACE inhibitors and ARBs are integral drugs in management. If either one is not well tolerated, the other drugs should be used. Either drug can be combined with a low-dose thiazide to achieve blood pressure targets.[38,63,64]

The ADA recommends ACE inhibitors in patients with diabetes who are older than 55 years at high risk for CVD, and a cardioselective beta$_1$-blocker for patients with existing CHD.[38] However, a BB may be less effective in a patient with diabetes with ischemic heart disease and may be less effective in preventing strokes than an ARB.[65] If patients are prescribed a BB, this may mask hypoglycemic symptoms, except sweating.

Management of patients with hypertension and HF starts with ACE inhibitors (via the reduction in the synthesis of angiotensin II by antagonism of the angiotensin-converting enzyme and inhibition of kininase II, which results in the accumulation of bradykinin).[5] With careful monitoring, ACE inhibitors can be used in patients with advanced kidney impairment.[18]

Managing Diabetes and Hypercoagulation: Antiplatelet therapy has become a major part of treating the patient with diabetes to prevent myocardial infarction or stroke. Antiplatelet therapy in patients with T2DM has significantly reduced the cardiovascular risk. The ADA 2011 guidelines recommend low-dose aspirin therapy (75-162 mg/day) as primary prevention therapy in patients with T1DM or T2DM who are at an increased cardiovascular risk (10-year risk >10%).[38] This includes men over the age of 50 years and women over the age of 60 years who have at least one major risk factor (e.g., family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). The ADA does not recommend aspirin for CVD prevention for adults with diabetes at low CVD risk because of the increased risk of bleeding. This includes men younger than 50 years and women younger than 60 years of age with no major additional risk factors. The ADA advised clinicians to use clinical judgement in treatment.[38] Aspirin (75-162 mg/day) is recommended as secondary prevention treatment in patients with diabetes with a history of CVD. If the patient is allergic to aspirin can be clopidogrel (75 mg/day) can be an alternative.[38,66] Combination therapy with aspirin and clopidogrel is accepted for up to 1 year after an acute coronary syndrome.

Other Management Therapies: If medical therapy has not been successful in preventing cardiovascular complications in patients with diabetes, surgical procedures are available. Patients with CHD can have coronary artery bypass surgery. Patients who may be at risk of having a stroke can undergo a surgical procedure to put a graft inside the carotid artery to ensure adequate blood flow to the brain. Patients with peripheral artery disease can undergo a bypass procedure of the offending arteries in the lower extremities.

Oral Antidiabetic Drugs: Role in Cardiovascular Disease Prevention

Metformin should be used with caution in patients with HF because it has been documented to can cause HF shortly after the start of therapy by increasing fluid retention in the body.[67] Metformin can be used with caution in patients with stable HF, but it is contraindicated in patients with advanced systolic HF.[68] Conversely, a recent 2010 study at the University of Califorina at Los Angeles suggests that in patients with both advanced HF and diabetes, use of metformin is safe and may be associated with better HF survival.[69]

Conclusions

High glucose levels alone are not the only factor in increasing the risk of developing cardiovascular/coronary heart problems in patients with diabetes.[48] Obesity and insulin resistance are together strong risk indicators for CHD and diabetes.[12] The triad of diabetes, dyslipidemia, and hypertension increases the risk of CHD. Strongly recommended are lipid and glycemic control (goal of HbA1c <7) and blood pressure management.[5,10,15] Strict glycemic control is important in preventing macrovascular and microvascular complications when blood glucose and A1C are at goal and may present cardiovascular benefits when treating new-onset T2DM without cardiovascular disease.

References available online at www.uspharmacist.com.

EXAMINATION

Select one correct answer for each question and record your responses on the examination answer sheet. Mail it to U.S. Pharmacist, address shown on the answer sheet (photocopies are acceptable). Please allow four weeks for processing. Alternatively, this exam can be taken online at www.uspharmacist.com. Please contact CE Customer Service at (800) 825-4696 or cecustomerservice@jobson.com with any questions.

Managing Heart-Related Complications in Patients With Diabetes

1. How many people in the world have diabetes mellitus (DM)?
A. 50 million
B. 100 million
C. 150 million
D. 220 million

2. Insulin is secreted by the:
A. Beta cells
B. Hepatocytes
C. Adrenal medulla
D. Adrenal cortex

3. Type 1 DM (T1DM) is characterized by:
A. Decreased production of insulin
B. Decreased secretion of insulin
C. Absolute lack of insulin
D. Excessive production of insulin

4. When glucose reaches the blood it:
A. Is taken up by cells and used for energy
B. Is immediately excreted in the urine
C. Undergoes first-pass effect
D. Undergoes enterohepatic recirculation

5. Which of the following is a macrovascular complication of DM?
A. Retinopathy
B. Neuropathy
C. Periodontal disease
D. Cardiovascular event

6. Which of the following predisposing factors affect the development of both cardiovascular disease (CVD) and DM?
A. Abdominal obesity
B. Hypertension
C. High serum cholesterol
D. All of the above

7. The overall mortality from cardiovascular disease is:
A. Twice as great in men and four to five times higher in women with diabetes
B. Three times greater in men than in women
C. Five times greater in women than in men
D. Ten times greater in women than in men

8. Which of the following factors is related to the metabolic syndrome?
A. Hypertension
B. Glucose intolerance
C. Central obesity
D. All of the above

9. The prevalence of CVD is from 2% to 4% in the population of patients without diabetes to as much as ___ in adult patients with diabetes.
A. 2%
B. 10%
C. 30%
D. 55%

10. The prothrombotic state in patients with diabetes is characterized by:
A. Hypercoagulation
B. Inhibition of platelet aggregation
C. Decreased fibrin
D. Decreased thrombosis formation

11. Which of the following statements about preventing a major cardiovascular event in an individual with type 2 DM (T2DM) is true?
A. Glycemic control is most important.
B. Reduction in serum LDL cholesterol is recommended if the patient is <40 years of age without risk factors for coronary artery disease.
C. Reduction in blood pressure to ≤140/90 is the goal.
D. Antiplatelet therapy is recommended.

12. Which of the following statements about patients with diabetes and serum lipid profile is true?
A. The target goal for LDL is ≤300 mg/dL.
B. HDL monitoring has a positive effect on the development of cardiovascular events in the patient with diabetes.
C. Total cholesterol lowering is the most important aspect of preventing cardiovascular complications.
D. Most patients do not have marked elevations of LDL cholesterol but still require therapy.

13. Which of the following antihypertensive drugs is usually initially started in patients with diabetes and hypertension?
A. ACE inhibitor
B. Thiazide diuretic

C. Loop diuretic
D. Calcium channel blocker

14. Which of the following statements about glycemic control in diabetes is true?
A. Postprandial blood glucose and fasting blood glucose are important.
B. Fasting blood glucose is more important.
C. There is no difference between postprandial and fasting blood glucose.
D. Glycemic control is not important.

15. Insulin resistance is best treated by:
A. Weight reduction and diet
B. Smoking cessation
C. Thiazide diuretics
D. ACE inhibitors

16. Hemoglobin A1c is used to:
A. Screen for fasting blood glucose
B. Monitor blood glucose over 2 to 3 months
C. Determine 2-hour postprandial blood glucose
D. Detect urinary glucose

17. In 2001, national inpatient hospital costs for diabetes with complications were nearly:
A. $600 million
B. $9.5 million
C. $1.5 billion
D. $3.8 billion

18. Which of the following conditions are together strong risk indications for CHD and diabetes?
A. Obesity and insulin resistance
B. Kidney failure and obesity
C. Neuropathy and insulin resistance
D. Hyperglycemia and obesity

19. Primary prevention of diabetes with cardiovascular risk factors includes:
A. Lifestyle modification
B. Aspirin use
C. Insulin use
D. Antihypertensive medication

20. According to the American Heart Association, the recommended management of individuals with new-onset diabetes to prevent cardiovascular events is to control:
A. Hyperglycemia only
B. Dyslipidemia only
C. Hyperglycemia, hypertension, dyslipidemia
D. Hypertension, dyslipidemia, hypercoagulation, hyperglycemia

Examination Answer Sheet
Credits: 2.0 hours (0.20 ceu)
Expires: February 28, 2014

This exam can be taken online at www.uspharmacist.com. Upon passing, you can print out your statement immediately and view your test history. Alternatively, you can mail this answer sheet to the address below. Please contact CE Customer Service at (800) 825-4696 or cecustomerservice@jobson.com with any questions.

Managing Heart-Related Complications in Patients With Diabetes

Directions: Select one answer for each question in the exam and completely darken the appropriate circle. A minimum score of 70% is required to earn credit. An identifier is required to process your exam. This is used for internal processing purposes only.

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1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
16.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
17.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

1 = Excellent 2 = Very Good 3 = Good 4 = Fair 5 = Poor

Rate the effectiveness of how well the activity:

21. Met objective 1:	①	②	③	④	⑤
22. Met objective 2:	①	②	③	④	⑤
23. Met objective 3:	①	②	③	④	⑤
24. Met objective 4	①	②	③	④	⑤
25. Related to your educational needs:	①	②	③	④	⑤
26. The active learning strategies (questions, cases, discussions) were appropriate and effective learning tools:	①	②	③	④	⑤
27. Avoided commercial bias:	①	②	③	④	⑤
28. How would you rate the overall usefulness of the material presented?	①	②	③	④	⑤
29. How would you rate the quality of the faculty?	①	②	③	④	⑤
30. How would you rate the appropriateness of the examination for this activity?	①	②	③	④	⑤

31. Comments on this activity:

Please retain a copy for your records. Please print clearly.

You must choose and complete ONE of the following three identifier types:

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② Last 4 digits of your SS # and date of birth ____ - ______
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Last Name _____
E-Mail _____

The following is your: ☐ Home Address ☐ Business Address

Business Name _____
Address _____
City _____ State ____
ZIP _____
Telephone # ___ - ___ - ____
Fax # ___ - ___ - ____
NABP e-Profile ID _____ Date of Birth (mmdd) ____

Profession: ☐ Pharmacist ☐ Other

By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature _____ Date _____

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Lesson 108058 Type of Activity: Knowledge **0430-0000-12-001-H01-P**