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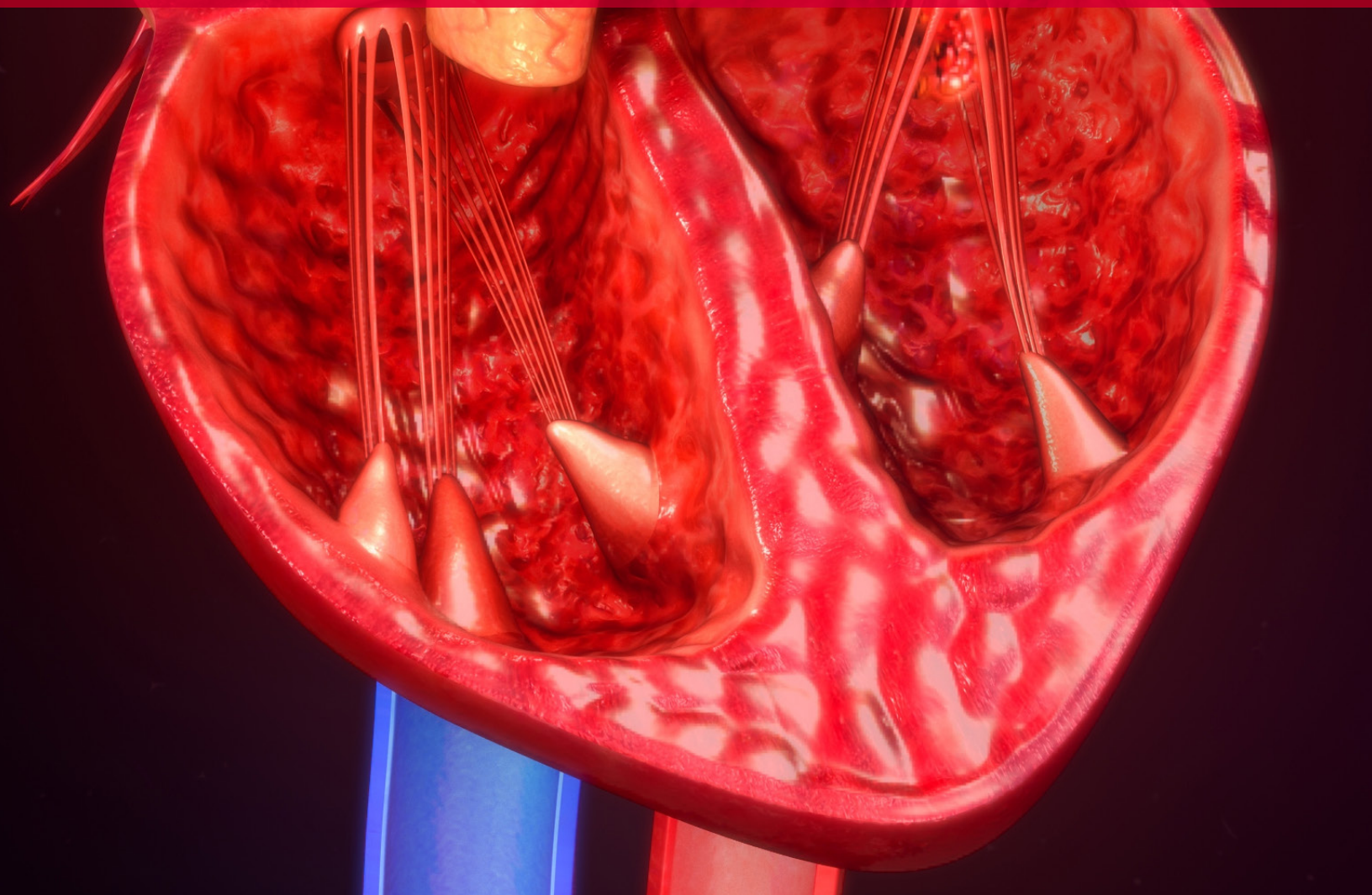
DIAGNOSTICS

Cardiac

Learning guide series



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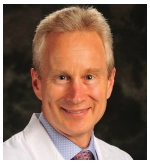

EDITOR

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Dr. Peter McCullough received a bachelor's degree from Baylor University and then earned a medical degree from the University of Texas Southwestern Medical School in Dallas where he was honored as a member of Alpha Omega Alpha. He continued his training with an internal medicine residency at the University of Washington in Seattle and a cardiology fellowship at William Beaumont Hospital in Michigan where he served as Chief Fellow. After completing his medical training, Dr. McCollough earned a master's degree in public health at the University of Michigan.

Dr. McCullough is an internationally recognized expert on the relationship between chronic kidney disease and cardiovascular disease. He is a leader in research on cardiac and renal disease and has contributed to the understanding of these disease processes through the publication of more than one thousand published medical communications. Likewise, he has successfully led many observational and randomized controlled trials and has also been involved in the U.S. Food and Drug Administration (FDA) approval process for numerous novel drugs and diagnostic tests.

Dr. McCullough's research and scholarship efforts have been recognized with both the Simon Dack Award from the American College of Cardiology and the International Vicenza Award in Critical Care Nephrology. In addition, he has been invited to lecture at many prominent institutions, including the New York Academy of Sciences, the National Institutes of Health, the FDA, and the European Medicines Agency.

Dr. McCullough continues to work on improving the medical community's understanding of cardiac and renal disease. He is a founding member and currently serves as president of the Cardio Renal Society of America. This organization promotes collaboration between cardiologists and nephrologists to identify and address the problem of cardiorenal syndromes. Moreover, Dr. McCullough serves as an editorial board member for multiple specialty journals and is also the co-editor of *Reviews in Cardiovascular Medicine* and the associate editor of the *American Journal of Cardiology*.

Currently, Dr. McCullough is the Vice Chief of Medicine at Baylor University Medical Center in Dallas and also serves as Principal Faculty in internal medicine for the Texas A&M University Health Sciences Center. He is board certified in internal medicine, cardiology, clinical lipidology, and echocardiography.

ABBOTT DIAGNOSTICS CARDIAC LEARNING GUIDE

INTENDED AUDIENCE

The Cardiac Learning Guide is intended to serve the basic educational needs of healthcare professionals who are involved in the laboratory or who manage patients who have or are at risk of developing heart disease. This includes, but is not limited to, laboratory technicians, laboratory technologists, supervisors and managers, nurses, suppliers, and other physician office and laboratory support personnel.

The guide contains:

- a review of the anatomy and physiology of a healthy heart
- an explanation of the pathophysiology of two common conditions – acute coronary syndrome and heart failure
- information on the role of cardiac biomarkers in the diagnosis, prognosis, risk stratification, and therapy monitoring of various heart conditions

HOW TO USE THIS LEARNING GUIDE

A set of learning objectives appear at the beginning of each section to help you focus on the key concepts being presented. Short quizzes at the end of the sections are designed to help you recall and retain important information. Answers are included to provide you with instant feedback; it is recommended that you revisit the topics you didn't recall correctly before moving to the next section.

A glossary of terms is also included at the end of this Learning Guide, featuring commonly used terms in cardiology.

CONTENTS

SECTION 1
ANATOMY AND PHYSIOLOGY OF THE HEART

LEARNING OBJECTIVES

When you complete this section, you will be able to:

1. Recognize key features of the cardiac anatomy including the heart chambers and coronary arteries
2. Describe how blood flows through the heart, lungs, and body
3. Understand basic characteristics of the heart's electrical conduction system
4. Explain systole and diastole and how this relates to blood flow

The heart, in the most simplistic of terms, is a pump. It continuously circulates blood through the body. The blood, in turn, delivers oxygen (bound to hemoglobin inside red blood cells) and nutrients to all of the organs and tissues. Blood also carries away the wastes and carbon dioxide produced by the organs and tissues so they can be removed from the body. This movement of blood throughout the body is almost entirely dependent on the heart's pumping ability.

BASIC HEART ANATOMY

A short review of cardiac anatomy is required to understand in more detail how the heart works. The heart is divided into two sides, right and left (**Figure 1-1**). The right side of the heart is further divided into a smaller, upper chamber called the right atrium and a lower, larger chamber called the right ventricle. Similarly, the left side is also divided into a smaller left atrium above and a larger left ventricle below.

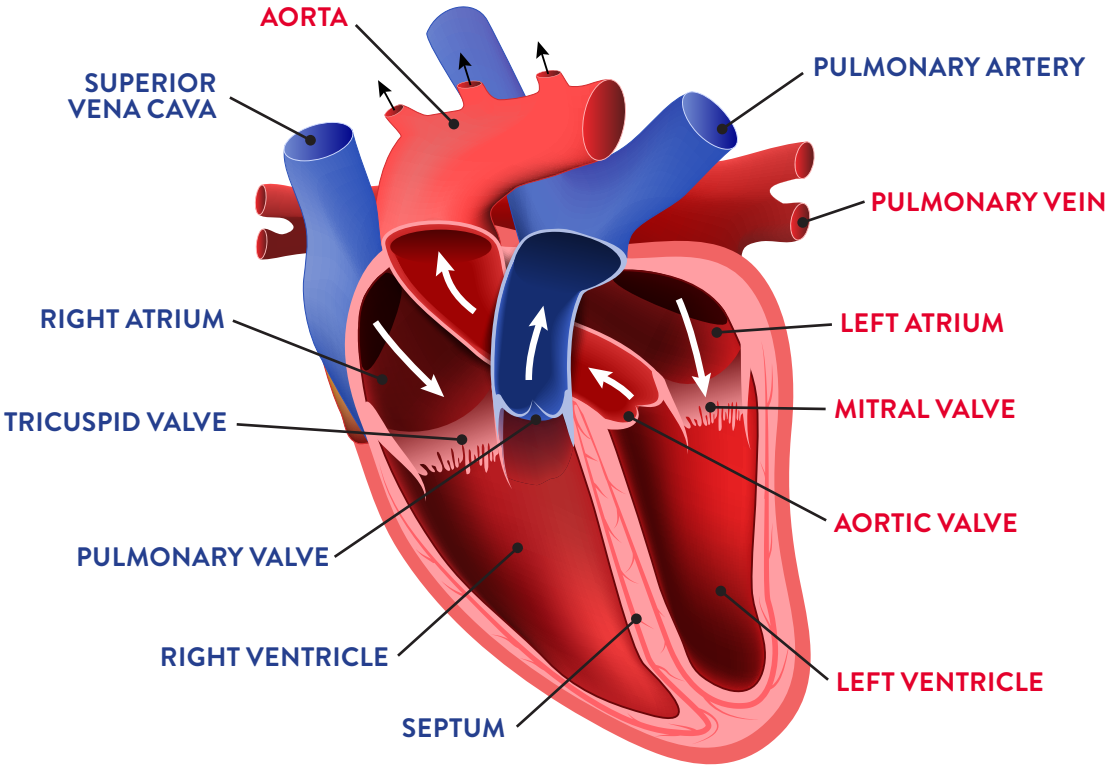


Figure 1-1. The four chambers of the heart and the major blood vessels that distribute and collect blood from other parts of the body

BLOOD FLOW THROUGH THE HEART AND BODY

Next, we must understand how blood circulates through the heart and body (**Figure 1-1**). Blood returning from the body arrives in the heart through two large veins, the superior vena cava and the inferior vena cava. This blood is oxygen-poor, meaning it contains a lower concentration of oxygen and carries a large amount of carbon dioxide produced by body tissues. From the vena cava, the oxygen-poor blood flows into the right atrium, then through a valve called the tricuspid valve, and into the right ventricle. From there, the blood is pumped out through the pulmonary valve, into the pulmonary artery, and to the lungs.

In the lungs, the blood moves into capillaries, which are tiny, thin-walled blood vessels that allow for the exchange of gases (like oxygen and carbon dioxide). The carbon dioxide in the oxygen-poor blood is exchanged for new oxygen from the air through the thin capillary walls. After this exchange, the blood contains high levels of oxygen and can be described as oxygen-rich. The oxygen-rich blood then returns to the heart through the pulmonary veins.

From the pulmonary veins, the oxygen-rich blood enters the left atrium. The blood continues from the left atrium, passes through the mitral valve, and empties into the left ventricle. The left ventricle, which is the largest and strongest of the four chambers of the heart, pumps the oxygen-rich blood through the aortic valve and out into a very large vessel called the aorta. From the aorta, blood travels into smaller arteries, then into arterioles, and finally capillaries of the organs and tissues of the body. It is here that oxygen is removed from the blood and carbon dioxide, a waste product from cells, replaces it. Finally, the blood that is now oxygen poor moves from the capillaries into venules, then into veins, and back into the superior or inferior vena cava to repeat the process.

THE CARDIAC TISSUE

For the heart to maintain this continuous pumping process, it also requires a large amount of oxygen. The heart is made up of a unique type of muscle tissue that is not found anywhere else in the body. This specialized muscle tissue of the heart is referred to as the myocardium. The cells that make up the myocardium are called cardiac myocytes. These myocytes are almost entirely dependent on aerobic metabolism, meaning they require oxygen to function normally and depend upon an oxygen-binding protein known as myoglobin.

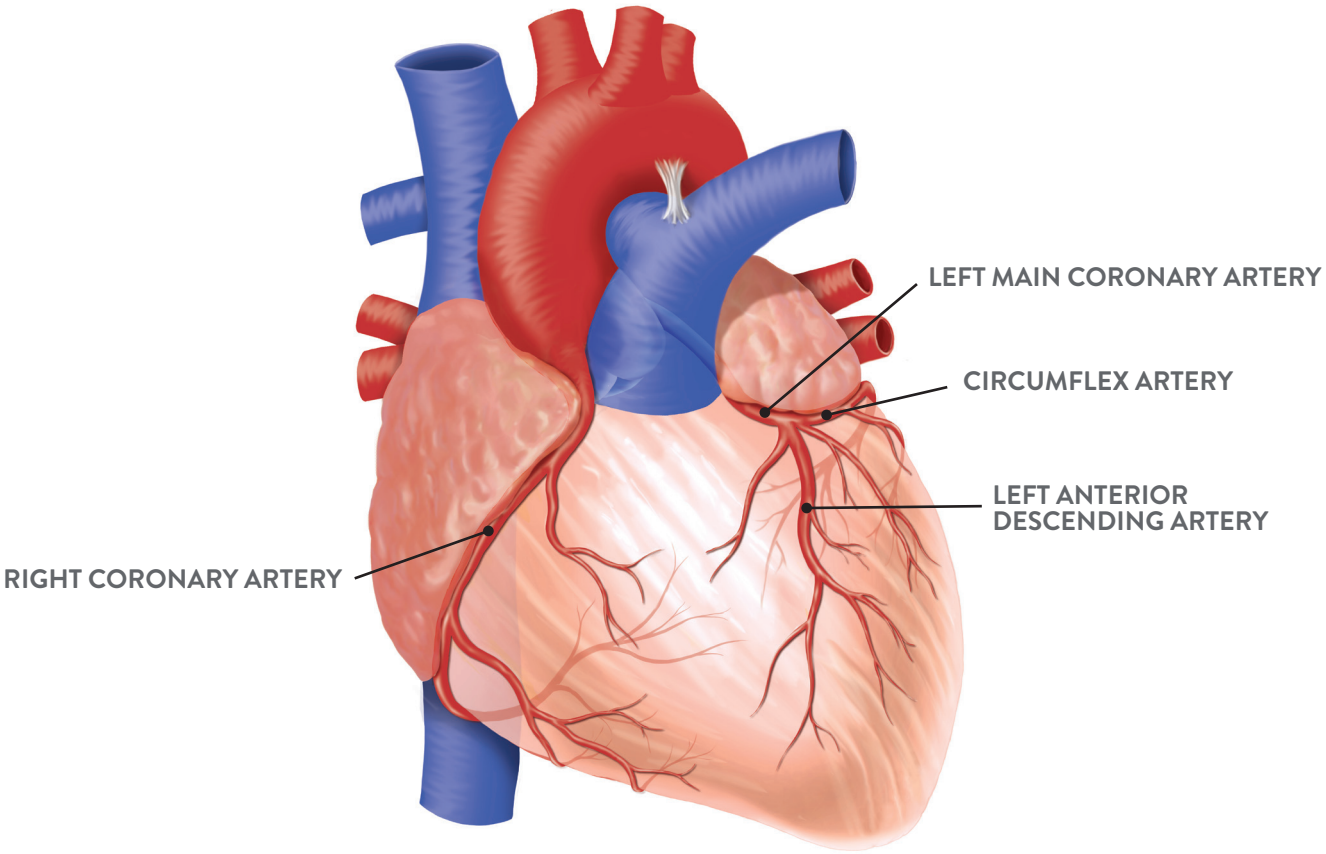
Blood Flow to the Myocardium

To continuously supply the heart muscle with oxygen, three major coronary arteries carry oxygen-rich blood from the aorta to the myocardium (**Figure 1-2**). Different coronary arteries supply blood to various parts of the myocardium. For example, the right coronary artery supplies blood to the right atrium, sections of both ventricles, and portions of the heart's electrical conduction system. Other major coronary arteries include the left main coronary artery, which divides into the left circumflex artery, and the left anterior descending artery, all of which are responsible for delivering blood to a particular part of the heart. In a similar network, several large cardiac veins, including the aptly named great cardiac vein, collect the oxygen-poor blood from the tissue and return it to the right atrium via the coronary sinus. Maintaining a healthy circulation of blood into the coronary arteries is necessary to assure optimal cardiac function. If an obstruction develops in any of the coronary arteries blocking the flow of blood, the myocytes that are supplied by the obstructed artery will experience distress, and there will be insufficient oxygen and nutrients flowing to that region of heart tissue.

Electrical Activity in the Heart

Cardiac muscle tissue has another distinctive quality. Unlike other types of muscle that require stimulation by a nerve or hormone to contract, the myocytes of the myocardium stimulate their own contraction. This self-stimulation is referred to as automaticity, and it means that the heart can stimulate its own muscle contraction without any input from the body.

Figure 1-2. Major arteries that supply blood to the myocardium



The electrical impulses that cause the heart muscle to contract, or beat, in a regular fashion originate in the sinoatrial node (SA node) which is located in the wall of the right atrium. Once the electrical activity in the SA node has begun, it travels through both atria, stimulating the muscle to contract (or beat). After stimulating the atria, the electrical impulse then travels to the atrioventricular node (AV node), down along a band of fibers (called the bundle of His) to the right and left bundles in the right and left ventricles, respectively. The electrical impulse then spreads to the walls of both ventricles through pathways called Purkinje fibers and triggers the ventricles to contract (or beat). These electrical impulses that stimulate contraction of the atrium and ventricles are what produce the rhythmic, coordinated pumping action of the heart. In turn, this pumping action generates the stroke volume which is felt as the pulse—the regular beat that can be monitored in the arteries throughout the body.

Although the heart creates its own electrical impulses, outside activity from nerves and hormones can influence how often and strongly the heart muscle contracts. For example, when a person experiences a sudden fright, the heart may beat much faster and more powerfully than normal. In this situation, the sympathetic nervous system and the adrenal glands release a hormone called norepinephrine. Norepinephrine changes how the heart responds to electrical stimulation resulting in an increased heart rate and contractility of the pumping chambers.

THE PUMPING ACTION OF THE HEART: SYSTOLE AND DIASTOLE

Another concept that is important to understand about the heart is systole and diastole. In simple terms, systole means contraction of the myocardium and diastole means relaxation of the myocardium. However, the atria and ventricles do not contract or relax at the same time. For a brief period, both atria and both ventricles are in diastole allowing blood from the vena cava or pulmonary veins to flow in passively. Once the SA node begins spreading its electrical impulse, the muscles of atria begin contracting to create atrial systole. During atrial systole, the walls of the left and right atrium contract to push blood into the ventricles (which are still in diastole). The atria quickly return to diastole and begin refilling with more blood in preparation for the next contraction. At this time, systole of the ventricles occurs, and the walls of both ventricles contract to push blood into the aorta and pulmonary artery (the right ventricle pumps to the pulmonary artery, and the left ventricle pumps to the aorta). After systole is complete, the ventricles return to diastole and begin refilling with blood again. Both systole and diastole are energy-dependent phases of the cardiac cycle, meaning the cardiac cells require energy to perform these functions. Dysfunction of either one or both of these phases can lead to heart failure.

In a healthy heart, the muscle tissue has an elastic quality, meaning it stretches easily but can quickly return to its original shape (similar to a rubber band). This quality is sometimes referred to as elasticity. During diastole, the muscle actively stretches as the heart fills with blood, and during systole, it springs back and contracts to smaller ventricular chamber sizes to pump the blood out.

Systole of the ventricles is significantly more powerful than systole of the atria because the ventricles are thicker and force the blood to travel much further. The left ventricle, the largest and thickest of the four heart chambers, creates the most powerful contraction during systole because it must pump blood to the entire body. Efficient pumping of the left ventricle is essential because it pushes the oxygenated blood to the tissues and organs and helps maintain the pressure required for the oxygen and carbon dioxide to be exchanged in the capillaries. If the left ventricle does not pump well, the tissues and organs of the body may not receive an adequate supply of oxygen to function normally.

Understanding the process of systole and diastole in the heart can also help explain a health parameter that is frequently measured in the clinical setting: blood pressure. More accurately termed arterial blood pressure, this is a measure of the pressure in the arteries during ventricular systole and the pressure at the end of ventricular diastole. For example, a blood pressure reading of 120/80 mmHg indicates that the blood vessels have a pressure of 120 mmHg during ventricular systole and 80 mmHg at the end of ventricular diastole. It is important that blood pressure not be too high or too low. Hypertension, the medical term for blood pressure that is too high, can damage organs and tissues of the body over time because of the high pressures. Correspondingly, hypotension, or blood pressure that is too low, will not create enough pressure to allow oxygen to be exchanged into organs and tissues. This can deprive the cells of oxygen needed for basic function and can lead to organ and tissue damage.

UNDERSTANDING EJECTION FRACTION

The last concept that is important to understand about the heart is ejection fraction. When a person is resting, only about 60 percent (normal range approximately 50-70 percent) of the blood that was in the ventricle at the end of diastole is pumped out (so the ventricle is never completely emptied). The percentage of blood pumped out during systole is called the ejection fraction. The actual number or percentage of ejection fraction can change as a result of physical activity or other demands on the cardiac muscle. Measuring ejection fraction is one of the ways clinicians can assess the health of a heart.

SECTION 1: REVIEW QUESTIONS

1. Place the following term in the correct order to describe the flow of blood through the heart, lungs, and body. Start with veins.

right atrium	pulmonary artery	right ventricle
veins	pulmonary vein	aorta
vena cava	left atrium	capillaries of organs and tissues
lungs	left ventricle	arteries

_____

_____

_____

_____

2. Which if the following statements about the heart is FALSE?

   a. The cells of the myocardium function using aerobic metabolism and require a steady supply of oxygen

   b. The cells of the heart generate their own electrical impulses to stimulate cardiac contraction; this electrical impulse originates in the SA node

   c. Arterial blood pressure is a measure of the pressure in the arteries during ventricular systole and at the end of ventricular diastole; it is important that blood pressure isn't too high or too low

   d. The right atrium and ventricle contract first, pushing blood to the lungs, and the left atrium and ventricle contract second, pushing blood to the rest of the body

3. _____ arteries supply the myocardium with oxygen-rich blood.

4. Systole means _____ and diastole means _____.

   The _____ ventricle creates the strongest contraction because it must pump blood to the entire body.

SECTION 2
ACUTE CORONARY SYNDROME

LEARNING OBJECTIVES

When you complete this section, you will be able to:

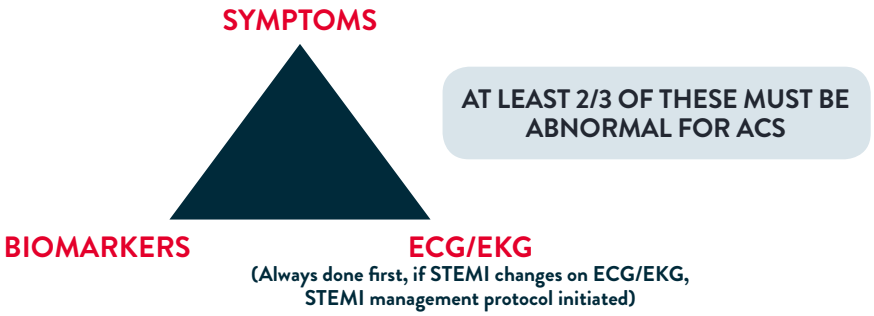
1. Describe the different types of acute coronary syndromes
2. Discuss the mechanisms of myocardial ischemia and infarction
3. Explain the process of diagnosing and risk stratifying patients with suspected acute coronary syndrome
4. Understand the role of cardiac biomarkers in diagnosis and risk stratification for patients with suspected acute coronary syndrome

Cardiovascular diseases are the most common causes of death worldwide, and they affect individuals from all backgrounds, incomes, and nations.[2] Of the estimated 17 million deaths attributed to cardiovascular disease worldwide in 2015, the World Health Organization estimates that 7.4 million were due to coronary heart disease, which is a disease of the coronary arteries.[2] Coronary heart disease manifests most often in the form of acute coronary syndrome, the general term used to describe a myocardial infarction (the medical term for heart attack) and unstable angina (the medical term for chest pain from heart disease). The American Heart Association estimates that in the United States, someone experiences a myocardial infarction every 42 seconds.[3] Of these individuals, approximately 15 percent will die within one year as a result of the myocardial infarction.[3] Similarly, in Europe, coronary heart disease is the single leading cause of mortality and the most common cause of premature death (before age 65 years).[4] Despite significant medical progress in diagnosing and treating cardiovascular diseases, the World Health Organization estimates that it will still be the most common cause of death worldwide in 2030.[5]

DEFINING ACUTE CORONARY SYNDROME

Acute coronary syndrome (ACS) is a general name for a group of conditions that indicate that the heart muscle is not receiving enough oxygen. This situation is termed myocardial ischemia. There are three subcategories of ACS: ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA).

Diagnosis of ACS



ST-Elevation Myocardial Infarction

An ST-elevation myocardial infarction (STEMI) is often the most severe form of ACS, and it is a type of myocardial infarction (MI). It is estimated that STEMI accounts for about 25 percent of all MI, but it carries a high risk of mortality with 10 percent of patients dying in the first 30 days after the event.[3] In a STEMI, characteristic changes occur on an electrocardiogram (ECG or sometimes referred to as EKG), a test that assesses electrical changes in the heart. If a STEMI is identified on an ECG, it indicates that an obstruction has occurred in one of the coronary arteries preventing the flow of oxygen-rich blood to the cardiac tissue.[6,7] This obstruction is usually caused by the rupture of plaque in the coronary artery. Plaque is a substance that can accumulate inside the coronary artery and is made up primarily of cholesterol, fat, and calcium. If plaque in a coronary artery ruptures, it triggers platelet activation and adhesion as well as the initiation of the clotting cascade that results in the production of fibrin. These events can lead to the formation of a clot or thrombus inside the coronary artery that completely blocks the flow of blood. As a result of this thrombus, the tissues and myocytes that the artery normally supplies blood to are deprived of oxygen. With time, the oxygen deprivation leads to the death of the myocytes and permanent damage to the myocardium resulting in a scar.

When a STEMI is identified on an ECG, immediate intervention is required to reopen the blocked coronary artery (the term reperfusion is often used to describe reopening the artery). Reperfusion can be accomplished by administration of an intravenous medication called a thrombolytic or, more optimally, by an immediate procedure called a primary percutaneous coronary intervention (primary PCI) performed at a hospital with cardiac catheterization facilities. Both of these procedures will be discussed in more detail later in this section. Any delay in the time to reperfusion can increase the amount of damage that occurs to the myocardium. Because a STEMI leads to the death of the cardiac myocytes, cardiac biomarkers are always elevated, but biomarker information is not required before proceeding to a reperfusion intervention.

A 12-lead ECG shows different views of the electrical activity in the heart from 12 distinct angles. During the test, a technician places a wire lead on 12 specific areas of the chest, arms, and legs. The ECG traces the view of the heart's electrical activity from each of these 12 areas of the body because they each reflect a unique view of the heart. On the ECG report, each lead produces a tracing, and the tracings are labeled I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, and V6. An ECG is useful for diagnosing a range of cardiac problems, including arrhythmias. In ACS, paramedics, nurses, and physicians use the ECG to differentiate a STEMI from other causes of ACS symptoms. An ECG can even identify which coronary artery is likely obstructed by looking at which leads have ST elevation (**Figure 2-1**).

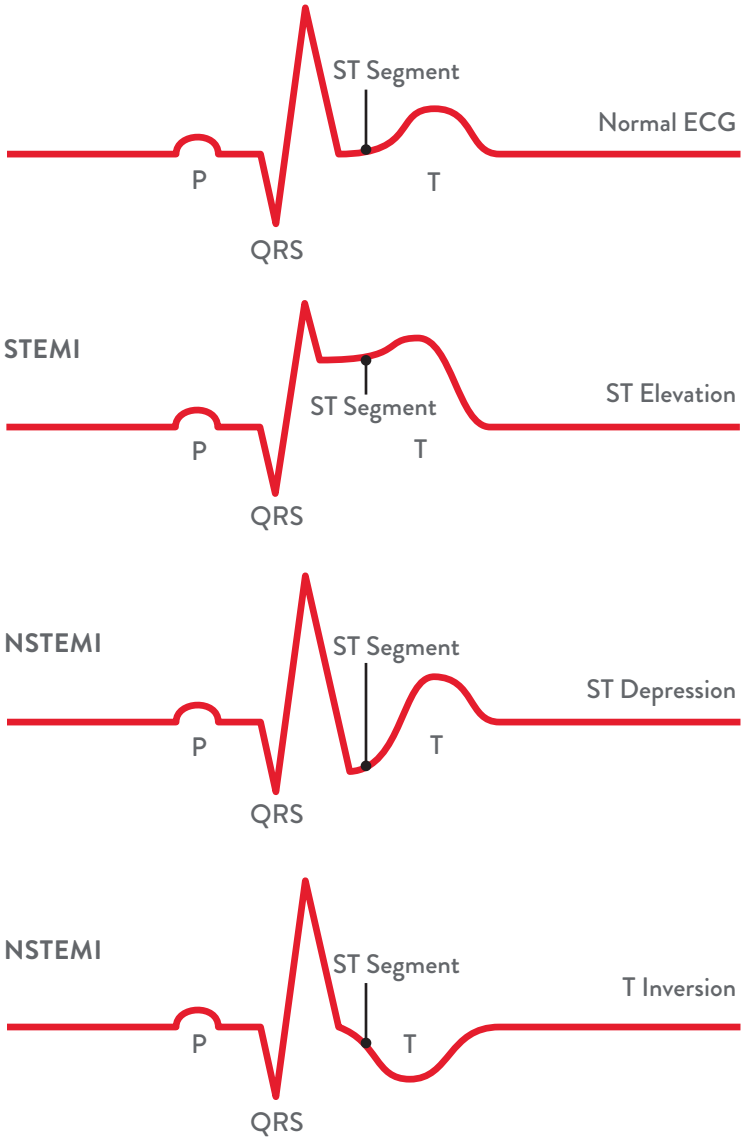


Figure 2-1. The name ST-elevation MI is describing the changes that happen during a STEMI on an ECG: the ST segment in the ECG tracing is more elevated than normal. This test is useful for distinguishing a STEMI from other types of MI.

Non-ST-Elevation Myocardial Infarction

The second type of ACS, non-ST-elevation myocardial infarction or NSTEMI, also has serious consequences for the heart. An NSTEMI is also a type of MI but is much more common than STEMI. Although estimates vary, approximately 75 percent of patients presenting with MI are diagnosed with NSTEMI, and this is associated with an 18 percent chance of death in the first 30 days after the event.[3] As the name implies, in an NSTEMI, the ECG does not have the characteristic ST elevation seen with STEMI. However, an NSTEMI shares many other similarities with a STEMI. An NSTEMI occurs when an obstruction occurs in the coronary artery that prevents adequate amounts of blood and oxygen to flow to the tissues, and with time, this results in tissue necrosis (tissue death).[6,7] Many things can cause this obstruction, but, similar to a STEMI, the most common cause is plaque rupture and subsequent thrombus formation in a coronary artery. Other less common causes include vasospasm of the coronary artery or an excessive accumulation of plaque inside the coronary artery that almost completely occludes blood flow. Regardless of the cause, an NSTEMI does cause ischemia in the cardiac myocytes because they are not receiving enough oxygen to function normally, and with time, this leads to the death of the myocytes and permanent damage to the myocardium. Elevated cardiac biomarkers are a confirmation of this damage and differentiate NSTEMI from unstable angina. Additionally, these elevated biomarkers, along with other clinical factors, help identify higher-risk patients with NSTEMI who require cardiac catheterization.

Unstable Angina

The third type of ACS is unstable angina (UA). Unlike STEMI and NSTEMI, traditional cardiac biomarkers are not elevated in UA, myocyte death does not appear to occur, and it is not classified an MI.[6,7] However, this understanding of UA is changing with the advent of more sensitive biomarker measurements, such as high-sensitivity troponin. Many experts now believe that most patients diagnosed with UA are likely experiencing an NSTEMI, but the conventional biomarker measurements are not sensitive enough to detect it.[8] As a result, the use of the term UA will likely be phased out over time. As in NSTEMI, cardiac catheterization is commonly performed in patients with UA.

Symptoms and Biomarkers in Diagnosing ACS

Regardless of whether it is classified as a STEMI or NSTEMI, an MI is caused by an ischemic event that results in death of the myocytes and permanent damage to the myocardium. The term necrosis is often used to describe the death of the myocytes. It is important to understand the criteria for recognizing necrosis and, in turn, diagnosing an acute MI (**Table 2-1**).

Although the assessment process for acute MI begins with an ECG, clinicians must also consider the symptoms the patient is experiencing and measure cardiac biomarkers. Cardiac troponins are the preferred biomarker in this clinical setting. The cells of the myocardium contain three types of troponin: troponin I, T, and C. Troponin C is also found in skeletal muscle, but troponins I and T are very specific to cardiac myocytes and are therefore clinically useful for measuring damage to the myocardium. When extended ischemia occurs, the cells die and begin to break apart releasing the troponin into the bloodstream.[6] If high levels of troponin T or I are measured in the blood, in the correct clinical setting, it is confirmation that there is necrosis in the cardiac tissue (**Table 2-1**).[6] To be diagnostic for MI, cardiac troponin must not only exceed the 99th percentile of the upper reference limit but also must be rising or falling in a characteristic pattern over time. Serial measurements of troponin can determine if concentrations are changing; when troponin concentrations remain constant over an extended duration, it suggests that an alternative diagnosis should be considered, such as renal failure, heart failure, or sepsis.[9]

Table 2-1.

FOURTH UNIVERSAL DEFINITION OF MI

Criteria for ACUTE myocardial infarction (Types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia
- New ischaemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology
- Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs)

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*.

Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*.

Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

There are additional types of MI (Types 4 and 5) that are very uncommon and are not included in this table. For details of these types of MI, see "Other Types of MI" on page 17.

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Cardiac troponin I (cTnI) and T (cTnT) are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart. Increases in cTnI values have not been reported to occur following injury to non-cardiac tissues. The situation is more complex for cTnT. Biochemical data indicate that injured skeletal muscle expresses proteins that are detected by the cTnT assay, leading to some situations where elevations of cTnT could emanate from skeletal muscle. cent data suggest that the frequency of such elevations in the absence of ischaemic heart disease may be higher than originally thought. cTnI and cTnT are the preferred biomarkers for the evaluation of myocardial injury, and high-sensitivity (hs)-cTn assays are recommended for routine clinical use. Other biomarkers, e.g., creatine kinase MB isoform (CKMB), are less sensitive and less specific. Myocardial injury is defined as being present when blood levels of cTn are increased above the 99th percentile upper reference limit (URL). The injury my be acute, as evidenced by a newly detected dynamic rising and/or falling pattern of cTn values above the 99th percentile URL, or chronic, in the setting of persistently elevated cTn levels.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology
- Patho-anatomical findings of a prior MI

From: Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Eur Heart J*. 2012; 33:2551–2567.

Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction. *JACC*. 2018.08.1038.

CLASSIFICATION OF MYOCARDIAL INFARCTIONS

For initial treatment stratification by emergency medicine providers and cardiologists, an MI is classified as a STEMI or NSTEMI. However, there are additional classifications for MI that further explain the mechanism leading to the ischemia. It is essential for providers to understand the cause of an MI to treat it appropriately.

Type 1: The Spontaneous MI

The most common type of MI is a spontaneous, or type 1, MI (**Figure 2-2**).[6] It is caused by rupture of plaque in a coronary artery. This rupture triggers the activation and aggregation of platelets, the initiation of the coagulation cascade to produce fibrin, and ultimately the formation of a thrombus which causes complete or partial occlusion of the artery. Plaque can accumulate inside any artery in the body, and the presence of plaque in the arteries is called atherosclerosis. The presence of plaque in the coronary arteries is particularly problematic, and when this occurs, it is termed coronary artery disease. Plaque changes how blood moves through the arteries because it stiffens the walls of the artery and narrows the artery lumen. Plaque is also less stable than walls of the artery and more prone to breakage or rupture. As blood travels through the coronary arteries, occasionally the plaque will rupture. If the subsequent platelet aggregation and fibrin formation result in a significant obstruction in the artery, a type 1 MI occurs. Since a type 1 MI is caused by plaque (and coronary artery disease), much of the prevention and long-term treatments focus on stabilizing current plaque (reducing the risk of rupture) and decreasing further plaque buildup.

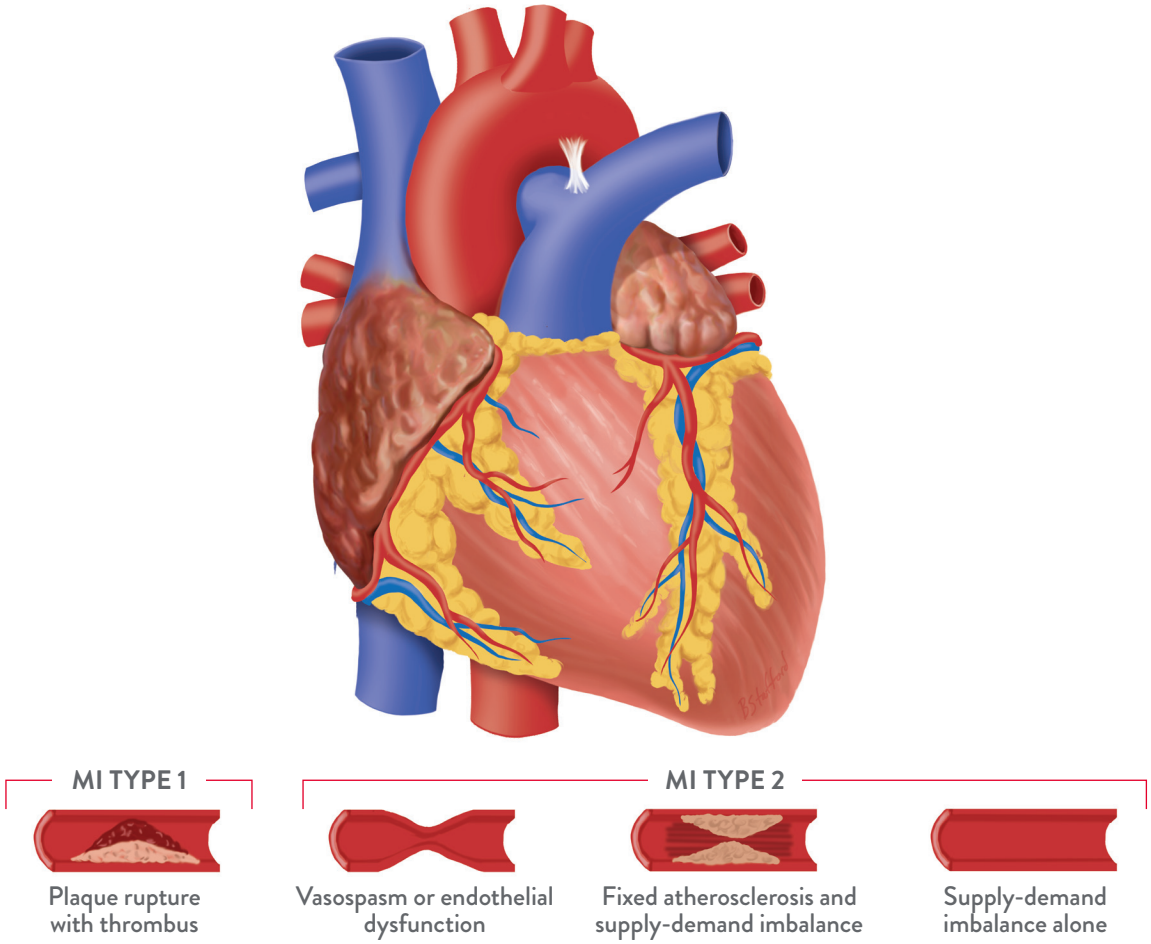


Figure 2-2. Differentiation between myocardial infarction (MI) types 1 and 2 according to the condition of the coronary arteries

Type 2: The Ischemic Imbalance MI
Unlike a type 1 MI, a type 2 MI is not triggered by a thrombus forming in a coronary artery. Instead, a type 2 MI is the result of supply and demand imbalance in the heart where the coronary arteries are not supplying adequate oxygen for the myocytes to function normally—the supply does not meet the demand. There are many reasons that this can occur (**Figure 2-2**). Some type 2 MIs are caused by a vasospasm, or spasm of the blood vessel wall, which can prevent blood from flowing appropriately to the myocardium, leading to ischemic damage. Others can be caused by coronary artery disease where plaque accumulation can limit the blood flow through a coronary artery. If the heart needs more oxygen because it is beating more rapidly than normal, as often occurs in a severe infection, and more oxygen is unable to flow to the tissue because of the plaque accumulation, then a type 2 MI occurs. Moreover, in some cases, the coronary arteries may be completely normal and healthy, but something else has led to an imbalance in the supply and demand resulting in an MI. Examples of this would include very high myocyte oxygen demand from an ongoing high heart rate or severe anemia where there are too few red blood cells circulating to bring the myocytes adequate oxygen.

Type 3: Cardiac Death MI
Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Other Types of MI
There are two other types of MI that should be mentioned for completeness. A type 4 MI is related to a percutaneous coronary intervention (PCI) procedure or a problem with a stent (a thin, mesh wire tube that props open a blood vessel) previously placed in a coronary artery.[6] Lastly, a type 5 MI results from a coronary artery bypass graft surgery (a surgical procedure that will be discussed later in this section).[6] Although all types of MI are clinically important, this guide will focus on type 1 and 2 as they are the most common in the clinical setting.

The key concept to appreciate about MI is that anything that prevents the myocardium from receiving adequate supplies of oxygen will lead to ischemia. If this ischemia is prolonged, it will lead to myocyte death and tissue necrosis.

Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction. *JACC*. 2018.08.1038.

THE PROCESS OF CARE IN MYOCARDIAL INFARCTION

Because damage to the cardiac tissue happens quickly once an obstruction occurs, it is essential that medical providers understand how to manage patients experiencing ACS efficiently. **Figure 2-3** is a flowchart explaining the process of care for patients with ACS. Any patient with ACS symptoms is classified as very high acuity in the emergency department and requires rapid assessment and close monitoring. Nurses, physicians, and other support staff must work together to ensure that this occurs in a timely and efficient manner.

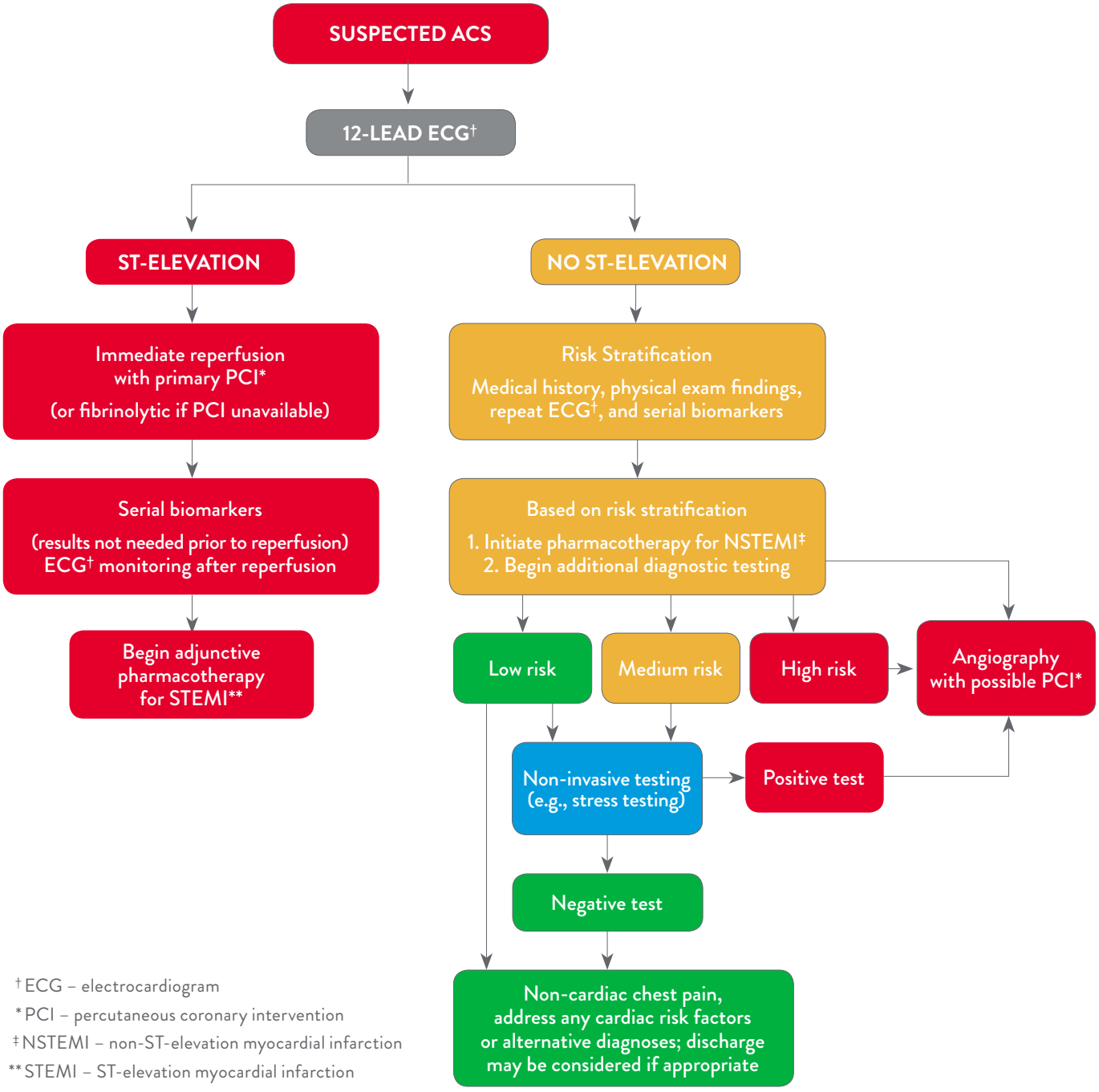


Figure 2-3. Process of care for patients with suspected acute coronary syndrome (ACS)[7,11,23]

ACS Symptoms

Any person experiencing symptoms of ACS should be evaluated immediately by a healthcare provider. Chest pain, sometimes radiating down the left arm, is probably the most widely recognized symptom. But many patients, especially women and the elderly, may experience other symptoms like chest pressure, nausea, sweating, jaw or back pain, shortness of breath, dizziness, or light-headedness.[10]

STEMI

The first step in the assessment of a patient with ACS symptoms is to perform an ECG (**Figure 2-4**). An ECG will be used to determine if the patient is experiencing a STEMI. The characteristic ST elevation on ECG, in conjunction with ACS symptoms and elevated cardiac biomarkers, are diagnostic for STEMI, but treatment should never be delayed waiting for biomarker results once STEMI has been identified on ECG.[6,11] A STEMI is most often a type 1 MI, and patients need immediate reperfusion therapy to open the occluded coronary artery and prevent further myocardial damage from occurring. The preferred treatment for a STEMI is a primary PCI performed as soon as possible after hospital arrival.

For the PCI procedure, the patient is promptly transferred to the cardiac catheterization laboratory (or cath lab). First, a specialized catheter is threaded through a large artery (either the femoral artery in the groin or the radial artery in the wrist) up into the heart. Next, the physician will use a dye to evaluate the blood flow through the coronary arteries (this is called an angiogram) and identify the exact area of occlusion. Finally, the blocked coronary artery is opened by inflating a tiny balloon-like device in the blocked region, and then a stent (or mesh wire tube) may be placed in the area of the blockage to prop the artery open.[12] The PCI procedure rapidly restores blood flow to the ischemic myocardium.

If PCI is unavailable, a physician will usually prescribe a thrombolytic drug for a patient experiencing a STEMI. A thrombolytic promotes degradation of the fibrin in the thrombus, to quickly lyse the clot in the coronary artery.[13]

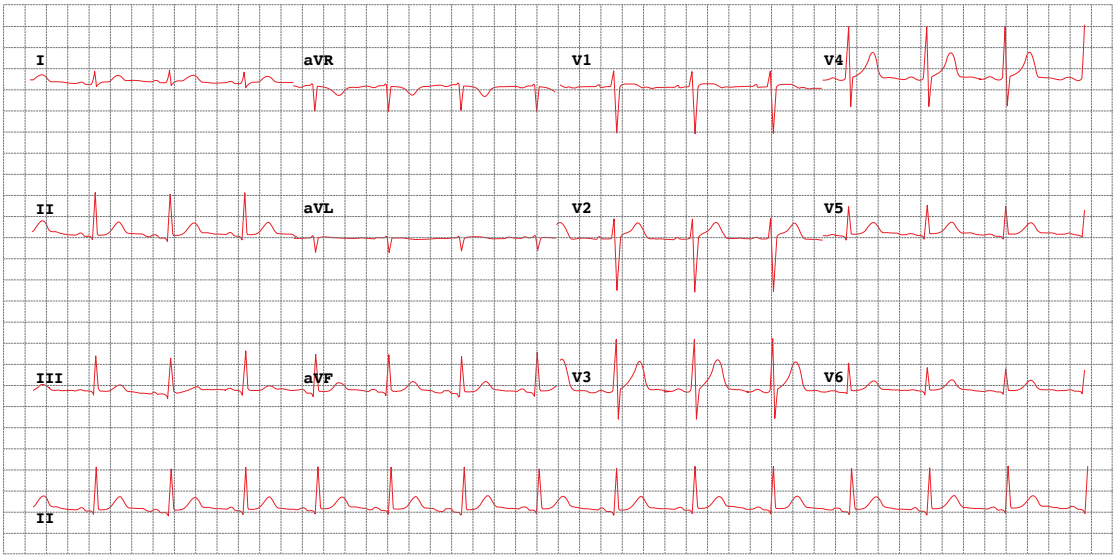


Figure 2-4. Example of a 12-lead ECG

Next Steps

Although STEMI is the first type of ACS to be screened for and diagnosed, the majority of MIs are not STEMI. It is estimated that approximately 75 percent of MIs are NSTEMI, and further testing is needed to establish this diagnosis (**Figure 2-3**).[3,11]

After the ECG is performed within 10 minutes of presentation and determined not to be a STEMI, cardiologists and emergency medicine providers will consider five different aspects of the patient's clinical status to further stratify the risk for MI and guide the next steps in treatment.

1 ECG Changes

After an initial ECG that is normal or non-diagnostic, current guidelines recommend that the ECG should be repeated several times during the first hour after presentation (usually at 15 or 30 minute intervals), especially if the patient's symptoms return.[7] This will allow physicians to evaluate for any new ECG changes that could indicate ischemia. Additionally, the ECG can be checked any time there is a change in patient status. It is common for patients with chest pain to have multiple ECGs over the course of evaluation in the emergency department or hospitalization.

2 Cardiac Biomarkers

It can be several hours after an ischemic event occurs before the cardiac troponin is detected in the blood using traditional assays; therefore, conventional cardiac troponins are measured several times in the first hours after symptom onset and presentation to the hospital.[7] The American Heart Association/ American College of Cardiology guidelines recommend measuring conventional cardiac troponin at the time of initial presentation and then repeating this measurement three to six hours after the symptoms began.[7] If high-sensitivity troponin is available, it is recommended that this test be repeated three hours after arrival in the emergency department for confirmation of a negative result.[14] It is also necessary for the diagnosis of MI to document that the cardiac troponin is rising or falling, rather than maintaining the same concentration. Accordingly, the series of cardiac troponins is usually continued even if the first measure is already elevated. Cardiac biomarkers will be discussed in more detail in Section 3.

3 Physical Exam Findings

On the initial physical exam, the clinician will determine if other, non-cardiac causes of chest pain need to be considered and will evaluate for signs of myocardial damage, such as heart failure symptoms.[7]

4 Risk Factors for ACS

Many factors increase a patient's risk for a cardiac event and need to be considered: older age, previous myocardial infarction, family history of heart disease, smoking, hypertension, hyperlipidemia, obesity, physical inactivity, and diabetes.[7,10]

5 Risk Assessment Tools

Clinicians will often use a risk prediction score such as the TIMI risk score, the GRACE score, or the HEART risk score. These tools not only assist in predicting an MI but they also help identify patients in need of urgent intervention with PCI and can estimate risk for death.[7]

NSTEMI

An NSTEMI is diagnosed when rising or falling cardiac biomarkers exceed the upper reference limit and the patient meets the criteria for MI listed in **Table 2-1** on page 15. Patients with NSTEMI are treated with antiplatelet medications, such as aspirin, and anticoagulant medications, such as heparin or enoxaparin, to prevent further extension of the thrombus.[7] However, thrombolytics are not used in NSTEMI.

In addition to treatment with medication, patients with NSTEMI usually undergo a coronary angiography (cardiac catheterization) procedure to examine the coronary arteries.[7] An angiography procedure, similar to what is done for STEMI, involves inserting a catheter into a large artery (in the groin or wrist) and threading it up to the heart. Once in the heart, a dye is released that will flow into the coronary arteries, and the physician will use an x-ray device to evaluate the flow of blood through the coronary arteries.[12] As the dye flows through, it will opacify the coronary arteries and display their branches like the branches of a tree (**Figure 2-5**). During this procedure, narrowings that indicate a blockage or lesion may be seen. If a blockage is identified, sometimes it can be opened using a balloon and stent (similar to the treatment of a STEMI), and sometimes extensive atherosclerosis of the coronary arteries is identified that cannot be treated with PCI and stenting. Severe, extensive atherosclerosis may be treated with coronary artery bypass grafting (CABG), which is sometimes referred to as open-heart bypass surgery. Occasionally, there is no atherosclerosis, and the MI was caused by something else (as sometimes occurs with type 2 MI). If this is the case, it is important to identify and treat the underlying cause of the MI to prevent further myocardial ischemia.

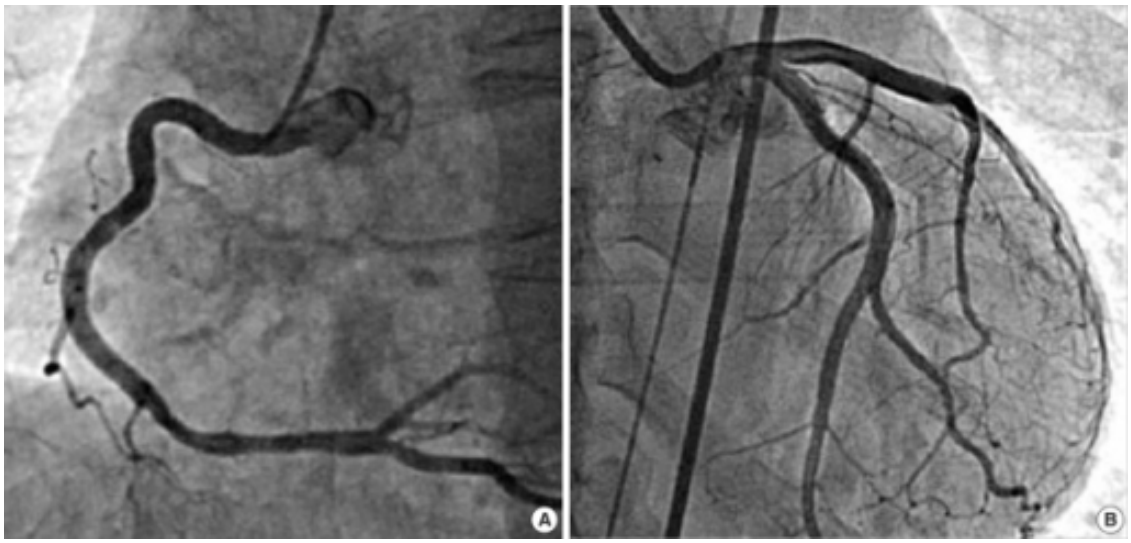


Figure 2-5. An x-ray evaluating blood flow through the coronary arteries during a coronary angiography

Attribution: Suh I-W, Lee CW, Kim Y-H, et al. "Catastrophic Catecholamine-Induced Cardiomyopathy Mimicking Acute Myocardial Infarction, Rescued by Extracorporeal Membrane Oxygenation (ECMO) in Pheochromocytoma." *Journal of Korean Medical Science*. 2008;23(2):350-354.

No MI Identified

In many cases, patients presenting with symptoms of ACS are not experiencing an MI. Patients who have negative biomarkers after repeat measurement are usually referred for additional testing based on their risk factors for ACS. Patients at high risk for coronary artery disease may still undergo an angiography procedure, but many patients, especially individuals with low or moderate risk for coronary artery disease, are referred for other types of tests. Treadmill ECG, stress myocardial perfusion imaging, coronary CT angiography, and other diagnostic tests are useful, non-invasive tools for identifying undiagnosed coronary artery disease in these patients.[7] If a patient is determined to have coronary artery disease, they are at an increased risk for having an MI. In this situation, doctors will work with the patient to lower the risk of a future MI with medication and lifestyle changes.[7]

SECTION 2: REVIEW QUESTIONS

1. Match the acronym or word with the correct description

   Atherosclerosis ____ PCI ____ MI ____ Troponin ____ Calcium ____

   a. A term used to describe an ischemic event that leads to permanent damage to the cardiac muscle
   b. A procedure used to reopen a blocked coronary artery
   c. A substance normally found in cardiac muscle cells that is released when the cells die
   d. A substance that is a part of plaque deposits in the coronary arteries
   e. A term used to describe plaque buildup inside the arteries

2. Describe the general mechanism for how myocardial damage occurs in a myocardial infarction

_____

_____

_____

_____

3. Select the statement(s) describing diagnostic requirements for a myocardial infarction

   a. Rising or falling cardiac biomarkers with at least one measured over the 99th percentile of the upper reference limit
   b. New changes to the ECG, imaging studies demonstrating new cardiac muscle damage, or symptoms of cardiac ischemia such as chest pain
   c. Low levels of oxygen (low oxygen saturations) measured on pulse oximetry
   d. A and B are both correct
   e. B and C are both correct
   f. All of the above are correct

4. The preferred cardiac biomarker for diagnosing MI is _____.

SECTION 3

THE ROLE OF CARDIAC BIOMARKERS IN ACUTE CORONARY SYNDROME (ACS)

LEARNING OBJECTIVES

When you complete this section, you will be able to:

1. Describe the role of troponin in ACS
2. Discuss differences between high-sensitivity and conventional troponin assays
3. Understand important considerations for implementing high-sensitivity troponin assays within an institution
4. Recognize other cardiac biomarkers with potential roles in ACS

As explained in Section 2, cardiac biomarkers, specifically cardiac troponin, are essential for the identification of myocardial necrosis and infarction. However, advances in the measurements of cardiac troponins are changing how acute coronary syndrome (ACS) patients are evaluated and risk-stratified. And new biomarkers are also emerging that, in the future, may have potential roles in diagnosis and prognostic evaluation of patients with ACS.

TROPONIN

Troponin is an abundant protein contained in the cardiac myocytes. It works inside the cell as part of the contractile mechanism to facilitate myocyte contraction. The troponin complex in a cardiac myocyte has three subunits, troponins C, T, and I (**Figure 3-1**).[15] Both skeletal and cardiac muscle synthesize troponin C, but troponin T and I are highly specific to cardiac muscle. Together, troponin T and I are considered the cardiac troponins. In the appropriate clinical setting, if significant elevations of these troponins are detected in the blood, and they are determined to be rising or falling, they are a useful tool for confirming cardiac necrosis.[15] Notably, most healthy individuals have small but measurable concentrations of troponin in the bloodstream in a normal physiologic state possibly as a result of cell turnover (the normal life and death cycle of a cell).[15] However, at these low concentrations, only high-sensitivity assays can detect it.[15]

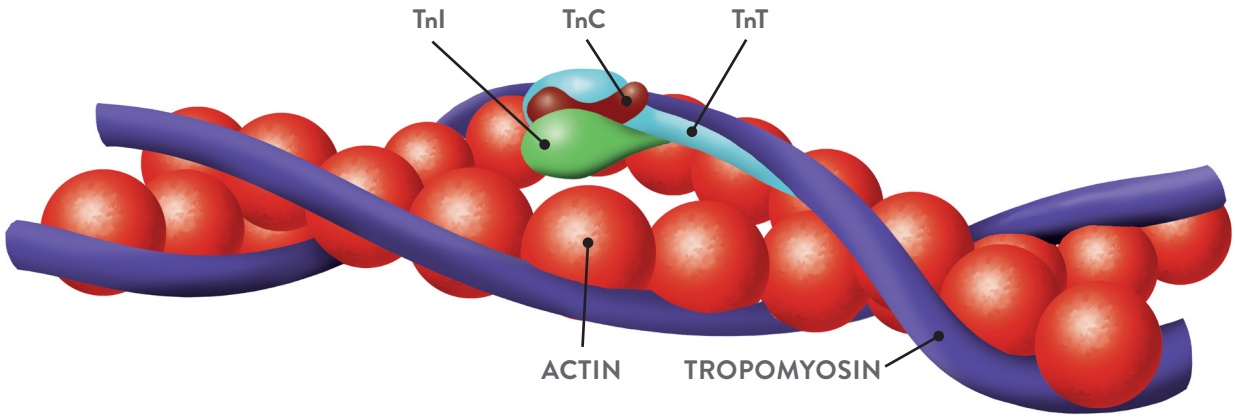


Figure 3-1. The troponin complex

Although the troponin protein was initially identified in 1965, the first assay for measuring troponin I in the serum was not developed until 1987.[16] An assay for troponin T followed in 1989.[16] Through the 1990s and 2000s, improvements in the immunoassays significantly increased the precision and sensitivity of these tests. The conventional troponin assays in current use are one hundred to one thousand times more sensitive than the original assays developed in the 1980s.[17]

Assays for troponins T and I are both used today in the care of patients with suspected ACS, which may exhibit one or more of the following biological variations:

1. Diurnal variation: The amount of circulating troponin may vary throughout the day in individuals not experiencing myocardial infarction (MI).[18]

2. Kidney disease and diseases of the skeletal muscle: Some assays measuring troponin in these settings exhibits less variation than other assays, and some troponins can be chronically elevated in patients with End Stage Renal Disease.[19,20,21,25]

3. ST-elevation myocardial infarction (STEMI): In this category of patients, the concentration of some subunits of troponin appear to follow a linear decline after the event, whereas some appear to decline and then peak again shortly after the MI.[22]

4. Macrotroponins: Consist of troponin bound to immunoglobulins (autoantibodies). Some assays may detect these autoantibodies.[150]

5. Biotin interference: It was recently reported that some immunoassays, including troponin assays, are susceptible to interference from biotin (or vitamin B7) supplements.[147] Laboratory personnel and clinicians should be mindful of this interaction when interpreting cardiac troponin results.

6. Hemolysis: A hemolyzed blood specimen can also result in inaccurate measurements of troponin assays. Thus, hemolysis needs should be noted when troponin concentrations are reported, and attempts should be made to redraw the specimen whenever possible.[38]

CONVENTIONAL TROPONIN ASSAYS

In the United States (US), conventional troponin I and T assays are still in widespread use. Although these assays are not sensitive enough to measure troponin in most healthy individuals, they are very reliable for detecting troponin levels that exceed the 99th percentile of a healthy reference population.[17] The performance target for these conventional assays is to measure troponins with a 10 percent coefficient of variation at the 99th percentile of their reference population, but not all currently available assays achieve this.[17]

With conventional assays, troponin I or T can be measured in the blood six to 12 hours after the onset of ACS symptoms.[7,15] After an MI, troponins will typically remain elevated for four to ten days.[7,15] The normal half-life for troponin in the plasma is about two hours, and it is at least partially removed by the kidneys.[15]

To meet the biomarker criteria for MI, not only must at least one troponin measurement be over the 99th percentile of the reference range but the troponin measurement must also be rising or falling in what is considered a characteristic pattern for MI.[7] The amount of rise or fall is not defined in the global consensus document, Third Universal Definition of MI, which requires the individual clinician to interpret the pattern of serial troponin values over time. A more specific definition is included in the American College of Cardiology and American Heart Association (ACC/AHA) non-ST-elevation MI (NSTEMI) guidelines; this document describes an increase or decrease of 20 percent from the initial elevated value when using conventional troponin assays.[7] In addition, these guidelines also suggest if the initial value is near or below the 99th percentile of the reference range, a change of ≥3 standard deviations of the variation from the initial value is required to meet the definition for rising or falling.[7] The ACC/AHA guidelines also stress that the clinical laboratory should clearly identify when a significant change has been identified in troponin concentrations during serial measurements.[7]

The reason for the rising or falling requirement for troponin is to aid in differentiating between a true MI and other potential causes for troponin elevation (**Table 3-1**). There are a variety of other cardiac conditions that can be associated with elevated troponin concentrations, sometimes chronically. These can include myocarditis, pericarditis, tachyarrhythmias, acute or chronic heart failure, and significant trauma to the heart.[7] Likewise, a myriad of non-cardiac problems, such as renal dysfunction, sepsis, burns, respiratory failure, and drug toxicity, can also cause elevations in troponin. Indeed, because troponin is partially removed by the kidney, individuals with end-stage renal disease may have chronic elevations of troponin.[7,24]

Table 3-1. Reasons for Troponin Elevations Not Related to Myocardial Infarction[15,17,23]

CARDIAC	NON-CARDIAC
Hypertensive emergency	Critical illness
Arrhythmias	Sepsis
Heart failure	Pulmonary embolism or hypertension
Myocarditis	Kidney dysfunction
Cardiomyopathy	Serious neurological events (e.g., stroke)
Aortic dissection	Thyroid disease
Structural heart disease (e.g., valve disease)	Drug toxicity (e.g., chemotherapy, cocaine)
Physical trauma to the heart	Extreme endurance exercise
Heart surgery/procedure (e.g., PCI*)	Rhabdomyolysis

*PCI – percutaneous coronary intervention

Because troponin elevation can have other, non-cardiac causes, it is essential that clinicians employ good clinical judgment during the risk stratification process for ACS. This process begins by taking a history from the patient and assessing symptoms, followed by a physical examination, an electrocardiogram (ECG), and then biomarker measurement. Only when all of these features are considered together can an accurate diagnosis be made.

The ACC/AHA guidelines for NSTEMI recommend measuring either troponin I or T when a patient with suspected ACS presents to the emergency department (ED).[7] This measurement should be repeated three to six hours after the symptoms started (or three to six hours after presentation) in all patients with ACS symptoms.[7] Additional measurements after six hours should be considered in patients who are stratified as moderate or high risk for ACS.[7]

LIMITATIONS TO CONVENTIONAL TROPONIN ASSAYS

Due to the extended time required to detect troponin in the blood using conventional assays, there can be a delay in the diagnosis of MI, which could also result in the delay of appropriate treatment. Following clinical evaluation and assessment for STEMI via ECG, most patients presenting to an emergency department (ED) with ACS symptoms will undergo a "rule-in" or "rule-out" protocol where serial cardiac markers are measured. Measuring the conventional troponin several times over a three- to six-hour period (or even longer period for higher risk patients) should yield a positive result if a patient is experiencing an NSTEMI. This process can result in prolonged ED admission times for patients who are ultimately "ruled out" (not experiencing an MI) and delays in initiation of treatments for patients who are eventually determined to be experiencing an NSTEMI.

Another limitation of conventional troponin assays is that they may lack enough sensitivity to detect small elevations in troponin that can occur in a less extensive MI or in those with lower circulating levels of troponin, such as women or patients presenting early after the onset of symptoms.[26,27] This scenario could cause an NSTEMI patient to be erroneously sent home, where they may go on to suffer cardiac complications or, in the worst case, may die.

The potential to miss the diagnosis of MI completely (incorrect "rule-out") and the extended time required to identify MI (delayed "rule-in") are the primary limitations of conventional troponin tests in clinical practice. The need to overcome these limitations led to the development of more sensitive and precise troponin assays.

HIGH-SENSITIVITY TROPONIN ASSAYS

Due to the shortcomings of conventional troponin measurements, high-sensitivity troponin (hsTn) assays have been developed. The hsTn assays have been used for several years outside the US. These assays are 10 to 100-fold more sensitive than the conventional troponin assays and can detect the very low levels of troponin that circulate in healthy individuals (**Figure 3-2**).[28] Though troponin was once thought only to enter the circulation when myocytes had been damaged, we now know that it can be found in normal individuals. The reasons for this have yet to be fully elucidated, but myocyte turnover and increased cell permeability have been suggested as mechanisms.[29,30]

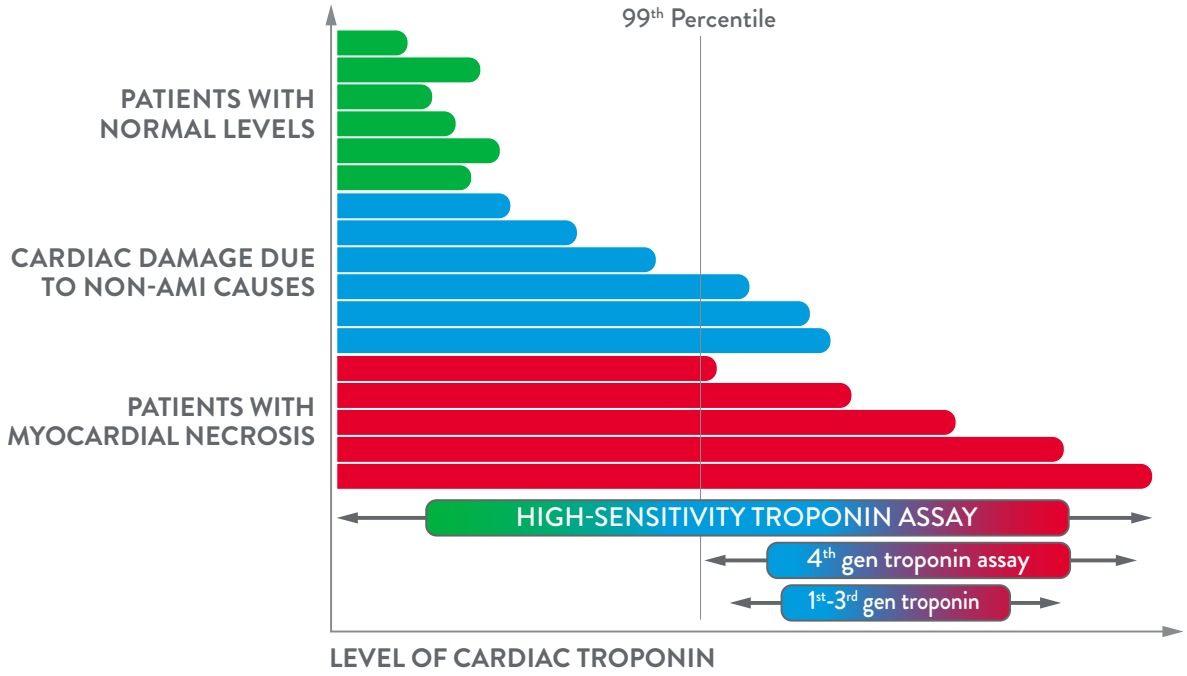


Figure 3-2. The sensitivity of high-sensitivity troponin assays allows for measurement of troponin in normal healthy individuals, whereas earlier generation assays were only sensitive enough to detect troponin elevation resulting from significant necrosis in MI, or occasionally, severe damage from other causes

Adapted from: Garg P, Morris P, Fazlanie AL, et al. "Cardiac Biomarkers of Acute Coronary Syndrome: from History to High-sensitivity Cardiac Troponin." *Internal and Emergency Medicine*. 2017;12(2):147-155. Used under CC BY http://creativecommons.org/licenses/by/4.0/ modified from original.

There have been varying proposals on how to define and differentiate high-sensitivity assays from conventional troponin assays. In 2012, a task force created by the International Federation of Clinical Chemistry (IFCC) proposed that hsTn assays be defined using two parameters:

- The total imprecision (coefficient of variation) at the 99th percentile value should be ≤10 percent[28]
- Measurable concentrations below the 99th percentile should be attainable with an assay at a concentration value above the assay's limit of detection (LOD) for at least 50 percent (and ideally >95 percent) of healthy individuals[28]
  - In 2018, the IFCC/AACC Task Force expanded on this point by requiring both men and women individually attain measurable concentrations, with at least 50% measurable concentrations above the assay's LoD[148]

Multiple high-sensitivity assays exist for troponin I, and one fifth-generation assay for troponin T is available. When compared directly, both types of troponin assays provide similar sensitivity and specificity for the biomarker requirement for MI.[27] The hsTnI assay may provide greater sensitivity for detecting acute MI in patients who present to the ED shortly after the onset of symptoms.[27] Both assays also provide prognostic information and have demonstrated the ability to predict mortality risk in ACS patients.

It should also be noted that there appear to be differences in troponin values based on age and sex, although this variation may depend on the assay used.[28] A study comparing women and men presenting with suspected ACS evaluated diagnostic thresholds using a hsTnI assay; researchers found that when using hsTnI, a sex-specific threshold for MI diagnosis doubled the diagnosis of MI in female participants.[26] Employing sex-specific thresholds also aided in identifying women at high risk for complications and death after MI.[26]

HIGH-SENSITIVITY TROPONIN ASSAYS IN PRACTICE: "RULE OUT" AND "RULE IN"

The hsTn assays have several significant advantages over the conventional assays that can be categorized as improving either "rule-in" or "rule-out" of MI.

Rule Out
One of the primary advantages of hsTn assays is that they have higher negative predictive value for acute MI than conventional tests. Since they can reliably detect very low levels of troponin, physicians can rule out MI in patients with these very low levels with more confidence than ever before (very low levels were unreportable with conventional assays). When studied in the clinical setting, the hsTn assays have shown a great deal of promise. There is increasing evidence to indicate that when patients with suspected ACS are tested with a hsTn assay on arrival to the ED using a risk-stratification algorithm, a negative hsTn measurement has over 95 percent negative predictive value for ruling out an MI.[14,31] At three hours after presentation, this number rises to over 99 percent, and accordingly, a repeat measurement of hsTn is recommended in all patients three to six hours after presentation.[32]

The ability to rule out an MI more quickly shortens the ED admission time for many patients, overcoming one of the primary limitations of conventional troponin assays (**Figure 3-3**).

Rule In
The other key advantage of hsTn assays is the ability to detect an acute MI very early before conventional tests would be positive.[23,27] Using conventional assays, there is a "troponin-blind" period during the first hours after the onset of MI when troponin concentrations are still reported as negative.[23] The hsTn assays significantly shorten this "troponin-blind" period, so patients experiencing an MI are more likely to have measurable troponin elevations when they first present to the ED.[23] Studies where hsTn have been measured at presentation and then repeated one-hour later have shown promise in improving early "rule-in" as well as "rule-out".[33] Moreover, this increase in sensitivity reduces the risk of missing an MI with less troponin elevation completely.[23] This can be a significant problem in women, and, predictably, the use of hsTn assays have demonstrated the ability to increase the diagnosis of MI in women.[26]

In identifying patients with MI earlier and more often, the hsTn assays also overcome two problems associated with the conventional assays. First, they reduce the delay to appropriate treatment for MI because it shortens the time for diagnosis in many situations. And second, it reduces the risk of missing an MI completely and the associated risk of cardiac complications and death (**Figure 3-3**).

HsTn Assays: Things to Consider

It is essential to emphasize that the high-sensitivity assays for troponin trade specificity for increased sensitivity. There may be more troponin elevations detected with hsTn assays that are not related to ACS. But it remains important for clinicians to be mindful that other conditions such as heart failure, sepsis, and kidney failure that can cause elevation of the conventional troponin assays also, to a greater degree, cause elevations of hsTn measures (**Table 3-1** on page 26). Multiple studies have found that the leading causes of "positive" high-sensitivity troponin elevations are not MI. Thus, each patient with an elevated value needs careful consideration for both the MI and non-MI determinants. As such, it is even more imperative that physicians employ good clinical judgment when evaluating patients with suspected ACS. All aspects of the patient's presentation should be assessed to appropriately stratify a patient's risk for ACS, including symptoms, medical history, physical exam information, ECG, and troponin concentrations.

It is also important to remember that to meet the biomarker criteria for an MI; troponin concentrations must be rising or falling over time. Given the increased sensitivity of these new assays, there has been renewed debate about how this rise or fall should be defined, and at the time of this publication, there is no formal consensus. Notably, none of the prior definitions of MI utilized high-sensitivity troponin values, and the AHA/ACC guideline recommendations on the percentage change in troponin concentrations required for MI are for conventional assays.[6,7] However, researchers have been exploring how these new high-sensitivity assays may modify the definition of change in troponin concentrations. A study by Keller et al. examining the use of high-sensitivity troponin assays for early rule-out of MI demonstrated the value of using a 50 percent change (or delta) between initial and three-hour troponin measurements, a strategy known as a scaled troponin approach.[34] Other groups have advocated for the use of an absolute change, rather than a percent change, for meeting the criteria of rising or falling troponin with high-sensitivity assays.[35] A position statement from the IFCC outlined the potential benefits of using this method although ultimately concluded that limitations exist for any method that defines troponin change in MI.[36]

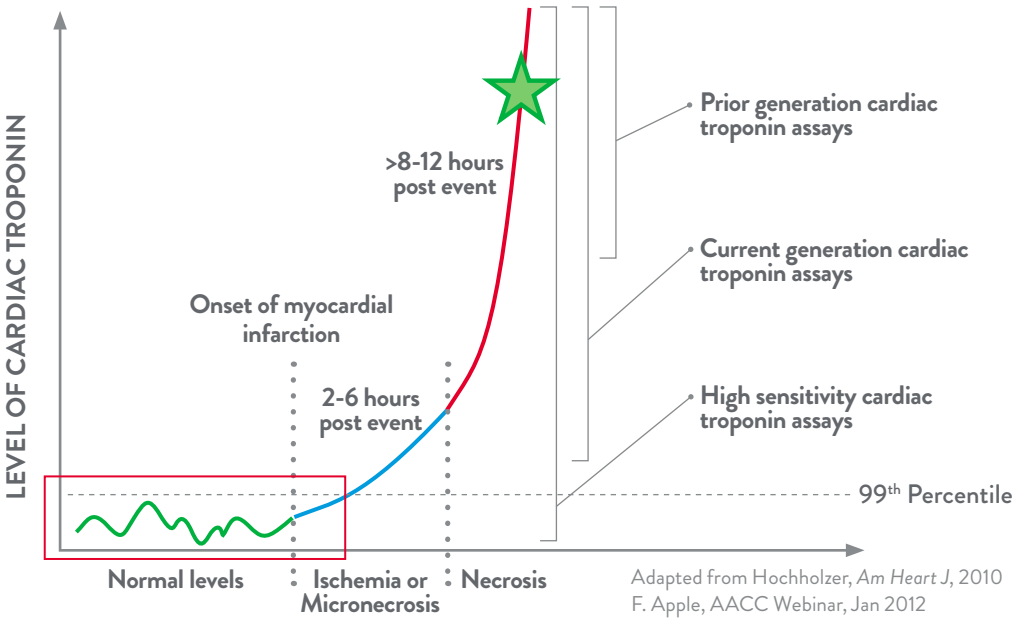


Figure 3-3. Troponin rise in the time after myocardial infarction. Older and current generation troponin assays cannot detect troponin increases as quickly as the high-sensitivity troponin assays

HnTn Assays: Effects on Patient Care

The high-sensitivity tests overcome the problem of prolonged diagnostic time for MI that can delay treatment. They can also dramatically shorten patient evaluation time in the ED and have demonstrated that they can reduce overall healthcare costs.[37] Furthermore, they avoid the predicament of potentially missing an MI with a lesser degree of troponin elevation.

However, with this increase in sensitivity, there is a loss of specificity. Clinicians need to be aware that there may be more troponin elevations reported with the new assays that are not related to ACS, and as indicated above, these cases will be in the majority. More than ever, troponins are only one piece to consider in the comprehensive evaluation of the patient. Despite these concerns, when used appropriately, these high-sensitivity tests have the potential to dramatically change how patients with ACS symptoms are managed, saving lives and money.

IMPLEMENTING HIGH-SENSITIVITY TROPONIN TESTING

When introducing hsTn testing to an institution, a variety of factors need to be considered. A multidisciplinary approach is essential, and representatives from all key areas affected by the change need to be included in the implementation process. Education is of particular importance; physicians, mid-level providers, nurses, and other healthcare personnel must understand the differences in sensitivity and specificity of the high-sensitivity assay.[38] Likewise, protocols and workflow, particularly in the ED, may need to be modified before implementing an assay with greater sensitivity.[38] The hsTn assays are most useful when they are used as part of an ACS risk assessment algorithm.[23] Importantly, it should be understood that simply replacing a conventional assay in an existing protocol with a hsTn assay does not allow the high-sensitivity assay to function to its full potential. Only when used in an algorithm that accounts for the increased sensitivity can it be effective for decreasing cost and ED admission time. Developing a new algorithm or modifying an existing algorithm for managing ACS patients will be important to promote appropriate use of the new test.[23] In addition, laboratory personnel will need to assess the quality control measures required for the new assay and will also need to work with other key stakeholders to decide on thresholds for the new assay, especially given that age and gender may influence normal values.[28,38] Practical considerations in the collection and processing of specimens need to be considered as well; hemolysis in the blood sample and the extent of centrifugation can both render the hsTn assays less accurate.[38] Similarly, practitioners should be reminded of other potential non-cardiac causes of troponin elevations, such as the increase in troponin T in patients with skeletal muscle disease or damage.[20,21]

In the 2015 NSTEMI guidelines, the European Society of Cardiology (ESC) recommends the use of hsTnT or hsTnI over conventional troponin assays.[23] In addition, ESC makes the general recommendation to measure hsTn at presentation and then repeat it 3 hours later as part of a rule-out algorithm.[23] The European guidelines also emphasize that hsTn is a quantitative measure, so the higher the number, the greater the likelihood of myocardial necrosis.[23] For example, a hsTn more than five-fold over the upper reference limit has a positive predictive value for a type 1 MI of over 90 percent, whereas elevations less than three-fold over the upper reference limit have a positive predictive value of only 50-60 percent. Importantly, these guidelines also highlight the benefit of developing new algorithms for the management of patients with ACS around the hsTn test that allow for the rapid assessment of patients presenting to the ED with ACS symptoms and the appropriate use of the hsTn test.[23]

Similarly, the National Institute for Health and Care Excellence (NICE) in the United Kingdom also recommends the use of hsTn as part of an early rule-out protocol for NSTEMI. According to the NICE recommendations, hsTn should be measured at presentation and repeated three hours later; if NSTEMI is not ruled out in this protocol, further evaluation is recommended.[39]

OTHER CARDIAC BIOMARKERS

Although troponin is central in the determination of myocardial necrosis, a variety of other markers have demonstrated some usefulness in the evaluation of patients with suspected ACS in the past, and more are under investigation.

Myoglobin, an oxygen-carrying protein, was one of the earliest biomarkers used for MI.[15] Although its concentrations rise in response to injury of the cardiac tissue, it is no longer recommended as a biomarker for ACS.[15]

Creatinine kinase MB (CK-MB) is a marker that is mostly specific to the cardiac tissue and was traditionally used in conjunction with older generation troponin assays. It remains elevated for a shorter time than troponin after MI, and it may provide additional clinical information regarding the timing of a myocardial injury and is sometimes useful for detecting an early reinfarction.[23] In current practice, routine measurements of CK-MB in patients with suspected ACS are no longer recommended.[23]

Copeptin is a small portion of a precursor for the arginine vasopressin hormone.[40] Although it is not specific to the cardiac tissue, copeptin does increase significantly in the early stages of MI.[40] In some studies, it has shown promise when used in conjunction with troponin for facilitating earlier rule-out of myocardial infarction to differentiate between patients with NSTEMI and no NSTEMI.[23,41] Copeptin concentrations may also provide prognostic information in ACS patients; higher copeptin levels have been correlated with greater mortality and risk for heart failure after an ACS event.[42] Although the US guidelines do not make a specific recommendation on it, the ESC guidelines on NSTEMI do suggest that copeptin may be useful to facilitate early rule-out of MI, especially if high-sensitivity troponin assays are unavailable.[23] Despite this recommendation, copeptin is infrequently used in clinical practice because it has not proved to be superior to troponin in identifying MI.

The natriuretic peptides, B-type natriuretic peptide (BNP) and its inactive counterpart N-terminal proBNP (NT-proBNP), are most often used in the setting of heart failure but also rise quickly after a myocardial ischemic event.[42] The natriuretic peptides can provide information about the size of the infarct area in the heart and also the function of the left ventricle before and during the ischemic event.[42] Perhaps more importantly, natriuretic peptides provide additional prognostic information for patients experiencing STEMI and NSTEMI and can predict mortality and heart failure after an ACS event.[42] BNP has been approved by the FDA as a prognostic aid in acute coronary syndromes.[43]

There are many other biomarkers currently being investigated for both diagnostic and prognostic use in ACS, and their exact role in the management of patients has not yet been defined. Ischemia-modified albumin has been cleared by the FDA as a diagnostic test for ischemia in patients with suspected acute coronary syndromes.[44] Cardiac myosin-binding protein C (or cMyC) recently demonstrated usefulness in early identification of acute MI, but researchers are still unsure if it offers any advantage over hsTn.[45] Similarly, two other emerging biomarkers have shown some promise for improving prognostic information in patients with ACS: GDF15 and ST2. The GDF15 protein is one of the transforming growth factor-ß cytokines. In studies, it has shown some usefulness in predicting future cardiovascular disease events and mortality.[42,46] Likewise, ST2, an FDA approved biomarker for ventricular strain in patients with heart failure, appears to provide additional prognostic information regarding mortality and complications after an ACS event.[42,46] Whether either GDF15 or ST2 provide additional prognostic information over currently used biomarkers remains to be determined.

SECTION 3: REVIEW QUESTIONS

1. CK-MB and troponin should always be used together to detect the presence of myocardial necrosis.

   ☐ **True** ☐ **False**

2. Which of the following statements accurately reflects the definition for rising or falling troponin concentrations using hsTn assays in an MI?

   a. A rise or fall indicative of cardiac necrosis is a 25 percent or more change from the initial elevated value

   b. There is no consensus on the exact amount or percentage of rise or fall required for troponin changes using hsTn assays to meet criteria for MI

   c. The IFCC states that a rise or fall in cardiac troponin over six hours of 50 percent of more is diagnostic for MI

   d. All of the above are correct

3. Which of the following statements about implementing hsTn is TRUE?

   a. The transition from a conventional troponin assay to a high-sensitivity assay requires education for laboratory personnel only

   b. When transitioning from conventional to high-sensitivity troponin measurements, a multidisciplinary team is needed

   c. Physicians need to be educated that a positive high-sensitivity troponin measurement is diagnostic for myocardial infarction

   d. Hemolysis does not affect a hsTn result

4. List four biomarkers (other than troponin) that have been studied in ACS patients and shown definite or possible benefit

_____

_____

SECTION 4
HEART FAILURE

LEARNING OBJECTIVES

When you complete this section, you will be able to:

1. Understand the mechanism of how heart failure occurs
2. Describe the different types of heart failure and classification systems
3. Recognize the consequences of heart failure
4. Explain tests that can be used to assess patients with heart failure

Heart failure, in the simplest of terms, indicates that a problem with the ventricles is preventing the heart from filling and/or pumping correctly. It is the result of a complex mechanical and neurohumoral syndrome resulting in stasis (or slow movement) of blood in the lungs and peripheral tissues. It is estimated that over 26 million people worldwide are living with heart failure, and it is the number one cause of hospitalization in the United States (US) and Europe.[47] In the US, it is estimated that over 6.5 million adults are living with heart failure and that figure is predicted to grow to over eight million by 2030.[48] Registries of heart failure patients in the US and Europe report mortality to be anywhere from 23 to 36 percent during the first year after a heart failure hospitalization.[49]

DEFINING HEART FAILURE

Heart failure initiates structural, functional, and neurohumoral abnormalities that prevent the ventricles from either properly filling with blood or properly ejecting blood. Regardless of the underlying mechanism, this results in poor cardiac performance. Section 1 of this guide described the basic consequences of poor cardiac performance: the tissues of the body may not receive enough oxygen if the heart is not providing enough pressure to allow for perfusion of oxygen and nutrients from the blood into the tissues. The body does attempt to compensate for this loss of perfusion. It begins to release hormones and neurotransmitters (chemical messengers in the body) that increase the blood pressure and promote retention of water by the kidneys to increase blood volume; this is termed neurohormonal activation.[50,51] In the short term, these compensation mechanisms are adaptive, but over the longer term, they clearly become maladaptive and are the targets for diagnostic tests and therapies. For example, neurohormonal activation facilitates the maintenance of perfusion to the organs if the body is experiencing acute blood loss, minimizing organ damage from this event. However, when neurohormonal activation occurs over a long period, as it does in heart failure, these compensations worsen the functional ability of the heart rather than improving it. [50,51]

DEFINING HEART FAILURE BY PUMP FUNCTION: HFPEF AND HFREF

To clarify the functional problem in heart failure, clinicians typically separate heart failure into two different categories: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) (**Figure 4-1**). In HFpEF, the primary problem is the left ventricle not filling properly with blood.[51] Conversely, in HFrEF, the primary problem is poor ejection of blood from the left ventricle.[51]

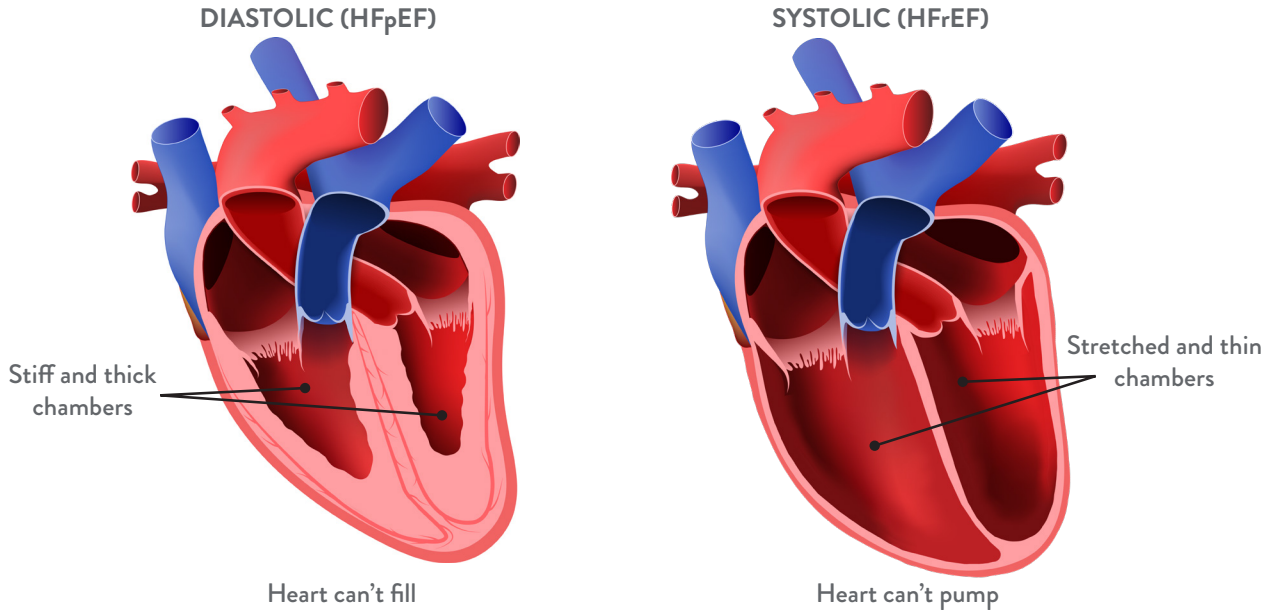


Figure 4-1. Structural changes to the ventricles of the heart in heart failure: in HFpEF (left) the ventricle walls stiffen and can't fill appropriately and in HFrEF (right) the ventricle dilates and the walls are stretched thin, impairing the normal pumping activity

Heart Failure and a Preserved Ejection Fraction (HFpEF)
In HFpEF, as the name implies, the ejection fraction of the left ventricle is normal (usually over 45 percent), so the heart is still pumping out the appropriate percentage of blood with each contraction.[51] However, the problem in HFpEF is an impairment in the heart's ability to relax during the process of filling with blood.[51,52] The left ventricle cannot relax and fill with blood normally because its walls are abnormally stiff and thickened; the walls of the ventricle are also not working in a coordinated fashion with the blood vessels that receive the blood.[51] This results in poor cardiac performance even though the ejection fraction is still within a normal range. Women, the obese, and elderly individuals are more likely to be diagnosed with HFpEF than men, individuals in a normal weight range, and younger people.[51,53] Heart failure with preserved ejection fraction can be more difficult to diagnose and manage than HFrEF, but almost half of the patients with heart failure in the US have HFpEF.[51,52,54] Unfortunately, at the time of this writing, there are no proven treatments for HFpEF that reduce the risk of heart failure hospitalization or cardiovascular death.

Heart Failure with Reduced Ejection Fraction (HFrEF)
In HFrEF, the ejection fraction of the left ventricle is reduced. This means that with each pumping contraction of the heart, a smaller percentage of blood, usually less than 45 percent, is forced out into the aorta. The interior cavity of the left ventricle is typically dilated in HFrEF, and the heart muscle is less effective when it contracts.[51] Unlike HFpEF, HFrEF is the more common cause of heart failure in men and younger individuals.[52] Approximately two-thirds of HFrEF is attributed to a prior myocardial infarction and damage to the heart resulting in scar formation.[55] Diagnosis is more straightforward in HFrEF than in HFpEF: patients with HFrEF are more likely than those with HFpEF to have common symptoms of heart failure. Also, because they are younger, patients with HFrEF are less likely than those with HFpEF to have other diseases that the symptoms could be attributed to, like chronic obstructive pulmonary disease.[51,52,54] Patients with HFrEF also respond more favorably to treatment with medications than those with HFpEF.[51,52] Indeed multiple classes of medications, as well as implantable devices, reduce the risk of heart failure hospitalization and cardiovascular death in HFrEF. These include medications such as ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, certain beta-blocking agents, valsartan/sacubitril, ivabradine, the combination of long-acting nitrates and hydralazine, and digoxin, as well as devices such as implantable cardioverter-defibrillators and cardiac resynchronization devices.[52,56]

What is a Normal Ejection Fraction?

Heart failure is often defined in terms of the heart's left ventricular ejection fraction (or EF), so what is a normal EF for the left ventricle? Although definitions vary, the normal range of EF (measured when a person is at rest) is generally described as approximately 50 to 70 percent. However, in 2015, the American Society of Echocardiography and the European Association of Cardiovascular Imaging released collaborative recommendations that offer a more precise definition. In this document, a normal left ventricular EF was defined as 52 to 72 percent for men and 54 to 74 percent for women.[57]

Heart Failure with Mid-Range Ejection Fraction (HFmrEF)
A new term, heart failure with mid-range ejection fraction, or HFmrEF, was recently described by the European Society of Cardiology (ESC). In the explanation for this new classification, the ESC defines HFmrEF with the same criteria used for HFpEF diagnosis but with an ejection fraction of 40-49 percent.[52] Their purpose in defining HFmrEF as a separate entity from HFpEF or HFrEF is to promote more study of interventions and outcomes in this very specific population of individuals with heart failure.[52] Because HFmrEF is a new term and is not included in other guidelines and literature, it will not be a focus of this guide.

DEFINING HEART FAILURE WITH CLASSIFICATION SYSTEMS: NYHA AND ACC/AHA

Several different classification schemes exist to quantify the severity of heart failure in a patient. The New York Heart Association (NYHA) classification system is based primarily on the effects the heart failure has on the patient's ability to perform physical activity. The categories progress from an NYHA class I, indicating the patient has no symptoms with normal physical activity, all the way to an NYHA class IV, indicating the patient has symptoms of heart failure at rest or with the slightest physical activity.[58] The NYHA classification system can predict mortality in heart failure and can be a useful way to monitor the effectiveness of treatment.[50,58]

Another classification scheme from the American College of Cardiology Foundation (ACC) and the American Heart Association (AHA) defines heart failure according to symptoms and structural changes to the heart (**Figure 4-2**). The ACC/AHA classification scheme for chronic heart failure begins with stage A, which indicates only that a patient is at high risk of developing heart failure as a result of comorbidities like coronary artery disease, diabetes, and hypertension.[58] Stage B in this classification scheme indicates that there is evidence of structural changes in the heart associated with heart failure, but the patient is not experiencing signs or symptoms.[58] In Stage C, patients have evidence of structural changes in the heart and also signs and symptoms of heart failure.[58] Finally, stage D indicates that the patient is experiencing end-stage heart failure: symptoms at rest or with minimal exertion despite maximized medical therapy.[58] Thus, the NYHA class is usually applied to patients with symptomatic Stage C and D heart failure.

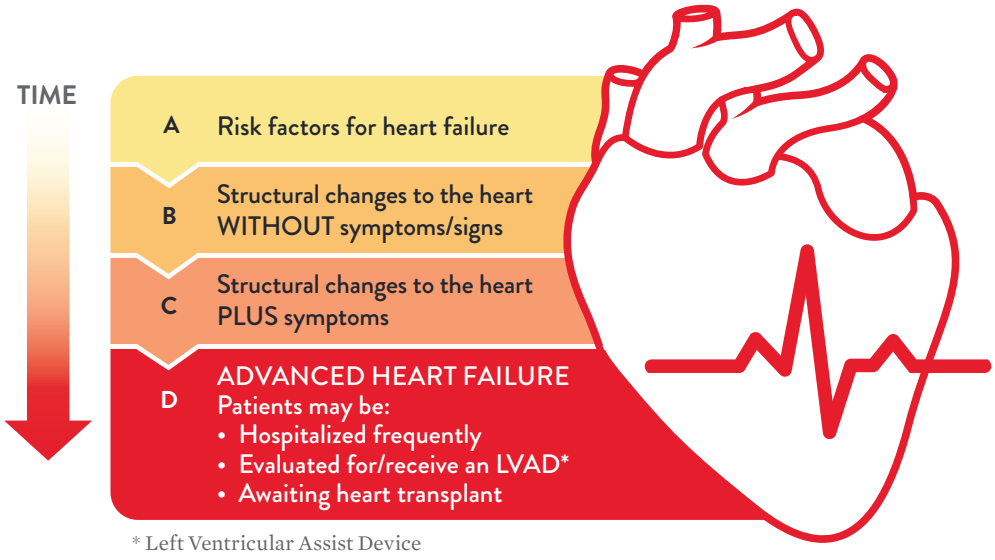


Figure 4-2. Stepwise progression of heart failure according to ACC/AHA stages

DEFINING HEART FAILURE BY PRESENTATION: ACUTE AND CHRONIC HEART FAILURE

Acute heart failure (AHF) is a term often used in the emergency department (ED) and hospital setting. This term refers to an acute, rapid worsening of heart failure symptoms that can be life-threatening.[52] Patients with AHF need prompt medical evaluation and treatment. In about two-thirds of cases, patients with AHF have already been diagnosed with heart failure, but in the other one-third, AHF is the first sign of a heart failure problem.[52,59] Often, a patient with stable heart failure experiences an event that triggers the AHF episode. This event can be something straightforward like neglecting to take prescribed heart failure medications or something more complex, such as a new MI, a superimposed infection, development of abnormal heart rhythm (atrial fibrillation), or dietary changes with increased intake of salt.[52]

Chronic heart failure, in contrast to acute, is the more stable, chronic manifestation of inadequate cardiac function. Chronic heart failure is the term used to describe patients with heart failure who are not experiencing an acute worsening of symptoms from AHF. The majority of patients with heart failure are classified as having chronic heart failure. They are managed in the outpatient setting, and they only convert to a diagnosis of acute heart failure in the setting of acute symptom worsening. Once a patient is hospitalized for heart failure, there is a much higher risk of repeat hospitalization within the next several months, and this often becomes a progressive cycle.

CAUSES OF HEART FAILURE

Anything that causes damage to the myocardium can lead to heart failure. Coronary artery disease is the most important predictor of heart failure, and it is estimated to be the primary cause of heart failure in over 60 percent of patients in the US.[55] However, other frequent causes of heart failure include hypertension (the medical term for high blood pressure), problems with the valves in the heart, or cardiomyopathy (maladaptive changes in heart structure caused by inflammation, infection, or unknown reasons).[50,52] Approximately 90 percent of all heart failure cases have antecedent hypertension (or hypertension before the diagnosis of heart failure). Thus it is believed that high blood pressure contributes to all forms of heart failure as an additional risk condition.[60] Other less common causes of heart failure include myocarditis, pericarditis, drug toxicities (e.g., certain types of chemotherapy, other cancer treatments, and alcohol), endocrine disorders like thyroid disease, collagen vascular diseases like scleroderma, and arrhythmias with persistently elevated heart rates.[50,52] In the absence of coronary artery disease, it is believed that most cases of HFrEF have a genetic predisposition with a superimposed insult such as longstanding hypertension, excessive alcohol intake, or viral syndrome.[61]

CONSEQUENCES OF HEART FAILURE

As discussed in Section 1, maintaining strong pumping ability is essential for the heart to function appropriately. When the heart doesn't pump effectively as a result of heart failure, a cascade of negative effects occurs throughout the body. Organs and tissues may not receive adequate oxygen to function appropriately, especially if any additional strain (like exercise or illness) is placed on the cardiac system.[62] The kidneys, in particular, are remarkably sensitive to the changes in cardiac performance and, as a result, many patients with heart failure have coexisting kidney disease.[62]

As a result of the continued neurohormonal activation in heart failure, the heart itself undergoes more changes. The structure of the ventricle undergoes further modification, causing it to be even less effective at pumping blood.[62] This process is often termed remodeling, and it is the consequence of scar formation in the cardiac tissue (this scarring is called cardiac fibrosis). Scar formation and fibrosis can initially be the result of a heart attack or may develop more diffusely over time as a result of the heart failure process itself.[63] The changes that lead to fibrosis occur on the cellular level within the cardiac myocytes. In response to the original damage that led to heart failure, the myocytes become enlarged and don't function as efficiently.[63] Poor myocyte function eventually leads to an excessive accumulation of proteins between the myocyte cells that prevent normal movement of the cells and cause stiffening of the myocytes. This stiffness of the myocytes produces the cardiac fibrosis.[63]

The consequences of these structural changes in the heart are profound for the rest of the body. Humans have a "closed circulatory system," like a closed circuit; this means that blood can only go "back" when it cannot go "forward." When the heart does not pump the blood forward effectively as a result of stiffness or pump failure, the blood begins to "back up" into the lungs. With blood moving more slowly through the pulmonary system, fluid leaks out into the lungs and begins to accumulate. When a patient with heart failure stands or sits upright, this fluid falls to the bottom of the lungs and may not interfere with breathing; however, when the patient lays down flat, the fluid pools throughout the lungs which may lead to difficulty breathing. Eventually, the increased pressure in the lungs may lead to congestion in the right ventricle. Because the right ventricle receives blood from the rest of the body, as the right ventricular performance is affected, a further "back up" of blood will occur into the peripheral tissues. This results in fluid accumulation in the peripheral tissues that manifests as swelling (or edema), first in the legs and feet (due to gravity), and then it may spread to the abdomen and even to organs such as the liver. This process whereby problems with the left ventricle lead to problems with the right ventricle, with congestion of the lungs as well as the peripheral tissues, underlies what most doctors regard as true "congestive heart failure."

SYMPTOMS AND SIGNS OF HEART FAILURE

One of the most important characteristics to evaluate in patients with heart failure is symptoms. Notably, many of the symptoms of heart failure can be traced back to the changes in cardiac performance and can be collectively termed "effort intolerance." Shortness of breath (sometimes called dyspnea) is the most common symptom of heart failure and is a sign that fluid is accumulating in the lungs as a result of poor left ventricular performance. Patients with heart failure often present with other symptoms as well, such as orthopnea (shortness of breath when lying down), paroxysmal nocturnal dyspnea (awakening from sleep with acute shortness of breath), exercise intolerance, weakness, fatigue, and swelling of the ankles and feet.[51,52] Again, these symptoms correlate with fluid accumulation in the lungs and body as a result of the "back up" of blood in the heart. Heart failure most often limits a persons' ability to perform strenuous or even low-intensity exercise. This can eventually progress to the point that symptoms interfere with very basic functions such as walking, showering, dressing, and eating food as described in NYHA class III and IV.[64]

On a physical exam, clinicians evaluate for signs of heart failure. In severe cases, the signs can be obvious; however, if the patient's heart failure has developed over a long time, the signs may be subtle. A patient may appear very congested (often referred to as "wet") or may not have obvious congestion at rest (referred to as "dry"). If "wet," fluid in the lungs can be heard with a stethoscope as crackles ("rales" or "crepitations"), and the patient may be visibly short of breath with evidence of low oxygen levels, such as blue skin. Fluid in the peripheral tissues can be seen and felt as swelling or edema (as described above). Evaluation of the jugular vein in the neck can show distension. Changes in how the heart sounds through a stethoscope and differences in where the heartbeat can be felt in the chest can also be signs of heart failure; the heart rate may increase to the point where it seems to "gallop" as it attempts to compensate for poor output.[50,52]

THE ROLE OF ECG AND IMAGING

Electrocardiogram (ECG)

Although the electrocardiogram or ECG (**Figure 4-3**) is essential in the assessment of patients with acute coronary syndrome (ACS) symptoms, it is a less specific tool in heart failure. Patients with heart failure can have mild or dramatic abnormalities on an ECG, but it can be a useful tool in several circumstances. First, an ECG can be helpful to rule out heart failure—very rarely would a patient with heart failure have a completely normal ECG.[52] Second, it may identify the etiology of the patient's heart failure, such as a previous MI.[52] And third, it may detect a coexisting problem such as atrial fibrillation (inappropriate, rapid beating of the atria) that requires treatment.[52] Importantly, in the setting of heart failure, there are electrical conduction disturbances that can lead to heart block (which is a lack of coordination of contraction of the ventricles). For example, in HFrEF, patients can experience several types of electrical conduction disturbances, such as right bundle branch block, left bundle branch block, or interventricular conduction delay; patients with these abnormalities may benefit from an implanted cardiac resynchronization device (discussed later in this section).[52]

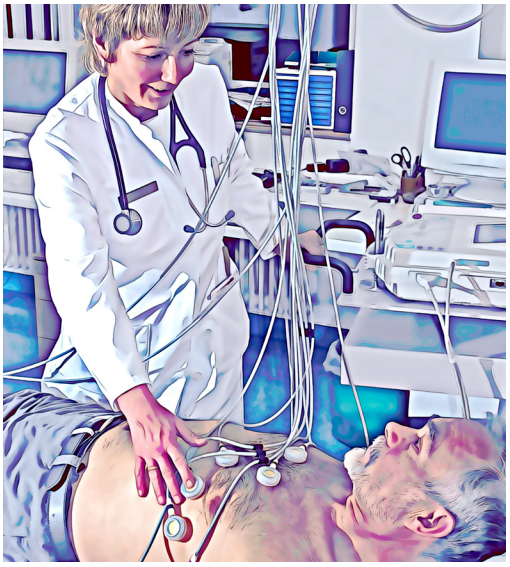


Figure 4-3. The electrocardiogram can be a useful tool in several circumstances

Echocardiogram

Echocardiography, or ultrasound of the heart, is an essential tool in the diagnosis of heart failure (the test itself is called an echocardiogram, often referred to as an echo). An echocardiogram provides information on the function of the heart muscle during relaxation and contraction, the size of the ventricular walls and the interior chamber, the performance of the valves, and the pressures in various parts of the heart.[52] The echocardiogram also measures ejection fraction and stiffness of the ventricle, necessary in the differentiation between HFrEF and HFpEF.[52]

Cardiac Magnetic Resonance (CMR)

Cardiac magnetic resonance (CMR), or magnetic resonance imaging (MRI) of the heart, is another useful tool for evaluating heart structure and characterizing changes in the cardiac tissue. It can be particularly helpful when echocardiography is not adequate to assess structural abnormalities in heart failure, especially the right side of the heart.[52] The European heart failure guidelines recommend the use of CMR in patients with complex congenital heart disease (a cardiac structure problem that a patient is born with) or with inadequate imaging with echocardiography.[52] Both the US and European heart failure guidelines also state that CMR can be helpful in establishing a cause of heart failure and characterizing the fibrotic changes in the cardiac tissue particularly in the setting of sarcoidosis.[52,58] Although CMR is the only imaging tool that can truly characterize the actual cardiac tissue, it is not suitable for everyone, such as patients with certain metal implants; it is also not available at all centers and may be more expensive than other imaging techniques.

Laboratory Testing

During an initial diagnostic workup for heart failure, a considerable amount of laboratory testing is performed. Renal and liver panels, lipid measurements, thyroid function tests, complete blood counts, and iron studies may be ordered to evaluate for underlying causes and comorbidities and also to assess the appropriateness of heart failure therapies.[52] In addition, several circulating biomarkers are useful in the diagnosis and management of heart failure.

Natriuretic Peptides
The natriuretic peptides (NPs), B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), play a central role in heart failure. Although BNP was initially called brain natriuretic peptide because it was first identified in the brains of pigs, this was a misnomer as it is very specific to the heart.[65] BNP is a hormone released by the cardiac myocytes when they are under strain, and NT-proBNP is an inactive fragment cleaved from the BNP molecule.[66] These NPs are released when the ventricles, particularly the left ventricle, experience volume and pressure overload and when neurohormonal activation occurs in response to heart failure.[66] Measuring NPs have shown benefit in almost every aspect of heart failure care. In the hospital setting, NPs can assist in distinguishing the cause of acute shortness of breath, determine prognostic information about mortality risk in AHF, and, when measured at discharge, can identify long-term prognosis after an AHF admission.[52,56,67] They can also be used as a screening tool in the outpatient setting to rule out heart failure or identify patients in need of early intervention to prevent heart failure.[52,56] Finally, they can provide long-term prognostic information for patients with chronic heart failure.[67] Section 5 will discuss the NPs in more detail.

Galectin-3
Galectin-3 is another biomarker that increases with worsening heart failure. Galectin-3 concentrations appear to increase when fibroblasts and macrophages are activated in the cardiac tissue.[63,68] These cells are involved in the remodeling of cardiac muscle that occurs in heart failure. Consequently, galectin-3 appears to be a good marker for the presence of cardiac remodeling and the development of cardiac fibrosis. In clinical studies, galectin-3 has demonstrated usefulness as a prognostic indicator and as a screening tool for assessing readmission risk after a heart failure hospitalization.[69,70] Section 5 will discuss galectin-3 in more detail.

Troponin
High-sensitivity troponin assays have an emerging role in heart failure and may provide useful prognostic information about the heart failure risk for patients experiencing an MI. Elevations in high-sensitivity troponin I concentrations in patients with suspected ACS strongly correlate with risk of future hospitalization for heart failure.[71] High-sensitivity troponin assays will be discussed in more detail in Section 5.

HEART FAILURE TREATMENT

Early identification, treatment of underlying causes, and control of risk factors are all essential first steps in the management of heart failure. Once those areas are addressed, patients should be counseled on lifestyle interventions such as eating a low-sodium diet, limiting fluid intake to a prescribed amount, weighing themselves daily, engaging in light aerobic exercise, understanding the need for follow-up appointments with their physician, and learning how best to manage the disease.[58,62]

Medications are typically prescribed to block the body's maladaptive neurohormonal response to heart failure. These can include drugs such as ACE inhibitors, beta-blockers, aldosterone antagonists, and diuretics.[62] It is essential that patients understand the importance of taking these medications because, when used appropriately, these drugs can prevent hospitalizations and decrease the risk of death from heart failure, especially in patients with HFrEF.[58,62] Although these medications can also be beneficial to patients with HFpEF, researchers are still attempting to determine the optimal drug regimens for treatment of HFpEF.[58,62]

Some patients with heart failure will also require intervention with cardiac devices. Certain individuals with severe heart failure who have electrical conduction abnormalities (as outlined in the previous discussion of ECG in heart failure) may be candidates for cardiac resynchronization therapy (often called a biventricular pacemaker), which is an implantable device that uses electrical impulses to aid both ventricles in contracting at the same time. Other patients with very low ejection fractions may require an implantable cardioverter-defibrillator, which can help the heart recover from life-threatening arrhythmias.[62] For patients experiencing the most severe heart failure symptoms (NYHA class IV and ACC/AHA stage D), a left-ventricular assist device (or LVAD) may be used to support cardiac function. An LVAD increases the output of blood from the heart using a pump implanted into the wall of the left ventricle.[62,72] Although the pump itself is implanted in the chest, a wire runs out of the device and through the skin to connect the LVAD to batteries and the control unit.[58,62] Finally, in the most critical cases, patients who are otherwise in good health and can tolerate the major surgery may undergo a cardiac transplant.[62] Only about 3,000 people receive heart transplants in the US each year.[73]

SECTION 4: REVIEW QUESTIONS

1. Decide which type of heart failure is being explained in each description (HFpEF, HFrEF, or AHF)
   a. A rapid worsening of symptoms that requires immediate evaluation _____
   b. This type of heart failure is easier to diagnose and is more responsive to chronic treatment _____
   c. This type of heart failure is more common in older individuals and women _____
   d. This can be triggered by failing to take prescribed medications for heart failure _____
   e. Heart failure resulting from the left ventricle's inability to relax _____
   f. Heart failure resulting from poor contractility of the left ventricle _____

2. List five symptoms of heart failure

_____

_____

_____

_____

_____

3. The most commonly used biomarker in heart failure is
   a. Galectin-3
   b. Natriuretic peptides
   c. Troponin
   d. All of the above

4. Fill in the blanks
   a. As a result of the poor cardiac pumping performance in heart failure, the body attempts to compensate by using _____ and _____ to raise blood pressure and retain more water. This is called _____ activation.
   b. The organs most sensitive to changes in cardiac performance are the _____.
   c. Serious, long-term structural changes occur in the heart as a result of heart failure. Cardiac _____ occurs as a result of the accumulation of proteins between the myocyte cells that causes the cells to stiffen.

SECTION 5

THE ROLE OF CARDIAC BIOMARKERS IN HEART FAILURE

LEARNING OBJECTIVES

When you complete this section, you will be able to:

1. Describe cardiac biomarkers used in heart failure
2. Explain the role of cardiac biomarkers in various aspects of heart failure care
3. Understand the guideline recommendations from several international organizations for the use of cardiac biomarkers in heart failure

As discussed in Section 4, the changes in cardiac function that occur in heart failure affect the entire body, so it is essential that clinicians monitor the status of heart failure patients with diligence. Circulating biomarkers can be especially helpful tools for gauging the presence, severity, and progression of heart failure. This section will build on the previous discussions of biomarkers used in heart failure and also introduce several emerging biomarkers for this disease process.

AS A GROUP, THE CARDIAC BIOMARKERS USED IN PATIENTS WITH HEART FAILURE CAN GENERALLY BE CLASSIFIED INTO THREE AREAS

- **Markers of myocardial stretch/pressure and neurohormonal activation**: These include natriuretic peptides and several emerging biomarkers (MR-proADM, copeptin). Rising concentrations of these biomarkers reflect increasing neurohormonal activation that can result from heart failure.
- **Markers of cardiac remodeling**: These include galectin-3 and several emerging biomarkers (ST2, GDF15). When markers in this group rise, they can indicate myocyte changes are occurring that lead to fibrosis in heart failure.
- **Markers of myocardial injury/ischemia**: These include cardiac troponins. Ischemia and injury may occur in heart failure, and biomarkers that reflect this process have demonstrated prognostic capability in heart failure patients. As discussed in Sections 2 and 3, the primary application of these markers is in patients with suspected acute coronary syndromes, but their potential utility in heart failure is outlined on page 48.

Evaluating each of these aspects of heart failure provides essential information on the status and prognosis of an individual patient. However, the usefulness of various biomarkers differs according to the clinical scenario.

MARKERS OF MYOCARDIAL STRETCH/PRESSURE AND NEUROHORMONAL ACTIVATION

Natriuretic Peptides

As discussed in Section 4, the natriuretic peptides (NPs), B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), play a central role in heart failure. BNP is a hormone released by the cardiac myocytes when they are under strain, and NT-proBNP is an inactive fragment cleaved from the BNP molecule.[66] These NPs are released when the ventricles, particularly the left ventricle, experience volume and pressure overload and when neurohormonal activation occurs in response to heart failure.[66] The NPs have shown benefit in almost every aspect of heart failure care. In the hospital setting, NPs can assist in distinguishing the cause of acute shortness of breath and determine prognostic information during the admission and after discharge.[52,56,67] They can be used as a screening tool in the outpatient setting to rule out heart failure or identify patients in need of early intervention to prevent heart failure.[52,56] They also provide prognostic information for patients with chronic heart failure.[67] This section will describe NPs in more detail and explain how they fit into the care of patients with heart failure.

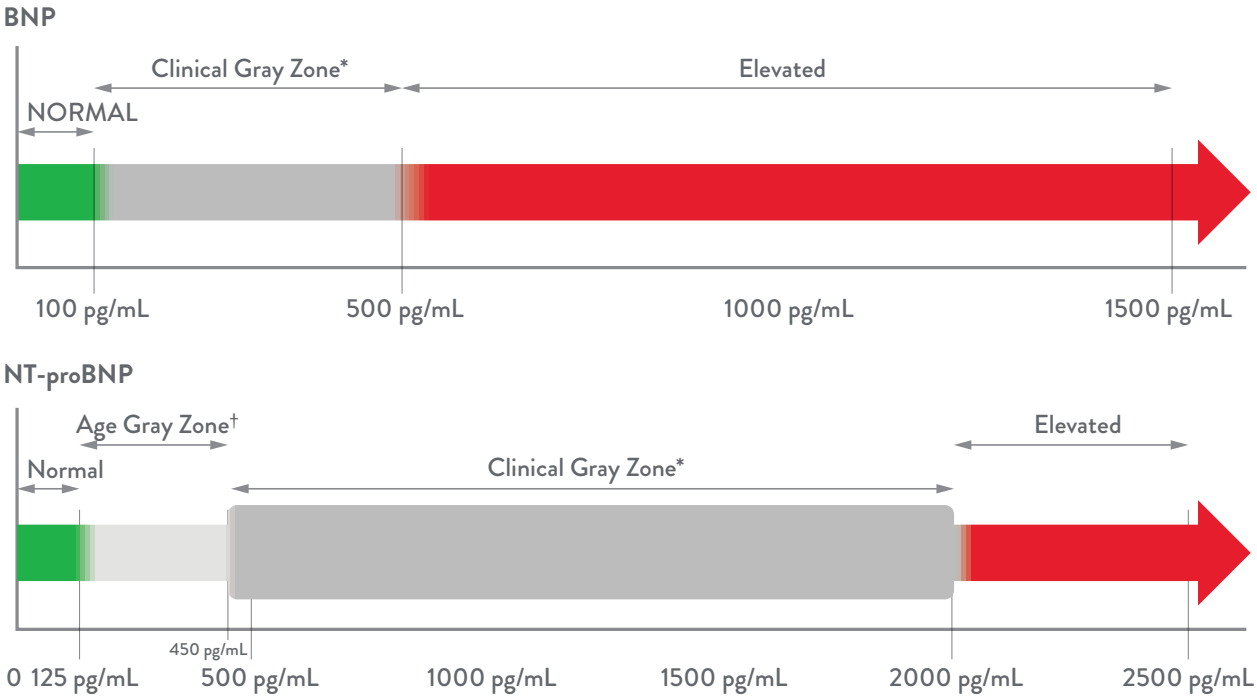
The NPs are hormones that influence fluid and sodium balance in the body.[74] Although only the B-type (BNP and NT-proBNP) are measured routinely in clinical medicine, three types have been identified in total:

- **Atrial NP** released from the atria
- **B-type NP** released from the ventricles
- **C-type NP**, which is found in the kidneys, blood vessels, and central nervous system[74]

Of note, BNP was originally called brain natriuretic peptide because it was first identified in the brains of pigs, but it was later determined to be a misnomer because it is released by the ventricles of the heart.[65] This guide will focus on the B-type NPs (BNP and NT-proBNP), subsequently referred to as NPs, because they are most specific to the pathophysiology of heart failure.

Differences in Natriuretic Peptide Assay Types

Although most studies indicate that BNP and NT-proBNP assays have similar sensitivity and specificity, clinicians should be aware of several differences.[66] For example, NT-proBNP has a longer half-life than BNP, although this does not appear to have significant clinical implications.[66] In addition, because the normal value ranges differ between the two types of assays, NT-proBNP concentrations measure higher and have more variability than BNP concentrations. It is essential that clinicians be aware of which assay is being used in the facility and be familiar with normal ranges of both tests (**Figure 5-1**).[66] Notably, BNP and NT-proBNP values are not interchangeable: there is no recognized "conversion factor" that works to convert a BNP result into an NT-proBNP result. Finally, all commercially available BNP assays standardize to an upper limit of normal of 100 pg/ml.[66] However, there is no universal cutpoint for normal for NT-proBNP. Most laboratories give a spectrum of upper limit values based on age categories ranging from 125 pg/mL to 2000 pg/mL, depending on the study population and assay used.[66]



* **Clinical Gray Zone:** other non-heart failure conditions may be contributing to elevation
† **Age Gray Zone:** age over 50 years or renal dysfunction

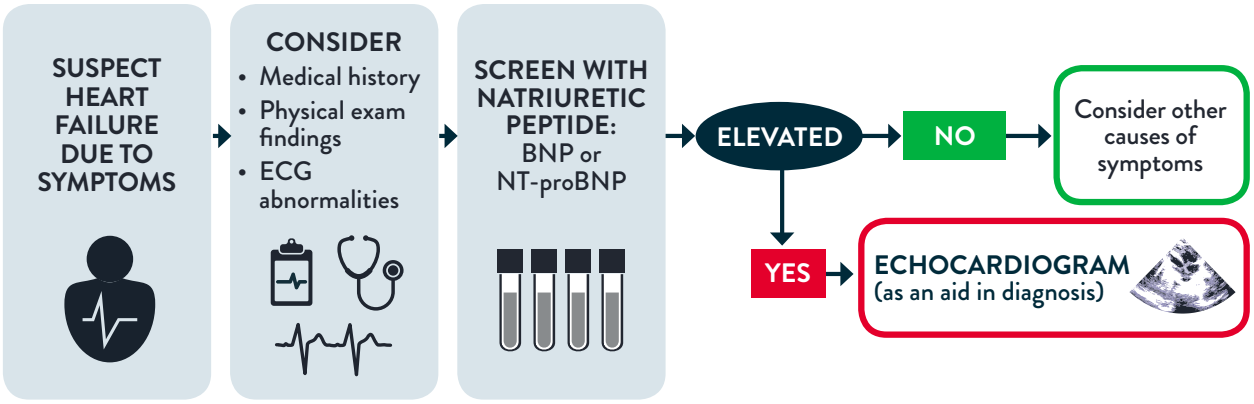
Figure 5-1. Ranges of normal, gray zone, and elevated BNP and NT-proBNP

USING NATRIURETIC PEPTIDES IN CLINICAL PRACTICE

Diagnosis of Acute and Chronic Heart Failure

For patients who seek emergency medical attention for acute shortness of breath, NPs are an essential test for determining the cause. These patients may be experiencing an episode of acute heart failure (AHF), and an NP measurement can assist clinicians in differentiating AHF from other causes of acute shortness of breath such as an exacerbation of chronic obstructive pulmonary disease or a pulmonary embolism.[56,75] NPs have very high negative predictive value (NPV) for AHF—if the NP value is not elevated, heart failure can usually be ruled out, and unnecessary heart failure treatment, such as diuretics (which could harm the kidneys if given to a patient who is not experiencing AHF), can be avoided.[56,75] This is also true for patients who present with shortness of breath in the outpatient setting; many of the signs and symptoms of heart failure are non-specific and can easily be attributable to other causes (like chronic obstructive pulmonary disease). Hence, a BNP or NT-proBNP measurement is a simple method to either exclude heart failure or identify patients who require more diagnostic testing to determine if heart failure is present (**Figure 5-2**).[52,56]

Figure 5-2. Using natriuretic peptides in clinical practice for non-acute symptoms[52,56]



Prognosis in Acute and Chronic Heart Failure

Another critical role for NPs in clinical practice is in providing prognostic information. For patients with AHF admitted to the hospital, high concentrations of NP upon admission are associated with increased risk of in-hospital mortality (for both cardiac causes and all causes).[56] In addition, measurement of BNP at discharge is useful for prediction of readmission within 30 and 60 days.[70] Readmission for heart failure shortly after discharge is often considered a preventable hospitalization, and it is a target of hospital and government quality improvement initiatives.[76] Consequently, identifying patients at high risk for this outcome is essential to improving quality of heart failure patient care.[76]

It is also well established that NP measurements can provide prognostic information in the outpatient setting. Increasing NP concentrations are associated with an increased mortality risk in ambulatory patients with heart failure.[58] NPs may also offer information about the changing status of heart failure within a patient and have been used to guide changes and adjustments to medication therapy; however, this is controversial, and due to conflicting evidence without a proven benefit in heart failure patient outcomes, guidelines do not recommend monitoring NP levels to guide therapy.[56,58,77]

Identifying Patients at Risk for Heart Failure

The natriuretic peptide assays BNP and NT-proBNP have established usefulness in stratifying patients who are at high risk for heart failure based on risk factors like diabetes, hypertension, and vascular disease.[56] Elevated NP concentrations have demonstrated utility in identifying patients in the general population who are at increased risk for developing heart failure, both in individuals who already have some high-risk characteristic and in individuals without high-risk characteristics (although NPs appear to be stronger predictors for individuals already at high risk).[75,78,79] However, they appear to be a better tool for identifying patients at risk for heart failure with reduced ejection fraction (HFrEF) than heart failure with preserved ejection fraction (HFpEF).[80] Importantly, NP measurements have demonstrated relevance in identifying patients who benefit from medical intervention to prevent heart failure, ultimately resulting in improved patient outcomes. In a large-scale trial (STOP-HF), NP concentrations were used to screen and stratify individuals at risk for heart failure; participants with BNP concentrations over 50 pg/mL in the intervention group were evaluated with echocardiography and received collaborative care interventions from primary care and cardiology specialists. Compared with participants in the control group (those who received usual care), participants in the screening and intervention group had lower rates of left ventricular dysfunction and heart failure several years later.[81] Section 6 will discuss biomarkers for screening of asymptomatic individuals in more detail.

Natriuretic Peptides in HFpEF versus HFrEF

Another important aspect of BNP and NT-proBNP measurements is that the type of heart failure influences the concentrations of NPs in the blood. As discussed in Section 4, HFpEF and HFrEF have different mechanisms in terms of how the cardiac dysfunction occurs. This difference also translates into disparities in NP release. In chronic HFpEF, NP elevations appear to be slightly more modest than what is measured in HFrEF.[75] They can even decrease to almost normal concentrations if the patient is free of symptoms.[75] Although NPs don't appear to be as elevated in patients with HFpEF compared to patients with HFrEF, they are still recommended as general screening tools for heart failure and are an essential component in establishing a diagnosis of HFpEF.[52,56] The ESC guidelines use the cutoff of BNP concentration over 35 pg/mL or an NT-proBNP concentration over 125 pg/mL for meeting the biomarker criteria for HFpEF.[52] Both of these cutpoints are well within the normal range of NPs for both tests and hence this recommendation should be viewed circumspectly. It should be noted that NP levels will be elevated in acute heart failure (AHF) regardless of whether the underlying mechanism is HFpEF or HFrEF.[75]

Interpretation of Natriuretic Peptide Results

As with other diagnostic tests, natriuretic peptide measurements should always be one of many considerations for clinicians during the evaluation of a patient with possible heart failure. The test itself may result in very elevated NP concentrations that strongly correlate to heart failure (BNP > 500 pg/mL or NT-proBNP > 2000 pg/mL), concentrations in the "gray-zone" indicating it could be heart failure or could be another problem (BNP 100–500 pg/mL or NT-proBNP 450–2000 pg/mL), or normal concentrations (BNP < 100 pg/mL or NT-proBNP < 125 pg/mL) (**Figure 5-1**).[66] Of note, compared with BNP, NT-proBNP has a much wider "gray zone" which may be attributed to advanced age (over 50 years) or renal dysfunction with NT-proBNP values in the range 125-450 pg/mL or higher.[82] This results in more "indeterminate" results when using this assay in older patients; BNP does not have this limitation.[82] Evaluating the entire patient presentation in addition to biomarker results, including symptoms, physical examination findings, and other diagnostic test results, is essential to establishing a correct diagnosis for every patient.

Confounding Factors in the Measurement of Natriuretic Peptides

Several disease processes and patient characteristics can confound the results of NP assays – clinicians must interpret the NP measurements with caution in these clinical scenarios. Because NT-proBNP is eliminated primarily by the kidneys and BNP is eliminated through multiple pathways, NT-proBNP is more susceptible to elevations in patients with kidney disease than BNP.[66] In severe kidney disease, BNP is also affected, but NT-proBNP continues to be more severely altered.[66] Likewise, several studies have also documented that NT-proBNP is increased in patients with atrial fibrillation; because this is a common comorbidity in patients with heart failure, clinicians must consider this when evaluating NT-proBNP measurements.[83,84] Increasing age and female sex both appear to increase the NP measurements regardless of underlying cardiac function, whereas obesity may decrease measured NP concentrations.[85] Lastly, a newer class of drug for heart failure, the angiotensin receptor neprilysin inhibitors (ARNI), may influence BNP concentrations because BNP is one of multiple peptides that can be cleaved by neprilysin. However, there is evidence that human BNP may be less sensitive to neprilysin degradation while retaining affinity for it. At the high concentrations of BNP (>916 pg/mL) that are frequently seen in HF patients, neprilysin activity may actually be inhibited or impaired.[86,87] This would limit the efficacy of drugs designed to inhibit the enzyme such as ARNI. Overall, there is insufficient evidence to determine if there are clinically significant differences in measured concentrations or adverse effects on patient outcomes and further research is ongoing.[88] Other common causes for NP elevation are included in **Table 5-1** on the next page.

Table 5-1. Conditions that Confound B-type Natriuretic Peptide Concentrations[56,85]

INFLUENCE ON B-TYPE NATRIURETIC PEPTIDE CONCENTRATIONS		
	BNP	**NT-proBNP**
Obesity	Decrease	Decrease
Kidney disease	Slight increase	Significant increase
Female sex	Increase	Increase
Increasing age	Increase	Increase
Severe pneumonia	Increase	Increase
Obstructive sleep apnea	Increase	Increase
Pulmonary hypertension	Increase	Increase
Severe burns	Increase	Increase
Critical illness	Increase	Increase
Sepsis	Increase	Increase
Atrial fibrillation	Increase	Increase
Acute coronary syndromes	Increase	Increase
Cardiac valve disease	Increase	Increase
Myocarditis/Pericarditis	Increase	Increase
Cardiac surgery	Increase	Increase
Cardioversion	Increase	Increase
Toxins (e.g., chemotherapy)	Increase	Increase

MARKERS OF CARDIAC REMODELING

Galectin-3

Galectin-3 is a protein that mediates inflammation and fibrosis throughout the body.[89] Elevated concentrations of galectin-3 are associated with a variety of diseases, including heart failure, cancer, liver disease, diabetes, and autoimmune diseases.[89] In heart failure, galectin-3 is secreted by macrophages in the myocardium after a cardiac injury.[90] It serves as a mediator for the development of fibrosis and also appears to contribute to inflammation in the cardiac tissue.[90] Galectin-3 can be categorized as a biomarker for cardiac remodeling because concentrations increase when the cardiac tissue experiences inflammation and progressing fibrosis.

In clinical studies of patients with heart failure, galectin-3 is more useful for long-term prognosis than initial diagnosis. When galectin-3 is measured over time, an increase of 15 percent or more has been correlated with an increased risk of mortality and rehospitalization for heart failure.[91] Galectin-3 has also shown added benefit when used in conjunction with NP measurements in patients presenting to the emergency department with acute shortness of breath. In this scenario, galectin-3 can provide long-term prognostic information about mortality, especially in individuals with low concentrations of NP on presentation.[92] Galectin-3 is also a useful marker to measure at discharge after a heart failure hospitalization, as it provides prognostic data on the likelihood of readmission within 60 days.[70] Importantly, galectin-3 has also shown particular promise in providing prognostic information in patients with HFpEF, which is an area where other biomarkers are less helpful.[70,93]

A key characteristic of galectin-3 is that concentrations appear to increase before heart failure manifests. As a result, it may be a useful screening tool for patients who are at risk for heart failure but have not developed it yet.[94] And it has demonstrated effectiveness for screening in a general population. In the PREVEND study, galectin-3 concentrations were strongly correlated with cardiovascular risk in the general population and also predicted all-cause mortality (death from any cause) in this same group.[95] Furthermore, in another study, serial measurements of galectin-3 in the general population also demonstrated the ability to identify individuals at high risk for a new onset of heart failure.[96]

Notably, in the PREVEND study, researchers found that women and older individuals had higher galectin-3 levels than men and younger individuals.[95] Hemolysis in the specimen, presence of rheumatoid factor, or anti-mouse antibodies can also contribute to inaccuracies in the galectin-3 results.[97]

MARKERS OF MYOCARDIAL STRESS OR INJURY/ISCHEMIA

High-Sensitivity Troponin

Although cardiac troponin assays such as high-sensitivity troponin (hsTn) were discussed extensively in Section 3, their utility in heart failure should also be mentioned. In the setting of heart failure, similar to its role in acute coronary syndrome (ACS), cardiac troponins are considered a biomarker for cardiac stress or injury.[98] Troponin elevations will occur in heart failure patients who are experiencing a myocardial infarction (MI), but they can also occur in acute or chronic heart failure as an indicator of myocardial stress.[99] With the development of high-sensitivity troponin assays, it has been established that most patients with heart failure have detectable troponin levels and many of these may be above the upper reference limit used to identify ACS.[98] Importantly, in this context, troponin elevations remain stable and do not demonstrate the rapid rise seen over several hours in ACS.[98] As such, cardiac troponins have demonstrated promise in providing additional prognostic information when measured in patients with heart failure and those at risk.

In patients presenting with ACS symptoms, hsTnI measurements over the upper reference limit may be useful predictors of heart failure hospitalizations during the 12 months after presentation.[71] Moreover, a recent study evaluated the combination of NT-proBNP and hsTnI for predicting heart failure in a population of individuals with risk factors. All study participants had at least one risk factor for heart failure, but normal left ventricular ejection fraction (approximately 50 percent or more); research found that the combination of the two biomarkers were better predictors of a heart failure hospitalization than either marker alone over a long period.[100] Another trial found that using a panel of biomarkers (that included hsTnI) in combination with a risk assessment model was more effective in predicting future heart failure risk in patients with coronary artery disease than the risk assessment model alone.[101]

The hsTn assays have also shown usefulness as prognostic tools in patients hospitalized for AHF; elevated hsTnI on admission has been associated with worsening heart failure during hospitalization and increased the length of stay.[102] Likewise, at discharge, elevations in hsTnI have been associated with increased risk for readmission and death in patients with AHF.[103] In addition, hsTn may aid in identifying patients with a low mortality risk during an episode of acute heart failure and may provide long-term mortality risk information in elderly patients with chronic heart failure.[104,105]

As noted in Section 3, hsTn assays are very sensitive tests, but with this sensitivity, there is a loss of specificity if specific protocols, particularly those involving “deltas” or changes over time, are not used. The other non-cardiac clinical scenarios that can cause hsTn elevations in ACS, such as sepsis and respiratory failure, also cause elevations when evaluating heart failure.

OTHER BIOMARKERS FOR HEART FAILURE

A number of other biomarkers are being studied for assessing different facets of heart failure. This section will discuss five that have demonstrated promise in heart failure management. Although researchers have identified these biomarkers as potentially useful in this population, none of these markers are currently used in routine clinical practice. Whether these emerging biomarkers provide additional clinical information beyond what can be gained from NPs and other established biomarkers remains to be determined.

Soluble ST2

Soluble ST2, or suppression of tumorigenicity 2, is a biomarker in the interleukin-1 receptor family that denotes biomechanical strain, myocardial stress, and fibrosis.[106] As such, it has been investigated as a marker for remodeling in heart failure. Unlike the NPs, ST2 concentrations do not appear to be influenced by age, gender, kidney function, or obesity.[106] In preliminary studies, measuring ST2 has shown usefulness in predicting the risk of death after an episode of acute heart failure.[106]

In addition, because it changes quickly, ST2 may eventually prove useful in providing clinical information for guiding heart failure therapies in the hospital setting when serial measurements are used.[106] For patients with chronic heart failure, it appears to predict the risk of death or cardiac transplantation, but whether this test provides any additional information over prognostic information available from NPs remains to be determined.[106]

GDF15

Growth differentiation factor 15 (GDF15) is a cytokine that is upregulated in the setting of inflammation.[107] Although it is also found in other body tissues, in the myocardium, it appears to be a marker for remodeling and may be a good prognosticator for mortality in individuals with heart failure.[107] It may also be useful in predicting the risk of heart failure and death after a myocardial infarction.[107] Similar to ST2, although GDF15 shows promise, it has not demonstrated superiority over biomarkers in current use.

MR-proADM

Several markers of neurohormonal activation in heart failure apart from the natriuretic peptides have been identified. One such biomarker is mid-regional pro-adrenomedullin (MR-proADM) which is measured because it is a precursor of adrenomedullin which has an array of neurohormonal effects in the body including dilation of the blood vessels.[108] Adrenomedullin and MR-proADM concentrations increase in heart failure.[108] Several studies have demonstrated that concentrations of MR-proADM are predictors of mortality as well as heart failure hospitalizations independent of NP measurements.[99] Although this biomarker appears promising, further study is needed to determine its place in heart failure management.

Copeptin

A second marker that primarily measures neurohormonal activation, copeptin, was discussed in Section 3 for ACS. It is a small part of a precursor for the arginine vasopressin hormone released from neurons that originate in the hypothalamus, and it serves as a surrogate marker for arginine vasopressin concentrations.[109] This biomarker has demonstrated prognostic usefulness in patients with acute heart failure, and it may identify patients at high risk of several endpoints: mortality within 90 days of presentation, heart failure hospitalizations, and emergency department visits.[109] Similar to other emerging biomarkers, research is still needed to determine if copeptin adds clinical value over biomarkers already in use.

MR-proANP

Another natriuretic peptide called mid-regional pro-atrial natriuretic peptide (MR-proANP) serves as a surrogate marker for atrial NP. It may be useful for diagnosing acute heart failure in patients presenting to the emergency departments with dyspnea.[110] Moreover, in preliminary studies, it has shown some effectiveness in predicting long-term risk of death after an episode of acute heart failure.[110] How MR-proANP may fit into the care of patients with acute heart failure remains to be determined.

GUIDELINES FOR BIOMARKERS

The European Society of Cardiology (ESC) recommends using the NPs as a method for screening patients with symptoms of heart failure. The screening cutoff point for ruling out stable, chronic heart failure in symptomatic individuals is a BNP < 35 pg/mL or an NT-proBNP < 125 pg/mL.[52] For any patient with concentrations measuring above these cutoff points, ESC recommends echocardiography for a definitive diagnosis.[52] The ESC Guidelines do not make any specific recommendations about other biomarkers for heart failure due to lack of conclusive evidence of benefit.[52]

Table 5-2. Biomarker Recommendations in the 2016 ESC Guidelines for Heart Failure[52]

USE	RECOMMENDATION	STRENGTH OF RECOMMENDATION AND LEVEL OF EVIDENCE TO SUPPORT RECOMMENDATION
DIAGNOSIS: NPs can be an initial diagnostic test in patients with suspected heart failure; recommended for ruling out rather than establishing a diagnosis		
DIAGNOSIS: Chronic setting	For patients with newly diagnosed HF, NPs should be considered to assess the appropriateness of specific therapies to identify reversible/treatable causes of HF and evaluate co-morbidities affecting HF	Moderate recommendation with a weak level of evidence **Should be considered**
DIAGNOSIS: Acute setting	For patients presenting with acute dyspnea and suspected heart failure, an NP measurement is recommended to aid in differentiating between AHF and other non-cardiac causes of acute dyspnea	Strong recommendation with a high level of evidence **Is recommended**

NP – natriuretic peptides; HF – heart failure; AHF – acute heart failure

In the 2017 focused update to the 2013 heart failure guidelines, the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) make a variety of recommendations about biomarkers. These are summarized in **Table 5-3** on the next page.

Table 5-3. Biomarker Recommendations in the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guidelines for the Management of Heart Failure[56]

USE	RECOMMENDATION	STRENGTH OF RECOMMENDATION AND LEVEL OF EVIDENCE TO SUPPORT RECOMMENDATION
DIAGNOSIS	The NP biomarkers are recommended for supporting or excluding a diagnosis of HF in a patient who presents with dyspnea	Strong recommendation for use with high-quality evidence **Is recommended**
PROGNOSIS OR RISK STRATIFICATION	In chronic HF, a BNP or NT-proBNP measurement is recommended for determining prognosis or disease severity	Strong recommendation for use with high-quality evidence **Is recommended**
	In AHF, measurement of an NP and/or cardiac troponin at the time of hospital admission is recommended to provide prognostic information	Strong recommendation for use with high-quality evidence **Is recommended**
	During hospitalization for HF, measurements of a predischarge NP level is reasonable to establish a prognosis after discharge	Moderate recommendation for use (reasonable to use) with a moderate quality of evidence from non-randomized trials* **Is reasonable**
	In chronic HF, it may be reasonable to use other clinically available tests (e.g., biomarkers of fibrosis or myocardial injury) for additional risk stratification	Weak recommendation for use (may be reasonable to use) with a moderate quality of evidence from non-randomized trials* **May be reasonable**
PREVENTION	In individuals at risk of developing HF, screening with an NP biomarker followed by a team-based intervention (which includes cardiovascular specialist care and optimization of GDMT) is reasonable to prevent new-onset HF or the development of left ventricular dysfunction	Moderate recommendation for use (reasonable to use) with a moderate quality of evidence from non-randomized trials* **Is reasonable**

NP – natriuretic peptide; HF – heart failure; AHF – acute heart failure; GDMT – guideline-directed medical therapy
*Randomized trials are preferred (and provide better evidence) over non-randomized trials

SECTION 5: REVIEW QUESTIONS

1. List one patient factor that can decrease measured levels of NP: _____. List five non-cardiac factors that can increase NP levels: _____, _____, _____, _____, and _____.

2. Match the biomarker with the aspect of heart failure that it evaluates.
   a. Marker for myocardial stress or injury
   b. Marker for neurohormonal activation
   c. Marker for cardiac remodeling

   Copeptin ____
   NP ____
   Galectin-3 ____
   hsTn ____
   Soluble ST2 ____
   GDF15 ____

3. The US and European guidelines recommend using a _____ assay for screening individuals with shortness of breath to support or exclude a diagnosis of heart failure. The US guidelines suggest that NP measurements can be helpful for _____ individuals who are at high risk of developing heart failure. They also recommend that _____ assays can be helpful for determining prognosis in acute and chronic heart failure and that other biomarkers that assess for _____ or _____ may be useful for risk stratification in patients with acute or chronic heart failure.

SECTION 6
PREVENTION OF CARDIOVASCULAR DISEASE

LEARNING OBJECTIVES

When you complete this section, you will be able to:

1. Describe the importance of prevention of cardiovascular diseases
2. Understand guideline recommendations for preventing cardiovascular diseases
3. Explain risk stratification tools and biomarkers used for assessing the risk of cardiovascular diseases in the general population

THE IMPORTANCE OF PREVENTING CARDIOVASCULAR DISEASES

Each year, over 17 million people across the globe die of cardiovascular diseases (**Figure 6-1**).[2] This number is projected to increase to over 23 million deaths per year by 2030.[5] The World Health Organization (WHO) emphasizes that although cardiovascular disease (CVD) is the number one cause of death worldwide, many of these deaths are preventable.[2] Modifiable behaviors, such as tobacco use, physical inactivity, poor dietary choices, and the resultant obesity are major contributors to CVD.[2] In addition, initiating therapies for diseases associated with CVD, such as hypercholesterolemia, diabetes, and hypertension, can also reduce risk.[2] Accurate risk stratification of patients at low, moderate, and high risk for developing CVD is a crucial component to reversing the advance of cardiovascular disease. For moderate and high-risk patients, accurate stratification allows for appropriate treatment to prevent the many complications that arise from cardiovascular disease, whereas in low-risk patients, it allows clinicians to avoid unnecessary investigation and treatment. If patients are not accurately risk stratified, patients who are truly high risk (but classified incorrectly as low or moderate risk) may not receive the needed preventative treatment. Likewise, patients who are low risk (but mistakenly classified as higher risk) will be exposed to treatments and tests that may be costly and may have serious adverse effects without experiencing a significant benefit.

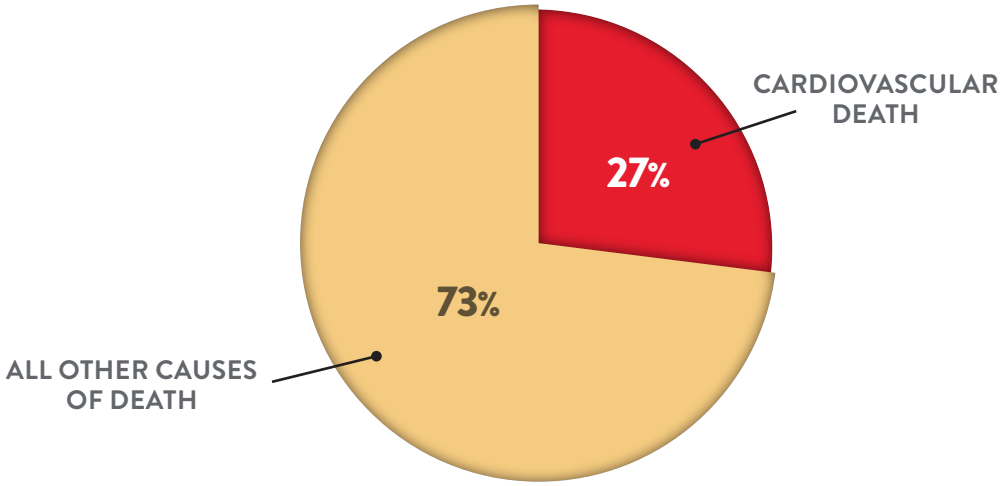


Figure 6-1. Cardiovascular disease was the most common cause of death worldwide in 2015[146]

GUIDELINE RECOMMENDATIONS FOR PREVENTING CARDIOVASCULAR DISEASES

American Guidelines

The American College of Cardiology and the American Heart Association (ACC/AHA) published guidelines in 2013 on the prevention of CVD. These guidelines focus on stratifying asymptomatic individuals based on their risk of experiencing a CVD event related to atherosclerosis in the next 10 years.[111] An atherosclerotic cardiovascular disease (ASCVD) scoring tool is recommended to provide an estimated 10-year risk for an ASCVD event and also an estimate of lifetime risk for an ASCVD event.[111] The ASCVD tool calculates risk using sex, race, cholesterol concentrations, smoking status, blood pressure, and several aspects of a patient's medical history.[111] In addition to the scoring tool, the guidelines suggest that other factors, including family history of CVD, the biomarker high-sensitivity C-reactive protein (hsCRP), and coronary artery calcium scoring (a method of visualizing coronary atherosclerosis by computed tomography) can be considered if there is still uncertainty about a person's risk for CVD disease.[111]

For anyone determined to be at high risk for ASCVD events in the next 10 years (typically a 10-year risk for an ASCVD event of 7.5 percent or more), the ACC/AHA guidelines recommend tailoring interventions to each patient.[111] Clinicians are referred to the specific guidelines available for the management of cholesterol, diabetes, hypertension, obesity, and lifestyle modifications.[111-13] Importantly, the prevention guidelines note that it is still appropriate for clinicians to counsel individuals with low or moderate estimated risk (a 10-year risk of less than 7.5 percent) on lifestyle interventions to reduce future risk of CVD.[111] The ACC/AHA guidelines recommend repeating assessment for ASCVD risk every four to six years in asymptomatic individuals.[111]

European Guidelines

A joint guideline on the prevention of cardiovascular disease was issued in 2016 by the European Society of Cardiology (ESC) in conjunction with 10 other groups. These guidelines do not recommend a risk stratification tool for asymptomatic individuals known to be at high or very high risk for CVD events, such as patients with diabetes who are over 40 years of age or individuals with specific high-risk characteristics such as familial hypercholesterolemia.[114] Instead, these patients should automatically be offered treatment to prevent CVD and the associated complications.[114] For other individuals over the age of 40, the European guidelines recommend the use of the SCORE tool, which estimates the 10-year risk of a fatal cardiovascular event.[114] The SCORE tool uses age, gender, smoking status, cholesterol, and blood pressure to assess overall risk. However, like the US guidelines, the European guidelines suggest that other factors should be considered when evaluating a patient's risk for CVD, particularly for individuals at a moderate 10-year risk for events. These factors include socioeconomic status, obesity, family history of premature CVD, coronary calcium scoring, and ankle-brachial index measurements.[114] Notably, the European guidelines do not recommend the use of biomarkers for risk stratification purposes.[114]

The European guidelines stress that the highest risk individuals benefit the most from preventative intervention, and they classify anyone with a risk of five percent or more as high risk and anyone over 10 percent as very high risk.[114] Specific targets are recommended for individuals in these risk groups, including avoidance of tobacco, eating a healthy diet, performing adequate amounts of physical activity, and achieving a healthy body mass index.[114] Blood pressure, glycemic, and cholesterol control should also be addressed and can be managed with or without medication.[114]

RISK STRATIFICATION TOOLS

Risk stratification tools are essential in the assessment of the many factors that contribute to CVD risk. As noted above, accurate CVD risk stratification allows for early intervention to prevent adverse events in the case of moderate and high-risk patients, and it avoids unnecessary investigation and treatment in individuals with low risk.[114] The ASCVD scoring tool from ACC/AHA and the SCORE tool have already been mentioned briefly, but a variety of other tools have been used to quantify the risk of cardiovascular disease in asymptomatic individuals. This guide will discuss four commonly employed CVD risk assessment tools.

- ASCVD from ACC/AHA
- SCORE
- Framingham General CVD Risk Tool
- Reynolds Risk Score

The ASCVD Tool

The ASCVD scoring tool was developed by the ACC/AHA workgroup during the development of the risk assessment guidelines published in 2013. The workgroup's goal was to create a tool that was representative of the population in the US, including data on African American, white, female, and male cohorts, which also provided relevant information about the risk for a first ASCVD event.[111] The group defined an ASCVD event as the first nonfatal stroke, first nonfatal myocardial infarction, or cardiac heart disease-related death.[111] The ASCVD tool is designed to be used in patients 40 to 79 years of age who do not have cardiovascular disease, and it was also incorporated into the ACC/AHA cholesterol guidelines issued in 2013.[111,113] **Table 6-1** provides the information assessed into the tool. An online calculator is also available at http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/.

The ASCVD tool has several limitations. First, the cohorts used to develop the tool did not include adequate numbers of people from other races (e.g., Asian, Hispanic, and Native American populations) so the tool may not be as useful in individuals who are not white or African American.[111] Second, there are also a variety of factors that the tool does not account for that can increase CVD risk, such as obesity, family history of CVD, and sedentary lifestyle (**Table 6-1**).[111]

SCORE

The Systemic Coronary Risk Estimation (or SCORE) tool was developed to guide risk assessment in the European population. The tool itself was created because other cohort risk calculators, such as the Framingham risk assessment tool, used data from cohorts living in the US rather than Europe; it was unclear if this appropriately predicted risk in non-American populations due to cultural and ethnic differences.[114] The SCORE tool was developed using data from 12 cohort studies in Europe that included 250,000 patients.[114]

The SCORE tool is designed to predict the 10-year risk of a fatal CVD event in individuals 40 to 65 years of age.[114] Although the tool itself does not incorporate this, the European guidelines suggest that overall risk for fatal plus non-fatal CVD events is approximately three times the risk calculated for fatal events.[114] It is important to note that the SCORE tool separates Europe into high- and low-risk countries, reflecting different CVD risk profiles in different regions. These charts can be accessed at https://www.escardio.org/static_file/Escardio/Subspecialty/EACPR/Documents/score-charts.pdf.

The SCORE tool has limitations similar to those found with ASCVD. Although it is specific to European populations, it may have less predictive capability for individuals in minority ethnic groups.[114] Like the ASCVD tool, it does not incorporate other known risk factors for CVD, as outlined in **Table 6-1**.[114]

Table 6-1. Comparison of Factors Used in Four Cardiovascular Disease Risk Stratification Tools[111,114-5,118-9]

	ASCVD	SCORE	FRAMINGHAM 2008	REYNOLDS RISK SCORE
Age	✓	✓	✓	✓
Sex	✓	✓	✓	✓
Race	✓*			
Cholesterol	✓‡	✓	✓§	✓
Blood pressure	✓‡	✓	✓‡	✓
Blood pressure treated with medication	✓		✓	
Smoking status	✓	✓	✓	✓
Diabetes	✓		✓	
BMI			✓§	
Country/Region		✓†		
Aspirin use	✓			
hsCRP				✓
Parental history of MI				✓

BMI – body mass index; hsCRP – high-sensitivity C-reactive protein; MI – myocardial infarction

* Only African American and White

† Differentiates between high- and low-risk countries in Europe

§ Framingham uses either cholesterol or BMI

‡ Incorporates treated and untreated

Framingham General CVD Risk Tool

The Framingham General CVD Risk Tool (sometimes known as Framingham 2008) was developed to predict the 10-year risk of CVD. It was a modification of an earlier tool, the Framingham risk assessment, which calculated risk for coronary heart disease. The Framingham General CVD tool broadened this focus to predict CVD risk, which included cerebrovascular events (such as stroke and transient ischemic attack), peripheral arterial disease, and heart failure in addition to coronary heart disease events.[115] It was developed using information from a US cohort, but it has been validated as a useful tool in other nations throughout the world.[116] The tool incorporates age, gender, smoking, blood pressure, diabetes diagnosis, and either cholesterol or body mass index to assess a 10-year risk for a CVD event.[115] An online risk calculator is available at https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php.

The Framingham General CVD tool can assess risk in a broader age range, 30 to 74 years, and it also incorporates obesity as a risk factor if the body mass index version is used.[115] Limitations of the Framingham CVD risk tool include that it is based on information from a comparatively small cohort of participants in the US and there are other major CVD risks not incorporated into the score, such as lifestyle factors and family history of CVD (**Table 6-1**).[117]

Reynolds Risk Score

The Reynolds risk score is another tool designed to predict the 10-year risk of cardiovascular disease in healthy individuals without diabetes.[118] Unlike the previously discussed tools, the Reynolds score incorporates a family history of CVD and the biomarker hsCRP into the risk calculation.[118-19] Smoking status, age, gender, blood pressure, and cholesterol measurements are also included in the score.[118-19] The Reynolds score was created with information from two US-based cohorts, the Women's Health Study and the Physicians Health Study-II.[118-19] An online calculator is available at http://www.reynoldsriskscore.org.

One of the significant limitations of the Reynolds score is that the cohorts it is modeled from are mostly comprised of white participants within a relatively specific socioeconomic range.[118-19] And although the Reynolds tool includes biomarker information and family history, other lifestyle factors are not incorporated into the risk score (**Table 6-1**).[118-19]

Limitations of Scoring Tools

Although an array of risk assessment tools are available for predicting CVD, there are significant limitations to using these tools alone for determining an individual's risk of developing CVD. First, many of the risk factors evaluated in these scoring tools are not specific to cardiac disease; elevations in blood pressure, for example, increase the risk of other problems, such as stroke. A second limitation is that many of these tools have not been externally validated (which means tested to determine if they are still accurate in other patient sample groups), and most have also not been compared head-to-head to provide clinicians with information about which tool has the best risk prediction capability.[120] Third, all scoring tools are based on a limited number of factors influencing CVD risk; because of this, an individual tool will not completely and accurately assess risk for all patients.[120] Finally, when these scoring tools have been compared and studied for external validation, their accuracy appears to be mixed. A study comparing the ASCVD tool, several Framingham risk scores (including the general CVD tool), and the Reynolds score in men and women used data from a multi-ethnic US cohort of individuals without cardiovascular disease. Researchers found that after monitoring participants for approximately 10 years, all tools overestimated risk of CVD in men, but the Reynolds score was the most accurately calibrated tool in this group.[121] Notably, most of the tools also overestimated risk in women, except the Reynolds score, which underestimated risk. The Framingham general CVD was the best-calibrated tool for women in this study.[121] As discussed previously, over and underestimation of risk have potentially serious consequences, so refining currently available tools to improve predictive accuracy for CVD is critical for appropriate patient care.

CONSIDERATIONS FOR BIOMARKERS IN CARDIOVASCULAR DISEASE RISK STRATIFICATION

To overcome the limitations presented by traditional scoring tools, researchers have begun focusing on circulating biomarkers as useful alternatives for assessing CVD risk. They comprise an easy, non-invasive test that may identify CVD risk more accurately than traditional risk-stratification tools alone. A number of biomarkers have demonstrated value in predicting CVD risk, and several have shown particular promise when used in conjunction with these traditional scoring tools. This portion of the guide will focus on specific considerations for using biomarkers in CVD risk assessment, discuss a number of biomarkers with data to support their use for CVD risk stratification, and briefly review several emerging biomarkers for CVD risk prediction.

Considerations for Biomarkers: Defining Normal

One difficulty in the assessment of CVD risk in an asymptomatic population is determining what the normal range for a biomarker should be. There is a great deal of variability in the way normal subjects are selected for determining normal ranges of clinical laboratory measures; some are screened using a simple method like a health questionnaire whereas others are subjected to more detailed assessments such as a physical examination by a clinician, electrocardiogram testing, or measurement of other surrogate biomarkers.[122] Resulting normal values can be quite variable given the variation in the selection process for normal subjects. Methods that determine if subjects are truly healthy (with biomarkers or ECG testing) are most likely better than those relying on self-reported information for identifying a biomarker's true normal range.[122] However, because there is no standard in how manufacturers or researchers determine the normal range for a biomarker, there is significant variation between studies in how this process occurs and how the normal range is defined.[122] This variation is of particular importance for high-sensitivity tests like troponin, where the accuracy of the 99th percentile measure may be impacting therapy decisions. Although there have been calls to make more specific determinations about defining a normal population, there remains significant variation in these practices, so it is up to the individual clinician to evaluate how normal values were obtained in various studies.[122] **Table 6-2** outlines one expert opinion on the best method for "coning," or selecting, participants for a normal reference population to define the 99th percentile value for cardiac troponin.[122]

Table 6-2. Useful Tools for Identifying Normal Individuals (a Normal Reference Population) to Determine 99th Percentile Values for Cardiac Troponin[122]

POTENTIAL PROBLEM IN NORMAL INDIVIDUALS	SURROGATE MARKER OR DEFINITION FOR SCREENING
Population diversity	• Minimum of 600 participants (50 percent male/female) • Diverse racial and ethnic backgrounds (40 percent white/40 percent African American/20 percent mix of Asian/Hispanic/other) • Age diversity (18 to 70+ years)
Clinical history	Assess for cardiovascular disease and medication use
Diabetes	Hemoglobin A1c
Myocardial dysfunction	BNP or NT-proBNP
Renal disease	Creatinine (for eGFR)
Coronary artery disease	Imaging to directly examine for atherosclerosis

Considerations for Biomarkers: Determining Clinical Value

Establishing the clinical value of a particular biomarker is another essential aspect in determining its role in patient care. Useful biomarkers will need to demonstrate two qualities: 1) accuracy in predicting future cardiac risk and 2) provision of additional information beyond what current methods offer.[123] These qualities can be evaluated using three complementary statistical techniques. First, a biomarker must demonstrate discrimination capability, or the ability to differentiate between individuals who will and will not develop a disease, which is usually evaluated with something called a c-statistic test.[123] Second, a biomarker must demonstrate through a statistical assessment that it is calibrated to what it measures, or that the biomarker's prediction aligns with the observed results.[123] And third, a biomarker must demonstrate that it improves a patient's risk characterization over previous methods, a concept known as net reclassification improvement.[123]

CARDIOVASCULAR RISK BIOMARKERS

Lipids

Circulating lipids often referred to as cholesterol, are essential building blocks for plaque in atherosclerotic disease. As such, lipid measurements are useful as predictors of cardiovascular disease and were some of the earliest circulating biomarkers used for assessing cardiovascular risk. Moreover, when medications, specifically statins, are employed to normalize certain lipid biomarkers, the rate of cardiovascular events and death is significantly reduced. As such, lipids are a cornerstone of cardiovascular risk assessment and are included in many risk prediction scoring tools.

TOTAL CHOLESTEROL

Higher concentrations of total cholesterol have long been associated with an increased risk for CVD.[124-25] Because of this correlation, total cholesterol concentrations are included in many CVD risk assessment tools. Although this measure remains a helpful tool for evaluating risk, it is no longer used as a target for intervention with lipid-lowering medication.

LOW-DENSITY LIPOPROTEIN

Low-density lipoprotein (LDL) is also very strongly correlated with risk of cardiovascular disease: as LDL concentrations increase, so does the risk for cardiovascular events.[113,124,126] Importantly, use of statin medication in patients with elevated LDL concentrations reduces the risk of cardiovascular events and death.[113,126] Both the US and European guidelines for lipid management use LDL as the primary biomarker for determining CVD risk and the need for intervention with medication therapy.[113,126] Of all the lipid markers, LDL is the most established for identifying risk and guiding medication interventions to lower risk of CVD and death.

HIGH-DENSITY LIPOPROTEIN

High-density lipoprotein (HDL), sometimes referred to as "good cholesterol," is inversely associated with CVD; so, unlike other forms of lipid biomarkers, as HDL increases, the risk of CVD declines.[124,127]
The concentrations of HDL are reported in most lipid panels and provide clinicians with additional insight about CVD risk. However, unlike LDL, drug therapies to raise HDL do not appear to reduce the risk of cardiovascular events in clinical trials, and it is unlikely that low HDL itself is a cause of CVD.[128-29]
Although lifestyle factors such as exercise and smoking cessation are interventions that can raise HDL and decrease cardiovascular risk, the benefits of these interventions are not entirely due to their effect on HDL.

TRIGLYCERIDES

Triglycerides are another lipid measurement typically reported on a lipid panel. Although some clinical trials examining the risk associated with triglyceride elevation have found a strong association with CVD, other lipid biomarkers may have better predictive power.[129] Moreover, at the time of this publication, studies of medications to lower triglycerides have not demonstrated improvement in cardiovascular outcomes, although there are ongoing clinical trials in this area.[129]

LIPID FRACTIONS

The term lipid fraction is used to describe different lipid measurements, including LDL, HDL, and triglycerides. This term is also used to describe newer lipid biomarkers, such as triglyceride-related lipoprotein and apolipoprotein B. And finally, lipid fraction can be used to describe the ratios in the concentration of two circulating lipids, such as triglyceride/HDL and total cholesterol/HDL. Studies are ongoing to identify the ideal lipid fraction for predicting CVD risk and to determine which lipid fractions are the best targets for medication therapies to reduce the rates of future CVD events.

High-Sensitivity C-Reactive Protein

Inflammation is an important mediator of cardiovascular disease and is linked to atherosclerosis, ischemic heart disease, and stroke.[130] High-sensitivity C-reactive protein, or hsCRP, becomes elevated in the presence of multiple cardiovascular risk factors including abdominal adiposity (fat accumulation in the abdomen), diabetes, hypertension, smoking, and hyperlipidemia (high lipid concentrations).[130] Hence, hsCRP is an integrated measure of CVD risk because of its complex associations with conventional risk factors. However, even when these other factors are considered, hsCRP has an independent risk relationship with CVD. As a biomarker for inflammation, hsCRP has demonstrated usefulness in identifying individuals at risk for CVD events.[118-19,131] Elevated hsCRP is associated with an increased risk of diabetes, cardiovascular disease, and mortality.[132] This predictive ability appears to improve when hsCRP is measured over time; prolonged elevations of hsCRP are stronger predictors of these outcomes than one-time measurements.[132] Importantly, hsCRP as a predictor for CVD events has been evaluated in different ethnic cohorts in different areas of the world.[130] Although studies indicate that there are race and geographic differences in normal hsCRP ranges (making the definition of normal ranges difficult to define for international populations), there is evidence that higher hsCRP concentrations correlate to a higher incidence of CVD events across all populations.[130]

One of the biggest shortcomings of hsCRP is its lack of specificity to the heart; any inflammatory condition, such as rheumatoid arthritis or inflammatory bowel disease, can cause elevations in hsCRP. In addition, hsCRP has not performed consistently in predicting CVD risk in several large study populations. Researchers evaluating the use of hsCRP in the participants of two large, long-term study groups, NHANES and ARIC, found that measuring hsCRP did not add any significant predictive effectiveness over traditional scoring tools and traditional risk factors (such as blood pressure and cholesterol).[133-34] Despite this, hsCRP was cited in the ACC/AHA guidelines as possibly helpful if the benefit of treatment is uncertain after traditional risk assessment with the ASCVD scoring tool.[111]

High-Sensitivity Troponin

Unlike hsCRP, high-sensitivity troponin (hsTn) T and I are biomarker assays that are very specific to the cardiac muscle.[149] Although they have demonstrated usefulness in acute coronary syndromes and heart failure, they also have recently established their value as prognostic indicators in the general, apparently-healthy population. In this context, the concentration of hsTn may be a reflection of the health of the myocardium. A long-term study of over 3,000 men with elevated cholesterol but no history of myocardial infarction, WOSCOPS, monitored participants for over five years and also assigned some participants to treatment with a statin.[135] Researchers measured hsTn at study entry and one year later; the change (rise or fall) in hsTn over that one-year period was strongly correlated with future risk of coronary disease, regardless of a change in cholesterol concentrations.[135] It was noted that treatment with the statin appeared to lower hsTn concentrations at the one-year measurement, which also correlated with a lower risk of coronary disease events.[135] Another trial, JUPITER, which examined the effectiveness of rosuvastatin (another statin medication) for preventing CVD events in individuals without cardiovascular disease, also evaluated hsTnI as a biomarker in over 12,000 participants.[136] In this trial, participants with the highest hsTnI concentrations also had the highest risk of a cardiovascular event or death from any cause.[136] Treatment with rosuvastatin lowered the risk of CVD events in individuals with and without elevated hsTnI concentrations.[136] Both of these trials highlight that the information provided by hsTnI can be used to help improve patient outcomes; not only is hsTnI useful in identifying patients who are at risk, but these patients will also benefit from intervention (treatment with a statin).

The use of hsTn in conjunction with traditional scoring tools has also been examined. In the BiomarCARE study, investigators examined data from multiple trials that included more than 74,000 European participants who were free from cardiovascular disease.[137] Researchers determined that hsTnI measurements provide better prognostic data for predicting CVD and CVD-related death when used in conjunction with the SCORE risk assessment tool than the SCORE tool alone.[137] In another study of over 9,000 individuals without cardiovascular disease, hsTnI performed better than hsCRP at predicting cardiovascular risk over more than 13 years of follow-up.[149] Furthermore, when hsTnI was added to established cardiovascular disease risk prediction models, it led to significantly greater net reclassification improvement than adding hsCRP to the models.[149]

An important difference in normal troponin concentrations between men and women has also been identified with the advent of high-sensitivity assays. The HUNT study found not only do women in a normal population have a lower hsTnI concentration than men, but hsTnI concentrations were stronger predictors of death due to cardiovascular disease in women than in men.[138] Another group of researchers used data from a long-term population study, the Dallas Heart Study, to evaluate sex-specific differences in an array of biomarkers, including hsTn.[139] Similar to findings in the HUNT study, women were found to have lower concentrations of hsTn than men.[139]

Evidence indicates that measuring circulating sensitive cardiac biomarkers such as hsTnI improves cardiovascular risk stratification in the general population; however the majority of the prior evidence and biomarker thresholds were derived in Western populations. Whether these data are similarly applicable to Asia Pacific populations and may be effectively used to target high risk individuals for primary prevention strategies warrant further study.[151]

Natriuretic Peptides

Although the natriuretic peptides (NPs) are used extensively in the management of patients with heart failure, they also have a role in screening the asymptomatic population for CVD. Even small elevations of NP levels, below the threshold for diagnosis of heart failure, have demonstrated usefulness as a prognostic marker for predicting the risk of cardiovascular events and death.[136,140] In a meta-analysis examining data from 11 studies on NT-proBNP for identification of risk in the general population, NT-proBNP elevation correlated with an increased cardiovascular mortality and mortality from any cause.[141] Moreover, there is also data to support that NPs are useful predictors of outcomes over long periods; BNP concentrations were strongly correlated with risk of CVD-related death in a cohort of middle-aged men followed for an average of 15 years.[142]

Importantly, the STOP-HF trial (as discussed in Section 5) evaluated interventions to prevent or delay the onset of heart failure in individuals with risk factors for heart failure. In the intervention group (the group that experienced the experimental care) of this trial, a BNP concentration over 50 pg/mL was used as a screening cutoff; patients with measurements above this received preventative interventions designed to reduce the risk for heart failure.[81] The participants that received the preventative interventions had lower rates of heart failure than the patients in the control group (the group that received normal care) at the end of the trial.[81] This trial highlights the real-world value of BNP as a biomarker for prevention. Patients were screened using BNP and received intervention if they were high-risk according to the biomarker; this intervention, in turn, resulted in improved patient outcomes (i.e., lower rates of heart failure).[81]

Other Biomarkers

A variety of other biomarkers have been evaluated to assess CVD risk in the general population, but their exact role in CVD risk assessment remains unclear. Lipoprotein (a) is a circulating lipoprotein similar to LDL, and its concentration in plasma has been consistently associated with CVD events.[143] Specific treatments to lower the production of Lp(a) are in development. Similarly, the total triglyceride concentration and the non-HDL fraction (total cholesterol minus HDL) of the lipid panel may reflect the "total atherogenicity" of the lipid profile and hence have been treatment targets in prior guidelines. Further study of these two lipid fractions is ongoing. Another biomarker, homocysteine, is an amino acid synthesized by the body. Elevated homocysteine concentrations are associated with inflammation and an increased risk of ischemic heart disease and stroke in a generally healthy population.[144] However, clinical trials evaluating folic acid and B-vitamins for decreasing homocysteine concentrations did not demonstrate any decrease in CVD risk. Finally, lipoprotein-associated phospholipase A2 (Lp-PLA2) is an enzyme linked to inflammation and instability in atherosclerotic plaques. Multiple studies have found an association between increasing Lp-PLA2 concentrations and increased risk of cardiac events.[145] But similar to homocysteine, clinical trials of specifics drugs for lowering Lp-PLA2 did not reduce the risk of CVD. Whether any of these markers provides an advantage over currently used prognostic tools has not been determined.

Biomarkers in Clinical Practice

Biomarkers for cardiovascular disease are continuously evolving, and although the roles for certain biomarkers, such as NPs and cardiac troponins, are well defined in specific aspects of cardiac care, the roles for many newer biomarkers are still being determined. One area that needs further clarification is how best to incorporate biomarker information into traditional risk stratification tools. Another area that requires more study is whether using a panel of biomarkers is better than measuring one or two individual markers. Theoretically, a panel may be a more useful approach because it includes markers for multiple pathways affected by CVD, but the value of this type of assessment is unclear in the clinical setting. Likewise, a third area that requires study is how incorporating biomarkers into risk assessment for CVD influences clinical outcomes in patients. Even with these unresolved questions, biomarker use in cardiovascular diseases will likely continue to evolve, ideally providing clinicians with better tools for caring for their patients.

SECTION 6: REVIEW QUESTIONS

1. Which of the following may be useful for determining an asymptomatic patient's risk for future CVD events?

   a. SCORE risk assessment tool

   b. A biomarker measurement, such as hsCRP or hsTnI

   c. Assessing other risk factors such as obesity, sedentary lifestyle, and family history of CVD events

   d. All of the above are useful considerations

2. The ACC/AHA guidelines recommend against the use of biomarkers to assess an asymptomatic patient's risk for future CVD events.

   ☐ **True** ☐ **False**

3. To demonstrate clinical usefulness, a biomarker needs to show all of the following EXCEPT...

   a. Net reclassification improvement

   b. Adherence to ACC/AHA guidelines

   c. Discrimination capability

   d. Calibration to what is measured

4. Which of the following statements is TRUE about normal values for biomarkers?

   a. A health questionnaire is preferred over surrogate biomarkers for determining normal values in a population

   b. A standardized, normal range must be established for every biomarker marketed in the US and Europe, and this standard must be adhered to by all manufacturers

   c. There is no standard for defining a normal population in studies of biomarkers or how that normal population is selected

   d. All of the above statements are true

APPENDIX

APPENDIX A: GLOSSARY OF TERMS

APPENDIX B: CORRECT RESPONSES

APPENDIX C: REFERENCES

APPENDIX A: GLOSSARY OF TERMS

A

ACE inhibitors: A class of medication used to treat heart failure and high blood pressure; in heart failure, these drugs block neurohormonal changes.

Acute coronary syndrome: A spectrum of problems ranging from ST-elevation MI to unstable angina that indicates the heart tissue is not receiving adequate supplies of oxygen.

Acute heart failure: Acute, rapid worsening of heart failure symptoms that can be life-threatening.

Adrenal glands: Glands that sit directly above the kidneys that produce a variety of hormones, including norepinephrine.

Aerobic exercise: Exercise that stimulates the heart rate and breathing rate to increase.

Aerobic respiration: The process used by the cells of the body to produce energy that relies on oxygen.

Aggregation (**of platelets**): Platelets clumping together in the process of forming a plug to stop bleeding from a blood vessel.

Aldosterone antagonists: Diuretic drugs used in heart failure that block the neurohormonal effects of heart failure.

Anemia: A condition resulting from an insufficient amount of healthy red blood cells circulating in the bloodstream.

Angina: The medical term for chest pain related to the heart.

Antibodies: Proteins used by the immune system to neutralize foreign, potentially harmful substances found in the body.

Anticoagulant: Medications that decrease the blood's ability to clot (thin the blood) by interfering with the body's normal clotting cascade.

Antiplatelet: Medications that decrease the blood's ability to clot (thin the blood) by interfering with the normal activity of platelets.

Angiography: A procedure done to examine the blood flow in the coronary arteries; it involves inserting a catheter into a large artery (in the groin or wrist) and threading it up to the heart. In the heart, a dye is released that will flow into the coronary arteries, and an x-ray device is used to evaluate the flow of blood through the coronary arteries.

Angiotensin receptor blocking agents (**ARB**): A class of medication used in patients with heart failure and high blood pressure; in heart failure, it can block some of the maladaptive neurohormonal activity.

Angiotensin II receptor-neprilysin inhibitors (ARNI): A new class of medication for heart failure that blocks the maladaptive neurohormonal response.

Aorta: The largest artery in the body; it receives blood pumped out of the left ventricle.

Artery: Blood vessels that carry oxygen-rich blood from the heart to the organs and tissues.

ASCVD scoring tool: A scoring tool used to assess risk for future atherosclerotic cardiovascular disease events in the general population of individuals without known cardiovascular disease.

Aspirin: An antiplatelet medication used to prevent blood from clotting; it is often used in the treatment and prevention of myocardial infarction.

Atherosclerosis: The buildup of plaque inside the arteries.

Atrial fibrillation: An abnormal heart rhythm where the atria beat inappropriately fast; this sometimes also results in the ventricles beating too fast.

Atrioventricular node (**AV node**): Part of the cardiac electrical conduction system, it receives impulses from the sinoatrial (SA) node and transmits them to the ventricles, stimulating the ventricles to beat.

Atrium (**plural: Atria**): The two upper chambers of the heart; they receive blood from the vena cava and the pulmonary vein and move it into the ventricles.

Autoimmune disease: A disease characterized by the body's immune system producing antibodies that attack its own tissue.

Automaticity: The heart tissue's ability to generate its own electrical impulses to stimulate contraction.

B

B-natriuretic peptide (**BNP**): A protein released by the ventricles of the heart when they are under strain or stress; most often used as a biomarker for diagnosing and monitoring heart failure.

Beta blocker: A medication used to slow the heart rate and control blood pressure; beta blockers are often used in patients who have had a myocardial infarction; some beta blockers are useful for blocking the neurohormonal changes associated with heart failure.

Biomarker: A measurable characteristic that can be used to evaluate normal body processes, disease, or response to treatment. This guide focuses on circulating biomarkers, which are markers that circulate in the bloodstream.

Blood: The liquid that travels through the blood vessels of the body that is made up of specific types of cells (i.e., red blood cells, white blood cells, platelets). Blood carries oxygen and nutrients to body tissues and carries waste and carbon dioxide away from tissues.

Blood pressure (**or arterial blood pressure**): The measure of pressure inside the arteries that is created by the force and rate of the heart beating and the elasticity of the arteries.

Blood vessel: A general term used to describe the tubes that carry blood through the body: arteries, veins, and capillaries.

Bundle of His: Part of the cardiac electrical conduction system, it transmits electrical signals from the atrioventricular (AV) node to the ventricles.

C

C-statistic test: A statistical test used to evaluate the discrimination capability of a particular test (e.g., the ability to differentiate between individuals who will and will not develop a disease).

Calcium: A chemical element that is very abundant in the body. Calcium is used to build bones and contract skeletal and cardiac muscle; it is needed for blood to clot normally.

Calibration (**or calibrated**): In statistics, how well a prediction aligns with the observed results.

Capillaries: The smallest blood vessels; they allow nutrients, oxygen, and carbon dioxide to be exchanged between cells and the blood.

Carbon dioxide: A gas which is a waste product of cell energy production.

Cardiac catheterization: See "angiography."

Cardiac catheterization laboratory (**cath lab**): The department within a facility (often a hospital) where angiography procedures are performed.

Cardiac magnetic resonance (**CMR**): A magnetic resonance imaging (or MRI) test that examines the structure of the heart.

Cardiac myosin-binding protein C (**cMyC**): An emerging, circulating biomarker that may be useful in early identification of myocardial infarction.

Cardiac resynchronization device/therapy: An implantable device that uses electrical impulses to aid both ventricles in contracting at the same time. It is used to treat certain electrical conduction abnormalities.

Cardiomyopathy: Maladaptive changes in heart structure caused by myocardial infarction, neurohormonal activation, genetic, abnormal cell signaling, or unknown reasons.

Cardioversion: A procedure used to treat an abnormal cardiac rhythm that involves either delivering a specific amount of electricity (a shock) to the heart or administering medication to promote return to a normal rhythm.

Cell: The smallest unit ("building block") within a living organism.

Cerebrovascular event: A term used to describe a situation where the brain is not receiving enough oxygen to function normally. This can mean a stroke (which results in permanent damage to the brain) or a transient ischemic attack (where symptoms are only temporary, and permanent damage does not occur).

Chemotherapy: A type of medication used to treat severe illnesses, such as cancer, that can be toxic to the cells of the body including cardiomyocytes.

Cholesterol: A fat-like substance found in body tissues that is necessary to make hormones, vitamin D, and parts of cells. Too much of certain types of cholesterol can raise the risk of heart disease.

Clot: A clump of blood composed of fibrin, platelets, and erythrocytes that are stuck together, usually to stop bleeding from a damaged blood vessel.

Clotting cascade (**or Coagulation cascade**): A complex series of reactions that occur within the body as a result of a blood vessel injury, ultimately resulting in the formation of a clot or thrombus.

Coefficient of variation (**CV**): A statistical measurement used to describe variation within a data sample; coefficient of variation is calculated by dividing the standard deviation (a measure that describes the amount of variation in a group of numbers) by the mean (or average) of those numbers. It is usually expressed as a percentage.

Congenital heart disease: A structural abnormality in the heart that is present at birth.

Coning: A term used to describe selection of a population for a scientific measurement.

Copeptin: An emerging, circulating biomarker that may be used for identifying myocardial infarction.

Coronary artery: An artery that supplies blood to the heart muscle.

Coronary artery bypass grafting (**CABG**): A type of surgery used to treat severe coronary heart disease. Surgeons use healthy blood vessels from another part of the body to create a new route for oxygen-rich blood to travel to the myocardium.

Coronary CT angiography: A type of imaging test that allows clinicians to visualize the inside of the coronary arteries using a powerful, detailed X-ray.

Coronary heart disease: A condition that results from atherosclerosis in the coronary arteries.

Contraction: Tension that occurs in the muscle fibers in response to a stimulus.

Creatinine kinase MB (**CK-MB**): An older circulating biomarker that was previously used to identify myocardial necrosis, related to myocardial infarction.

D

Degradation: Breaking down into parts.

Delta: A change or difference between two numbers measuring the same thing.

Diabetes: A disease characterized by either the inability to make insulin or resistance to insulin that results in elevated concentrations of glucose (a basic form of sugar) in the body. Diabetes significantly increases the risk of heart disease.

Diastole: The relaxation phase of the heart pumping cycle that results in relaxation of the heart muscle, allowing the heart chambers to fill with blood.

Digoxin: A medication used to treat symptoms of heart failure or control the heart rate in atrial fibrillation.

Discrimination: In statistics, the ability to differentiate between individuals who will and will not develop a disease; usually measured with the c-statistic test.

Diurnal variation: A scenario where concentrations of substances in the body vary throughout different times of the day.

Diuretic: A type of medication used in patients with heart failure that triggers the kidneys to remove more water from the body (in the urine).

Dyspnea: Difficulty breathing.

E

Echocardiography: A test the uses ultrasound to visualize the heart and its function.

Ejection fraction: The percentage of blood pumped out of the left ventricle with each contraction; normal range is approximately 55-75%.

Elasticity: Stretchiness.

Electrocardiogram (**ECG or EKG**): A test that measures the electrical activity of the heart, visualizing the electrical activity of the heart from 12 different angles; used to evaluate for a type of myocardial infarction, cardiac arrhythmias, and other cardiac abnormalities.

End-stage renal disease (**ESRD**): Chronic, irreversible failure of the kidneys; patients require either dialysis or a kidney transplant at this stage.

Enoxaparin: A medication that interferes with the clotting cascade used to thin the blood; it is used in many clinical scenarios, including myocardial infarction.

Enzyme: A protein produced by the body that encourages a chemical or biological reaction to occur more quickly.

F

Fat: An oily substance found in the body and also ingested in food; it is a building block for many substances in the body.

Fibrin: A protein formed after activation of the clotting cascade that creates a clot or thrombus.

Fibrinolytic: A medication that breaks down fibrin and a fibrin-based clot.

Fibrosis: In the heart, scar formation in tissue in response to an injury.

Framingham general CVD risk score: A scoring tool for predicting risk of a cardiovascular event in individuals without known cardiovascular disease.

G

Galectin-3: A protein that mediates inflammation and fibrosis throughout the body; as a circulating biomarker, it is useful for providing prognostic information in patients with heart failure.

Growth-differentiation factor-15 (**GDF15**): A cytokine that is upregulated in the setting of inflammation; it may be useful as an emerging, circulating biomarker for cardiac remodeling and a prognostic indicator for individuals with heart failure.

GRACE score: A scoring tool used to risk stratify a patient with suspected acute coronary syndrome.

H

Half-life: In the body, the time it takes for the concentration of a substance to decrease by half (e.g., a half-life of 20 hours would mean it takes 20 hours for a drug's concentration in the body to drop from 10 ng/mL to 5 ng/mL).

Heart: The organ in the body responsible for pumping blood to other body organs and tissues.

Heart failure: A condition in which a problem with the ventricles is preventing the heart from pumping correctly; it is the result of a complex mechanical and neurohumoral syndrome resulting in stasis (or slow movement) of blood in the lungs and peripheral tissues.

HEART score: A scoring tool used to risk stratify a patient with suspected acute coronary syndrome.

Hemoglobin: The protein in red blood cells that carries oxygen.

Hemolysis: Rupture or breaking apart of red blood cells; this rupture of red blood cells can occur in a specimen collection tube (during or after removing the blood from the body) and can affect the accuracy of certain laboratory tests.

Heparin: A medication that interferes with the clotting cascade used to thin the blood; it is used in many clinical scenarios, including myocardial infarction.

HFmrEF (**Heart failure with mid-range ejection fraction**): A newer heart failure classification used to describe patients with heart failure symptoms and a left ventricular ejection fraction of 40- 49 percent.

HFpEF (**Heart failure with preserved ejection fraction**): A heart failure classification used to describe patients with heart failure symptoms and an ejection fraction in the normal range, usually over 45 percent.

HFrEF (**Heart failure with reduced ejection fraction**): A heart failure classification used to describe patients with heart failure symptoms and a reduced ejection fraction, usually under 45 percent.

High-sensitivity C-reactive protein (**hsCRP**): A circulating biomarker for inflammation in the body; in cardiology practice, it can be used as a screening tool for identifying patients at risk for cardiac disease when other tools are not adequate.

Homocysteine: An amino acid synthesized by the body; elevated concentrations are associated with inflammation and an increased risk of ischemic heart disease and stroke in a generally healthy population, but its usefulness as a screening tool is uncertain.

Hormone: A "messenger" substance produced by the body that is released into body fluids to stimulate the activity of a different tissue or organ.

Hydralazine: A medication used for blood pressure that has also shown benefit in certain heart failure patients, particularly those of African descent, when used in combination with another medication (a long-acting nitrate).

Hyperlipidemia: The medical term for higher-than-normal cholesterol concentrations in the blood.

Hypertension: The medical term for high blood pressure that indicates that the pressure inside the arteries is higher than normal.

Hypotension: The medical term for low blood pressure that indicates that the pressure inside the arteries is too low and may not be adequate for perfusion of oxygen into the tissues.

I

Ischemia: A scenario where tissues are not receiving enough oxygen.

Immunoassay: A test that measures the presence or concentrations of proteins (often antibodies) in a fluid (usually blood).

Implantable cardioverter-defibrillator: An implantable device that can detect abnormal, dangerous cardiac rhythms and can send a small, electrical shock to the heart to return it to a normal rhythm.

Ischemia modified albumin: An FDA-approved, circulating biomarker for identifying myocardial infarction.

J

K

Kidneys: The organs of the body that create urine, remove waste from the blood, and regulate fluid balance.

Kidney failure (**or renal failure**): Impairment of normal kidney function; there is a spectrum of impairment that occurs, ranging from mild to chronic, irreversible impairment (known as end-stage renal disease).

L

Left-ventricular assist device (**LVAD**): An implantable device, using a pump implanted into the wall of the left ventricle, which is used in patients with end-stage heart failure to support cardiac function. The pump itself is implanted in the chest, but a wire runs out of the device and through the skin to connect the LVAD to the external batteries and control unit.

Lesion: In the coronary arteries, another name for an area inside the artery with plaque buildup.

Lipoprotein-associated phospholipase A2 (**Lp-PLA2**): An enzyme linked to inflammation and instability in atherosclerotic plaques; it has been studied as a possible biomarker for screening asymptomatic populations for cardiovascular disease.

Low-sodium diet: A diet low in salt.

Lumen: An opening; in the case of blood vessels, this term describes the opening inside the vessel.

M

Maladaptive: Counterproductive; inadequate adjustment to a change or environment.

Mineralocorticoid receptor antagonist: See "Aldosterone antagonist."

Mortality: Death or dying.

MR-proADM: An emerging, circulating biomarker for neurohormonal activation in heart failure.

MR-proANP: An emerging, circulating biomarker for neurohormonal activation in heart failure.

Myocardial: Relating to the heart.

Myocardial infarction: Permanent damage to the heart as a result of inadequate blood flow to the cardiac tissue.

Myocarditis: Inflammation of the heart muscle, often as a result of a viral infection.

Myocardium: The heart's muscle tissue.

Myocyte: A cell in the heart tissue.

Myoglobin: An oxygen-binding protein similar to hemoglobin; it was one of the earliest circulating biomarkers for myocardial infarction, but it is no longer used for this purpose.

N

Natriuretic peptide: Hormones that influence fluid and sodium balance in the body. Although there are several other known natriuretic peptides, this term is often used to describe BNP and its inactive counterpart, NT-proBNP.

Necrosis: Death of all or most of the cells in an area of the body.

Negative predictive value (**NPV**): The probability that an individual with a negative result on a screening test does not have a disease or problem.

Neprilysin: An enzyme involved in an array of biochemical processes in the body; neprilysin is involved in the breakdown of BNP.

Net reclassification improvement: In statistics, the ability of a new test or marker to demonstrate that it improves predictive ability over previously used methods (e.g., more individuals were provided with accurate predictions with the new method than with previous methods).

Neurohormonal activation: The release of hormones and neurotransmitters that increase the blood pressure and promote retention of water by the kidneys to increase blood volume. This occurs in response to a loss of perfusion and can be helpful for short-term problems, like acute blood loss, or harmful in the case of heart failure.

Neurotransmitter: Chemical messengers in the body that stimulate a nerve.

Nitrate (**long-acting**): A type of medication used for patients with certain cardiac problems; in heart failure, they can be beneficial when used in combination with hydralazine, especially in individuals of African descent.

Norepinephrine (**or Noradrenaline**): A hormone released by the adrenal glands and certain nerves that promotes vasoconstriction (narrowing of the blood vessels) and increases in the blood pressure.

NSTEMI (**pronounced: en-stem-eee**): A type of myocardial infarction that does not result in characteristic ST-elevation on an electrocardiogram.

NT-proBNP: An inactive fragment cleaved from BNP; used clinically as a circulating biomarker in patients with heart failure.

O

Obese: Significantly overweight.

Obesity: The state of being significantly overweight.

Obstructive sleep apnea: A sleep disorder in which patients stop and restart breathing many times through the night; it has a variety of negative health implications and is a risk factor for certain cardiac problems.

Occlusion: Blockage.

Organ: A self-contained part of the body that has a specific function.

Oxygen: An element and a gas necessary for normal function of the body cells.

P

Percutaneous coronary intervention (**PCI**): An angiography procedure done to treat a blockage in a coronary artery that involves threading a wire device into the coronary artery, opening the blocked artery with a tiny, balloon-like device, and then propping the artery open with a mesh wire tube called a stent.

Perfusion: Passage of fluid (in this case, blood) into the capillaries of an organ or tissue.

Pericarditis: Inflammation of the lining around the heart, often due to a viral infection.

Peripheral/periphery: Situated away from the center; in the case of the body, this often refers to the arms, legs, hands, and feet.

Permeability: How well liquids and other substances can pass through a structure.

Plaque: A substance that can accumulate inside an artery; it is made up primarily of cholesterol, fat, and calcium.

Pneumonia: An infection in the lungs, caused by either a bacterium or a virus.

Prognostic: Predicting the likelihood of something.

Pulmonary embolism: A potentially life-threatening event caused by a substance (usually a blood clot) that travels through the veins, then gets wedged into a branch of the pulmonary artery and creates a blockage.

Pulmonary hypertension: A life-threatening disease that causes high blood pressure in the arteries of the lungs and the right side of the heart.

Pulmonary veins: The veins that bring oxygenated blood from the lungs back to the heart.

Purkinje fibers: Fibers in the heart that conduct electrical impulses to the left and right ventricle, to stimulate the heart to beat.

Q

Quantitative: Measuring the quantity of something; in the laboratory setting, quantitative measures provide an exact number describing the concentration of a substance (this is in contrast to a qualitative measure, which tells only if a substance is present or not).

R

Remodeling: In the heart, the process of structural changes to the cardiac tissue as a result of heart failure, tissue injury, or other factors.

Renal: See "kidney."

Renal Failure: See "kidney failure."

Reperfusion: Restoring blood flow to a tissue or organ.

Retention: Holding on to a substance.

Reynolds risk score: A scoring tool used to assess risk for future cardiovascular events in the general population of individuals without cardiovascular disease.

Rheumatoid factor: An antibody directed against the body's own tissue; elevated concentrations can be a sign of an autoimmune disease such as rheumatoid arthritis.

S

Sarcoidosis: A chronic inflammatory disease that causes abnormal tissue to form in different parts of the body, including the lungs, skin, and heart.

Sepsis: The body's response to a serious infection that can be life-threatening if not treated promptly.

Sinoatrial node (**SA node**): The area of the right atrium where electrical impulses originate.

Skeletal muscle: A muscle connected to the skeleton that participates in the mechanical, voluntary movement of the body.

Smooth muscle: Muscles in the gut and other internal organs that move involuntarily (i.e., not conscientiously controlled).

Standard deviation: In statistics, a number that specifies how much members of a group differ from the group average.

Stasis: A slow down or complete stoppage of a normal flow.

STEMI (**pronounced: stem–eee**): A type of myocardial infarction characterized by ST-elevation on an electrocardiogram test.

ST2: An emerging circulating biomarker used in heart failure and acute coronary syndromes.

Stent: Mesh wire tube placed inside a blood vessel to prop it open.

Stress myocardial perfusion imaging: An imaging test that evaluates how well blood flows into the cardiac tissue.

Stethoscope: A medical instrument most often used to externally evaluate the heart and lungs; one end of the device fits into the clinician's ears and the other, round end is placed against the chest wall.

Stroke: A potentially life-threatening event where adequate blood supply to a portion of the brain is cutoff, resulting in permanent damage. There are two primary mechanisms for this: 1) ischemic, which is usually caused by a blood clot and 2) hemorrhagic, which is caused by a blood vessel in the brain bursting.

Superimposed: Occurring in addition to or on top of something else.

Systole: The phase of the cardiac pumping cycle that involves contraction of the heart muscle, pushing out blood.

T

Tachyarrhythmia: A general term describing an abnormal, fast, heart rhythm.

Thrombin: An enzyme in the blood that works in the clotting cascade to create fibrin.

Thrombolytic: A medication that breaks down or dissolves a blood clot.

Thrombosis: The process of a blood clot forming inside a blood vessel.

Thrombus: A blood clot.

TIMI score: A scoring tool used to risk stratify patients with suspected acute coronary syndrome.

Tissue: Material inside the body made up of specialized cells.

Transient ischemic attack (**TIA**): A temporary period of abnormal brain functioning caused by temporary loss of blood flow to an area of the brain; sometimes called a "mini-stroke," it is a risk factor for future strokes.

Treadmill ECG: A test for coronary artery disease where a patient undergoes continuous ECG monitoring while doing exercise, such as running on a treadmill or riding a bicycle.

Troponin: A protein that is abundant in the cardiac myocytes; it works inside the cell as part of the contractile mechanism to facilitate myocyte contraction; troponins T and I are both useful as biomarkers in the evaluation of individuals with possible myocardial infarction.

U

Unstable angina: A type of acute coronary syndrome where cardiac biomarkers are not elevated and myocyte death does not appear to occur; it is not classified a myocardial infarction.

V

Valsartan/sacubitril: A medication used for heart failure that blocks the body's maladaptive neurohormonal response.

Vascular disease: A type of disease characterized by blood vessel abnormalities; it is a general classification that encompasses an array of different conditions, including coronary heart disease.

Vasospasm: Spasm of the blood vessel wall.

Vein: Blood vessels that carry oxygen-poor blood from the capillaries back to the heart.

Vena cava: The largest vein in the body which delivers blood into the right ventricle.

Ventricles: The larger, lower two chambers of the heart.

Venules: Smaller veins that deliver blood to the capillaries.

W

X

Y

Z

APPENDIX B: CORRECT RESPONSES

SECTION 1

1. Veins >> vena cava >> right atrium >> right ventricle >> pulmonary artery >> lungs >> pulmonary veins >> left atrium >> left ventricle >> aorta >> arteries >> capillaries of organs and tissues
2. d
3. Coronary
4. Contraction, relaxation, left

SECTION 2

1. Atherosclerosis: e
   PCI: b
   MI: a
   Troponin: c
   Calcium: d
2. In a myocardial infarction, adequate amounts of blood and oxygen cannot reach a portion of the myocardial tissue. This leads to the death of the cells in the affected area. Most often, an MI is caused by a thrombus forming in a coronary artery as a result of plaque rupture, but it can also be caused by a spasm of the blood vessel, excessive plaque buildup, or anything that causes inadequate flow of oxygen into the tissues.
3. d
4. Cardiac troponin

SECTION 3

1. False
2. b
3. b
4. Any four of the following: copeptin, BNP, NT-proBNP, cMyC, GDF15, ST2

SECTION 4

1. a. AHF b. HFrEF c. HFpEF d. AHF e. HFpEF f. HFrEf
2. Any 5 of the following: dyspnea (shortness of breath), orthopnea (shortness of breath when lying down), paroxysmal nocturnal dyspnea (awakening from sleep with acute shortness of breath), exercise intolerance, weakness, fatigue, swelling of the ankles or feet
3. b
4. Blanks are:
   a. Hormones and neurotransmitters, neurohormonal
   b. Kidneys
   c. Fibrosis

SECTION 5

1. Obesity; any 5 of the following: kidney disease, female sex, increasing age, severe pneumonia, obstructive sleep apnea, pulmonary hypertension, severe burns, critical illness
2. Copeptin: b
   NP: b
   Galectin-3: c
   hsTn: a
   Soluble ST2: c
   GDF15: c
3. NP, screening, NP, fibrosis or myocardial injury

SECTION 6

1. d
2. False
3. b
4. c

APPENDIX C: REFERENCES

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