Diabetes and the Cardiovascular, Renal, Metabolism cluster

Introduction

Worldwide, over 500 million adults, which is one in ten, are living with diabetes. This condition has important links with both heart and kidney disease, forming a disease cluster called "CVRM". Learn how these conditions are interconnected and how best to combat them for great overall health.[1]

Contents:

What is CVRM?

Each organ of the body performs a specific task, but also depends on the other organs to function well. When one part isn't working properly, it places stress on the others, negatively affecting your health as a whole.

An important example of this interconnection is how the heart, kidneys and pancreas affect one another, and the corresponding links between cardiovascular disease, chronic kidney disease and Type 2 diabetes.

These organ systems can be collectively termed "**CVRM: Cardiovascular, Renal, Metabolic**":
CV: Cardiovascular refers to the circulatory system - the heart and blood vessels.
R: Renal refers to the kidneys, which can develop chronic kidney disease (CKD). With CKD, the kidneys can't properly perform their function of removing waste and toxins from the blood.
M: Metabolic refers to the pancreas, which produces enzymes and hormones, notably insulin, that help break down food and control blood sugar levels. Type 2 diabetes is the most common associated condition.[2,3]

What is type 2 diabetes?

In Type 2 diabetes, blood sugar levels rise above normal. The food we consume breaks down into glucose, a simple sugar, which circulates in our bloodstream. The pancreas secretes the hormone insulin to help transform glucose into energy that the body's cells can utilise. However, in the case of Type 2 diabetes, the body either produces insufficient insulin or struggles to use its insulin effectively. This leads to difficulties in processing glucose, causing an unhealthy accumulation of sugar in the bloodstream.

Elevated blood sugar levels can harm both the major vessels serving the heart, brain and legs, as well as the smaller ones impacting the eyes, kidneys, nerves and feet.[4,5,6]

Causes and risk factors

Certain lifestyle factors raise your risk of developing type 2 diabetes, including unhealthy diet, obesity, sedentary lifestyle and smoking.

Diabetes also has a genetic component: if you have family members with diabetes, you have increased risk of also developing the condition.

Type 2 diabetes is associated with ageing - older people are more likely to have problems with their pancreas.[6]

Symptoms

Diagnosing diabetes based solely on symptoms can be challenging, as these might not be readily apparent, particularly in the initial stages of the condition. Later symptoms may include:

- Frequent urination
- Unintentional weight loss
- Fatigue
- Increased thirst
- Blurred vision
- Slow wound healing
- Numbness or tingling in hands and feet.[5]

Diagnosis

Should you exhibit symptoms of diabetes, your physician will assess your blood sugar levels through a blood test. However, it's advisable not to wait for symptoms to show up. Everyone aged 35 and above should undergo blood glucose testing, and those with risk factors for diabetes, such as obesity, should begin even earlier. It's far better to know if you have diabetes because the sooner you start treatment, the better the outcome.[7,8]

Treatment

A diabetes treatment plan usually includes medication, home blood sugar monitoring and healthy lifestyle changes.

Common medications include:

- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose co-transporter-2 inhibitors (SGLT2), which help the kidneys remove excess glucose via the urine.
- Metformin – reduces blood glucose, helps your own insulin work more effectively.
- Insulin – supplements your body's insulin to help lower blood sugar.
- Dipeptidyl peptidase-4 (DPP-4) inhibitors – control insulin and glucose levels by blocking specific enzymes.

You may experience incidents of low blood sugar (hypoglycaemia) after starting on diabetic medication, so it's important to carry a glucose-containing snack. Ask your doctor about recognising and managing hypoglycaemia. [5,8,9]

Links between diabetes and cardiovascular disease

Three common diseases of lifestyle - diabetes, cardiovascular disease and chronic kidney disease (CKD) - are interconnected. When you have dysfunction in one of these areas, it can put stress on the others and cause problems there also.

There is a strong link between high blood sugar and cardiovascular disease. If your blood sugar isn't well controlled and remains high, it can damage blood vessels and nerves in your heart.

When your heart isn't functioning at its best, it elevates your risk for ailments like heart attacks and strokes.

However, the close connection between type 2 diabetes and the heart means that if you undergo appropriate treatment and lifestyle changes that improve the health of one of these organ systems, you will likely also improve the health of the other.[2,10]

Links between diabetes and kidney disease

People with type 2 diabetes frequently experience kidney problems if their blood sugar level is poorly controlled. High blood sugar levels can significantly damage your kidneys, making them less efficient.

Type 2 diabetes can also contribute to high blood pressure, a major cause of CKD. Doctors often prescribe treatment to help control blood pressure alongside those to control blood sugar, to protect the kidneys.

Getting diabetes under control can have a positive impact on the kidneys, given the close connection between these organ systems.[2,10]

Take charge of your health

Being diagnosed with type 2 diabetes and needing to make lifestyle changes may feel daunting initially. Start with small, manageable changes and you'll soon adapt to a healthy routine. These actions help to lower the risk both for developing diabetes, and for further damage if you are already diagnosed:[7-13]

- **Schedule regular medical checkups** for ongoing treatment, monitoring and guidance on managing your diabetes, as well as related issues such as cardiovascular disease. Plaque can build up "silently" in your blood vessels for years, so it's recommended that cardiovascular risk factors are assessed at least annually.
- **Take medications** as prescribed, so they work effectively.
- **Stop smoking.** Smokers are 30%-40% more likely to develop type 2 diabetes than non-smokers. People with diabetes who smoke are more likely to have difficulty with insulin dosing and blood sugar management.
- **Get regular exercise.** Choose a physical activity you enjoy, and gradually increase to at least 150 minutes cardio per week. Activities like walking, housework and gardening count too. Take the stairs, weed the beds, dance in your living room – it all adds up. Blood sugar

monitoring before, during and after exercise sessions may be necessary, especially if you're on insulin - check with your doctor.

- **Follow a healthy diet** recommended by your doctor or nutritionist: high in fruit and vegetables, whole grains and lean protein; low in processed food, added sugar and salt. Also aim to maintain a healthy weight. Dietary tips:
  - Beware of hidden sugar in drinks and baked goods.
  - Retire the salt shaker – make food tasty with salt alternatives, herbs and spices.
  - Instead of animal fats like butter, use healthier vegetable oils (in moderation). Eat fish, seeds and nuts containing heart-healthy fats.
  - Swap refined white flour, rice and pasta for high-fibre whole grains.
- **Get support** from friends, family and the patient community, and ask your doctor to recommend a therapist if you're feeling overwhelmed or down - especially for longer than two weeks. Make contact with Diabetes South Africa https://www.diabetessa.org.za/ for a wealth of information and resources, including support groups near you or online.

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Source texts

Relevant sections highlighted

1.International Diabetes Federation, 2022 IDF Diabetes Atlas 2022. [online] Available at: www.diabetesatlas.org [Accessed 24 June 2024].

Key global findings 2021
The IDF Diabetes Atlas 10th edition reports a continued global increase in diabetes prevalence, confirming diabetes as a significant global challenge to the health and well-being of individuals, families and societies.

Download the IDF Diabetes Atlas 10th Edition and other resources.

View all the latest national and regional data in our data portal

Diabetes around the world in 2021:
537 million adults (20-79 years) are living with diabetes - 1 in 10. This number is predicted to rise to 643 million by 2030 and 783 million by 2045.
Over 3 in 4 adults with diabetes live in low- and middle-income countries.Diabetes is responsible for 6.7 million deaths in 2021 - 1 every 5 seconds.Diabetes caused at least USD 966 billion dollars in health expenditure – a 316% increase over the last 15 years.
541 million adults have Impaired Glucose Tolerance (IGT), which places them at high risk of type 2 diabetes.

2.Centers for Disease Control, 2024. Chronic Kidney Disease, Diabetes, and Heart Disease. [online] Available at: https://www.cdc.gov/kidneydisease/publications-resources/link-between-ckd-diabetes-heart-disease.html [Accessed 24 June 2024]

Chronic Kidney Disease, Diabetes, and Heart Disease
KEY POINTS
Chronic kidney disease (CKD), diabetes, and heart disease are connected.
Find out why and how you can prevent or manage all three.
About CKD, diabetes, and heart disease
The relationship between CKD, diabetes, and heart disease is one example of the ways our organs are connected. When one organ isn’t working properly, it can put stress on other organs, causing them to stop working properly as well.

Your body uses a hormone called insulin that moves sugars from the blood and into your body's cells for energy. If someone has diabetes, they either don't make enough insulin or can't use the insulin well.

If someone has CKD, their kidneys don't filter out toxins and waste from their blood as well as they should.

Heart disease refers to several types of heart conditions. The most common condition, coronary artery disease, leads to changes in blood flow to the heart. This can cause a heart attack.

Make the connection
So how are these three conditions connected? Risk factors for each condition are similar and include:

High blood sugar.
High blood pressure.
Family history.
Obesity.
Unhealthy diet.
Physical inactivity.
High blood sugar can slowly damage the kidneys. Over time, they may stop filtering blood as well as they should, leading to CKD. Approximately 1 in 3 U.S. adults with diabetes has CKD.

When the kidneys don't work well, it puts stress on the heart. When someone has CKD, their heart needs to pump harder to get blood to the kidneys. This can lead to heart disease, the leading cause of death in the United States. Change in blood pressure is also a CKD complication that can lead to heart disease.

Tips to prevent or manage all three
The good news is that you can manage or prevent CKD, diabetes, and heart disease all at once. These five tips can help you get started:

Get active
Being active can help prevent or manage CKD, diabetes, and heart disease. Find an activity you like, start small, and get moving!

Choose healthy foods and drinks
This is an important way to give your body the fuel it needs to function properly. Adding more fruits and veggies to your plate can also help you keep a healthy weight. This is a great way to prevent or manage CKD, diabetes and heart disease.

Quit smoking
Quitting is one of the best things you can do for your health. It'll help you prevent CKD, type 2 diabetes, and heart disease. It also helps to improve any of these conditions if you have them. You don't have to do it alone! For support, visit I'm Ready To Quit.

Find out your risk for prediabetes
Know where you stand by taking this 1-minute prediabetes risk test. If your risk is high, talk to your doctor about taking action to prevent or delay type 2 diabetes. The lifestyle change program through CDC's National Diabetes Prevention Program can help you build the healthy habits you need to succeed.

Get your annual flu shot
People with chronic diseases are more likely to have health complications if they catch the flu. These complications can worsen an existing condition and can even be fatal.

Protect your heart if you have CKD
Over time, CKD often gets worse and can lead to kidney failure. People with kidney failure will need regular dialysis (a treatment that filters the blood) or a kidney transplant to survive.

Heart disease is the most common cause of death for someone on dialysis. When your kidneys don't function properly, the heart has to work harder to circulate blood. This may lead to high blood pressure and possibly heart disease.

Tips to help protect your heart and kidneys:
Choose foods that are healthiest for your heart and your kidneys. Ask your doctor for a referral to a dietitian to understand which foods and drinks are best for you. Learn more about dialysis and a healthy diet.

Get regular physical activity to help lower your blood pressure and improve your heart health. And remember that moving more doesn't have to be strenuous. Some great ways to get active are gardening, yoga, or brisk walking around the block. Ask your doctor about which activities are best for you and if there are any you should avoid.

Manage your weight and blood sugar by changing your diet and activity routine. For extra help, you can work with a dietitian to create an eating plan that works for you and your kidneys.

3.American Heart Association, 2024. What is cardiovascular disease? [online] Available at: https://www.heart.org/en/health-topics/consumer-healthcare/what-is-cardiovascular-disease [Accessed 24 June 2024]

What is Cardiovascular Disease?
Cardiovascular disease can refer to a number of conditions:

Heart disease
Heart and blood vessel disease, also called heart disease, includes numerous problems, many of which are related to atherosclerosis.

Atherosclerosis is a condition that develops when a substance called plaque builds up in the walls of the arteries. This buildup narrows the arteries, making it harder for blood to flow through. If a blood clot forms, it can block the blood flow. This can cause a heart attack or stroke.

Heart attack

A heart attack occurs when the blood flow to a part of the heart is blocked by a blood clot. If this clot cuts off the blood flow completely, the part of the heart muscle supplied by that artery begins to die.

Most people survive their first heart attack and return to their normal lives, enjoying many more productive years. But having a heart attack does mean that you need to make some changes.

The medications and lifestyle changes that your health care professional recommends may vary according to how badly your heart was damaged, and to what degree of heart disease caused the heart attack.

Learn more about heart attack.

Stroke

An ischemic stroke, which is the most common type of stroke, occurs when a blood vessel that feeds the brain gets blocked, usually from a blood clot.

When the blood supply to a part of the brain is cut off, some brain cells will begin to die. This can result in the loss of functions controlled by that part of the brain, such as walking or talking.

A hemorrhagic stroke occurs when a blood vessel within the brain bursts. This is most often caused by uncontrolled high blood pressure.

Some effects of stroke are permanent if too many brain cells die after being starved of oxygen. These cells are never replaced.

The good news is that sometimes brain cells don't die during stroke — instead, the damage is temporary. Over time, as injured cells repair themselves, previously impaired function improves. In other cases, undamaged brain cells nearby may take over for the areas of the brain that were injured.

Either way, strength may return, speech may get better and memory may improve. This recovery process is what stroke rehabilitation is all about.

Learn more about stroke.

Heart failure

Heart failure, sometimes called congestive heart failure, means the heart isn't pumping blood as well as it should. Heart failure does not mean that the heart stops beating — that's a common misperception. Instead, the heart keeps working, but the body's need for blood and oxygen isn't being met.

Heart failure can get worse if left untreated. If your loved one has heart failure, it's very important to follow their health care professional's treatment plan.

Learn more about heart failure.

Arrhythmia

Arrhythmia refers to an abnormal heart rhythm. There are various types of arrhythmias. The heart can beat too slow, too fast or irregularly.

Bradycardia, or a heart rate that's too slow, is when the heart rate is less than 60 beats per minute. Tachycardia, or a heart rate that's too fast, refers to a heart rate of more than 100 beats per minute.

An arrhythmia can affect how well your heart works. With an irregular heartbeat, your heart may not be able to pump enough blood to meet your body's needs.

Learn more about arrhythmia.

Heart valve problems

When heart valves don't open enough to allow the blood to flow through as it should, a condition called stenosis results. When the heart valves don't close properly and thus allow blood to leak through, it's called regurgitation. If the valve leaflets bulge or prolapse back into the upper chamber, it's a condition called prolapse. Discover more about the roles your heart valves play in healthy circulation.

Learn more about heart valve disease.

Common treatments

Here are some common treatments for different types of cardiovascular disease:

Heart valve problems
Medications
Heart valve surgery
Arrhythmia
Medications
Pacemaker
Electric cardioversion
Catheter ablation
Lifestyle changes
Heart attack
Medications
Coronary angioplasty
Coronary artery bypass graft surgery
Heart transplant or other heart surgery
Radiofrequency ablation
Stent procedure
Transmyocardial revascularization
Lifestyle changes

Stroke
Medications
Carotid endarterectomy (PDF)(link opens in new window)
Thrombectomy
Aneurysm clipping
Coil embolization
Blood transfusion
Lifestyle changes
Diagnostic tests, surgical procedures and medications
In the hospital and during the first few weeks at home, your health care professional may perform several tests and procedures. These tests help them determine what caused the stroke or heart attack, and how much damage was done. Some tests monitor your progress to see if the treatment is working.

Learn more about diagnostic tests and procedures.

Learn more about surgical procedures that may have been performed at the hospital.

Cardiac medications
The medications prescribed after a cardiovascular event can aid in recovery and help prevent another heart attack or stroke.

If you're a caregiver, make sure your loved one takes their medications as directed and on time. Learn about the medications that your loved takes. Know what those medicines do, and what their goal is.

It's important to follow your health care professional's directions closely, so ask questions and take notes.

It's important to follow your doctor's directions closely, so ask questions and take notes. Learn more about cardiac medications.

Written by American Heart Association editorial staff and reviewed by science and medicine advisors.
See our editorial policies and staff.

Last Reviewed: Jan 10, 2024

4.The Heart and Stroke Foundation of South Africa, 2023. Diabetes. [online] Available at: https://www.heartfoundation.co.za/diabetes/ [Accessed 24 June 2024].

DIABETES
What is diabetes?
Diabetes is a condition that occurs when the levels of glucose (sugar) in the body are too high, either because the body doesn't produce enough insulin or the body doesn't use the insulin it produces, effectively Insulin is a hormone necessary to carry glucose from the bloodstream into the cells where it is used for energy. If there is too little insulin or resistance to insulin, blood glucose levels continue to rise,

because glucose is not removed from the bloodstream. There are 3 main types of Diabetes:
Type 1 (insulin-dependent), usually affects younger people
Type 2 (also known as maturity-onset or non-insulin-dependent diabetes), tends to develop gradually in adults and is much more common
Gestational Diabetes, is high glucose levels only during pregnancy. This type of diabetes can be resolved after giving birth, but can also increase the risks of Type 2 diabetes developing later in life
You are more likely to develop diabetes if you have one or more of the following risk factors:
Overweight or obese
Physical inactivity
Unhealthy diet
Family history of diabetes
Previous diabetes in pregnancy (gestational diabetes)
It has been estimated that there are about 1 in 10 South Africans with diabetes, but roughly 1 in 2 of these individuals don't know it because it has not been diagnosed!
How does diabetes affect your heart?
Heart disease and strokes are the leading cause of death in people living with diabetes. The constant high blood sugar causes damage and narrowing of the blood vessels, increased blood triglycerides (a type of fat), decreased levels of "good" HDL cholesterol, high blood pressure and increased risk of a heart attack or stroke. People living with diabetes are also more prone to the development of atherosclerosis and blood clots. Diabetes also accelerates the damage done by smoking, high blood pressure and high cholesterol. Diabetes can even affect the heart muscle itself, making it a less efficient pump. As diabetes can affect the nerves to the heart, symptoms of angina may not be felt in the usual way and may be passed off as indigestion or an upset stomach. This leads to delays and difficulties in diagnosing angina and heart attacks. As you can see, diabetes increases the risk of stroke and heart disease, especially if other risk factors are already present. The risks multiply! The good news is that there are many things that you can do to control your diabetes, reduce your risks and stay healthy.
HOW IS IT DIAGNOSED?
DIETARY ADVICE FOR MANAGING DIABETES
TIPS TO LOWER RISK OF HEART DISEASE & STROKE
SYMPTOMS & COMPLICATIONS OF DIABETES
Symptoms are a result of having too much glucose (sugar) in the blood and not enough in the cells of the body. Symptoms vary from individual to individual and elderly people may not present any symptoms. Some of the symptoms may include:

Constant thirst
Passing more urine than normal
Tiredness
Unexplained weight loss
Blurred vision
Regular episodes of thrush
In uncontrolled diabetes, high levels of glucose over many years can damage many different parts of the body:

Aggravates atherosclerosis in the heart and blood vessels (hardening and narrowing of blood vessels by fatty deposits), causing coronary artery disease, stroke and blood circulation problems.
Eye damage, causing reduced vision which may lead to blindness
Kidney disease and kidney failure
Ulcers, infections, or gangrene in the feet

Nerve damage causing loss of sensation, especially in the feet and legs; pins and needles; and impotence

5.National Institute of Diabetes and Digestive and Kidney Diseases, 2017. Type 2 Diabetes. [online] Available at: https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/type-2-diabetes [Accessed 24 June 2024]

Type 2 Diabetes

What is type 2 diabetes?
Type 2 diabetes, the most common type of diabetes, is a disease that occurs when your blood glucose, also called blood sugar, is too high. Blood glucose is your main source of energy and comes mainly from the food you eat. Insulin, a hormone made by the pancreas, helps glucose get into your cells to be used for energy. In type 2 diabetes, your body doesn't make enough insulin or doesn't use insulin well. Too much glucose then stays in your blood, and not enough reaches your cells.

The good news is that you can take steps to prevent or delay the development of type 2 diabetes.

Who is more likely to develop type 2 diabetes?
You can develop type 2 diabetes at any age, even during childhood. However, type 2 diabetes occurs most often in middle-aged and older people. You are more likely to develop type 2 diabetes if you are age 45 or older, have a family history of diabetes, or are overweight or have obesity. Diabetes is more common in people who are African American, Hispanic/Latino, American Indian, Asian American, or Pacific Islander.

Physical inactivity and certain health problems such as high blood pressure affect your chances of developing type 2 diabetes. You are also more likely to develop type 2 diabetes if you have prediabetes or had gestational diabetes when you were pregnant. Learn more about risk factors for type 2 diabetes.

Type 2 diabetes occurs most often in middle-aged and older people.
What are the symptoms of diabetes?
Symptoms of diabetes include

increased thirst and urination
increased hunger
feeling tired
blurred vision
numbness or tingling in the feet or hands
sores that do not heal
unexplained weight loss
Symptoms of type 2 diabetes often develop slowly—over the course of several years—and can be so mild that you might not even notice them. Many people have no symptoms. Some people do not find out they have the disease until they have diabetes-related health problems, such as blurred vision or heart disease.

What causes type 2 diabetes?

Type 2 diabetes is caused by several factors, including

overweight and obesity
not being physically active
insulin resistance
genes
Learn more about the causes of type 2 diabetes.

How do health care professionals diagnose type 2 diabetes?
Your health care professional can diagnose type 2 diabetes based on blood tests. Learn more about blood tests for diabetes and what the results mean.

How can I manage my type 2 diabetes?
Managing your blood glucose, blood pressure, and cholesterol, and quitting smoking if you smoke, are important ways to manage your type 2 diabetes. Lifestyle changes that include planning healthy meals, limiting calories if you are overweight, and being physically active are also part of managing your diabetes. So is taking any prescribed medicines. Work with your health care team to create a diabetes care plan that works for you.

Following your meal plan helps you manage your diabetes.
What medicines do I need to treat my type 2 diabetes?
Along with following your diabetes care plan, you may need diabetes medicines, which may include pills or medicines you inject under your skin, such as insulin. Over time, you may need more than one diabetes medicine to manage your blood glucose. Even if you don't take insulin, you may need it at special times, such as during pregnancy or if you are in the hospital. You also may need medicines for high blood pressure, high cholesterol, or other conditions.

What health problems can people with diabetes develop?
Following a good diabetes care plan can help protect against many diabetes-related health problems. However, if not managed, diabetes can lead to problems such as

heart disease and stroke
nerve damage
kidney disease
foot problems
eye disease
gum disease and other dental problems
sexual and bladder problems
Many people with type 2 diabetes also have nonalcoholic fatty liver disease (NAFLD). Losing weight if you are overweight or have obesity can improve NAFLD. Diabetes is also linked to other health problems such as sleep apnea, depression, some types of cancer, and dementia NIH external link.

You can take steps to lower your chances of developing these diabetes-related health problems.

How can I lower my chances of developing type 2 diabetes?
Research such as the Diabetes Prevention Program External link, sponsored by the National Institutes of Health, has shown that you can take steps to reduce your chances of developing type 2 diabetes if you have risk factors for the disease. Here are some things you can do to lower your risk:

Lose weight if you are overweight, and keep it off. You may be able to prevent or delay diabetes by losing 5 to 7 percent of your current weight.1 For instance, if you weigh 200 pounds, your goal would be to lose about 10 to 14 pounds.

Diabetes Risk Management Calculator
Losing 5% to 7% of your body weight may reduce your risk of diabetes.†

Move more. Get at least 30 minutes of physical activity, such as walking, at least 5 days a week. If you have not been active, talk with your health care professional about which activities are best. Start slowly and build up to your goal.
Eat healthy foods. Eat smaller portions to reduce the amount of calories you eat each day and help you lose weight. Choosing foods with less fat is another way to reduce calories. Drink water instead of sweetened beverages.
Ask your health care team what other changes you can make to prevent or delay type 2 diabetes.

Most often, your best chance for preventing type 2 diabetes is to make lifestyle changes that work for you long term. Get started with Your Game Plan to Prevent Type 2 Diabetes.

References
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Last Reviewed May 2017

6a. Organ Talks, 2022. Essential diabetes information. [online] Available at: https://www.organs-talk.com/t2d [Accessed 24 June 2024]

What is type 2 diabetes?
Amongst other components, the food we eat is broken down by the body to create glucose, a type of sugar in the blood that gives us energy. Insulin is a hormone produced by your pancreas, that helps the body to utilize this sugar to turn it into fuel for the body.1,2

When you have type 2 diabetes, your body either doesn't make enough insulin, or it doesn't use its own insulin as well as it should, which makes it harder for your body to utilize glucose. As a result, the sugar level stays high in your blood which can have harmful effects on the body.3

Type 2 diabetes is a common condition, and it can cause damage to the large blood vessels of the heart, brain, and legs, as well as to smaller blood vessels, causing problems in the eyes, kidneys, feet, and nerves.3

what-is-type-2-diabetes
did-you-know1
Did you know:
Diabetes affects 463 million people worldwide.3

What causes type 2 diabetes?
There are many factors that can put you at risk of developing type 2 diabetes, these include:3,4

Food
An unhealthy diet
Not getting enough exercise
An inactive lifestyle
Being overweight or obese
Obesity
Family
Family history
Watch
Aging
Type 2 diabetes is often associated with being overweight or inactive, and although these factors increase the likelihood of developing the disease, they aren't the only cause. Aging and a family history of diabetes could mean that you have a higher-than-average chance of having problems with your pancreas.3,4

What are some of the signs and symptoms of type 2 diabetes?
Signs and symptoms of type 2 diabetes aren't always obvious and can sometimes be subtle enough to go unnoticed, so it's important you are aware of what to look out for.

Signs and symptoms can include:5
Urinating more often, especially at night

Unexpected weight loss

Increased thirst

Feeling more tired than usual

Vision problems

Wounds taking longer to heal

Signs and symptoms
If you or your loved one is experiencing any of these symptoms, talk to your doctor right away.
How is type 2 diabetes diagnosed?
It's important that you visit your doctor if you're experiencing any symptoms of type 2 diabetes. The earlier you get diagnosed, the earlier you can begin to take control of your health, which will decrease your chances of the disease affecting other organs, such as your heart and kidneys.

Testing for type 2 diabetes is a relatively straightforward process that usually involves:6

Talking to your doctor about your symptoms
a-blood-test-to-check-your-blood-sugar-level
A blood test to check your blood sugar level
If the results of these tests indicate that you have type 2 diabetes, then your doctor will discuss a plan of

action with you.

7. Cleveland Clinic, 2021. Diabetes; an overview. [online] Available at: https://my.clevelandclinic.org/health/diseases/7104-diabetes-mellitus-an-overview [Accessed 24 June 2024]

Diabetes
Diabetes is a common condition that affects people of all ages. There are several forms of diabetes. Type 2 is the most common. A combination of treatment strategies can help you manage the condition to live a healthy life and prevent complications.

What is diabetes?
Diabetes is a condition that happens when your blood sugar (glucose) is too high. It develops when your pancreas doesn't make enough insulin or any at all, or when your body isn't responding to the effects of insulin properly. Diabetes affects people of all ages. Most forms of diabetes are chronic (lifelong), and all forms are manageable with medications and/or lifestyle changes.

Glucose (sugar) mainly comes from carbohydrates in your food and drinks. It's your body's go-to source of energy. Your blood carries glucose to all your body's cells to use for energy.

When glucose is in your bloodstream, it needs help — a "key" — to reach its final destination. This key is insulin (a hormone). If your pancreas isn't making enough insulin or your body isn't using it properly, glucose builds up in your bloodstream, causing high blood sugar (hyperglycemia).

Over time, having consistently high blood glucose can cause health problems, such as heart disease, nerve damage and eye issues.

The technical name for diabetes is diabetes mellitus. Another condition shares the term "diabetes" — diabetes insipidus — but they're distinct. They share the name "diabetes" because they both cause increased thirst and frequent urination. Diabetes insipidus is much rarer than diabetes mellitus.

What are the types of diabetes?
There are several types of diabetes. The most common forms include:

Type 2 diabetes: With this type, your body doesn't make enough insulin and/or your body's cells don't respond normally to the insulin (insulin resistance). This is the most common type of diabetes. It mainly affects adults, but children can have it as well.
Prediabetes: This type is the stage before Type 2 diabetes. Your blood glucose levels are higher than normal but not high enough to be officially diagnosed with Type 2 diabetes.
Type 1 diabetes: This type is an autoimmune disease in which your immune system attacks and destroys insulin-producing cells in your pancreas for unknown reasons. Up to 10% of people who have diabetes have Type 1. It's usually diagnosed in children and young adults, but it can develop at any age.
Gestational diabetes: This type develops in some people during pregnancy. Gestational diabetes usually goes away after pregnancy. However, if you have gestational diabetes, you're at a higher risk of developing Type 2 diabetes later in life.
Other types of diabetes include:

Type 3c diabetes: This form of diabetes happens when your pancreas experiences damage (other than autoimmune damage), which affects its ability to produce insulin. Pancreatitis, pancreatic cancer, cystic fibrosis and hemochromatosis can all lead to pancreas damage that causes diabetes. Having your pancreas removed (pancreatectomy) also results in Type 3c.
Latent autoimmune diabetes in adults (LADA): Like Type 1 diabetes, LADA also results from an autoimmune reaction, but it develops much more slowly than Type 1. People diagnosed with LADA are usually over the age of 30.
Maturity-onset diabetes of the young (MODY): MODY, also called monogenic diabetes, happens due to an inherited genetic mutation that affects how your body makes and uses insulin. There are currently over 10 different types of MODY. It affects up to 5% of people with diabetes and commonly runs in families.
Neonatal diabetes: This is a rare form of diabetes that occurs within the first six months of life. It's also a form of monogenic diabetes. About 50% of babies with neonatal diabetes have the lifelong form called permanent neonatal diabetes mellitus. For the other half, the condition disappears within a few months from onset, but it can come back later in life. This is called transient neonatal diabetes mellitus.
Brittle diabetes: Brittle diabetes is a form of Type 1 diabetes that's marked by frequent and severe episodes of high and low blood sugar levels. This instability often leads to hospitalization. In rare cases, a pancreas transplant may be necessary to permanently treat brittle diabetes.
How common is diabetes?
Diabetes is common. Approximately 37.3 million people in the United States have diabetes, which is about 11% of the population. Type 2 diabetes is the most common form, representing 90% to 95% of all diabetes cases.

About 537 million adults across the world have diabetes. Experts predict this number will rise to 643 million by 2030 and 783 million by 2045.

Symptoms and Causes
Symptoms of diabetes include increased thirst, frequent urination and slow-healing cuts and sores. The severity of symptoms can vary based on the type of diabetes you have. These symptoms are usually more intense in Type 1 diabetes than Type 2 diabetes.
What are the symptoms of diabetes?
Symptoms of diabetes include:

Increased thirst (polydipsia) and dry mouth.
Frequent urination.
Fatigue.
Blurred vision.
Unexplained weight loss.
Numbness or tingling in your hands or feet.
Slow-healing sores or cuts.
Frequent skin and/or vaginal yeast infections.
It's important to talk to your healthcare provider if you or your child has these symptoms.

Additional details about symptoms per type of diabetes include:

Type 1 diabetes: Symptoms of T1D can develop quickly — over a few weeks or months. You may develop additional symptoms that are signs of a severe complication called diabetes-related ketoacidosis (DKA). DKA is life-threatening and requires immediate medical treatment. DKA symptoms include vomiting,

stomach pains, fruity-smelling breath and labored breathing.
Type 2 diabetes and prediabetes: You may not have any symptoms at all, or you may not notice them since they develop slowly. Routine bloodwork may show a high blood sugar level before you recognize symptoms. Another possible sign of prediabetes is darkened skin on certain parts of your body (acanthosis nigricans).
Gestational diabetes: You typically won't notice symptoms of gestational diabetes. Your healthcare provider will test you for gestational diabetes between 24 and 28 weeks of pregnancy.
What causes diabetes?
Too much glucose circulating in your bloodstream causes diabetes, regardless of the type. However, the reason why your blood glucose levels are high differs depending on the type of diabetes.

Causes of diabetes include:

Insulin resistance: Type 2 diabetes mainly results from insulin resistance. Insulin resistance happens when cells in your muscles, fat and liver don't respond as they should to insulin. Several factors and conditions contribute to varying degrees of insulin resistance, including obesity, lack of physical activity, diet, hormonal imbalances, genetics and certain medications.
Autoimmune disease: Type 1 diabetes and LADA happen when your immune system attacks the insulin-producing cells in your pancreas.
Hormonal imbalances: During pregnancy, the placenta releases hormones that cause insulin resistance. You may develop gestational diabetes if your pancreas can't produce enough insulin to overcome the insulin resistance. Other hormone-related conditions like acromegaly and Cushing syndrome can also cause Type 2 diabetes.
Pancreatic damage: Physical damage to your pancreas — from a condition, surgery or injury — can impact its ability to make insulin, resulting in Type 3c diabetes.
Genetic mutations: Certain genetic mutations can cause MODY and neonatal diabetes.
Long-term use of certain medications can also lead to Type 2 diabetes, including HIV/AIDS medications and corticosteroids.

What are the complications of diabetes?
Diabetes can lead to acute (sudden and severe) and long-term complications — mainly due to extreme or prolonged high blood sugar levels.

Acute diabetes complications
Acute diabetes complications that can be life-threatening include:

Hyperosmolar hyperglycemic state (HHS): This complication mainly affects people with Type 2 diabetes. It happens when your blood sugar levels are very high (over 600 milligrams per deciliter or mg/dL) for a long period, leading to severe dehydration and confusion. It requires immediate medical treatment.
Diabetes-related ketoacidosis (DKA): This complication mainly affects people with Type 1 diabetes or undiagnosed T1D. It happens when your body doesn't have enough insulin. If your body doesn't have insulin, it can't use glucose for energy, so it breaks down fat instead. This process eventually releases substances called ketones, which turn your blood acidic. This causes labored breathing, vomiting and loss of consciousness. DKA requires immediate medical treatment.
Severe low blood sugar (hypoglycemia): Hypoglycemia happens when your blood sugar level drops below the range that's healthy for you. Severe hypoglycemia is very low blood sugar. It mainly affects people with diabetes who use insulin. Signs include blurred or double vision, clumsiness, disorientation and seizures. It requires treatment with emergency glucagon and/or medical intervention.

Long-term diabetes complications
Blood glucose levels that remain high for too long can damage your body's tissues and organs. This is mainly due to damage to your blood vessels and nerves, which support your body's tissues.

Cardiovascular (heart and blood vessel) issues are the most common type of long-term diabetes complication. They include:

Coronary artery disease.
Heart attack.
Stroke.
Atherosclerosis.
Other diabetes complications include:

Nerve damage (neuropathy), which can cause numbness, tingling and/or pain.
Nephropathy, which can lead to kidney failure or the need for dialysis or transplant.
Retinopathy, which can lead to blindness.
Diabetes-related foot conditions.
Skin infections.
Amputations.
Sexual dysfunction due to nerve and blood vessel damage, such as erectile dysfunction or vaginal dryness.
Gastroparesis.
Hearing loss.
Oral health issues, such as gum (periodontal) disease.
Living with diabetes can also affect your mental health. People with diabetes are two to three times more likely to have depression than people without diabetes.

Diagnosis and Tests
Diagnosing Diabetes
How is diabetes diagnosed?
Healthcare providers diagnose diabetes by checking your glucose level in a blood test. Three tests can measure your blood glucose level:

Fasting blood glucose test: For this test, you don't eat or drink anything except water (fast) for at least eight hours before the test. As food can greatly affect blood sugar, this test allows your provider to see your baseline blood sugar.
Random blood glucose test: "Random" means that you can get this test at any time, regardless of if you've fasted.
A1c: This test, also called HbA1C or glycated hemoglobin test, provides your average blood glucose level over the past two to three months.
To screen for and diagnose gestational diabetes, providers order an oral glucose tolerance test.

The following test results typically indicate if you don't have diabetes, have prediabetes or have diabetes. These values may vary slightly. In addition, healthcare providers rely on more than one test to diagnose diabetes.

Type of test	In-range (mg/dL)	Prediabetes (mg/dL)	Diabetes (mg/L)
Fasting blood glucose test	Less than 100.	100 to 125.	126 or higher.

Random blood glucose test N/A. N/A. 200 or higher (with classic symptoms of hyperglycemia or hyperglycemic crisis).
A1c Less than 5.7%. 5.7% to 6.4%. 6.5% or higher.

Management and Treatment

Managing Diabetes

How is diabetes managed?

Diabetes is a complex condition, so its management involves several strategies. In addition, diabetes affects everyone differently, so management plans are highly individualized.

The four main aspects of managing diabetes include:

Blood sugar monitoring: Monitoring your blood sugar (glucose) is key to determining how well your current treatment plan is working. It gives you information on how to manage your diabetes on a daily — and sometimes even hourly — basis. You can monitor your levels with frequent checks with a glucose meter and finger stick and/or with a continuous glucose monitor (CGM). You and your healthcare provider will determine the best blood sugar range for you.
Oral diabetes medications: Oral diabetes medications (taken by mouth) help manage blood sugar levels in people who have diabetes but still produce some insulin — mainly people with Type 2 diabetes and prediabetes. People with gestational diabetes may also need oral medication. There are several different types. Metformin is the most common.
Insulin: People with Type 1 diabetes need to inject synthetic insulin to live and manage diabetes. Some people with Type 2 diabetes also require insulin. There are several different types of synthetic insulin. They each start to work at different speeds and last in your body for different lengths of time. The four main ways you can take insulin include injectable insulin with a syringe (shot), insulin pens, insulin pumps and rapid-acting inhaled insulin.
Diet: Meal planning and choosing a healthy diet for you are key aspects of diabetes management, as food greatly impacts blood sugar. If you take insulin, counting carbs in the food and drinks you consume is a large part of management. The amount of carbs you eat determines how much insulin you need at meals. Healthy eating habits can also help you manage your weight and reduce your heart disease risk.
Exercise: Physical activity increases insulin sensitivity (and helps reduce insulin resistance), so regular exercise is an important part of management for all people with diabetes.
Due to the increased risk for heart disease, it's also important to maintain a healthy:

Weight.
Blood pressure.
Cholesterol.

Prevention

How can I prevent diabetes?

You can't prevent autoimmune and genetic forms of diabetes. But there are some steps you can take to lower your risk for developing prediabetes, Type 2 diabetes and gestational diabetes, including:

Eat a healthy diet, such as the Mediterranean diet.
Get physically active. Aim for 30 minutes a day at least five days a week.
Work to achieve a weight that's healthy for you.
Manage your stress.
Limit alcohol intake.
Get adequate sleep (typically 7 to 9 hours) and seek treatment for sleep disorders.
Quit smoking.

Take medications as directed by your healthcare provider to manage existing risk factors for heart disease.
It's important to note that there are some diabetes risk factors you can't change, such as your genetics/family history, age and race. Know that Type 2 diabetes is a complex condition that involves many contributing factors.

Outlook / Prognosis
What is the prognosis for diabetes?
The prognosis (outlook) for diabetes varies greatly depending on several factors, including:

The type of diabetes.
How well you manage the condition over time and your access to diabetes care.
Your age at diagnosis/how long you've had diabetes.
If you have other health conditions.
If you develop diabetes complications.
Chronic high blood sugar can cause severe complications, which are usually irreversible. Several studies have shown that untreated chronic high blood sugar shortens your lifespan and worsens your quality of life.

In the United States, diabetes is the eighth leading cause of death. A large number of people with diabetes will die from a heart attack or stroke.

However, it's important to know that you can live a healthy life with diabetes. The following are key to a better prognosis:

Lifestyle changes.
Regular exercise.
Dietary changes.
Regular blood sugar monitoring.
Studies show that people with diabetes may be able to reduce their risk of complications by consistently keeping their A1c levels below 7%.

Living With
When should I see my healthcare provider?
If you haven't been diagnosed with diabetes, you should see a healthcare provider if you have any symptoms of diabetes, such as increased thirst and frequent urination.

If you have diabetes, you should see your provider who helps you manage diabetes (such as an endocrinologist) regularly.

A note from Cleveland Clinic

Being diagnosed with diabetes is a life-changing event, but it doesn't mean you can't live a happy and healthy life. Managing diabetes involves consistent care and diligence. While it'll likely be very overwhelming at first, over time you'll get a better grasp on managing the condition and being in tune with your body.

Be sure to see your healthcare provider(s) regularly. Managing diabetes involves a team effort — you'll

want medical professionals, friends and family on your side. Don’t be afraid to reach out to them if you need help.

8. Mayo Clinic, n.d. Diabetes diagnosis and treatment. [online] Available at: https://www.mayoclinic.org/diseases-conditions/diabetes/diagnosis-treatment/drc-20371451#:~:text [Accessed 24 June 2024]

Type 1 diabetes symptoms often start suddenly and are often the reason for checking blood sugar levels. Because symptoms of other types of diabetes and prediabetes come on more gradually or may not be easy to see, the American Diabetes Association (ADA) has developed screening guidelines. The ADA recommends that the following people be screened for diabetes:

- Anyone with a body mass index higher than 25 (23 for Asian Americans), regardless of age, who has additional risk factors. These factors include high blood pressure, non-typical cholesterol levels, an inactive lifestyle, a history of polycystic ovary syndrome or heart disease, and having a close relative with diabetes.
- Anyone older than age 35 is advised to get an initial blood sugar screening. If the results are normal, they should be screened every three years after that.
- Women who have had gestational diabetes are advised to be screened for diabetes every three years.
- Anyone who has been diagnosed with prediabetes is advised to be tested every year.
- Anyone who has HIV is advised to be tested.

Tests for type 1 and type 2 diabetes and prediabetes

- A1C test. This blood test, which doesn't require not eating for a period of time (fasting), shows your average blood sugar level for the past 2 to 3 months. It measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells. It's also called a glycated hemoglobin test.
  The higher your blood sugar levels, the more hemoglobin you'll have with sugar attached. An A1C level of 6.5% or higher on two separate tests means that you have diabetes. An A1C between 5.7% and 6.4% means that you have prediabetes. Below 5.7% is considered normal.
- Random blood sugar test. A blood sample will be taken at a random time. No matter when you last ate, a blood sugar level of 200 milligrams per deciliter (mg/dL) — 11.1 millimoles per liter (mmol/L) — or higher suggests diabetes.
- Fasting blood sugar test. A blood sample will be taken after you haven't eaten anything the night before (fast). A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, you have diabetes.
- Glucose tolerance test. For this test, you fast overnight. Then, the fasting blood sugar level is measured. Then you drink a sugary liquid, and blood sugar levels are tested regularly for the next two hours.
  A blood sugar level less than 140 mg/dL (7.8 mmol/L) is normal. A reading of more than 200 mg/dL (11.1 mmol/L) after two hours means you have diabetes. A reading between 140 and 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) means you have prediabetes.

If your provider thinks you may have type 1 diabetes, they may test your urine to look for the presence of ketones. Ketones are a byproduct produced when muscle and fat are used for energy. Your provider will also probably run a test to see if you have the destructive immune system cells associated with type 1 diabetes called autoantibodies.

Your provider will likely see if you're at high risk for gestational diabetes early in your pregnancy. If you're at high risk, your provider may test for diabetes at your first prenatal visit. If you're at average risk, you'll probably be screened sometime during your second trimester.

Treatment

Depending on what type of diabetes you have, blood sugar monitoring, insulin and oral drugs may be part of your treatment. Eating a healthy diet, staying at a healthy weight and getting regular physical activity also are important parts of managing diabetes.

Treatments for all types of diabetes

An important part of managing diabetes — as well as your overall health — is keeping a healthy weight through a healthy diet and exercise plan:

- Healthy eating. Your diabetes diet is simply a healthy-eating plan that will help you control your blood sugar. You'll need to focus your diet on more fruits, vegetables, lean proteins and whole grains. These are foods that are high in nutrition and fiber and low in fat and calories. You'll also cut down on saturated fats, refined carbohydrates and sweets. In fact, it's the best eating plan for the entire family. Sugary foods are OK once in a while. They must be counted as part of your meal plan.
  Understanding what and how much to eat can be a challenge. A registered dietitian can help you create a meal plan that fits your health goals, food preferences and lifestyle. This will likely include carbohydrate counting, especially if you have type 1 diabetes or use insulin as part of your treatment.
- Physical activity. Everyone needs regular aerobic activity. This includes people who have diabetes. Physical activity lowers your blood sugar level by moving sugar into your cells, where it's used for energy. Physical activity also makes your body more sensitive to insulin. That means your body needs less insulin to transport sugar to your cells.
  Get your provider's OK to exercise. Then choose activities you enjoy, such as walking, swimming or biking. What's most important is making physical activity part of your daily routine.
  Aim for at least 30 minutes or more of moderate physical activity most days of the week, or at least 150 minutes of moderate physical activity a week. Bouts of activity can be a few minutes during the day. If you haven't been active for a while, start slowly and build up slowly. Also avoid sitting for too long. Try to get up and move if you've been sitting for more than 30 minutes.

Treatments for type 1 and type 2 diabetes

Treatment for type 1 diabetes involves insulin injections or the use of an insulin pump, frequent blood sugar checks, and carbohydrate counting. For some people with type 1 diabetes, pancreas transplant or islet cell transplant may be an option.

Treatment of type 2 diabetes mostly involves lifestyle changes, monitoring of your blood sugar, along with oral diabetes drugs, insulin or both.

Monitoring your blood sugar

Depending on your treatment plan, you may check and record your blood sugar as many as four times a day or more often if you're taking insulin. Careful blood sugar testing is the only way to make sure that your blood sugar level remains within your target range. People with type 2 diabetes who aren't taking insulin generally check their blood sugar much less often.

People who receive insulin therapy also may choose to monitor their blood sugar levels with a continuous glucose monitor. Although this technology hasn't yet completely replaced the glucose meter, it can lower the number of fingersticks necessary to check blood sugar and provide important information about trends in blood sugar levels.

Even with careful management, blood sugar levels can sometimes change unpredictably. With help from your diabetes treatment team, you'll learn how your blood sugar level changes in response to food, physical activity, medications, illness, alcohol and stress. For women, you'll learn how your blood sugar level changes in response to changes in hormone levels.

Besides daily blood sugar monitoring, your provider will likely recommend regular A1C testing to measure your average blood sugar level for the past 2 to 3 months.

Compared with repeated daily blood sugar tests, A1C testing shows better how well your diabetes treatment plan is working overall. A higher A1C level may signal the need for a change in your oral drugs, insulin regimen or meal plan.

Your target A1C goal may vary depending on your age and various other factors, such as other medical conditions you may have or your ability to feel when your blood sugar is low. However, for most people with diabetes, the American Diabetes Association recommends an A1C of below 7%. Ask your provider what your A1C target is.

Insulin

People with type 1 diabetes must use insulin to manage blood sugar to survive. Many people with type 2 diabetes or gestational diabetes also need insulin therapy.

Many types of insulin are available, including short-acting (regular insulin), rapid-acting insulin, long-acting insulin and intermediate options. Depending on your needs, your provider may prescribe a mixture of insulin types to use during the day and night.

Insulin can't be taken orally to lower blood sugar because stomach enzymes interfere with insulin's

action. Insulin is often injected using a fine needle and syringe or an insulin pen — a device that looks like a large ink pen.

An insulin pump also may be an option. The pump is a device about the size of a small cellphone worn on the outside of your body. A tube connects the reservoir of insulin to a tube (catheter) that's inserted under the skin of your abdomen.

A continuous glucose monitor, on the left, is a device that measures blood sugar every few minutes using a sensor inserted under the skin. An insulin pump, attached to the pocket, is a device that's worn outside of the body with a tube that connects the reservoir of insulin to a catheter inserted under the skin of the abdomen. Insulin pumps are programmed to deliver specific amounts of insulin continuously and with food.

A tubeless pump that works wirelessly is also now available. You program an insulin pump to dispense specific amounts of insulin. It can be adjusted to give out more or less insulin depending on meals, activity level and blood sugar level.

A closed loop system is a device implanted in the body that links a continuous glucose monitor to an insulin pump. The monitor checks blood sugar levels regularly. The device automatically delivers the right amount of insulin when the monitor shows that it's needed.

The Food and Drug Administration has approved several hybrid closed loop systems for type 1 diabetes. They are called "hybrid" because these systems require some input from the user. For example, you may have to tell the device how many carbohydrates are eaten, or confirm blood sugar levels from time to time.

A closed loop system that doesn't need any user input isn't available yet. But more of these systems currently are in clinical trials.

Oral or other drugs

Sometimes your provider may prescribe other oral or injected drugs as well. Some diabetes drugs help your pancreas to release more insulin. Others prevent the production and release of glucose from your liver, which means you need less insulin to move sugar into your cells.

Still others block the action of stomach or intestinal enzymes that break down carbohydrates, slowing their absorption, or make your tissues more sensitive to insulin. Metformin (Glumetza, Fortamet, others) is generally the first drug prescribed for type 2 diabetes.

Another class of medication called SGLT2 inhibitors may be used. They work by preventing the kidneys from reabsorbing filtered sugar into the blood. Instead, the sugar is eliminated in the urine.

Transplantation

In some people who have type 1 diabetes, a pancreas transplant may be an option. Islet transplants are being studied as well. With a successful pancreas transplant, you would no longer need insulin therapy.

But transplants aren't always successful. And these procedures pose serious risks. You need a lifetime of immune-suppressing drugs to prevent organ rejection. These drugs can have serious side effects. Because of this, transplants are usually reserved for people whose diabetes can't be controlled or those who also need a kidney transplant.

Bariatric surgery

Some people with type 2 diabetes who are obese and have a body mass index higher than 35 may be helped by some types of bariatric surgery. People who've had gastric bypass have seen major improvements in their blood sugar levels. But this procedure's long-term risks and benefits for type 2 diabetes aren't yet known.

Treatment for gestational diabetes

Controlling your blood sugar level is essential to keeping your baby healthy. It can also keep you from having complications during delivery. In addition to having a healthy diet and exercising regularly, your treatment plan for gestational diabetes may include monitoring your blood sugar. In some cases, you may also use insulin or oral drugs.

Your provider will monitor your blood sugar level during labor. If your blood sugar rises, your baby may release high levels of insulin. This can lead to low blood sugar right after birth.

Treatment for prediabetes

Treatment for prediabetes usually involves healthy lifestyle choices. These habits can help bring your blood sugar level back to normal. Or it could keep it from rising toward the levels seen in type 2 diabetes. Keeping a healthy weight through exercise and healthy eating can help. Exercising at least 150 minutes a week and losing about 7% of your body weight may prevent or delay type 2 diabetes.

Drugs — such as metformin, statins and high blood pressure medications — may be an option for some people with prediabetes and other conditions such as heart disease.

Signs of trouble in any type of diabetes

Many factors can affect your blood sugar. Problems may sometimes come up that need care right away.

High blood sugar

High blood sugar (hyperglycemia in diabetes) can occur for many reasons, including eating too much, being sick or not taking enough glucose-lowering medication. Check your blood sugar level as directed by your provider. And watch for symptoms of high blood sugar, including:

- Urinating often
- Feeling thirstier than usual
- Blurred vision

- Tiredness (fatigue)
- Headache
- Irritability

If you have hyperglycemia, you'll need to adjust your meal plan, drugs or both.

Increased ketones in your urine

Diabetic ketoacidosis is a serious complication of diabetes. If your cells are starved for energy, your body may begin to break down fat. This makes toxic acids known as ketones, which can build up in the blood. Watch for the following symptoms:

- Nausea
- Vomiting
- Stomach (abdominal) pain
- A sweet, fruity smell on your breath
- Shortness of breath
- Dry mouth
- Weakness
- Confusion
- Coma

You can check your urine for excess ketones with a ketones test kit that you can get without a prescription. If you have excess ketones in your urine, talk with your provider right away or seek emergency care. This condition is more common in people with type 1 diabetes.

Hyperglycemic hyperosmolar nonketotic syndrome

Hyperosmolar syndrome is caused by very high blood sugar that turns blood thick and syrupy.

Symptoms of this life-threatening condition include:

- A blood sugar reading over 600 mg/dL (33.3 mmol/L)
- Dry mouth
- Extreme thirst
- Fever
- Drowsiness
- Confusion
- Vision loss
- Hallucinations

This condition is seen in people with type 2 diabetes. It often happens after an illness. Call your provider or seek medical care right away if you have symptoms of this condition.

Low blood sugar (hypoglycemia)

If your blood sugar level drops below your target range, it's known as low blood sugar (diabetic

hypoglycemia). If you're taking drugs that lower your blood sugar, including insulin, your blood sugar level can drop for many reasons. These include skipping a meal and getting more physical activity than normal. Low blood sugar also occurs if you take too much insulin or too much of a glucose-lowering medication that causes the pancreas to hold insulin.

Check your blood sugar level regularly and watch for symptoms of low blood sugar, including:

- Sweating
- Shakiness
- Weakness
- Hunger
- Dizziness
- Headache
- Blurred vision
- Heart palpitations
- Irritability
- Slurred speech
- Drowsiness
- Confusion
- Fainting
- Seizures

Low blood sugar is best treated with carbohydrates that your body can absorb quickly, such as fruit juice or glucose tablets.

9. Organ Talks, 2021. Living life with type 2 diabetes [online] Available at: https://www.organs-talk.com/t2d/living-life-with-t2d [Accessed 24 June 2024].

Living life with type 2 diabetes
'The most important thing for me in life is my health'

background-image@3x
How can my healthcare team help?
Regular communication with your healthcare team is an important part of managing and controlling your type 2 diabetes, so that you can keep living life how you want. Care for type 2 diabetes can vary depending on your own personal needs and where you are located, but generally they can support by:

offering
Offering
healthcare support and advice

Helping
Helping
you to understand your treatment options

Providing
Providing

tools and resources to support your lifestyle goals

Living with a long-term condition like type 2 diabetes can be challenging, so it's really important that you feel confident in communicating with your healthcare team. To help you feel more confident in your conversations with your doctor, it may help to try the following tips:1

write-down-any-questions
Write down any questions
or talking points beforehand. This will help to structure your conversation during your appointment.

honest
Be completely honest
about your experiences and concerns. That way, your doctor can give you the best advice for you.

Seek support
if you would feel more confident with extra support, you could even take someone with you to your appointment to help you keep track of all the information that you're given.

Treatments for type 2 diabetes
You'll likely have questions about how your type 2 diabetes will be treated. Your healthcare team will be able to answer these questions and prescribe the recommended treatment for you.

It is important to keep in mind that risk factors like blood sugar, body weight, blood pressure and the protection of the heart and the kidneys are all interconnected. In the best case, medications should help manage more than one individual risk factor.2

treatments
There are lots of different types of medication to help manage your type 2 diabetes, including:3,4
Metformin – Reduces the amount of glucose in the blood and helps the insulin produced by your body to work more effectively

Sodium-glucose cotransporter 2 (SGLT2) inhibitors – Reduce the amount of glucose in your blood by helping the kidneys pass excess glucose through the urine

Glucagon-like peptide 1 (GLP-1) receptor agonists or GLP-1 analogues – Increase the amount of insulin released by the pancreas which reduces the amount of glucose in your blood

Dipeptidyl peptidase-4 (DPP-4) inhibitors – Block the action of an enzyme called DPP-4. This inhibition helps your body to regulate insulin and glucose levels

Sulfonylureas – Reduce the amount of glucose in your blood by helping the pancreas produce more insulin

Insulin – Supplements the natural insulin your body produces to help reduce the amount of glucose in your blood

T2D
Each therapy has a different role in managing your condition, so be sure to take your treatments as

directed by your doctor.
Your doctor will also advise you to make some lifestyle changes, such as changes to your diet and more regular exercise, to help manage your blood sugar level.4

Staying on top of your type 2 diabetes
Speaking to your doctor about your symptoms can ensure that your symptoms are managed in a way that is most appropriate for your situation.

Your doctor may have suggested that a change of lifestyle is necessary to help manage your type 2 diabetes and help control your symptoms. While there are many benefits to a healthy diet and regular exercise, changing your lifestyle can seem like an overwhelming task, but you don't have to make these changes all at once. The key is to make small, practical changes, such as:5

Walking
Walking
If and when you can – this could be as simple as: taking the stairs instead of the elevator; parking the car, a little further away; getting off the bus one stop earlier.

do-household-chores
Do household chores
These allow you to move and stretch a lot, like raking leaves, washing the car or gardening.

active-play-with-children-and-pets
Active play with children and pets
Or, alternatively taking a walk in the park with friends.

tracking-your-food-intake
Tracking your food intake
Using a journal or app can help you identify habits of overeating and gives you better control over your diet.

swapping-sugary-drinks
Swapping sugary drinks
For example fruit juices, out with water if you can, or drinking no added sugar versions of drinks.

adapting-your-diet
Adapting your diet
Eating more foods rich in heart-healthy fats such as fish, nuts and seeds. Also, think about using vegetable oils as an alternative to frying with butter, ghee or lard.

reducing-carbohydrate-intake
Reducing carbohydrate intake
Try and cut down on the number of carbohydrates in your meals. Replace some of the white rice or pasta on your plate with green vegetables or try whole grain alternatives which are less processed.

reducing-alcohol-intake
Reducing alcohol intake

Lower the amount of alcohol you drink. The recommended daily limit for people with diabetes is one drink a day for women, and two for men.

reducing-salt-intake
Reducing salt intake
Cutting down on your salt intake, buying low salt versions and not adding extra salt to your meals.

Your emotional experience with type 2 diabetes
Type 2 diabetes is not only a physical disease; it can also have a significant impact on your mental health.6 Rapidly changing blood-sugar level, fatigue and the daily responsibilities associated with managing a long-term condition aren't always easy to deal with, but it's important to be kind to yourself, and to know where you can turn for help if you need it.

Your emotional experience with type 2 diabetes
anger-denial-fear-and-depression
Anger, denial, fear and depression
are common responses to a type 2 diabetes diagnosis.6 Being diagnosed with a long-term condition is tough and it will take some time to adjust to your new routines. In the meantime, it's important to be kind to yourself and take things day-by-day until you get adjusted.

speaking-to-close-friends-or-loved-ones
Speaking to close friends or loved ones
about the way you are feeling might help to lighten the load and support you as you get used to your new routine.

living life T2D
Joining online communities or support groups
can provide extra help and encouragement along your journey with type 2 diabetes. The people within these support groups can also help to address your concerns and can give advice based on real life experiences with the condition.

Depression and anxiety are serious conditions
Depression and anxiety are serious conditions
that are common among people living with type 2 diabetes.6 There are a lot of different reasons that you might be feeling depressed or anxious but it's important not to ignore the signs – your mental health is extremely important and plays a huge role in your quality of life.

For further information, or if you just want to talk, there are various helplines available that can offer support.

Did you know:
As many as 40% of people with type 2 diabetes said they have struggled with their psychological wellbeing since being diagnosed.6
There are links between type 2 diabetes and depression, so it's important to seek help from your healthcare team if you've not been feeling like yourself for an extended period of time.6

10.Organ Talks, 2021. Learn about type 2 diabetes and the interconnected systems [online] Available

at: https://www.organs-talk.com/t2d/interconnected-systems [Accessed 24 June 2024].

Learn about type 2 diabetes and the interconnected systems
What is the connection between type 2 diabetes and the heart?
Type 2 diabetes and the heart are interconnected. The high blood sugar that people with type 2 diabetes have means they are at an increased risk of developing heart disease.1

High blood sugar resulting from unmanaged type 2 diabetes can cause damage to the blood vessels and nerves that help your heart to work as it should. If left unchecked this can eventually lead to cardiovascular disease, like a heart attack or heart failure.1,2

The close relationship between type 2 diabetes and the heart also means that when a person adapts their lifestyle to improve the health of one of these organ systems, positive improvements are likely to be seen in other areas.1

What is the connection between type 2 diabetes and the heart
did you know
Did you know:
At least one in three people with type 2 diabetes have cardiovascular disease.3
People with type 2 diabetes are up to four times more likely to develop heart disease than people without diabetes.4
If you have questions or concerns about the interconnectivity of these conditions, speak to your doctor.

What is the connection between type 2 diabetes and the kidneys?
Blood sugar level and the kidneys are interconnected, meaning that when a person has type 2 diabetes, they are likely to experience kidney problems if their blood sugar level isn't controlled.1

The uncontrolled high blood sugar caused by type 2 diabetes can cause significant damage to your kidneys, making them work less efficiently. Proper management of your type 2 diabetes, through changes in lifestyle and adequate treatments, can stabilize your kidney health and reduce the chances of further damage being caused.1

Type 2 diabetes can also cause high blood pressure which is one of the major causes of chronic kidney disease.3 Doctors will often prescribe treatments to help control your blood pressure alongside medicine to control your blood sugar, to prevent damage to your kidneys.1

Once you have your type 2 diabetes under control, this can have a positive impact on the kidneys, due to the close connection between the organ systems.

What is the connection between type 2 diabetes and the kidneys
Approximately half of people with type 2 diabetes
Did you know:
Approximately half of people with type 2 diabetes have some level of kidney disease.5
If you have questions or concerns about the interconnectivity of these conditions, speak to your doctor.

11. American Diabetes Association, 2023. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2023 [online] Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9810475/ [Accessed 24 June 2024]

Diabetes Care. 2023 Jan; 46(Suppl 1): S158–S190.
Published online 2022 Dec 12. doi: 10.2337/dc23-S010
PMCID: PMC9810475
PMID: 36507632
10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2023

Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and results in an estimated $37.3 billion in cardiovascular-related spending per year associated with diabetes (1). Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors are addressed simultaneously. Under the current paradigm of aggressive risk factor modification in people with diabetes, there is evidence that measures of 10-year CHD risk among U.S. adults with diabetes have improved significantly over the past decade (2) and that ASCVD morbidity and mortality have decreased (3,4).

Heart failure is another major cause of morbidity and mortality from cardiovascular disease. Recent studies have found that rates of incident heart failure hospitalization (adjusted for age and sex) were twofold higher in people with diabetes compared with those without (5,6). People with diabetes may have heart failure with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). Hypertension is often a precursor of heart failure of either type, and ASCVD can coexist with either type (7), whereas prior myocardial infarction (MI) is often a major factor in HFrEF. Rates of heart failure hospitalization have been improved in recent trials including people with type 2 diabetes, most of whom also had ASCVD, with sodium–glucose cotransporter 2 (SGLT2) inhibitors (8–11).

A recent meta-analysis indicated that SGLT2 inhibitors reduce the risk of heart failure hospitalization, cardiovascular mortality, and all-cause mortality in people with (secondary prevention) and without (primary prevention) cardiovascular disease (12).

For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all people with diabetes. These risk factors include duration of diabetes, obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease (CKD), and the presence of albuminuria. Modifiable abnormal risk factors should be treated as described in these guidelines. Notably, the majority of evidence supporting interventions to reduce cardiovascular risk in diabetes comes from trials of people with type 2 diabetes. No randomized trials have been specifically designed to assess the impact of cardiovascular risk reduction strategies in people with type 1 diabetes. Therefore, the recommendations for cardiovascular risk factor modification for people with type 1 diabetes are extrapolated from data obtained in people with type 2 diabetes and are similar to those for people with type 2 diabetes.

As depicted in Fig. 10.1, a comprehensive approach to the reduction in risk of diabetes-related

complications is recommended. Therapy that includes multiple, concurrent evidence-based approaches to care will provide complementary reduction in the risks of microvascular, kidney, neurologic, and cardiovascular complications. Management of glycemia, blood pressure, and lipids and the incorporation of specific therapies with cardiovascular and kidney outcomes benefit (as individually appropriate) are considered fundamental elements of global risk reduction in diabetes.

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Figure 10.1
Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

Go to:
The Risk Calculator
The American College of Cardiology/American Heart Association ASCVD risk calculator (Risk Estimator Plus) is generally a useful tool to estimate 10-year risk of a first ASCVD event (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus). The calculator includes diabetes as a risk factor, since diabetes itself confers increased risk for ASCVD, although it should be acknowledged that these risk calculators do not account for the duration of diabetes or the presence of diabetes complications, such as albuminuria. Although some variability in calibration exists in various subgroups, including by sex, race, and diabetes, the overall risk prediction does not differ in those with or without diabetes (13–16), validating the use of risk calculators in people with diabetes. The 10-year risk of a first ASCVD event should be assessed to better stratify ASCVD risk and help guide therapy, as described below.

Recently, risk scores and other cardiovascular biomarkers have been developed for risk stratification of secondary prevention patients (i.e., those who are already high risk because they have ASCVD) but are not yet in widespread use (17,18). With newer, more expensive lipid-lowering therapies now available, use of these risk assessments may help target these new therapies to “higher risk” ASCVD patients in the future.

Go to:
Hypertension/Blood Pressure Control
Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg (19). This is in agreement with the definition of hypertension by the American College of Cardiology and American Heart Association (19). Hypertension is common among people with either type 1 or type 2 diabetes. Hypertension is a major risk factor for both ASCVD and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the American Diabetes Association position statement “Diabetes and Hypertension” for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (20) and recent updated hypertension guideline recommendations (19,21,22).

Screening and Diagnosis
Recommendations
10.1 Blood pressure should be measured at every routine clinical visit. When possible, individuals found to have elevated blood pressure (systolic blood pressure 120–129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. A Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg based on an average of ≥2 measurements obtained on ≥2 occasions.

A Individuals with blood pressure ≥180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. E
10.2 All people with hypertension and diabetes should monitor their blood pressure at home. A
Blood pressure should be measured at every routine clinical visit by a trained individual and should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference. Elevated values should preferably be confirmed on a separate day; however, in individuals with cardiovascular disease and blood pressure ≥180/110 mmHg, it is reasonable to diagnose hypertension at a single visit (21). Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and "true" blood pressure (23,24). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. Studies of individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (23,24). Moreover, home blood pressure monitoring may improve patient medication taking and thus help reduce cardiovascular risk (25).

Treatment Goals
Recommendations
10.3 For people with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. B
10.4 People with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. B
10.5 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational age birth weight. A There are limited data on the optimal lower limit, but therapy should be lessened for blood pressure <90/60 mmHg. E A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. A
Randomized clinical trials have demonstrated unequivocally that treatment of hypertension reduces cardiovascular events as well as microvascular complications (26–32). There has been controversy on the recommendation of a specific blood pressure goal in people with diabetes. The committee recognizes that there has been no randomized controlled trial to specifically demonstrate a decreased incidence of cardiovascular events in people with diabetes by targeting a blood pressure <130/80 mmHg. The recommendation to support a blood pressure goal of <130/80 mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association (20), the International Society of Hypertension (21), and the European Society of Cardiology (22). The committee's recommendation for the blood pressure target of <130/80 mmHg derives primarily from the collective evidence of the following randomized controlled trials. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that treatment to a target systolic blood pressure of <120 mmHg decreases cardiovascular event rates by 25% in high-risk patients, although people with diabetes were excluded from this trial (33). The recently completed Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial included nearly 20% of people with diabetes and noted

decreased cardiovascular events with treatment of hypertension to a blood pressure target of <130 mmHg (34). While the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial (ACCORD BP) did not confirm that targeting a systolic blood pressure of <120 mmHg in people with diabetes results in decreased cardiovascular event rates, the prespecified secondary outcome of stroke was reduced by 41% with intensive treatment (35). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial revealed that treatment with perindopril/indapamide to an achieved systolic blood pressure of ~135 mmHg significantly decreased cardiovascular event rates compared with a placebo treatment with an achieved blood pressure of 140 mmHg (36). Therefore, it is recommended that people with diabetes who have hypertension should be treated to blood pressure targets of <130/80 mmHg. Notably, there is an absence of high-quality data available to guide blood pressure targets in people with type 1 diabetes, but a similar blood pressure target of <130/80 mmHg is recommended in people with type 1 diabetes. As discussed below, treatment should be individualized and treatment should not be targeted to <120/80 mmHg, as a mean achieved blood pressure of <120/80 mmHg is associated with adverse events.

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control SPRINT provides the strongest evidence to support lower blood pressure goals in patients at increased cardiovascular risk, although this trial excluded people with diabetes (33). The trial enrolled 9,361 patients with a systolic blood pressure of ≥130 mmHg and increased cardiovascular risk and treated to a systolic blood pressure target of <120 mmHg (intensive treatment) versus a target of <140 mmHg (standard treatment). The primary composite outcome of myocardial infarction (MI), coronary syndromes, stroke, heart failure, or death from cardiovascular causes was reduced by 25% in the intensive treatment group. The achieved systolic blood pressures in the trial were 121 mmHg and 136 mmHg in the intensive versus standard treatment group, respectively. Adverse outcomes, including hypotension, syncope, electrolyte abnormality, and acute kidney injury were more common in the intensive treatment arm; risk of adverse outcomes needs to be weighed against the cardiovascular benefit of more intensive blood pressure lowering.
ACCORD BP provides the strongest direct assessment of the benefits and risks of intensive blood pressure control in people with type 2 diabetes (35). In the study, a total of 4,733 with type 2 diabetes were assigned to intensive therapy (targeting a systolic blood pressure <120 mmHg) or standard therapy (targeting a systolic blood pressure <140 mmHg). The mean achieved systolic blood pressures were 119 mmHg and 133 mmHg in the intensive versus standard group, respectively. The primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes was not significantly reduced in the intensive treatment group. The prespecified secondary outcome of stroke was significantly reduced by 41% in the intensive treatment group. Adverse events attributed to blood pressure treatment, including hypotension, syncope, bradycardia, hyperkalemia, and elevations in serum creatinine occurred more frequently in the intensive treatment arm than in the standard therapy arm (Table 10.1).

Table 10.1
Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (35)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death

• Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment
• Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE (36) 11,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors Intervention: a single-pill, fixed-dose combination of perindopril and indapamide
Achieved (mean) SBP/DBP: 136/73 mmHg Control: placebo
Achieved (mean) SBP/DBP: 141.6/75.2 mmHg • Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)
• 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (242)
HOT (37) 18,790 participants, including 1,501 with diabetes DBP target: ≤80 mmHg
Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group DBP target: ≤90 mmHg • In the overall trial, there was no cardiovascular benefit with more intensive targets
• In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (43) 9,361 participants without diabetes SBP target: <120 mmHg
Achieved (mean): 121.4 mmHg SBP target: <140 mmHg
Achieved (mean): 136.2 mmHg • Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD)
• Intensive target reduced risk of death 27%
• Intensive therapy increased risks of electrolyte abnormalities and AKI
STEP (34) 8,511 participants aged 60–80 years, including 1,627 with diabetes SBP target: <130 mmHg
Achieved (mean): 127.5 mmHg SBP target: <150 mmHg
Achieved (mean): 135.3 mmHg • Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes)
• Intensive target reduced risk of cardiovascular death 28%
• Intensive therapy increased risks of hypotension
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ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; STEP, Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; T2D, type 2 diabetes.

Of note, the ACCORD BP and SPRINT trials targeted a similar systolic blood pressure <120 mmHg, but in contrast to SPRINT, the primary composite cardiovascular end point was nonsignificantly reduced in ACCORD BP. The results have been interpreted to be generally consistent between both trials, but ACCORD BP was viewed as underpowered due to the composite primary end point being less sensitive to blood pressure regulation (33).

The more recent STEP trial assigned 8,511 patients aged 60–80 years with hypertension to a systolic blood pressure target of 110 to <130 mmHg (intensive treatment) or a target of 130 to <150 mmHg (34).

In this trial, the primary composite outcome of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes was reduced by 26% in the intensive treatment group. In this trial, 18.9% of patients in the intensive treatment arm and 19.4% in the standard treatment arm had a diagnosis of type 2 diabetes. Hypotension occurred more frequently in the intensive treatment group (3.4%) compared with the standard treatment group (2.6%), without significant differences in other adverse events, including dizziness, syncope, or fractures.

In ADVANCE, 11,140 people with type 2 diabetes were randomized to receive either treatment with fixed combination perindopril/indapamide or matching placebo (36). The primary end point, a composite of cardiovascular death, nonfatal stroke infarction, or worsening renal or diabetic eye disease, was reduced by 9% in the combination treatment. The achieved systolic blood pressure was ~135 mmHg in the treatment group and 140 mmHg in the placebo group.

The Hypertension Optimal Treatment (HOT) trial enrolled 18,790 patients and targeted diastolic blood pressure <90 mmHg, <85 mmHg, or <80 mmHg (37). The cardiovascular event rates, defined as fatal or nonfatal MI, fatal and nonfatal strokes, and all other cardiovascular events, were not significantly different between diastolic blood pressure targets (≤90 mmHg, ≤85 mmHg, and ≤80 mmHg), although the lowest incidence of cardiovascular events occurred with an achieved diastolic blood pressure of 82 mmHg. However, in people with diabetes, there was a significant 51% reduction in the treatment group with a target diastolic blood pressure of <80 mmHg compared with a target diastolic blood pressure of <90 mmHg.

Meta-analyses of Trials To clarify optimal blood pressure targets in people with diabetes, multiple meta-analyses have been performed. One of the largest meta-analyses included 73,913 people with diabetes. Compared with a less tight blood pressure control, allocation to a tighter blood pressure control significantly reduced the risk of stroke by 31% but did not reduce the risk of MI (38). Another meta-analysis of 19 trials including 44,989 patients showed that a mean blood pressure of 133/76 mmHg is associated with a 14% risk reduction for major cardiovascular events compared with a mean blood pressure of 140/81 mmHg (32). This benefit was greatest in people with diabetes. An analysis of trials including people with type 2 diabetes and impaired glucose tolerance with achieved systolic blood pressures of <135 mmHg in the intensive blood pressure treatment group and <140 mmHg in the standard treatment group revealed a 10% reduction in all-cause mortality and a 17% reduction in stroke (30). More intensive reduction to <130 mmHg was associated with a further reduction in stroke but not other cardiovascular events.
Several meta-analyses stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention (or intensive treatment) arm. Based on these analyses, antihypertensive treatment appears to be most beneficial when mean baseline blood pressure is ≥140/90 mmHg (19,26,27,29–31). Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident.

Individualization of Treatment Targets Patients and clinicians should engage in a shared decision-making process to determine individual blood pressure targets (19). This approach acknowledges that the benefits and risks of intensive blood pressure targets are uncertain and may vary across patients and is consistent with a patient-focused approach to care that values patient priorities and health care professional judgment (39). Secondary analyses of ACCORD BP and SPRINT suggest that clinical factors can help determine individuals more likely to benefit and less likely to be harmed by intensive blood

pressure control (40,41).
Absolute benefit from blood pressure reduction correlated with absolute baseline cardiovascular risk in SPRINT and in earlier clinical trials conducted at higher baseline blood pressure levels (13,41). Extrapolation of these studies suggests that people with diabetes may also be more likely to benefit from intensive blood pressure control when they have high absolute cardiovascular risk. This approach is consistent with guidelines from the American College of Cardiology and American Heart Association, which also advocate a blood pressure target of <130/80 mmHg for all people, with or without diabetes (20).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, acute kidney injury, and electrolyte abnormalities) should also be taken into account (33,35,42,43). Individuals with older age, CKD, and frailty have been shown to be at higher risk of adverse effects of intensive blood pressure control (43). In addition, individuals with orthostatic hypotension, substantial comorbidity, functional limitations, or polypharmacy may be at high risk of adverse effects, and some patients may prefer higher blood pressure targets to enhance quality of life. However, in ACCORD BP, it was found that intensive blood pressure lowering decreased the risk of cardiovascular events irrespective of baseline diastolic blood pressure in patients who also received standard glycemic control (44). Therefore, the presence of low diastolic blood pressure is not necessarily a contraindication to more intensive blood pressure management in the context of otherwise standard care.

Pregnancy and Antihypertensive Medications There are few randomized controlled trials of antihypertensive therapy in pregnant individuals with diabetes. A 2014 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension that included 49 trials and over 4,700 women did not find any conclusive evidence for or against blood pressure treatment to reduce the risk of preeclampsia for the mother or effects on perinatal outcomes such as preterm birth, small-for-gestational-age infants, or fetal death (45). The Control of Hypertension in Pregnancy Study (CHIPS) (46) enrolled mostly women with chronic hypertension. In CHIPS, targeting a diastolic blood pressure of 85 mmHg during pregnancy was associated with reduced likelihood of developing accelerated maternal hypertension and no demonstrable adverse outcome for infants compared with targeting a higher diastolic blood pressure. The mean systolic blood pressure achieved in the more intensively treated group was 133.1 ± 0.5 mmHg, and the mean diastolic blood pressure achieved in that group was 85.3 ± 0.3 mmHg. A similar approach is supported by the International Society for the Study of Hypertension in Pregnancy, which specifically recommends use of antihypertensive therapy to maintain systolic blood pressure between 110 and 140 mmHg and diastolic blood pressure between 80 and 85 mmHg (47).
The more recent Chronic Hypertension and Pregnancy (CHAP) trial assigned pregnant individuals with mild chronic hypertension to antihypertensive medications to target a blood pressure goal of <140/90 mmHg (active treatment group) or to control treatment, in which antihypertensive therapy was withheld unless severe hypertension (systolic pressure ≥160 mmHg or diastolic pressure ≥105 mmHg) developed (control group) (48). The primary outcome, a composite of preeclampsia with severe features, medically indicated preterm birth at <35 weeks of gestation, placental abruption, or fetal/neonatal death, occurred in 30.2% of female participants in the active treatment group vs. 37.0% in the control group ($P < 0.001$). The mean systolic blood pressure between randomization and delivery was 129.5 mmHg in the active treatment group and 132.6 mmHg in the control group.

Current evidence supports controlling blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension but also to minimize impairment of fetal growth. During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), and spironolactone are

contraindicated as they may cause fetal damage. Special consideration should be taken for individuals of childbearing potential, and people intending to become pregnant should switch from an ACE inhibitor/ARB or spironolactone to an alternative antihypertensive medication approved during pregnancy. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine, while hydralzine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (49). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (49,50). The American College of Obstetricians and Gynecologists also recommends that postpartum individuals with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and for 7–10 days postpartum. Long-term follow-up is recommended for these individuals as they have increased lifetime cardiovascular risk (51). See Section 15, “Management of Diabetes in Pregnancy,” for additional information.

Treatment Strategies
Lifestyle Intervention
Recommendation
10.6 For people with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. A Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. Lifestyle therapy consists of reducing excess body weight through caloric restriction (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”), at least 150 min of moderate-intensity aerobic activity per week (see Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities”), restricting sodium intake (<2,300 mg/day), increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (52), and increasing activity levels (53) (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”).

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic >120 mmHg or diastolic >80 mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (Fig. 10.2) (53). A lifestyle therapy plan should be developed in collaboration with the patient and discussed as part of diabetes management. Use of internet or mobile-based digital platforms to reinforce healthy behaviors may be considered as a component of care, as these interventions have been found to enhance the efficacy of medical therapy for hypertension (54,55).

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Figure 10.2
Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for individuals with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker (CCB). BP,

blood pressure. Adapted from de Boer et al. (20).

Pharmacologic Interventions

Recommendations

10.7 Individuals with confirmed office-based blood pressure ≥130/80 mmHg qualify for initiation and titration of pharmacologic therapy to achieve the recommended blood pressure goal of <130/80 mmHg. A

10.8 Individuals with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in people with diabetes. A

10.9 Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people with diabetes. A ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. A

10.10 Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should not be used. A

10.11 An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in people with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine A or 30–299 mg/g creatinine. B If one class is not tolerated, the other should be substituted. B

10.12 For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. B

Initial Number of Antihypertensive Medications. Initial treatment for people with diabetes depends on the severity of hypertension (Fig. 10.2). Those with blood pressure between 130/80 mmHg and 160/100 mmHg may begin with a single drug. For patients with blood pressure ≥160/100 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended in order to more effectively achieve adequate blood pressure control (56–58). Single-pill antihypertensive combinations may improve medication taking in some patients (59).

Classes of Antihypertensive Medications. Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in people with diabetes: ACE inhibitors (60,61), ARBs (60,61), thiazide-like diuretics (62), or dihydropyridine calcium channel blockers (63). In people with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension (64–66). For patients with albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), initial treatment should include an ACE inhibitor or ARB to reduce the risk of progressive kidney disease (20) (Fig. 10.2). In patients receiving ACE inhibitor or ARB therapy, continuation of those medications as kidney function declines to estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 may provide cardiovascular benefit without significantly increasing the risk of end-stage kidney disease (67). In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection when compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (68). β-Blockers are indicated in the setting of prior MI, active angina, or HfrEF but have not been shown to reduce mortality as blood pressure-lowering agents in the absence of these conditions (28,69,70).

Multiple-Drug Therapy. Multiple-drug therapy is often required to achieve blood pressure targets (Fig. 10.2), particularly in the setting of diabetic kidney disease. However, the use of both ACE inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is contraindicated given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and acute kidney injury (AKI) (71–73). Titration of and/or addition of further

blood pressure medications should be made in a timely fashion to overcome therapeutic inertia in achieving blood pressure targets.

Bedtime Dosing. Although prior analyses of randomized clinical trials found a benefit to evening versus morning dosing of antihypertensive medications (74,75), these results have not been reproduced in subsequent trials. Therefore, preferential use of antihypertensives at bedtime is not recommended (76).

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors or ARBs can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (77,78). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (79). Therefore, serum creatinine and potassium should be monitored during treatment with an ACE inhibitor, ARB, or diuretic, particularly among patients with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (77,78,80).

Resistant Hypertension

Recommendation

10.13 Individuals with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. A

Resistant hypertension is defined as blood pressure ≥140/90 mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs with complementary mechanisms of action at adequate doses. Prior to diagnosing resistant hypertension, a number of other conditions should be excluded, including missed doses of antihypertensive medications, white coat hypertension, and secondary hypertension. In general, barriers to medication taking (such as cost and side effects) should be identified and addressed (Fig. 10.2). Mineralocorticoid receptor antagonists, including spironolactone and eplerenone, are effective for management of resistant hypertension in people with type 2 diabetes when added to existing treatment with an ACE inhibitor or ARB, thiazide-like diuretic, or dihydropyridine calcium channel blocker (81). In addition, mineralocorticoid receptor antagonists reduce albuminuria in people with diabetic nephropathy (82–84). However, adding a mineralocorticoid receptor antagonist to a regimen including an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these patients, and long-term outcome studies are needed to better evaluate the role of mineralocorticoid receptor antagonists in blood pressure management.

Go to:

Lipid Management

Lifestyle Intervention

Recommendations

10.14 Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) eating pattern; reduction of saturated fat and trans fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease in people with diabetes. A

10.15 Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women). C

Lifestyle intervention, including weight loss in people with overweight or obesity (when appropriate) (85), increased physical activity, and medical nutrition therapy, allows some patients to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each patient's age, pharmacologic treatment, lipid levels, and medical conditions.

Recommendations should focus on application of a Mediterranean (83) or Dietary Approaches to Stop Hypertension (DASH) eating pattern, reducing saturated and trans fat intake and increasing plant stanols/sterols, n-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus) intake (86,87). Glycemic control may also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional nutrition information.

Ongoing Therapy and Monitoring with Lipid Panel

Recommendations

10.16 In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. E

10.17 Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication taking. E

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in patients <40 years of age. In younger people with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable. A lipid panel should also be obtained immediately before initiating statin therapy. Once a patient is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and on an individual basis (e.g., to monitor for medication taking and efficacy). If LDL cholesterol levels are not responding in spite of medication taking, clinical judgment is recommended to determine the need for and timing of lipid panels. In individual patients, the highly variable LDL cholesterol–lowering response seen with statins is poorly understood (88). Clinicians should attempt to find a dose or alternative statin that is tolerable if side effects occur. There is evidence for benefit from even extremely low, less than daily statin doses (89).

Go to:

Statin Treatment

Primary Prevention

Recommendations

10.18 For people with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. A

10.19 For people with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. C

10.20 For people with diabetes aged 40–75 at higher cardiovascular risk, including those with one or more atherosclerotic cardiovascular disease risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by ≥50% of baseline and to target an LDL cholesterol goal of <70 mg/dL. B

10.21 For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple atherosclerotic cardiovascular disease risk factors and an LDL cholesterol ≥70 mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. C

10.22 In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin treatment. B

10.23 In adults with diabetes aged >75 years, it may be reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks. C

10.24 Statin therapy is contraindicated in pregnancy. B

Secondary Prevention

Recommendations

10.25 For people of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. A

10.26 For people with diabetes and atherosclerotic cardiovascular disease, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL. Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. B

10.27 For individuals who do not tolerate the intended intensity, the maximum tolerated statin dose should be used. E

Initiating Statin Therapy Based on Risk

People with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subjects with and without CHD (90,91). Subgroup analyses of people with diabetes in larger trials (92–96) and trials in people with diabetes (97,98) showed significant primary and secondary prevention of ASCVD events and CHD death in people with diabetes. Meta-analyses, including data from over 18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol (99). The cardiovascular benefit in this large meta-analysis did not depend on baseline LDL cholesterol levels and was linearly related to the LDL cholesterol reduction without a low threshold beyond which there was no benefit observed (99).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. Table 10.2 shows the two statin dosing intensities that are recommended for use in clinical practice: high-intensity statin therapy will achieve approximately a ≥50% reduction in LDL cholesterol, and moderate-intensity statin regimens achieve 30–49% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in people with diabetes but is sometimes the only dose of statin that a patient can tolerate. For patients who do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.

Table 10.2

High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
Simvastatin 20–40 mg	
Pravastatin 40–80 mg	
Lovastatin 40 mg	
Fluvastatin XL 80 mg	
Pitavastatin 1–4 mg	

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*Once-daily dosing. XL, extended release.

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk (known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD

are convincing (100,101). The relative benefit of lipid-lowering therapy has been uniform across most subgroups tested (91,99), including subgroups that varied with respect to age and other risk factors.

Primary Prevention (People without ASCVD) For primary prevention, moderate-dose statin therapy is recommended for those aged ≥40 years (93,100,101), although high-intensity therapy should be considered in the context of additional ASCVD risk factors. The evidence is strong for people with diabetes aged 40–75 years, an age-group well represented in statin trials showing benefit. Since cardiovascular risk is enhanced in people with diabetes, as noted above, patients who also have multiple other coronary risk factors have increased risk, equivalent to that of those with ASCVD. Therefore, current guidelines recommend that in people with diabetes who are at higher cardiovascular risk, especially those with one or more ASCVD risk factors, high-intensity statin therapy should be prescribed to reduce LDL cholesterol by ≥50% from baseline and to target an LDL cholesterol of <70 mg/dL (102–104). Since in clinical practice it is frequently difficult to ascertain the baseline LDL cholesterol level prior to statin therapy initiation, in those individuals, a focus on an LDL cholesterol target level of <70 mg/dL rather than the percent reduction in LDL cholesterol is recommended. In those individuals, it may also be reasonable to add ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy to maximum tolerated statin therapy if needed to reduce LDL cholesterol levels by ≥50% and to achieve the recommended LDL cholesterol target of <70 mg/dL (14). The evidence is lower for patients aged >75 years; relatively few older people with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants (91,98,99), and because older age confers higher risk, the absolute benefits are actually greater (91,105). Moderate-intensity statin therapy is recommended in people with diabetes who are ≥75 years of age. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of dose performed as needed. See Section 13, “Older Adults,” for more details on clinical considerations for this population.

Age <40 Years and/or Type 1 Diabetes. Very little clinical trial evidence exists for people with type 2 diabetes under the age of 40 years or for people with type diabetes of any age. For pediatric recommendations, see Section 14, “Children and Adolescents.” In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 people with type 1 diabetes had a proportionately similar, although not statistically significant, reduction in risk to that in people with type 2 diabetes (93). Even though the data are not definitive, similar statin treatment approaches should be considered for people with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Patients <40 years of age have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and suffering an MI, stroke, or cardiovascular death is high. For people who are <40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the patient and health care professional discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy. Please refer to “Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association” (106) for additional discussion.

Secondary Prevention (People with ASCVD) Because cardiovascular event rates are increased in people with diabetes and established ASCVD, intensive therapy is indicated and has been shown to be of benefit in multiple large meta-analyses and randomized cardiovascular outcomes trials (91,99,105,107,108). High-intensity statin therapy is recommended for all people with diabetes and ASCVD to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL. Based on the evidence discussed below, addition of ezetimibe or a PCSK9 inhibitor is recommended if this goal is not achieved on maximum tolerated statin therapy. These recommendations are based on the observation that high-intensity versus moderate-intensity statin therapy reduces cardiovascular event rates in high-risk individuals with established cardiovascular disease in randomized trials (95,107). In addition,

the Cholesterol Treatment Trialists' Collaboration involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins (99), showed a 21% reduction in major cardiovascular events in people with diabetes for every 39 mg/dL of LDL cholesterol lowering, irrespective of baseline LDL cholesterol or patient characteristics (99). However, the best evidence to support lower LDL cholesterol targets in people with diabetes and established cardiovascular disease derives from multiple large randomized trials investigating the benefits of adding nonstatin agents to statin therapy. As discussed in detail below, these include combination treatment with statins and ezetimibe (105,109) or PCSK9 inhibitors (108,110–112). Each trial found a significant benefit in the reduction of ASCVD events that was directly related to the degree of further LDL cholesterol lowering. These large trials included a significant number of participants with diabetes and prespecified analyses on cardiovascular outcomes in people with and without diabetes (109,111,112). The decision to add a nonstatin agent should be made following a clinician-patient discussion about the net benefit, safety, and cost of combination therapy.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial in 18,144 patients comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone (105). Individuals were ≥50 years of age, had experienced a recent acute coronary syndrome (ACS) and were treated for an average of 6 years. Overall, the addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events (atherosclerotic cardiovascular events), with the degree of benefit being directly proportional to the change in LDL cholesterol, which was 70 mg/dL in the statin group on average and 54 mg/dL in the combination group (105). In those with diabetes (27% of participants), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45% cumulative incidence at 7 years) and a relative risk reduction of 14% (hazard ratio [HR] 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (109).

Statins and PCSK9 Inhibitors Placebo-controlled trials evaluating the addition of the PCSK9 inhibitors evolocumab and alirocumab to maximum tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36 to 59%. These agents have been approved as adjunctive therapy for individuals with ASCVD or familial hypercholesterolemia who are receiving maximum tolerated statin therapy but require additional lowering of LDL cholesterol (113,114). No cardiovascular outcome trials have been performed to assess whether PCSK9 inhibitor therapy reduces ASCVD event rates in individuals without established cardiovascular disease (primary prevention).

The effects of PCSK9 inhibition on ASCVD outcomes was investigated in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, which enrolled 27,564 individuals with prior ASCVD and an additional high-risk feature who were receiving their maximum tolerated statin therapy (two-thirds were on high-intensity statin) but who still had LDL cholesterol ≥70 mg/dL or non-HDL cholesterol ≥100 mg/dL (108). Patients were randomized to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month based on patient preference) versus placebo. Evolocumab reduced LDL cholesterol by 59% from a median of 92 to 30 mg/dL in the treatment arm.

During the median follow-up of 2.2 years, the composite outcome of cardiovascular death, MI, stroke, hospitalization for angina, or revascularization occurred in 11.3% vs. 9.8% of the placebo and evolocumab groups, respectively, representing a 15% relative risk reduction ($P < 0.001$). The combined end point of cardiovascular death, MI, or stroke was reduced by 20%, from 7.4 to 5.9% ($P < 0.001$). Evolocumab therapy also significantly reduced all strokes (1.5% vs. 1.9%; HR 0.79 [95% CI 0.66–0.95]; $P = 0.01$) and ischemic stroke (1.2% vs. 1.6%; HR 0.75 [95% CI 0.62–0.92]; $P = 0.005$) in the total population,

with findings being consistent in individuals with or without a history of ischemic stroke at baseline (115). Importantly, similar benefits were seen in a prespecified subgroup of people with diabetes, comprising 11,031 patients (40% of the trial) (112).

In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 18,924 patients (28.8% of whom had diabetes) with recent acute coronary syndrome were randomized to the PCSK9 inhibitor alirocumab or placebo every 2 weeks in addition to maximum tolerated statin therapy, with alirocumab dosing titrated between 75 and 150 mg to achieve LDL cholesterol levels between 25 and 50 mg/dL (110). Over a median follow-up of 2.8 years, a composite primary end point (comprising death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospital admission) occurred in 903 patients (9.5%) in the alirocumab group and in 1,052 patients (11.1%) in the placebo group (HR 0.85 [95% CI 0.78–0.93]; P < 0.001). Combination therapy with alirocumab plus statin therapy resulted in a greater absolute reduction in the incidence of the primary end point in people with diabetes (2.3% [95% CI 0.4–4.2]) than in those with prediabetes (1.2% [0.0–2.4]) or normoglycemia (1.2% [–0.3 to 2.7]) (111).

In addition to monoclonal antibodies targeting PCSK9, the siRNA inclisiran has been developed and has recently become available in the U.S. In the Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10) and Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11) trials (116), individuals with established cardiovascular disease or ASCVD risk equivalent were randomized to receive inclisiran or placebo. Inclisiran allows less frequent administration compared with monoclonal antibodies and was administered on day 1, on day 90, and every 6 months in these trials. In the ORION-10 trial, 47.5% of patients in the inclisiran group and 42.4% in the placebo group had diabetes; in the ORION-11 trial, 36.5% of patients in the inclisiran group and 33.7% in the placebo group had diabetes. The coprimary end point of placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 was 52.3% in the ORION-10 trial and 49.9% in the ORION-11 trial. In an exploratory analysis, the prespecified cardiovascular end point, defined as a cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal MI, or stroke, occurred in 7.4% of the inclisiran group and 10.2% of the placebo group in the ORION-10 trial and in 7.8% of the inclisiran group and 10.3% of the placebo group in the ORION-11 trial. A cardiovascular outcome trial using inclisiran in people with established cardiovascular disease is currently ongoing (117).

Statins and Bempedoic Acid Bempedoic acid is a novel LDL cholesterol–lowering agent that is indicated as an adjunct to diet and maximum tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of LDL cholesterol. A pooled analysis suggests that bempedoic acid therapy lowers LDL cholesterol levels by about 23% compared with placebo (118). At this time, there are no completed trials demonstrating a cardiovascular outcomes benefit to use of this medication; however, this agent may be considered for patients who cannot use or tolerate other evidence-based LDL cholesterol-lowering approaches, or for whom those other therapies are inadequately effective (119).

Treatment of Other Lipoprotein Fractions or Targets

Recommendations

10.28 For individuals with fasting triglyceride levels ≥500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. C

10.29 In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors

(diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. C

10.30 In individuals with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. A

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including weight loss and abstinence from alcohol (120). Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL and especially >1,000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis. Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see statin treatment). In people with moderate hypertriglyceridemia, lifestyle interventions, treatment of secondary factors, and avoidance of medications that might raise triglycerides are recommended.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) enrolled 8,179 adults receiving statin therapy with moderately elevated triglycerides (135–499 mg/dL, median baseline of 216 mg/dL) who had either established cardiovascular disease (secondary prevention cohort) or diabetes plus at least one other cardiovascular risk factor (primary prevention cohort) (121). Patients were randomized to icosapent ethyl 4 g/day (2 g twice daily with food) versus placebo. The trial met its primary end point, demonstrating a 25% relative risk reduction ($P < 0.001$) for the primary end point composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. This reduction in risk was seen in people with or without diabetes at baseline. The composite of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 26% ($P < 0.001$). Additional ischemic end points were significantly lower in the icosapent ethyl group than in the placebo group, including cardiovascular death, which was reduced by 20% ($P = 0.03$). The proportions of patients experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups. It should be noted that data are lacking with other n-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products (121). As an example, the addition of 4 g per day of a carboxylic acid formulation of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n-3 carboxylic acid) to statin therapy in patients with atherogenic dyslipidemia and high cardiovascular risk, 70% of whom had diabetes, did not reduce the risk of major adverse cardiovascular events compared with the inert comparator of corn oil (122).

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in people with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy (123). In a large trial in people with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (124).

Other Combination Therapy

Recommendations

10.31 Statin plus fibrate combination therapy has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. A

10.32 Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. A

Statin and Fibrate Combination Therapy Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate) (125).

In the ACCORD study, in people with type 2 diabetes who were at high risk for ASCVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared with simvastatin alone. Prespecified subgroup analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥204 mg/dL (2.3 mmol/L) and an HDL cholesterol level ≤34 mg/dL (0.9 mmol/L) (126).

Statin and Niacin Combination Therapy The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized over 3,000 people (about one-third with diabetes) with established ASCVD, LDL cholesterol levels <180 mg/dL [4.7 mmol/L], low HDL cholesterol levels (men <40 mg/dL [1.0 mmol/L] and women <50 mg/dL [1.3 mmol/L]), and triglyceride levels of 150–400 mg/dL (1.7–4.5 mmol/L) to statin therapy plus extended-release niacin or placebo. The trial was halted early due to lack of efficacy on the primary ASCVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (127).
The much larger Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial also failed to show a benefit of adding niacin to background statin therapy (128). A total of 25,673 individuals with prior vascular disease were randomized to receive 2 g of extended-release niacin and 40 mg of laropiprant (an antagonist of the prostaglandin D2 receptor DP1 that has been shown to improve participation in niacin therapy) versus a matching placebo daily and followed for a median follow-up period of 3.9 years. There was no significant difference in the rate of coronary death, MI, stroke, or coronary revascularization with the addition of niacin–laropiprant versus placebo (13.2% vs. 13.7%; rate ratio 0.96; P = 0.29). Niacin–laropiprant was associated with an increased incidence of new-onset diabetes (absolute excess, 1.3 percentage points; P < 0.001) and disturbances in diabetes management among those with diabetes. In addition, there was an increase in serious adverse events associated with the gastrointestinal system, musculoskeletal system, skin, and, unexpectedly, infection and bleeding.

Therefore, combination therapy with a statin and niacin is not recommended given the lack of efficacy on major ASCVD outcomes and increased side effects.

Diabetes Risk with Statin Use
Several studies have reported a modestly increased risk of incident diabetes with statin use (129,130), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (131). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin developed diabetes) (131). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 patients (130).

Lipid-Lowering Agents and Cognitive Function
Although concerns regarding a potential adverse impact of lipid-lowering agents on cognitive function have been raised, several lines of evidence point against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement (132). First, there are three large randomized trials of statin versus placebo where specific cognitive tests were performed, and no differences were seen

between statin and placebo (133–136). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (105) or PCSK9 inhibitors (108,137) to statin therapy, including among patients treated to very low LDL cholesterol levels. In addition, the most recent systematic review of the U.S. Food and Drug Administration's (FDA's) postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data do not reveal an adverse effect of statins on cognition (138). Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD (138).

Go to:

Antiplatelet Agents

Recommendations

10.33 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. A

10.34 For individuals with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. B

10.35 Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome and may have benefits beyond this period. A

10.36 Long-term treatment with dual antiplatelet therapy should be considered for individuals with prior coronary intervention, high ischemic risk, and low bleeding risk to prevent major adverse cardiovascular events. A

10.37 Combination therapy with aspirin plus low-dose rivaroxaban should be considered for individuals with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events. A

10.38 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. A

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention) and is strongly recommended. In primary prevention, however, among patients with no previous cardiovascular events, its net benefit is more controversial (129,140).

Previous randomized controlled trials of aspirin specifically in people with diabetes failed to consistently show a significant reduction in overall ASCVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes, although some sex differences were suggested (141–143).

The Antithrombotic Trialists' Collaboration published an individual patient–level meta-analysis (139) of the six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (relative risk 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (relative risk 0.95 [95% CI 0.78–1.15]) or total stroke.

Most recently, the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial randomized 15,480 people with diabetes but no evident cardiovascular disease to aspirin 100 mg daily or placebo (144). The

primary efficacy end point was vascular death, MI, or stroke or transient ischemic attack. The primary safety outcome was major bleeding (i.e., intracranial hemorrhage, sight-threatening bleeding in the eye, gastrointestinal bleeding, or other serious bleeding). During a mean follow-up of 7.4 years, there was a significant 12% reduction in the primary efficacy end point (8.5% vs. 9.6%; P = 0.01). In contrast, major bleeding was significantly increased from 3.2 to 4.1% in the aspirin group (rate ratio 1.29; P = 0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There were no significant differences by sex, weight, or duration of diabetes or other baseline factors including ASCVD risk score.

Two other large, randomized trials of aspirin for primary prevention, in people without diabetes (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) (145) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (146), which included 11% with diabetes, found no benefit of aspirin on the primary efficacy end point and an increased risk of bleeding. In ARRIVE, with 12,546 patients over a period of 60 months follow-up, the primary end point occurred in 4.29% vs. 4.48% of patients in the aspirin versus placebo groups (HR 0.96 [95% CI 0.81–1.13]; P = 0.60). Gastrointestinal bleeding events (characterized as mild) occurred in 0.97% of patients in the aspirin group vs. 0.46% in the placebo group (HR 2.11 [95% CI 1.36–3.28]; P = 0.0007). In ASPREE, including 19,114 individuals, for cardiovascular disease (fatal CHD, MI, stroke, or hospitalization for heart failure) after a median of 4.7 years of follow-up, the rates per 1,000 person-years were 10.7 vs. 11.3 events in aspirin vs. placebo groups (HR 0.95 [95% CI 0.83–1.08]). The rate of major hemorrhage per 1,000 person-years was 8.6 events vs. 6.2 events, respectively (HR 1.38 [95% CI 1.18–1.62]; P < 0.001).

Thus, aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk. The main adverse effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1,000 per year in real-world settings. However, for adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (147).

Recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease) (148–151). Noninvasive imaging techniques such as coronary calcium scoring may potentially help further tailor aspirin therapy, particularly in those at low risk (152,153). For people >70 years of age (with or without diabetes), the balance appears to have greater risk than benefit (144,146). Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk, but generally not in older adults. Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.

For people with documented ASCVD, use of aspirin for secondary prevention has far greater benefit than risk; for this indication, aspirin is still recommended (139).

Aspirin Use in People <50 Years of Age

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding. Clinical judgment should be used for those at intermediate risk (younger patients

with one or more risk factors or older patients with no risk factors) until further research is available. Patients' willingness to undergo long-term aspirin therapy should also be considered (154). Aspirin use in patients aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving people with diabetes ranged from 50 mg to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose but using the lowest possible dose may help to reduce side effects (155). In the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial of individuals with established cardiovascular disease, 38% of whom had diabetes, there were no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily (156). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from people with diabetes have altered function, it is unclear what, if any, effect that finding has on the required dose of aspirin for cardioprotective effects in people with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A2 and thus are not sensitive to the effects of aspirin (157). "Aspirin resistance" has been described in people with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B2) (158), but other studies suggest no impairment in aspirin response among people with diabetes (159). A trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (160); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. Another meta-analysis raised the hypothesis that low-dose aspirin efficacy is reduced in those weighing >70 kg (161); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would thus not validate this suggested hypothesis (144). It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Receptor Antagonist Use

A P2Y12 receptor antagonist in combination with aspirin is reasonable for at least 1 year in patients following an ACS and may have benefits beyond this period. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (162). In people with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events including cardiovascular and CHD death (163). Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in people with diabetes and stable coronary artery disease (164,165). However, a higher incidence of major bleeding, including intracranial hemorrhage, was noted with dual antiplatelet therapy. The net clinical benefit (ischemic benefit vs. bleeding risk) was improved with ticagrelor therapy in the large prespecified subgroup of patients with history of percutaneous coronary intervention, while no net benefit was seen in patients without prior percutaneous coronary intervention (165). However, early aspirin discontinuation compared with continued dual antiplatelet therapy after coronary stenting may reduce the risk of bleeding without a corresponding increase in the risks of mortality and ischemic events, as shown in a prespecified analysis of people with diabetes enrolled in the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial and a recent meta-analysis (166,167).

Combination Antiplatelet and Anticoagulation Therapy

Combination therapy with aspirin plus low dose rivaroxaban may be considered for people with stable coronary and/or peripheral artery disease to prevent major adverse limb and cardiovascular complications. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies)

trial of 27,395 individuals with established coronary artery disease and/or peripheral artery disease, aspirin plus rivaroxaban 2.5 mg twice daily was superior to aspirin plus placebo in the reduction of cardiovascular ischemic events including major adverse limb events. The absolute benefits of combination therapy appeared larger in people with diabetes, who comprised 10,341 of the trial participants (168,169). A similar treatment strategy was evaluated in the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial (170), in which 6,564 individuals with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban 2.5 mg twice daily plus aspirin or placebo plus aspirin. Rivaroxaban treatment in this group of patients was also associated with a significantly lower incidence of ischemic cardiovascular events, including major adverse limb events. However, an increased risk of major bleeding was noted with rivaroxaban added to aspirin treatment in both COMPASS and VOYAGER PAD.

The risks and benefits of dual antiplatelet or antiplatelet plus anticoagulant treatment strategies should be thoroughly discussed with eligible patients, and shared decision-making should be used to determine an individually appropriate treatment approach. This field of cardiovascular risk reduction is evolving rapidly, as are the definitions of optimal care for patients with differing types and circumstances of cardiovascular complications.

Go to:

Cardiovascular Disease

Screening

Recommendations

10.39 In asymptomatic individuals, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. A

10.40 Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). E

Treatment

Recommendations

10.41 Among people with type 2 diabetes who have established atherosclerotic cardiovascular disease or established kidney disease, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (Table 10.3B and Table 10.3C) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. A

Table 10.3B

Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists

	ELIXA (208)	LEADER (203)	SUSTAIN-6 (204)*	EXSCEL (209)	REWIND (207)	PIONEER-6 (205)
	(n = 6,068)	(n = 9,340)	(n = 3,297)	(n = 14,752)	(n = 9,901)	(n = 3,183)
Intervention	Lixisenatide/placebo	Liraglutide/placebo	Semaglutide s.c. injection/placebo	Exenatide QW/ placebo	Dulaglutide/placebo	Semaglutide oral/ placebo
Main inclusion criteria	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes with or without		

preexisting CVD	Type 2 diabetes and prior ASCVD event or risk factors for ASCVD			Type 2 diabetes and high CV risk (age of ≥50 years with established CVD or CKD, or age of ≥60 years with CV risk factors only)						
A1C inclusion criteria (%)	5.5–11.0			≥7.0	≥7.0	6.5–10.0		≤9.5	None	
Age (years)†	60.3	64.3	64.6	62	66.2	66				
Race (% White)	75.2	77.5	83.0	75.8	75.7	72.3				
Sex (% male)	69.3	64.3	60.7	62	53.7	68.4				
Diabetes duration (years)†	9.3	12.8	13.9	12	10.5	14.9				
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3				
Statin use (%)	93	72	73	74	66	85.2 (all lipid-lowering)				
Metformin use (%)	66	76	73	77	81	77.4				
Prior CVD/CHF (%)	100/22	81/18	60/24	73.1/16.2		32/9	84.7/12.2			
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	7.4	8.2				
Mean difference in A1C between groups at end of treatment (%)	−0.3‡^	−0.4‡	−0.7 or −1.0^	−0.53‡^	−0.61‡	−0.7				
Year started/reported	2010/2015	2010/2016	2013/2016	2010/2017	2011/2019	2017/2019				
Primary outcome§	4-point MACE 1.02 (0.89–1.17)	3-point MACE 0.87 (0.78–0.97)	3-point MACE 0.74 (0.58–0.95)	3-point MACE 0.91 (0.83–1.00)	3-point MACE 0.88 (0.79–0.99)	3-point MACE 0.79 (0.57–1.11)				
Key secondary outcome§	Expanded MACE 1.02 (0.90–1.11)	Expanded MACE 0.88 (0.81–0.96)	Expanded MACE 0.74 (0.62–0.89)	Individual components of MACE (see below)						
Composite microvascular outcome (eye or renal outcome)	0.87 (0.79–0.95)	Expanded MACE or HF hospitalization 0.82 (0.61–1.10)								
Cardiovascular death§	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78–1.06)	0.49 (0.27–0.92)				
MI§	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79–1.15)	1.18 (0.73–1.90)				
Stroke§	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.76 (0.61–0.95)	0.74 (0.35–1.57)				
HF hospitalization§	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.93 (0.77–1.12)	0.86 (0.48–1.55)				
Unstable angina hospitalization§	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	1.14 (0.84–1.54)	1.56 (0.60–4.01)				
All-cause mortality§	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.51 (0.31–0.84)				
Worsening nephropathy§‖	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.85 (0.77–0.93)	—				

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—, not assessed/reported; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of Diabetes Care.

*Powered to rule out a hazard ratio of 1.8; superiority hypothesis not prespecified.

†Age was reported as means in all trials; diabetes duration was reported as means in all trials except EXSCEL, which reported medians.

‡Significant difference in A1C between groups ($P < 0.05$).

^AIC change of 0.66% with 0.5 mg and 1.05% with 1 mg dose of semaglutide.
§Outcomes reported as hazard ratio (95% CI).
‖Worsening nephropathy is defined as the new onset of urine albumin-to-creatinine ratio >300 mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of <45 mL/min/1.73 m2, the need for continuous renal replacement therapy, or death from renal disease in LEADER and SUSTAIN-6 and as new macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy in REWIND. Worsening nephropathy was a prespecified exploratory adjudicated outcome in LEADER, SUSTAIN-6, and REWIND.

Table 10.3C

Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

	EMPA-REG OUTCOME (8) (n = 7,020)		CANVAS Program (9) (n = 10,142)		DECLARE-TIMI 58 (196) (n = 17,160)		CREDENCE (194) (n = 4,401)	DAPA-CKD (197,239) (n = 4,304; 2,906 with diabetes)		VERTIS CV (201,240) (n = 8,246)	DAPA-HF (11) (n = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (200) (n = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (189,241) (n = 5,988; 2,938 with diabetes)	DELIVER (199) (n = 6,263; 2,807 with diabetes)
Intervention	Empagliflozin/placebo		Canagliflozin/placebo		Dapagliflozin/placebo		Canagliflozin/placebo	Dapagliflozin/placebo		Ertugliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo*	Empagliflozin/placebo	Dapagliflozin/placebo
Main inclusion criteria	Type 2 diabetes and preexisting CVD		Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 CV risk factors at ≥50 years of age		Type 2 diabetes and established ASCVD or multiple risk factors for ASCVD		Type 2 diabetes and albuminuric kidney disease	Albuminuric kidney disease, with or without diabetes		Type 2 diabetes and ASCVD	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction >40%	NYHA class II, III, or IV heart failure and an ejection fraction >40% with or without diabetes
A1C inclusion criteria (%)	7.0–10.0		7.0–10.5		≥6.5		6.5–12	—		7.0–10.5	—	—	—	—
Age (years)†	63.1	63.3	64.0	63	61.8	64.4	66	67.2, 66.5		71.8, 71.9	71.7			
Race (% White)	72.4	78.3	79.6	66.6	53.2	87.8	70.3	71.1, 69.8		76.3, 75.4	71.2			
Sex (% male)	71.5	64.2	62.6	66.1	66.9	70	76.6	76.5, 75.6		55.4, 55.3	56.1			
Diabetes duration (years)†	57% >10		13.5	11.0	15.8		12.9							
Median follow-up (years)	3.1	3.6	4.2	2.6	2.4	3.5	1.5	1.3	2.2	2.3				
Statin use (%)	77	75	75 (statin or ezetimibe use)		69	64.9	—	—	—	68.1, 68.8	—			
Metformin use (%)	74	77	82	57.8	29	51.2% (of people with diabetes)		—	—	—				
Prior CVD/CHF (%)	99/10	65.6/14.4		40/10	50.4/14.8	37.4/10.9		99.9/23.1	100% with CHF	100% with CHF	100% with CHF	100% with CHF		
Mean baseline A1C (%)	8.1	8.2	8.3	8.3	7.1% (7.8% in those with diabetes)			8.2						

— — — 6.6
Mean difference in A1C between groups at end of treatment (%) −0.3^ −0.58‡ −0.43‡ −0.31 —
−0.48 to −0.5 — — — —
Year started/reported 2010/2015 2009/2017 2013/2018 2017/2019 2017/2020
2013/2020 2017/2019 2017/2020 2017/2020 2018/2022
Primary outcome§ 3-point MACE 0.86 (0.74–0.99) 3-point MACE 0.86 (0.75–0.97) 3-point MACE
0.93 (0.84–1.03)
CV death or HF hospitalization 0.83 (0.73–0.95) ESRD, doubling of creatinine, or death from renal or CV
cause 0.70 (0.59–0.82) ≥50% decline in eGFR, ESKD, or death from renal or CV cause 0.61 (0.51–0.72)
3-point MACE 0.97 (0.85–1.11) Worsening heart failure or death from CV causes 0.74 (0.65–0.85)
Results did not differ by diabetes status CV death or HF hospitalization 0.75 (0.65–0.86) CV death or HF
hospitalization 0.79 (0.69–0.90) Worsening HF or CV death 0.82 (0.73–0.92)
Key secondary outcome§ 4-point MACE 0.89 (0.78–1.01) All-cause and CV mortality (see below)
Death from any cause 0.93 (0.82–1.04)
Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m2, new ESRD, or death from renal or
CV causes 0.76 (0.67–0.87) CV death or HF hospitalization 0.69 (0.57–0.83)
3-point MACE 0.80 (0.67–0.95) ≥50% decline in eGFR, ESKD, or death from renal cause 0.56 (0.45–0.68)
CV death or HF hospitalization 0.71 (0.55–0.92)
Death from any cause 0.69 (0.53–0.88) CV death or HF hospitalization 0.88 (0.75–1.03)
CV death 0.92 (0.77–1.11)
Renal death, renal replacement therapy, or doubling of creatinine 0.81 (0.63–1.04) CV death or HF
hospitalization 0.75 (0.65–0.85) Total HF hospitalizations 0.70 (0.58–0.85)
Mean slope of change in eGFR 1.73 (1.10–2.37) All HF hospitalizations (first and recurrent) 0.73
(0.61–0.88)
Rate of decline in eGFR (−1.25 vs. −2.62 mL/min/1.73 m2; P < 0.001) Total number worsening HF and
CV deaths 0.77 (0.67–0.89)
Change in KCCQ TSS at month 8 1.11 (1.03–1.21)
Mean change in KCCQ TSS 2.4 (1.5–3.4)
All-cause mortality 0.94 (0.83–1.07)
Cardiovascular death§ 0.62 (0.49–0.77) 0.87 (0.72–1.06) 0.98 (0.82–1.17) 0.78
(0.61–1.00) 0.81 (0.58–1.12) 0.92 (0.77–1.11) 0.82 (0.69–0.98) 0.92
(0.75–1.12) 0.91 (0.76–1.09) 0.88 (0.74–1.05)
MI§ 0.87 (0.70–1.09) 0.89 (0.73–1.09) 0.89 (0.77–1.01) — — 1.04
(0.86–1.26) — — — —
Stroke§ 1.18 (0.89–1.56) 87 (0.69–1.09) 1.01 (0.84–1.21) — — 1.06
(0.82–1.37) — — — —
HF hospitalization§ 0.65 (0.50–0.85) 67 (0.52–0.87) 0.73 (0.61–0.88) 0.61
(0.47–0.80) — 0.70 (0.54–0.90) 0.70 (0.59–0.83) 0.69 (0.59–0.81) 0.73
(0.61–0.88) 0.77 (0.67–0.89)
Unstable angina hospitalization§ 0.99 (0.74–1.34) — — — — —
— — — — —
All-cause mortality§ 0.68 (0.57–0.82) 87 (0.74–1.01) 0.93 (0.82–1.04) 0.83
(0.68–1.02) 0.69 (0.53–0.88) 0.93 (0.80–1.08) 0.83 (0.71–0.97) 0.92
(0.77–1.10) 1.00 (0.87–1.15) 0.94 (0.83–1.07)
Worsening nephropathy§‖ 0.61 (0.53–0.70) 0.60 (0.47–0.77) 0.53 (0.43–0.66)
(See primary outcome) (See primary outcome) (See secondary outcomes) 0.71 (0.44–1.16)
Composite renal outcome 0.50 (0.32–0.77) Composite renal outcome** 0.95 (0.73–1.24) —
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—, not assessed/reported; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MACE, major adverse cardiovascular event; Ml, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; NYFIA, New York Fleart Association. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of Diabetes Care.

*Baseline characteristics for EMPEROR-Reduced displayed as empagliflozin, placebo.
†Age was reported as means in all trials; diabetes duration was reported as means in all trials except EMPA-REG OUTCOME, which reported as percentage of population with diabetes duration >10 years, and DECLARE-TIMI 58, which reported median.
‡Significant difference in A1C between groups ($P < 0.05$).
^AIC change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin).
§Outcomes reported as hazard ratio (95% Cl).
‖Definitions of worsening nephropathy differed between trials.
**Composite outcome in EMPEROR-Preserved: time to first occurrence of chronic dialysis, renal transplantation; sustained reduction of ≥40% in eGFR, sustained eGFR <15 mL/min/1.73 m2 for individuals with baseline eGFR ≥30 mL/min/1.73 m2.
10.41a In people with type 2 diabetes and established atherosclerotic cardiovascular disease, multiple atherosclerotic cardiovascular disease risk factors, or diabetic kidney disease, a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. A
10.41b In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. A
10.41c In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, combined therapy with a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit and a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit may be considered for additive reduction in the risk of adverse cardiovascular and kidney events. A
10.42a In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. A
10.42b In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to improve symptoms, physical limitations, and quality of life. A
10.43 For people with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or angiotensin receptor blocker, addition of finerenone is recommended to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression. A
10.44 In people with known atherosclerotic cardiovascular disease, particularly coronary artery disease, ACE inhibitor or angiotensin receptor blocker therapy is recommended to reduce the risk of cardiovascular events. A
10.45 In people with prior myocardial infarction, β-blockers should be continued for 3 years after the event. B
10.46 Treatment of individuals with heart failure with reduced ejection fraction should include a

β-blocker with proven cardiovascular outcomes benefit, unless otherwise contraindicated. A
10.47 In people with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if estimated glomerular filtration rate remains >30 mL/min/1.73 m2 but should be avoided in unstable or hospitalized individuals with heart failure. B

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with 1) typical or atypical cardiac symptoms and 2) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

Screening Asymptomatic Patients

The screening of asymptomatic patients with high ASCVD risk is not recommended (171), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides benefit similar to invasive revascularization (172,173). There is also some evidence that silent ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies (174). In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in people with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (175–177). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic people with type 2 diabetes and normal ECGs (178). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, indiscriminate screening is not considered cost-effective. Studies have found that a risk factor-based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which people with type 2 diabetes will have silent ischemia on screening tests (179,180).

Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven in asymptomatic people with diabetes, though research is ongoing. Since asymptomatic people with diabetes with higher coronary disease burden have more future cardiac events (175,181,182), these additional imaging tests may provide reasoning for treatment intensification and/or guide informed patient decision-making and willingness for medication initiation and participation.

While coronary artery screening methods, such as calcium scoring, may improve cardiovascular risk assessment in people with type 2 diabetes (183), their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Lifestyle and Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Action for Health in Diabetes (Look AHEAD) trial may be considered for improving glucose control, fitness, and some ASCVD risk factors (184). Patients at increased ASCVD

risk should receive statin, ACE inhibitor, or ARB therapy if the patient has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class. Clear benefit exists for ACE inhibitor or ARB therapy in people with diabetic kidney disease or hypertension, and these agents are recommended for hypertension management in people with known ASCVD (particularly coronary artery disease) (65,66,185). People with type 2 diabetes and CKD should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of CKD progression (186–189). β-Blockers should be used in individuals with active angina or HFrEF and for 3 years after MI in those with preserved left ventricular function (190,191).

Glucose-Lowering Therapies and Cardiovascular Outcomes

In 2008, the FDA issued a guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment for type 2 diabetes amid concerns of increased cardiovascular risk (192). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular and renal outcomes in people with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease (Table 10.3A, Table 10.3B, and Table 10.3C). An expanded review of the effects of glucose-lowering and other therapies in people with CKD is included in Section 11, "Chronic Kidney Disease and Risk Management."

Table 10.3A

Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: DPP-4 inhibitors

SAVOR-TIMI 53 (224)	EXAMINE (235)	TECOS (226)	CARMELINA (193,236)	CAROLINA (193,237)
(n = 16,492)	(n = 5,380)	(n = 14,671)	(n = 6,979)	(n = 6,042)
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo	Linagliptin/placebo	Linagliptin/glimepiride
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and high CV and renal risk	Type 2 diabetes and high CV risk
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	6.5–10.0	6.5–8.5
Age (years)†	65.1	61.0	65.4	65.8	64.0
Race (% White)	75.2	72.7	67.9	80.2	73.0
Sex (% male)	66.9	67.9	70.7	62.9	60.0
Diabetes duration (years)†	10.3	7.1	11.6	14.7	6.2
Median follow-up (years)	2.1	1.5	3.0	2.2	6.3
Statin use (%)	78	91	80	71.8	64.1
Metformin use (%)	70	66	82	54.8	82.5
Prior CVD/CHF (%)	78/13	100/28	74/18	57/26.8	34.5/4.5
Mean baseline A1C (%)	8.0	8.0	7.2	7.9	7.2
Mean difference in A1C between groups at end of treatment (%)	−0.3‡	−0.3‡	−0.3‡	−0.36‡	0
Year started/reported	2010/2013	2009/2013	2008/2015	2013/2018	2010/2019
Primary outcome§	3-point MACE 1.00 (0.89–1.12)	3-point MACE 0.96 (95% UL ≤1.16)	4-point MACE 0.98 (0.89–1.08)	3-point MACE 1.02 (0.89–1.17)	3-point MACE 0.98 (0.84–1.14)
Key secondary outcome§	Expanded MACE 1.02 (0.94–1.11)	4-point MACE 0.95 (95% UL ≤1.14)	3-point MACE 0.99 (0.89–1.10)	Kidney composite (ESRD, sustained ≥40% decrease in eGFR, or renal death) 1.04 (0.89–1.22)	4-point MACE 0.99 (0.86–1.14)
Cardiovascular death§	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.96 (0.81–1.14)	1.00 (0.81–1.24)

MI§ 0.95 (0.80–1.12) 1.08 (0.88–1.33) 0.95 (0.81–1.11) 1.12 (0.90–1.40) 1.03 (0.82–1.29)
Stroke§ 1.11 (0.88–1.39) 0.91 (0.55–1.50) 0.97 (0.79–1.19) 0.91 (0.67–1.23) 0.86 (0.66–1.12)
HF hospitalization§ 1.27 (1.07–1.51) 1.19 (0.90–1.58) 1.00 (0.83–1.20) 0.90 (0.74–1.08) 1.21 (0.92–1.59)
Unstable angina hospitalization§ 1.19 (0.89–1.60) 0.90 (0.60–1.37) 0.90 (0.70–1.16) 0.87 (0.57–1.31) 1.07 (0.74–1.54)
All-cause mortality§ 1.11 (0.96–1.27) 0.88 (0.71–1.09) 1.01 (0.90–1.14) 0.98 (0.84–1.13) 0.91 (0.78–1.06)
Worsening nephropathy§‖ 1.08 (0.88–1.32) — — Kidney composite (see above) —
Open in a separate window
—, not assessed/reported; ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; UL, upper limit. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of Diabetes Care.

†Age was reported as means in all trials except EXAMINE, which reported medians; diabetes duration was reported as means in all trials except SAVOR-TIMI 53 and EXAMINE, which reported medians.
‡Significant difference in A1C between groups ($P < 0.05$).
§Outcomes reported as hazard ratio (95% CI).
‖Worsening nephropathy is defined as a doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L) in SAVOR-TIMI 53. Worsening nephropathy was a prespecified exploratory adjudicated outcome in SAVOR-TIMI 53.
Cardiovascular outcomes trials of dipeptidyl peptidase 4 (DPP-4) inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. In addition, the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes) study demonstrated noninferiority between a DPP-4 inhibitor, linagliptin, and a sulfonylurea, glimepiride, on cardiovascular outcomes despite lower rates of hypoglycemia in the linagliptin treatment group (193). However, results from other new agents have provided a mix of results.

SGLT2 Inhibitor Trials The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, an SGLT2 inhibitor, versus placebo on cardiovascular outcomes in 7,020 people with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group, HR in the empagliflozin group 0.86 [95% CI 0.74–0.99]; $P = 0.04$ for superiority) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%, HR 0.62 [95% CI 0.49–0.77]; $P < 0.001$) (8).
Two large outcomes trials of the SGLT2 inhibitor canagliflozin have been conducted that separately assessed 1) the cardiovascular effects of treatment in patients at high risk for major adverse cardiovascular events (9) and 2) the impact of canagliflozin therapy on cardiorenal outcomes in people with diabetes-related CKD (194). First, the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program integrated data from two trials. The CANVAS trial that started in 2009 was partially unblinded prior to completion because of the need to file interim cardiovascular outcomes data for regulatory

approval of the drug (195). Thereafter, the post approval CANVAS-Renal (CANVAS-R) trial was started in 2014. Combining both trials, 10,142 participants with type 2 diabetes were randomized to canagliflozin or placebo and were followed for an average 3.6 years. The mean age of patients was 63 years, and 66% had a history of cardiovascular disease. The combined analysis of the two trials found that canagliflozin significantly reduced the composite outcome of cardiovascular death, MI, or stroke versus placebo (occurring in 26.9 vs. 31.5 participants per 1,000 patient-years; HR 0.86 [95% CI 0.75–0.97]). The specific estimates for canagliflozin versus placebo on the primary composite cardiovascular outcome were HR 0.88 (95% CI 0.75–1.03) for the CANVAS trial and 0.82 (0.66–1.01) for CANVAS-R, with no heterogeneity found between trials. Of note, there was an increased risk of lower-limb amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 patient-years; HR 1.97 [95% CI 1.41–2.75]) (9). Second, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial randomized 4,401 people with type 2 diabetes and chronic diabetes-related kidney disease (UACR >300 mg/g and eGFR 30 to <90 mL/min/1.73 m2) to canagliflozin 100 mg daily or placebo (194). The primary outcome was a composite of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes. The trial was stopped early due to conclusive evidence of efficacy identified during a prespecified interim analysis with no unexpected safety signals. The risk of the primary composite outcome was 30% lower with canagliflozin treatment when compared with placebo (HR 0.70 [95% CI 0.59–0.82]). Moreover, it reduced the prespecified end point of end-stage kidney disease alone by 32% (HR 0.68 [95% CI 0.54–0.86]). Canagliflozin was additionally found to have a lower risk of the composite of cardiovascular death, MI, or stroke (HR 0.80 [95% CI 0.67–0.95]), as well as lower risk of hospitalizations for heart failure (HR 0.61 [95% CI 0.47–0.80]) and of the composite of cardiovascular death or hospitalization for heart failure (HR 0.69 [95% CI 0.57–0.83]). In terms of safety, no significant increase in lower-limb amputations, fractures, acute kidney injury, or hyperkalemia was noted for canagliflozin relative to placebo in CREDENCE. An increased risk for diabetic ketoacidosis was noted, however, with 2.2 and 0.2 events per 1,000 patient-years noted in the canagliflozin and placebo groups, respectively (HR 10.80 [95% CI 1.39–83.65]) (194).

The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial was another randomized, double-blind trial that assessed the effects of dapagliflozin versus placebo on cardiovascular and renal outcomes in 17,160 people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD (196). Study participants had a mean age of 64 years, with ~40% of study participants having established ASCVD at baseline—a characteristic of this trial that differs from other large cardiovascular trials where a majority of participants had established cardiovascular disease. DECLARE-TIMI 58 met the prespecified criteria for noninferiority to placebo with respect to major adverse cardiovascular events but did not show a lower rate of major adverse cardiovascular events when compared with placebo (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93 [95% CI 0.84–1.03]; P = 0.17). A lower rate of cardiovascular death or hospitalization for heart failure was noted (4.9% vs. 5.8%; HR 0.83 [95% CI 0.73–0.95]; P = 0.005), which reflected a lower rate of hospitalization for heart failure (HR 0.73 [95% CI 0.61–0.88]). No difference was seen in cardiovascular death between groups.

In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial (197), 4,304 individuals with CKD (UACR 200–5,000 mg/g and eGFR 25–75 mL/min/1.73 m2), with or without diabetes, were randomized to dapagliflozin 10 mg daily or placebo. The primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Over a median follow-up period of 2.4 years, a primary outcome event occurred in 9.2% of participants in the dapagliflozin group and 14.5% of those in the placebo group. The risk of the primary composite outcome was significantly lower with dapagliflozin therapy compared with placebo

(HR 0.61 [95% CI 0.51–0.72]), as were the risks for a renal composite outcome of sustained decline in eGFR of at least 50%, endstage kidney disease, or death from renal causes (HR 0.56 [95% CI 0.45–0.68]), and a composite of cardiovascular death or hospitalization for heart failure (HR 0.71 [95% CI 0.55–0.92]). The effects of dapagliflozin therapy were similar in individuals with and without type 2 diabetes.

Results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF), and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER), which assessed the effects of dapagliflozin and empagliflozin in individuals with established heart failure (11,189,198,199,200), are described below in glucose-lowering therapies and heart failure.

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) (201) was a randomized, double-blind trial that established the effects of ertugliflozin versus placebo on cardiovascular outcomes in 8,246 people with type 2 diabetes and established ASCVD. Participants were assigned to the addition of 5 mg or 15 mg of ertugliflozin or to placebo once daily to background standard care. Study participants had a mean age of 64.4 years and a mean duration of diabetes of 13 years at baseline and were followed for a median of 3.0 years. VERTIS CV met the prespecified criteria for noninferiority of ertugliflozin to placebo with respect to the primary outcome of major adverse cardiovascular events (11.9% in the pooled ertugliflozin group and 11.9% in the placebo group; HR 0.97 [95% CI 0.85–1.11]; $P < 0.001$). Ertugliflozin was not superior to placebo for the key secondary outcomes of death from cardiovascular causes or hospitalization for heart failure; death from cardiovascular causes; or the composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level. The HR for a secondary outcome of hospitalization for heart failure (ertugliflozin vs. placebo) was 0.70 [95% CI 0.54–0.90], consistent with findings from other SGLT2 inhibitor cardiovascular outcomes trials.

Sotagliflozin, an SGLT1 and SGLT2 inhibitor not currently approved by the FDA in the U.S., lowers glucose via delayed glucose absorption in the gut in addition to increasing urinary glucose excretion and has been evaluated in the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial (202). A total of 10,584 people with type 2 diabetes, CKD, and additional cardiovascular risk were enrolled in SCORED and randomized to sotagliflozin 200 mg once daily (uptitrated to 400 mg once daily if tolerated) or placebo. SCORED ended early due to a lack of funding; thus, changes to the prespecified primary end points were made prior to unblinding to accommodate a lower than anticipated number of end point events. The primary end point of the trial was the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. After a median of 16 months of follow-up, the rate of primary end point events was reduced with sotagliflozin (5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group [HR 0.74 (95% CI 0.63–0.88); $P < 0.001$]). Sotagliflozin also reduced the risk of the secondary end point of total number of hospitalizations for heart failure and urgent visits for heart failure (3.5% in the sotagliflozin group and 5.1% in the placebo group; HR 0.67 [95% CI 0.55–0.82]; $P < 0.001$) but not the secondary end point of deaths from cardiovascular causes. No significant between-group differences were found for the outcome of all-cause mortality or for a composite renal outcome comprising the first occurrence of long-term dialysis, renal transplantation, or a sustained reduction in eGFR. In general, the adverse effects of sotagliflozin were similar to those seen with use of SGLT2 inhibitors, but they also

included an increased rate of diarrhea potentially related to the inhibition of SGLT1.

GLP-1 Receptor Agonist Trials The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, versus placebo on cardiovascular outcomes in 9,340 people with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease (203). Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, LEADER showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) (HR 0.87 [95% CI 0.78–0.97]; P < 0.001 for noninferiority; P = 0.01 for superiority). Deaths from cardiovascular causes were significantly reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (HR 0.78 [95% CI 0.66–0.93]; P = 0.007) (203).
Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (204). Semaglutide is a once-weekly GLP-1 receptor agonist approved by the FDA for the treatment of type 2 diabetes. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) was the initial randomized trial powered to test noninferiority of semaglutide for the purpose of regulatory approval (204). In this study, 3,297 people with type 2 diabetes were randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 2 years. The primary outcome (the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) occurred in 108 patients (6.6%) in the semaglutide group vs. 146 patients (8.9%) in the placebo group (HR 0.74 [95% CI 0.58–0.95]; P < 0.001). More patients discontinued treatment in the semaglutide group because of adverse events, mainly gastrointestinal. The cardiovascular effects of the oral formulation of semaglutide compared with placebo have been assessed in Peptide Innovation for Early Diabetes Treatment (PIONEER) 6, a preapproval trial designed to rule out an unacceptable increase in cardiovascular risk (205). In this trial of 3,183 people with type 2 diabetes and high cardiovascular risk followed for a median of 15.9 months, oral semaglutide was noninferior to placebo for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (HR 0.79 [95% CI 0.57–1.11]; P < 0.001 for noninferiority) (205). The cardiovascular effects of this formulation of semaglutide will be further tested in a large, longer-term outcomes trial.

The Harmony Outcomes trial randomized 9,463 people with type 2 diabetes and cardiovascular disease to once-weekly subcutaneous albiglutide or matching placebo, in addition to their standard care (206). Over a median duration of 1.6 years, the GLP-1 receptor agonist reduced the risk of cardiovascular death, MI, or stroke to an incidence rate of 4.6 events per 100 person-years in the albiglutide group vs. 5.9 events in the placebo group (HR ratio 0.78, P = 0.0006 for superiority) (206). This agent is not currently available for clinical use.

The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial was a randomized, double-blind, placebo-controlled trial that assessed the effect of the once-weekly GLP-1 receptor agonist dulaglutide versus placebo on major adverse cardiovascular events in ~9,990 people with type 2 diabetes at risk for cardiovascular events or with a history of cardiovascular disease (207). Study participants had a mean age of 66 years and a mean duration of diabetes of ~10 years. Approximately 32% of participants had history of atherosclerotic cardiovascular events at baseline. After a median follow-up of 5.4 years, the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes occurred in 12.0% and 13.4% of participants in the dulaglutide and placebo treatment groups, respectively (HR 0.88 [95% CI 0.79–0.99]; P = 0.026). These findings equated to incidence rates of 2.4 and 2.7 events per 100 person-years, respectively. The results were consistent

across the subgroups of patients with and without history of CV events. Allcause mortality did not differ between groups (P = 0.067).

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial studied the once-daily GLP-1 receptor agonist lixisenatide on cardiovascular outcomes in people with type 2 diabetes who had had a recent acute coronary event (208). A total of 6,068 people with type 2 diabetes with a recent hospitalization for MI or unstable angina within the previous 180 days were randomized to receive lixisenatide or placebo in addition to standard care and were followed for a median of ~2.1 years. The primary outcome of cardiovascular death, MI, stroke, or hospitalization for unstable angina occurred in 406 patients (13.4%) in the lixisenatide group vs. 399 (13.2%) in the placebo group (HR 1.2 [95% CI 0.89–1.17]), which demonstrated the noninferiority of lixisenatide to placebo (P < 0.001) but did not show superiority (P = 0.81).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial also reported results with the once-weekly GLP-1 receptor agonist extended-release exenatide and found that major adverse cardiovascular events were numerically lower with use of extended-release exenatide compared with placebo, although this difference was not statistically significant (209). A total of 14,752 people with type 2 diabetes (of whom 10,782 [73.1%] had previous cardiovascular disease) were randomized to receive extended-release exenatide 2 mg or placebo and followed for a median of 3.2 years. The primary end point of cardiovascular death, MI, or stroke occurred in 839 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR 0.91 [95% CI 0.83–1.00]; P < 0.001 for noninferiority), but exenatide was not superior to placebo with respect to the primary end point (P = 0.06 for superiority). However, all-cause mortality was lower in the exenatide group (HR 0.86 [95% CI 0.77–0.97]). The incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

In summary, there are now numerous large randomized controlled trials reporting statistically significant reductions in cardiovascular events for three of the FDA-approved SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, with lesser benefits seen with ertugliflozin) and four FDA-approved GLP-1 receptor agonists (liraglutide, albiglutide [although that agent was removed from the market for business reasons], semaglutide [lower risk of cardiovascular events in a moderate-sized clinical trial but one not powered as a cardiovascular outcomes trial], and dulaglutide). Meta-analyses of the trials reported to date suggest that GLP-1 receptor agonists and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in people with type 2 diabetes and established ASCVD (210,211). SGLT2 inhibitors also reduce risk of heart failure hospitalization and progression of kidney disease in people with established ASCVD, multiple risk factors for ASCVD, or albuminuric kidney disease (212,213). In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. For many patients, use of either an SGLT2 inhibitor or a GLP-1 receptor agonist to reduce cardiovascular risk is appropriate. Emerging data suggest that use of both classes of drugs will provide an additive cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist may be considered to provide the complementary outcomes benefits associated with these classes of medication. Evidence to support such an approach includes findings from AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes), an outcomes

trial of people with type 2 diabetes and either cardiovascular or kidney disease plus at least one other risk factor randomized to the investigational GLP-1 receptor agonist efpeglenatide or placebo (214). Randomization was stratified by current or potential use of SGLT2 inhibitor therapy, a class ultimately used by >15% of the trial participants. Over a median follow-up of 1.8 years, efpeglenatide therapy reduced the risk of incident major adverse cardiovascular events by 27% and of a composite renal outcome event by 32%. Importantly, the effects of efpeglenatide did not vary by use of SGLT2 inhibitors, suggesting that the beneficial effects of the GLP-1 receptor agonist were independent of those provided by SGLT2 inhibitor therapy (215). Efpeglenatide is currently not approved by the FDA for use in the U.S.

Glucose-Lowering Therapies and Heart Failure As many as 50% of people with type 2 diabetes may develop heart failure (216). These conditions, which are each associated with increased morbidity and mortality, commonly coincide, and independently contribute to adverse outcomes (217). Strategies to mitigate these risks are needed, and the heart failure-related risks and benefits of glucose-lowering medications should be considered carefully when determining a regimen of care for people with diabetes and either established heart failure or high risk for the development of heart failure.
Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure (218–220). Therefore, thiazolidinedione use should be avoided in people with symptomatic heart failure. Restrictions to use of metformin in people with medically treated heart failure were removed by the FDA in 2006 (221). Observational studies of people with type 2 diabetes and heart failure suggest that metformin users have better outcomes than individuals treated with other antihyperglycemic agents (222); however, no randomized trial of metformin therapy has been conducted in people with heart failure. Metformin may be used for the management of hyperglycemia in people with stable heart failure as long as kidney function remains within the recommended range for use (223).

Recent studies examining the relationship between DPP-4 inhibitors and heart failure have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that patients treated with the DPP-4 inhibitor saxagliptin were more likely to be hospitalized for heart failure than those given placebo (3.5% vs. 2.8%, respectively) (224). However, three other cardiovascular outcomes trials—Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (225), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (226), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (193)—did not find a significant increase in risk of heart failure hospitalization with DPP-4 inhibitor use compared with placebo. No increased risk of heart failure hospitalization has been identified in the cardiovascular outcomes trials of the GLP-1 receptor agonists lixisenatide, liraglutide, semaglutide, exenatide once-weekly, albiglutide, or dulaglutide compared with placebo (Table 10.3B) (203,204,207–209).

Reduced incidence of heart failure has been observed with the use of SGLT2 inhibitors (8,194,196). In EMPA- REG OUTCOME, the addition of empagliflozin to standard care led to a significant 35% reduction in hospitalization for heart failure compared with placebo (8). Although the majority of patients in the study did not have heart failure at baseline, this benefit was consistent in patients with and without a history of heart failure (10). Similarly, in CANVAS and DECLARE-TIMI 58, there were 33% and 27% reductions in hospitalization for heart failure, respectively, with SGLT2 inhibitor use versus placebo (9,196). Additional data from the CREDENCE trial with canagliflozin showed a 39% reduction in hospitalization for heart failure, and 31% reduction in the composite of cardiovascular death or hospitalization for heart failure, in a diabetic kidney disease population with albuminuria (UACR >300 to 5,000 mg/g) (194). These combined findings from four large outcomes trials of three different SGLT2

inhibitors are highly consistent and clearly indicate robust benefits of SGLT2 inhibitors in the prevention of heart failure hospitalizations. The EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE trials suggested, but did not prove, that SGLT2 inhibitors would be beneficial in the treatment of people with established heart failure. More recently, the placebo-controlled DAPA-HF trial evaluated the effects of dapagliflozin on the primary outcome of a composite of worsening heart failure or cardiovascular death in patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less. Of the 4,744 trial participants, 45% had a history of type 2 diabetes. Over a median of 18.2 months, the group assigned to dapagliflozin treatment had a lower risk of the primary outcome (HR 0.74 [95% CI 0.65–0.85]), lower risk of first worsening heart failure event (HR 0.70 [95% CI 0.59–0.83]), and lower risk of cardiovascular death (HR 0.82 [95% CI 0.69–0.98]) compared with placebo. The effect of dapagliflozin on the primary outcome was consistent regardless of the presence or absence of type 2 diabetes (11).

EMPEROR-Reduced assessed the effects of empagliflozin 10 mg once daily versus placebo on a primary composite outcome of cardiovascular death or hospitalization for worsening heart failure in a population of 3,730 patients with NYHA class II, III, or IV heart failure and an ejection fraction of 40% or less (200). At baseline, 49.8% of participants had a history of diabetes. Over a median follow-up of 16 months, those in the empagliflozin-treated group had a reduced risk of the primary outcome (HR 0.75 [95% CI 0.65–0.86]; P < 0.001) and fewer total hospitalizations for heart failure (HR 0.70 [95% CI 0.58–0.85]; P < 0.001). The effect of empagliflozin on the primary outcome was consistent irrespective of diabetes diagnosis at baseline. The risk of a prespecified renal composite outcome (chronic dialysis, renal transplantation, or a sustained reduction in eGFR) was lower in the empagliflozin group than in the placebo group (1.6% in the empagliflozin group vs. 3.1% in the placebo group; HR 0.50 [95% CI 0.32–0.77]).

EMPEROR-Preserved, a randomized double-blinded placebo-controlled trial of 5,988 adults with NYHA functional class I–IV chronic HFpEF (left ventricular ejection fraction >40%), evaluated the efficacy of empagliflozin 10 mg daily versus placebo on top of standard of care on the primary outcome of composite cardiovascular death or hospitalization for heart failure (189). Approximately 50% of subjects had type 2 diabetes at baseline. Over a median of 26.2 months, there was a 21% reduction (HR 0.79 [95% CI 0.69–0.90]; P < 0.001) of the primary outcome. The effects of empagliflozin were consistent in people with or without diabetes (189).

In the DELIVER trial, 6,263 individuals with heart failure and an ejection fraction >40% were randomized to receive either dapagliflozin or placebo (199). The primary outcome of a composite of worsening heart failure, defined as hospitalization or urgent visit for heart failure, or cardiovascular death was reduced by 18% in patients treated with dapagliflozin compared with placebo (HR 0.82 [95% CI 0.73–0.92]; P < 0.001). Approximately 44% of patients randomized to either dapagliflozin or placebo had type 2 diabetes, and results were consistent regardless of the presence of type 2 diabetes.

A large recent meta-analysis (227) including data from EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, DELIVER, and Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) included 21,947 patients and demonstrated reduced risk for the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, first hospitalization for heart failure, and all-cause mortality. The findings on the studied end points were consistent in both trials of heart failure with mildly reduced or preserved ejection fraction and in all five trials combined. Collectively, these studies indicate that SGLT2 inhibitors reduce the risk for heart failure hospitalization and cardiovascular death in a wide range of people with heart failure.

Additional data are accumulating regarding the effects of SGLT inhibition in people hospitalized for acute decompensated heart failure and in people with heart failure and HFpEF. As an example, the investigational SGLT1 and SGLT2 inhibitor sotagliflozin has also been studied in the SOLOIST-WHF trial (228). In SOLOIST-WHF, 1,222 people with type 2 diabetes who were recently hospitalized for worsening heart failure were randomized to sotagliflozin 200 mg once daily (with uptitration to 400 mg once daily if tolerated) or placebo either before or within 3 days after hospital discharge. Patients were eligible if hospitalized for signs and symptoms of heart failure (including elevated natriuretic peptide levels) requiring treatment with intravenous diuretic therapy. Exclusion criteria included end-stage heart failure or recent acute coronary syndrome or intervention, or an eGFR <30 mL/min/1.73 m2). Patients were required to be clinically stable prior to randomization, defined as no use of supplemental oxygen, a systolic blood pressure ≥100 mmHg, and no need for intravenous inotropic or vasodilator therapy other than nitrates. Similar to SCORED, SOLOIST-WHF ended early due to a lack of funding, resulting in a change to the prespecified primary end point prior to unblinding to accommodate a lower than anticipated number of end point events. At a median follow-up of 9 months, the rate of primary end point events (the total number of cardiovascular deaths and hospitalizations and urgent visits for heart failure) was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; HR 0.67 [95% CI 0.52–0.85]; P < 0.001). No significant between-group differences were found in the rates of cardiovascular death or all-cause mortality. Both diarrhea (6.1% vs. 3.4%) and severe hypoglycemia (1.5% vs. 0.3%) were more common with sotagliflozin than with placebo. The trial was originally also intended to evaluate the effects of SGLT inhibition in people with HFpEF, and ultimately no evidence of heterogeneity of treatment effect by ejection fraction was noted. However, the relatively small percentage of such patients enrolled (only 21% of participants had ejection fraction >50%) and the early termination of the trial limited the ability to determine the effects of sotagliflozin in HFpEF specifically.

In addition to the hospitalization and mortality benefit in people with heart failure, several recent analyses have addressed whether SGLT2 inhibitor treatment improves clinical stability and functional status in individuals with heart failure. In 3,730 patients with NYHA class II–IV heart failure with an ejection fraction of ≤40%, treatment with empagliflozin reduced the combined risk of death, hospitalization for heart failure, or an emergent/urgent heart failure visit requiring intravenous treatment and reduced the total number of hospitalizations for heart failure requiring intensive care, a vasopressor or positive inotropic drug, or mechanical or surgical intervention (229). In addition, patients treated with empagliflozin were more likely to experience an improvement in NYHA functional class (229). In people hospitalized for acute de novo or decompensated chronic heart failure, initiation of empagliflozin treatment during hospitalization reduced the primary outcome of a composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (230). Furthermore, PRESERVED-HF, a multicenter study (26 sites in the U.S.) showed that dapagliflozin treatment leads to significant improvement in both symptoms and physical limitation, as well as objective measures of exercise function in people with chronic HFpEF, regardless of diabetes status (198). Finally, canagliflozin improved heart failure symptoms assessed using the Kansas City Cardiomyopathy Questionnaire Total Symptom Score, irrespective of left ventricular ejection fraction or the presence of diabetes (231). Therefore, in people with type 2 diabetes and established HFpEF or HFrEF, an SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce the risk of worsening heart failure and cardiovascular death. In addition, an SGLT2 inhibitor is recommended in this patient population to improve symptoms, physical limitations, and quality of life. The benefits seen in this patient population likely represent a class effect, and they appear unrelated to glucose lowering given comparable outcomes in people with heart failure with and without diabetes.

Finerenone in People with Type 2 Diabetes and Chronic Kidney Disease As discussed in detail in Section 11, “Chronic Kidney Disease and Risk Management,” people with diabetes are at an increased risk for CKD, which increases cardiovascular risk (232). Finerenone, a selective nonsteroidal mineralocorticoid antagonist, has been shown in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial to improve CKD outcomes in people with type 2 diabetes with stage 3 or 4 CKD and severe albuminuria (233). In the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial, 7,437 patients with UACR 30–300 mg/g and eGFR 25–90 mL/min/1.73 m2 or UACR 300–5,000 and eGFR ≥60 mL/min/1.73 m2 on maximum dose of renin-angiotensin system blockade were randomized to receive finerenone or placebo (186). The HR of the primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization from heart failure was reduced by 13% in patients treated with finerenone. A prespecified subgroup analysis from FIGARO-DKD further revealed that in patients without symptomatic HFrEF, finerenone reduces the risk for new-onset heart failure and improves heart failure outcomes in people with type 2 diabetes and CKD (187). Finally, in the pooled analysis of 13,026 people with type 2 diabetes and CKD from both FIDELIO-DKD and FIGARO-DKD, the HRs for the composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure as well as a composite of kidney failure, a sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death were 0.86 and 0.77, respectively (188). These collective studies indicate that finerenone improves cardiovascular and renal outcomes in people with type 2 diabetes. Therefore, in people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, addition of finernone should be considered to improve cardiovascular outcomes and reduce the risk of CKD progression.
Clinical Approach As has been carefully outlined in Fig. 9.3 in the preceding Section 9, “Pharmacologic Approaches to Glycemic Treatment,” people with type 2 diabetes with or at high risk for ASCVD, heart failure, or CKD should be treated with a cardioprotective SGLT2 inhibitor and/or GLP-1 receptor agonist as part of the comprehensive approach to cardiovascular and kidney risk reduction. Importantly, these agents should be included in the regimen of care irrespective of the need for additional glucose lowering, and irrespective of metformin use. Such an approach has also been described in the American Diabetes Association–endorsed American College of Cardiology “2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes” (234). Figure 10.3, reproduced from that decision pathway, outlines the approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy.
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Figure 10.3
Approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy. Reprinted with permission from Das et al. (234).

Adoption of these agents should be reasonably straightforward in people with established cardiovascular or kidney disease who are later diagnosed with diabetes, as the cardioprotective agents can be used from the outset of diabetes management. On the other hand, incorporation of SGLT2 inhibitor or GLP-1 receptor agonist therapy in the care of individuals with more long-standing diabetes may be more challenging, particularly if patients are using an already complex glucose-lowering regimen. In such patients, SGLT2 inhibitor or GLP-1 receptor agonist therapy may need to replace some or all of their existing medications to minimize risks of hypoglycemia and adverse side effects, and potentially to minimize medication costs. Close collaboration between primary and specialty care professionals can

help to facilitate these transitions in clinical care and, in turn, improve outcomes for highrisk people with type 2 diabetes.

12.Centers for Disease Control, 2023. Smoking and diabetes. [online] Available at: https://www.cdc.gov/tobacco/campaign/tips/diseases/diabetes.html# [Accessed 24 June 2024].

Diabetes is a chronic (long-lasting) health condition that affects how your body turns food into energy.1 Most of the food a person eats is turned into glucose (a kind of sugar) for the body's cells to use for energy. The pancreas, an organ near the stomach, makes a hormone called insulin that helps glucose get into the body's cells.

When you have diabetes, your body either doesn't make enough insulin or can't use insulin very well. When there isn't enough insulin, or cells stop responding to insulin, too much sugar stays in your bloodstream. Over time, that can cause serious health problems, such as heart disease, vision loss, and kidney disease.1

There are three types of diabetes:

- Type 1 diabetes is thought to be caused by an autoimmune reaction (the body attacks itself by mistake) that stops your body from making insulin. Fewer people have type 1 diabetes, which is most often diagnosed in children, adolescents, or young adults.1
- Type 2 diabetes develops over many years and is usually diagnosed in adults, but is increasingly being diagnosed in children, teens, and young adults. About 90%-95% of people with diabetes have type 2. Type 2 diabetes can be prevented or delayed with healthy lifestyle changes, such as losing weight, eating healthy foods, and being active. 1
- Gestational diabetes develops in pregnant women who have never had diabetes. While it usually goes away after pregnancy, gestational diabetes increases a woman's risk for type 2 diabetes later in life. The condition can also increase a baby's risk for health problems.1

For additional information about diabetes, including symptoms, risk factors, and testing, please visit CDC's Diabetes Basics.

How Is Smoking Related to Diabetes?

We now know that smoking is one cause of type 2 diabetes.2 In fact, people who smoke cigarettes are 30%–40% more likely to develop type 2 diabetes than people who don't smoke.2,3 People with diabetes who smoke are more likely than those who don't smoke to have trouble with insulin dosing and with managing their condition.2,3 The more cigarettes you smoke, the higher your risk for type 2 diabetes.2,3

No matter what type of diabetes you have, smoking makes your diabetes harder to manage. If you have diabetes and you smoke, you are more likely to have serious health problems from diabetes, including:3

- Heart disease
- Kidney disease
- Poor blood flow in the legs and feet that can lead to infections, ulcers, and possible amputation (removal of a body part by surgery, such as toes or feet)
- Retinopathy (an eye disease that can cause blindness)
- Peripheral neuropathy (damaged nerves to the arms and legs that cause numbness, pain, weakness,

and poor coordination)

If you have diabetes and you smoke, quitting smoking will benefit your health right away. People with diabetes who quit are better able to manage their blood sugar levels.3

Can diabetes be prevented?

- Don't smoke. Smoking increases your chance of having type 2 diabetes.3
- Lose weight if you are overweight.4
- Stay active. Physical activity can prevent or delay type 2 diabetes in adults who are at high risk for the condition.4

The CDC-led National Diabetes Prevention Program (National DPP) lifestyle change program has been proven to help people make the changes needed to prevent or delay type 2 diabetes, improve their overall health, and build healthy habits for life. First, find out your risk by taking the 1-minute prediabetes risk test (available in Spanish and English). Then, learn more about the National DPP lifestyle change program and find a class near you (or online).

How Is Diabetes Treated?

Diabetes treatment and management can include:5

- A healthy diet and physical activity program
- Weight loss (if overweight)
- Medicines to manage blood sugar by helping the body use insulin better
- Insulin taken by injection or by using an insulin pump
- Diabetes self-management education and support to address problem-solving and coping skills needed to help manage diabetes and its complications
- Medicines to manage cholesterol and blood pressure

13.Organs Talk, 2021. About the connectivity of organ systems. [online] Available at: https://www.organs-talk.com/ [Accessed 24 June 2024].

About the connectivity of organ systems

What is the link between type 2 diabetes, the heart and the kidneys, and how does it affect the body?

Type 2 diabetes, the heart and the kidneys have an important connection as they have the potential to both positively and negatively impact each other.1 They are linked to one another through blood flow, hormones and the central nervous system.

The pancreas produces enzymes and hormones which help break down the food we eat and regulate blood sugar levels. Type 2 diabetes, which is mainly caused by pancreatic dysfunction and insulin resistance, affects how the kidneys filter blood and blood pressure, and therefore the health of the cardiovascular system.2

The heart pumps blood throughout the body to all organs, including the pancreas and kidneys. If the flow of blood to the organs is reduced, they will not be able to function as they should.3

The kidneys filter the blood and remove any waste or toxins that may be present. If they are unable to do this correctly, blood pressure in the body can increase, impacting the health of the other organs.4,5

The interconnectivity between these organs means that when a person experiences disease in one of these areas, it increases the chances of one or all the other systems being affected. This can result in worsening of the disease overall.4,6

This also means that when improvements are made in one area through lifestyle changes and appropriate care, positive improvements are likely to be seen in other organs and systems.4,6

By taking actions such as healthy eating, moving more, taking medication and not smoking, it is possible to reduce the risk of further damage and to prevent or delay organs from getting worse.7,8,9

Interconnectivity
Did you know?
T2D
At least one in three people with heart failure have type 2 diabetes10
CVD
At least one in three people with chronic kidney disease have cardiovascular disease11
CKD
At least one in three people with heart failure have chronic kidney disease12
What can be done about it?
When addressing the challenges that link diabetes and conditions of the heart and kidneys, achieving balanced health across all is key. Looking at the bigger picture of how each system interconnects is fundamental to treatment.

Life shouldn't be put on hold. Through careful management and lifestyle changes, such as diet and exercise, it can be possible to lead a normal and happy life. By taking care of yourself and improving lifestyle through diet and exercise, you can reduce complications and improve your overall wellbeing.

Appropriate steps include:
Understanding
your disease/s and how to manage them, considering treatment as well as lifestyle.

Having
informed conversations with your doctor(s) about the care that is most appropriate for you.

Making
changes to your lifestyle (e.g., more activity or a healthier diet), which could make significant improvements to your overall health.

Where can I find support to help me stay on track?

It is important to acknowledge that there may be some mental and emotional health challenges following diagnosis of conditions of the heart and kidneys or a diabetes diagnosis.13 Therefore, it is important to reach out for support if you need it. There are various support groups and online communities that can help to support you, both physically and mentally. Speak to your doctor or healthcare team about what resources are available to you.

You might also find it helpful to speak to close friends or loved ones to help you to wrap your head around things. At the very least, sharing with someone close to you can help lighten the load.

Talking to your doctor and healthcare team regularly is vital to managing your condition and supporting your overall health. Your doctor may suggest simple changes to lifestyle, such as healthier eating and doing more regular exercise, to help improve your health and reduce your risk of further complications