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Summary and Quick Facts for Heart Failure

- Heart failure is a general term describing a syndrome in which the heart cannot pump enough blood to meet the body's needs. About 5.7 million adults in the United States have heart failure and approximately 550,000 cases are diagnosed in the United States each year.
- This protocol will review the causes of and risk factors for heart failure, along with current standards of care and a number of emerging treatment strategies. Dietary and lifestyle strategies that can support overall cardiovascular health will also be reviewed, as will a variety of natural, integrative interventions shown in studies to support heart health.
- Standard treatment options for heart failure focus on limiting symptoms and attempting to reduce progression and mortality. A comprehensive strategy for minimizing risk and improving heart failure outcomes should address its underlying causes.

Heart failure is a condition in which the heart cannot pump enough blood to meet the body's demands. Most cases of heart failure begin with the left ventricle being unable to pump blood efficiently to the body. As heart failure progresses, the body tries to keep up with tissue oxygen demands, but it cannot maintain this indefinitely.

Heart failure can occur when the heart becomes weakened or damaged. Many conditions can cause heart failure, the most common being coronary artery disease and ischemic heart disease.

The mortality rate from heart failure remains high despite medical advances. Natural integrative ingredients such as **coenzyme Q10** and **hawthorn** may help improve outcomes for patients with heart failure.

What are the Risk Factors for Heart Failure?

- Family history of heart disease and other heart-related diseases
- Excessive alcohol consumption
- Smoking
- Lack of physical activity
- Poor dietary habits
- Obesity/overweight
- Concurrent health conditions, including:
 - History of heart disease
 - Diabetes
 - High blood pressure
 - Chronic obstructive pulmonary disease
 - Kidney disease
 - Depression
 - Sleep apnea
- Certain medications, including some cancer drugs and antidepressants

What are the Signs and Symptoms of Heart Failure?

- Fatigue
- Difficulty breathing
- Decreased capacity for physical activity
- Fluid retention
- Frequent nighttime urination
- Irregular heartbeat
- Decreased appetite and/or nausea
- Difficulty concentrating, less alert
- In advanced heart failure, wheezing, cough with pink-tinged frothy sputum, abdominal discomfort or swelling, anorexia, and weight loss may occur

What are Conventional Medical Treatments for Heart Failure?

Note: Treatment considerations/recommendations vary depending on disease severity.

Stages A and B: For patients at high risk of heart failure, but without structural disease or symptoms of heart failure (**Stage A**); or patients with structural heart disease but without signs or symptoms of heart failure (**Stage B**):

- Diet and lifestyle improvement
- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for high blood pressure
- Beta blockers to lower heart rate and blood pressure
- Statins to lower cholesterol levels

Stage C: For patients who have structural heart disease with prior or current symptoms of heart failure, the same treatments are recommended, with the possible addition of:

- Angiotensin receptor-neprilysin inhibitors (ARNIs)
- Diuretics
- Aldosterone antagonists
- Cardiac glycosides
- Anticoagulants
- Sinoatrial current inhibitor
- SGLT2 inhibitors
- Medical devices, such as a pacemaker
- Continuous positive airway pressure (CPAP) (for patients with sleep apnea)
- Medically supervised exercise program
- Cardiac rehabilitation

Stage D: For patients with treatment-resistant heart failure:

- Heart transplant
- Biventricular pacemaker
- Left ventricle assist devices

What are Emerging Therapies for Heart Failure?

- Stem cell therapy
- Testosterone replacement therapy
- Vagus nerve stimulation
- Trimetazine, and others

What Dietary and Lifestyle Changes Can Be Beneficial for Heart Failure?

- Quit smoking and limit alcohol intake
- Follow a heart-healthy diet, such as DASH or the Mediterranean diet
- Ensure you are getting enough micronutrients, like potassium, magnesium, and B vitamins

- Physical activity (someone with heart failure should undergo exercise programs that are medically supervised)
- Manage stress and anxiety
- Maintain healthy blood sugar levels

What Natural Interventions May Be Beneficial for Heart Failure?

- **Coenzyme Q10.** Coenzyme Q10 (CoQ10) is essential for energy production in the mitochondria and is concentrated in heart muscle. CoQ10 deficiency is associated with heart failure. Several clinical studies have shown benefits from CoQ10 supplementation in heart failure, including lower risk of adverse cardiac events or death.
- **Hawthorn.** Extracts from hawthorn contain many beneficial phytochemicals, including oligomeric procyanidins. Hawthorn has been shown to improve left ventricle ejection fraction, cardiac efficiency, and blood pressure in patients with heart failure.
- **Pyrroloquinoline quinone (PQQ).** PQQ, like CoQ10, is involved in generating energy in the mitochondria. Preclinical studies suggest PQQ may benefit the heart muscle.
- **Fish oil.** Omega-3 fatty acids are well known for their positive impact on heart health. Clinical studies indicate supplementation with fish oil may improve certain parameters in patients with heart failure.
- **Carnitine.** Carnitine is important for cardiac energy metabolism. Clinical trials have shown that carnitine supplementation improved cardiac efficiency, left ventricle ejection fraction, and 3-year survival rates in heart failure patients.
- Many other ingredients may be beneficial for patients with heart failure, including **creatine, taurine, D-ribose**, and more.

2 Introduction

Heart failure is a general term describing a syndrome in which the heart cannot pump enough blood to meet the body's needs. Heart failure can develop rapidly or gradually, and is most commonly caused by coronary artery disease, which occurs when fatty plaque deposits build up in the arteries supplying blood to the heart muscle.¹ Other factors that can contribute to heart failure include structural heart muscle defects, cardiac valve disease, lung disease, coronary artery disease due to atherosclerosis, thyroid disease, and anemia.²⁻⁷

About 5.7 million adults in the United States have heart failure, and approximately 550,000 cases are diagnosed in the United States each year.⁸ Standard treatment options for heart failure focus on limiting symptoms and attempting to reduce progression and mortality. Despite medical advances, heart failure continues to reduce quality of life for those it affects, and the mortality rate due to heart failure remains high.^{9,10} However, several novel and integrative strategies appear promising.

For instance, an important insight in heart failure research came in 2014 with the publication of results of the Q-SYMBIO coenzyme Q10 (CoQ10) trial. This groundbreaking two-year study showed that CoQ10 supplementation significantly reduced the risk of a major cardiovascular event compared with placebo in subjects with moderate-to-severe heart failure.¹¹ CoQ10 supplementation is especially important for individuals taking cholesterol-lowering statin drugs because statins block the biosynthesis of both cholesterol and CoQ10.¹²⁻¹⁶

A comprehensive strategy for minimizing risk and improving heart failure outcomes should also address its underlying causes. Therefore, readers are encouraged to review additional Life Extension protocols on [atherosclerosis and cardiovascular](#)

disease, high blood pressure, cardiac arrhythmia, cholesterol management, weight loss, diabetes, kidney disease, and hyperthyroidism and hypothyroidism.

This protocol will review the causes of and risk factors for heart failure, along with current standards of care and a number of emerging treatment strategies. Dietary and lifestyle strategies that can support overall cardiovascular health will be reviewed as well, as will a variety of natural, integrative interventions shown in studies to support heart health.

3 Understanding the Heart and Heart Failure

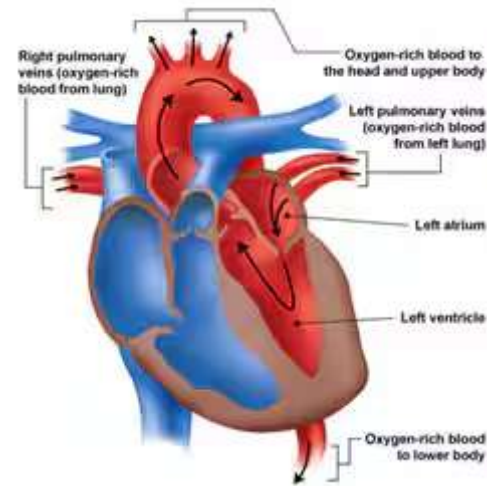
The human heart consists of left and right halves, which behave as two parallel “pumps” with distinct roles in circulation. Both the left and right side of the heart contain two chambers: a smaller atrium, at the top, which receives blood and transfers it to a larger, more muscular ventricle. The ventricles, situated at the bottom of the heart, pump blood from the heart into circulation.¹⁷

The right atrium receives low-oxygen blood from systemic circulation, and the right ventricle then pumps it to the lungs to become re-oxygenated. The left atrium of the heart receives high-oxygen blood from the lungs (pulmonary circulation), and the left ventricle then pumps it into systemic circulation. Thus, the two sides of the heart work in conjunction to collect oxygen-poor blood from peripheral tissues, send it to the lungs to pick up oxygen and deposit carbon dioxide, and redistribute the newly oxygenated blood to tissues and organs.¹⁷

Heart failure can occur when the heart becomes weakened or damaged (see “Heart Failure: Causes and Risk Factors”). The ventricles may become too stiff to fill properly or stretch too much to pump blood efficiently. Ejection fraction (EF) is a measure of the percentage of blood ejected from the left ventricle with each heartbeat, reflecting the efficiency of the heart’s pumping action. A normal left

ventricular EF is 52 – 72% for men and 54 – 74% for women.⁴⁰¹ In other words, a normally functioning heart will eject somewhere in the range of 50 – 75% of the total blood in the left ventricle with each heartbeat. Heart failure can occur with reduced EF or preserved EF. Whether EF is reduced or preserved may influence treatment decisions and the course of the condition.

As the heart begins to fail, the body tries to compensate to ensure that adequate oxygen is delivered to tissues. Signals from the nervous system, kidneys, and blood vessels result in fluid retention (to increase blood pressure in an attempt to better distribute oxygenated blood), increased heart rate and contractile force, and dilatation of the ventricle (to hold more blood) to increase ejection force.



Increases in blood volume and ventricular filling pressures cause blood to “back up” in systemic or pulmonary circulation and leak fluid into peripheral tissues, causing edema (swelling) in the lungs, abdomen, and extremities. This is termed “congestive” heart failure.¹⁸ Fluid can sometimes collect in the lungs, hindering breathing. This is known as pulmonary edema, which can cause respiratory distress if untreated.¹⁹

As heart failure progresses, the body tries to keep up with tissue oxygen demands. However, the heart is restricted in how much it can expand to hold more blood or increase its contractile force and rate, and the kidneys can only process so much water before fluid infiltrates other organs and tissues. Once compensation limits have been reached, the cardiovascular system can no longer satisfy tissue oxygen

demands. This is called decompensated heart failure, which requires immediate medical intervention.^{18,20}

Types of Heart Failure

Distinction is sometimes made between “left-sided” and “right-sided” heart failure. In left-sided heart failure, the left ventricle is primarily affected. Right-sided heart failure usually arises after left-sided heart failure progresses, and typically does not occur independently. In less common conditions, such as cor pulmonale (a lung problem), the right side of the heart may be primarily affected.

Left-sided heart failure: reduced and preserved ejection fraction. The left ventricle, the largest and most muscular of the four heart chambers, must generate a substantial amount of force to pump blood into the systemic circulation. Generally, heart failure begins with the left ventricle.¹ In left-sided heart failure, the ability of the left ventricle to push oxygenated blood into circulation is compromised, meaning the heart must work harder to pump the same amount of blood.

There are two types of left-sided heart failure: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).²¹ As previously noted, ejection fraction is a measure of the amount of blood that leaves the left ventricle and enters systemic circulation with each heartbeat. It represents how efficiently the left ventricle empties itself. In HFrEF, the ventricle cannot contract normally and lacks the force to adequately eject blood. In HFpEF, the ventricle is unable to relax and fill properly. Patients with HFrEF typically respond well to standard treatments and have a more favorable prognosis than those with HFpEF.²²

Ejection fractions between 40–55% may indicate cardiac damage, and an ejection fraction < 40%, termed reduced ejection fraction, indicates heart failure or significant heart muscle damage.²³ An ejection fraction of > 75% may indicate

hypertrophic cardiomyopathy, in which abnormally thick heart muscle makes it difficult for the heart to pump out enough blood.

The most common causes of heart failure are ischemic heart disease and coronary artery disease. Other causes include high blood pressure, valvular heart disease, congenital heart disease, and a variety of cardiomyopathies.^{24,25}

Right-sided heart failure. The right side of the heart pumps oxygen-poor blood to the lungs so it can be oxygenated. Right-sided heart failure usually occurs as a result of left-sided failure. When the left ventricle fails, increased fluid pressure backs up through the pulmonary circulation and increases the resistance against which the right ventricle must pump. As the right side of the heart fails, blood backs up in the body's veins. This may cause swelling in the legs, ankles, and abdomen.²⁶

4 Heart Failure: Causes and Risk Factors

Heart failure may be due to a variety of factors and causes, such as damage to the heart muscle of unknown origin (idiopathic cardiomyopathy), developmental abnormalities (eg, atrial septal defect), thyroid disease (eg, hyperthyroidism), and cardiac valve disease, among others. The most common cause of heart failure is ischemic heart disease due to coronary artery atherosclerosis. Recognition and mitigation of the various contributing factors may reduce heart failure risk and improve prognosis.^{27,28}

Genetics and Family History

A family history of heart failure, cardiomyopathy (dysfunction of heart muscle), atherosclerotic disease, arrhythmia, skeletal myopathy (muscle disease involving skeletal muscle), or sudden cardiac death are well-known risk factors for heart failure.²⁸⁻³⁰

Diet and Lifestyle

Dietary and lifestyle factors associated with increased risk of heart failure include excessive alcohol consumption and nutritional deficiencies (B vitamins).³⁰⁻³²

Smoking is a major risk factor for developing heart failure, and quitting smoking was shown to have a significant effect on lowering morbidity and the risk of death in people with left ventricular dysfunction, an effect that was comparable to currently approved drugs.^{33,34}

Physical inactivity, a known risk factor for many cardiovascular diseases, was shown to worsen the survival rate of patients with heart failure; a study reported that 2.5 years after being admitted to the hospital, only 25% of patients with a sedentary lifestyle were alive compared with 75% of physically active patients.³⁵

Insufficient intake of fruits and vegetables is another risk factor associated with heart failure. A 22-year, prospective cohort study including 20,900 men assessed the association between heart failure and body weight, smoking, exercise, alcohol intake, and dietary habits, including fruit, vegetable, and breakfast cereal consumption. Healthy lifestyle habits were individually and jointly linked to a lower lifetime risk of heart failure, with the lowest risk (1 in 10) in the men who adhered to four or more factors, and the highest risk (1 in 5) in the men who adhered to none of the six factors.³⁶ In addition, a diet with too much added sugar has been shown to increase risk of cardiovascular disease and mortality.³⁷

Health Conditions Associated with Heart Failure

Heart disease. Atrial fibrillation, valve disease (including aortic stenosis, mitral regurgitation, tricuspid regurgitation), ischemic heart disease due to coronary artery **atherosclerosis**, and prior heart attack are associated with an increased risk of heart failure.^{30,38} **Heart arrhythmias**; cardiomyopathy caused by drug use, disease, infection, or alcohol abuse; and myocarditis from an infection may also cause heart disease. In addition, congenital heart defects may lead to heart failure.¹

Hypertension. Hypertension (high blood pressure) increases heart failure risk two-to three-fold.^{39,40} Half of patients with acute heart failure have systolic blood pressure over 140 mmHg, and 70% have a history of high blood pressure.⁴¹ For more information, refer to the [High Blood Pressure](#) protocol.

Diabetes. Diabetics have a high rate of heart failure, and their heart failure prognosis is usually worse than in non-diabetics.⁴² Diabetics often have elevated lipid levels and hypertension, both risk factors for heart failure.

Chronic obstructive pulmonary disease (COPD). Long-standing obstructive pulmonary disease, often caused by tobacco abuse, is associated with heart failure, and when the two occur simultaneously, prognosis is worse than either alone.⁴³ Advanced COPD typically contributes to right-sided heart failure (cor pulmonale).

Renal insufficiency/kidney disease. Heart failure can reduce blood flow to the kidneys, which may cause kidney failure if untreated. Evidence suggests heart failure is widespread in patients with chronic kidney disease and end-stage renal disease, and its prevalence increases with decreasing kidney function. Heart diseases is a strong predictor of mortality in dialysis patients.⁴⁴

Overweight/obesity. The heart of an obese person must work harder than for a non-obese person. Having a high body mass index (BMI) is a risk factor for developing heart failure.⁴⁵ Being overweight is linked to heart failure risk factors such as high blood pressure, diabetes, high blood lipid levels, metabolic syndrome, and an enlarged left ventricle. Obesity is also associated with sleep apnea and cardiomyopathy.¹⁹

Depression. Depression and heart failure often occur together, especially in older people. These conditions also seem to worsen one another in older individuals, a phenomenon termed “negative synergism.” Depression is often under-recognized in heart failure patients. Proper mental health screening and support is an important

part of optimal care for those affected by heart failure.⁴⁶ More information is available in Life Extension's [Depression](#) protocol.

Other conditions. Other conditions less well-recognized to be linked with increased heart failure risk include iron overload, rheumatologic and connective tissue disorders, infection (HIV, infectious myocarditis), endocrine disorders (thyroid disease and growth hormone disorders), and amyloidosis and sarcoidosis.⁴⁷

Obstructive Sleep Apnea—A Hidden Epidemic with Deadly Consequences

Obstructive sleep apnea, a common and potentially lethal sleep disorder, results from the upper airway collapsing during sleep, reducing oxygen flow. The resulting low oxygen in the bloodstream arouses the individual, resulting in disrupted sleep. Between 2% and 7% of adults have obstructive sleep apnea, causing signs and symptoms including intractable fatigue and sleepiness during the day, frequent loud snoring, long periods without breathing (known as apnea events, observed by another person), and poor concentration.^{48,49} Research suggests 30–50% of heart failure patients have sleep apnea, which contributes to the progression of heart failure and associated morbidity and mortality.⁵⁰

This underdiagnosed and often overlooked sleep disorder represents a major risk factor for cardiovascular disease, including hypertension, coronary artery disease, cardiac arrhythmias, sudden cardiac death, and heart failure.⁵¹

Obstructive sleep apnea has been associated with a 68% increase in coronary heart disease in men.⁵²

One theory suggests sleep apnea generates oxidative stress, inflammation, and endothelial dysfunction, which further cardiovascular issues.⁵⁰ Obstructive sleep apnea may also be associated with increased cholesterol levels and increased rates of hypertension,^{53,54} type 2 diabetes,⁵⁵ cancer mortality,⁵⁶ stroke, and death.⁵⁷

More information is available in the [Sleep Apnea](#) protocol.

Medications That May Increase Heart Failure Risk

Certain medications may cause or worsen heart failure through toxicity, worsening hypertension levels, increasing the sodium load, or drug-drug interactions.⁵⁸ Some drugs that cause or exacerbate heart failure include⁵⁸:

- thiazolidinediones (a class of diabetes medications)
- antiarrhythmics (eg, dronedarone)
- anti-cancer drugs (eg, anthracyclines)
- targeted cancer therapies (eg, bevacizumab and lapatinib)
- hematologic medications (eg, anagrelide)
- certain antidepressants (eg, citalopram)
- pergolide (an anti-Parkinson medication)
- certain appetite suppressants
- pulmonary medications (eg, bosentan and epoprostenol)
- tumor necrosis factor-alpha (TNF- α) inhibitors

Prognostic Factors

Predictors of poor outcome and mortality in heart failure include having a reduced VO₂ max capacity (the maximum intake of oxygen with increasing exercise intensity), older age, male gender, diabetes, a left ventricular ejection fraction of <45%, and a more advanced New York Heart Association (NYHA) heart failure classification.²² Anemia and depression have also been associated with poor outcomes in heart failure.^{59,60}

Complications of Heart Failure

The prognosis of heart failure depends on the patient's age and overall health, as well as the cause and severity of heart failure. Complications may include liver or kidney damage or failure, problems with the heart valves or heart rhythm, pulmonary congestion, anemia, muscle wasting, stroke, or pulmonary embolism. While there is no cure for heart failure, some people may experience improvements in heart function and symptoms with proper treatment, including medications, weight loss, exercise, a healthy diet, stress reduction, and dietary supplements, such as CoQ10, fish oil, and carnitine.¹

5 What are the Signs and Symptoms of Heart Failure?

Some of the most prominent symptoms of heart failure are listed below.⁶¹ Some symptoms may not be apparent in mild heart failure, but will emerge as heart failure advances to moderate or severe stages.

- Fatigue and difficulty breathing (dyspnea), which can lead to decreased capacity for physical activity (exercise intolerance). In cases of mild heart failure, it may be difficult to breathe during physical activity, while in advanced heart failure it may be difficult for patients to breathe even at rest.
- Fluid retention, which may result in peripheral or pulmonary edema.²⁸ However, not all people with heart failure will exhibit both exercise intolerance and edema.
- Frequent nighttime urination (nocturia).
- Rapid or irregular heartbeat.
- Lack of appetite or nausea.
- Decreased mental alertness or difficulty concentrating.
- In advanced heart failure, wheezing, cough that produces pink-tinged frothy sputum, abdominal discomfort or swelling, anorexia, and weight loss may occur.

Some signs that may suggest heart failure include changes in heart size (cardiomegaly) and/or rhythm, impaired lung function, evidence of low blood oxygen, and abdominal swelling. These signs are typically progressive with the severity of heart failure.²

Classification and Staging of Heart Failure

Classifying heart failure on the basis of severity and clinical manifestations helps clarify what kinds of interventions may be necessary and what the prognosis may be. The New York Heart Association (NYHA) Functional Classification classifies patients with cardiac disease into one of four classes, based on symptoms and their degree of comfort at different levels of physical activity.

NYHA Functional Classification

- Class I patients have no physical limitations or any symptoms such as fatigue, palpitations, breathlessness, or chest pain.
- Class II patients are comfortable at rest and can typically perform everyday activities. Physical activity may result in fatigue, palpitations, breathlessness, or chest pain.
- Class III patients are comfortable at rest, but everyday activities cause fatigue, palpitations, breathlessness, or chest pain.
- Class IV patients cannot engage in any physical activity without discomfort. Symptoms of heart failure or chest pain may be present even at rest.⁶²

Although the NYHA classification system helps cardiologists guide therapy for individual patients, it is subject to inter-observer variability. A second approach to heart failure classification was developed by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines and is sometime used to supplement NYHA classification in the clinical setting.^{63,64}

This system accounts for both the development and progression of heart failure.⁶³ It identifies four stages, the first two (A and B) of which are not considered overt heart failure, but rather risk factors that predispose to heart failure. This scale attempts to help healthcare providers identify at-risk patients early.²⁸

American College of Cardiology Foundation/American Heart Association Staging

At Risk for Heart Failure

- **Stage A.** These patients are at a high risk for heart failure, but do not have structural disease or symptoms of heart failure. This includes those with coronary artery disease or diabetes.
- **Stage B.** This stage includes those who have structural heart disease, such as left ventricular hypertrophy/dysfunction or chamber enlargement, but who do not have signs or symptoms of heart failure.

Heart Failure

- **Stage C.** These patients have structural heart disease with prior or current symptoms of clinical heart failure.
- **Stage D.** These patients have treatment-resistant heart failure requiring specialized intervention, such as transplantation, biventricular pacemakers, or left ventricle assist devices.²⁸

Note that in the ACCF/AHA classification system, a patient cannot move backwards to a prior stage. That is, once a patient is classified as Stage C, they cannot be in Stage B again. In the NYHA system, which is based solely on symptoms, patients can move between classes.⁶⁵

The initial approach to a patient with suspected heart failure relies heavily on a thorough medical history and careful clinical exam. However, signs and symptoms of heart failure are non-specific—they might be caused by a number of other conditions—so further testing is often necessary to make a conclusive diagnosis. A complete blood count, chemistry panel, and urinalysis, as well as a chest X-ray, are generally part of this workup. Blood testing for natriuretic peptides (BNP or N-terminal prohormone of brain natriuretic peptide [NT-proBNP]), an electrocardiogram, and an echocardiogram are also standard parts of an initial assessment.^{22,47,66}

Electrocardiography and Imaging

An electrocardiogram (ECG) can be used to measure electric abnormalities, enlargement of the heart chambers, and arrhythmia. It is recommended as part of an initial evaluation of individuals with suspected heart failure.^{3,47,66}

An echocardiogram is among the most useful diagnostic tests for heart failure.⁶⁶ Echocardiography is an ultrasound technique that displays real-time images of the heart to visualize abnormalities in the heart muscle or valves, quantitate changes in the size of heart chambers, or detect abnormalities in blood flow. When combined with Doppler flow studies (which help visualize blood flow through the heart), it represents an important diagnostic approach for patients with heart failure.³ Echocardiography is also an important technique to estimate and monitor changes in left ventricular ejection fraction.

Other imaging techniques may also be used to evaluate the size and thickness of the heart chambers, detect myocardial damage, or detect pulmonary edema, including chest radiography (X-rays), computed tomography (CT or CAT scans), and magnetic resonance imaging (MRI).^{3,19,67,68} In particular, MRI is useful in helping

determine the cause of heart failure and establishing prognosis. It can also help guide treatment.⁶⁹

Biomarker Testing

B-type natriuretic peptide (BNP), a peptide hormone released mostly by cells of the ventricle (cardiomyocytes) in response to heart muscle stretch or injury, is a valuable biomarker both for diagnosing acute heart failure and predicting clinical outcomes.⁷⁰⁻⁷³ BNP normally functions to signal the kidneys to release sodium and water into the urine to lower blood volume, and thus, blood pressure. Serum levels of BNP, and its precursor fragment (NT-proBNP), rise proportionally with risk for cardiovascular disease.⁷¹ In one prospective cohort study of 380 people in Sweden, having a low BNP was one of the best predictors of survival to age 90 in men.⁷⁴

Cardiac troponins (cTnI and cTnT) are regulatory proteins associated with muscle fibers in the heart that can be released into circulation upon cardiomyocyte damage or death. Quantitation of serum cardiac troponins is the gold standard for detecting acute damage to the heart muscle, such as from a heart attack.⁷⁵ Cardiac troponins may also leak from cells during chronic diseases, such as heart failure.⁷⁶ Measuring serum cTnT using a high-sensitivity assay (hs-cTnT) can be used in heart failure diagnosis and risk assessment.⁷⁷⁻⁷⁹ A recent meta-analysis of 16 studies with over 67,000 subjects found that there is a strong association between heart failure and cardiac troponins, and that its measurement was predictive of a heart failure event.⁸⁰

In addition to these biomarkers, other markers of inflammation, oxidative stress, vascular dysfunction, and myocardial problems can mark heart failure.^{81,82}

Measurements of soluble ST2, a member of the interleukin 1 receptor family and marker of cardiac distress,⁸³ and galectin-3, a protein that plays a role in inflammation, cancer, and heart disease,⁸⁴ can predict hospitalization and death.

Monitoring multiple biomarkers may be useful to target heart failure therapies in the future, but further research is needed.

Additional tests that may help diagnose and monitor heart failure include thyroid function tests, especially thyroid-stimulating hormone (TSH), as hyperthyroidism and untreated hypothyroidism can cause heart failure. Standard blood tests to measure electrolyte levels and assess liver and kidney function (such as a chemistry panel and complete blood count [CBC]) may also be useful.^{47,66}

Cardiovascular risk markers, such as homocysteine, insulin-like growth factor 1, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6), may also be assessed,³⁰ although they are not specific for heart failure and may be more relevant for prognosis than diagnosis.⁸⁵

Iron and Heart Failure

Iron overload and iron deficiency are associated with heart failure, but in different circumstances. Iron can accumulate in cardiac muscles in hereditary iron metabolism diseases (primary hemochromatosis) or following multiple blood transfusions, leading to cell death via oxidative stress. This phenomenon, called iron-overload cardiomyopathy, is a major cause of heart failure in people with iron overload disorders. A blood test called transferrin saturation can be used to screen for iron overload. Physicians may test for iron excess in heart failure patients with a personal or family history of iron metabolism diseases, or if iron overload is suspected for another reason.⁸⁶⁻⁸⁸

The prevalence of iron deficiency in heart failure with reduced ejection fraction (HFrEF) may be as high as 50%. Mechanisms leading to this deficiency include poor absorption, gastrointestinal losses, and diminished bioavailability. Iron deficiency is associated with an increased risk of cardiovascular morbidity and

mortality.⁸⁹ Individuals with heart failure may develop iron deficiency as their condition progresses. In an analysis of studies including more than 1,500 heart failure patients, 50% of subjects were found to be iron deficient.⁹⁰ Also, a 2013 study on 552 subjects with chronic heart failure found that iron deficiency was strongly associated with reduced quality of life.⁹¹

Iron supplementation in heart failure patients with iron deficiency is associated with improved symptoms, functional capacity, quality of life, and reduced hospital admissions.⁹²⁻⁹⁴ The specific mechanisms by which iron deficiency negatively impacts heart failure outcomes are not clearly defined, but may be due to iron-deficiency-related anemia in some cases and the direct effects of depleted iron stores in others.⁹⁵ An iron and total iron binding capacity (TIBC) test can be used to screen for iron deficiency.

Anemia is fairly common among individuals with heart failure and is associated with poor outcomes. Iron deficiency is a prominent cause of anemia in many situations, but anemia can occur independently of iron deficiency in heart failure. More severe anemia is associated with more severe heart failure, and iron deficiency is associated with a reduced exercise capacity.⁹⁶

Other possible causes of anemia in heart failure include impaired production of erythropoietin (a hormone that controls red blood cell production), kidney problems, and problems with fluid retention.⁹⁷ Recognition and management of anemia is an important component of heart failure care.^{95,98-100} Several blood tests can be useful for screening for anemia and may help guide treatment, including ferritin, TIBC, vitamin B12, folate, and reticulocyte (immature red blood cell) count.

The role of iron supplementation in heart failure patients remains controversial. Iron Repletion Effects on Oxygen Uptake in Heart Failure (IRONOUT-HF), a

randomized, double-blind, placebo-controlled trial involving supplementation of 150 mg of oral iron polysaccharide twice daily in patients with HFrEF, found no clinical effect after supplementation, even when iron stores were repleted, suggesting poor oral iron absorption in HFrEF patients. A recent re-analysis of the trial did not support iron supplementation in iron deficient patients with HFrEF.⁸⁹ Additional research may be needed to clarify the role of iron supplementation in patients with heart failure.

7 Heart Failure Treatment

The suggested optimal treatment of heart failure is outlined in guidelines issued by the American College of Cardiology Foundation and American Heart Association (ACCF/AHA). These guidelines were updated in 2022.³³¹ Recommendations in the guidelines are stratified by disease severity.

Treatment Recommendations for Patients at Risk for Heart Failure (ACCF/AHA stage A)

Patients with stage A heart failure have no symptoms of heart failure and no structural problems in their heart but are at high risk due to high blood pressure, atherosclerosis, type 2 diabetes, obesity, and/or metabolic syndrome. This category also includes those with a family history or genetic marker indicating high risk of cardiomyopathy, as well as those who have been exposed to cardiac toxins (eg, the anticancer drugs doxorubicin [Adriamycin] and daunomycin [Cerubidine]).³³¹

The treatment approach to stage A heart failure begins with adopting a healthy diet and lifestyle, including exercising regularly, maintaining healthy body weight, and not smoking. Because of the close relationship between hypertension and heart

failure, treatment of high blood pressure is paramount in patients with stage A heart failure.³³¹

Medications

Antihypertensives. Use of antihypertensives (ie, medications that lower blood pressure) has been found to reduce the risk of developing heart failure.³³² Intensive antihypertensive therapy targeting an optimal systolic blood pressure of <120 mm Hg may be indicated for those with high risk of heart failure who also have high blood pressure, but in general a treatment goal of <130/80 mm Hg is recommended.³³¹

Sodium/glucose cotransporter-2 (SGLT2) inhibitors. SGLT2 inhibitors are a newer class of antidiabetic drugs that also protect the heart and kidneys. Canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance) are drugs in this class. A growing body of evidence shows treatment with SGLT2 inhibitors reduces the risk of symptomatic heart failure and improves outcomes in symptomatic (stage C) heart failure patients with or without diabetes.^{333,334} Based on the strength of the evidence, SGLT2 inhibitor therapy is now recommended for stage A heart failure patients with type 2 diabetes, established cardiovascular disease, or high cardiovascular risk.³³¹ Potential adverse side effects include urogenital yeast infections, especially in women, and potentially dangerous diabetic ketoacidosis.³³⁵

Cardiovascular medications. Any medications needed to treat existing cardiovascular risk factors like high cholesterol levels, atrial fibrillation, or peripheral or coronary artery disease are important for protecting patients with high risk of heart failure.³³¹ Examples include cholesterol-lowering statins, aspirin, antiplatelet drugs, and anticoagulants.^{336,337}

Treatment Recommendations for Patients with Pre-Heart Failure (ACCF/AHA stage B)

Stage B heart failure involves changes in structure and function of the heart, such as heart chamber enlargement, abnormal wall movement, valve disorders, or reduced ejection fraction. High levels of B-type natriuretic peptide (BNP) or cardiac troponin levels, which reflect heart muscle dysfunction, are also indicative of pre-heart failure. However, signs and symptoms of heart failure are not present in stage B.³³¹

As in stage A, dietary and lifestyle strategies are paramount in managing stage B heart failure. In addition, therapies aimed at specific co-existing conditions affecting cardiovascular health continue to be important in stage B.³³¹

Medications

The medical approach to treatment of stage A is also indicated for stage B heart failure patients, including SGLT2 inhibitor therapy if diabetes is present and cardiovascular medications as indicated for the individual.³³¹ Additional medical recommendations are:

Antihypertensives. Guidelines for antihypertensive therapy are more specific for those with stage B heart failure than stage A.

- **Angiotensin-converting enzyme (ACE) inhibitors.** ACE inhibitors lower blood pressure by inhibiting activity of ACE and reducing synthesis of angiotensin II, a hormone that causes constriction of blood vessels and raises blood pressure. Enalapril (Vasotec) and lisinopril (Zestril) are examples of commonly prescribed ACE inhibitors. ACE inhibitors have been found to reduce progression, hospitalization, and death due to heart failure in patients with reduced left ventricular ejection fraction ($\leq 40\%$).^{331,338}

Not all patients are able to tolerate ACE inhibitors with cough being a common side effect. ACE inhibitors can also cause a type of severe skin swelling called

angioedema and must be used with caution in patients with low blood pressure, advanced kidney disease, and elevated blood potassium.³³⁹

- **Angiotensin II receptor blockers (ARBs).** ARBs lower blood pressure by blocking interactions between angiotensin II and its receptors, limiting blood vessel constriction. Commonly prescribed ARBs include candesartan (Atacand) and valsartan (Diovan). Intriguingly, the ARB telmisartan (Micardis) has also been shown to reduce insulin resistance, a major contributor to heart disease.³⁴⁰ ARBs have been found to reduce death and heart failure-related illness in patients with a low ejection fraction and a previous heart attack.³³¹ However, because evidence of their benefits is not as strong as for ACE inhibitors, their use is usually restricted to cases of intolerance to ACE inhibitors due to cough or angioedema.^{341,342} Like ACE inhibitors, ARBs must be used with caution in patients with high blood potassium levels, advanced kidney disease, and low blood pressure.³⁴²
- **Beta blockers.** Beta blockers lower blood pressure, heart rate, and heart contraction force by blocking a type of adrenaline receptor called beta-adrenoceptors. Beta blockers are added to treatment with ACE inhibitors or ARBs to improve their effectiveness in patients with pre-heart failure and reduced ejection fraction.³⁴³ Beta blockers such as carvedilol (Coreg), bisoprolol (Zebeta), and metoprolol (Lopressor) have been found to reduce damage to cardiac structure and function and improve outcomes in patients with reduced ejection fraction, with most of the evidence being in those who have had a heart attack.^{331,344,345} A meta-analysis of 11 randomized controlled trials including over 14,000 patients found beta blockers improved ejection fraction in heart failure patients with ejections fractions as high as 40–49%.³⁴⁶

Common adverse side effects of beta blockers include fatigue, dizziness, nausea, and constipation; less commonly, difficulty breathing, increased blood glucose levels, insomnia, edema, and worsening of Raynaud syndrome may occur. Individuals with low blood pressure or a low heart rate may not be able to use beta blockers.³⁴⁷

Treatment Considerations for Patients with Heart Failure (ACCF/AHA stage C)

Patients with stage C heart failure have structural changes to the heart muscle and have or have experienced heart failure symptoms. The guideline recognizes the importance of self-care, patient education, social support, and an integrated team of healthcare providers to meet the complex needs of heart failure patients.³³¹ A healthy diet and lifestyle are important for slowing progression; however, a sodium-restricted diet is no longer emphasized in recommendations due to lack of evidence of its benefit.^{331,348} Exercise training or cardiac rehabilitation may improve health-related quality of life.³⁴⁹ Annual influenza vaccination has been found to lower the rate of hospitalization and death, whether due to cardiovascular reasons or any cause, in heart failure patients, with cumulative benefits seen in those who were vaccinated regularly.³⁵⁰

Medications

Pharmacological treatment for stage C heart failure relies on the same key medications as stages A and B, with treatment beginning at very low doses that can be gradually increased as needed. Importantly, SGLT2 inhibitor therapy is a core recommendation for both diabetic and non-diabetic stage C heart failure patients. Additional medications recommended for stage C heart failure are:

Angiotensin receptor-neprilysin (ARN) inhibitors. The only ARN inhibitor with current FDA approval, Entresto, contains two agents: sacubitril and the ARB valsartan. By inhibiting the activity of the enzyme neprilysin, sacubitril slows the

breakdown of natriuretic peptides. The combined effect of the two agents leads to blood vessel dilation and improved fluid balance. Sacubitril-valsartan appears to be more effective than traditionally used ACE inhibitors and ARBs for reducing hospitalizations and deaths in patients with mild-to-moderate symptomatic heart failure with reduced ejection fraction, and is recommended as an alternative to ACE inhibitors or ARBs in these patients.^{331,351,352} A meta-analysis determined the combination of ARN inhibitor, beta blocker, mineralocorticoid receptor antagonist (MRA), and a SGLT2 inhibitor reduced deaths more than any other treatment regimen in heart failure patients with reduced ejection fraction.³⁵³

Like ACE inhibitors, sacubitril-valsartan can cause angioedema, as well as low blood pressure, cough, high blood potassium levels, and kidney damage.³⁵⁴ Despite its relatively high cost, some evidence suggests including an ARN inhibitor early in heart failure treatment may ultimately save money.³⁵⁵

Mineralocorticoid receptor antagonists (MRAs). MRAs inhibit aldosterone, a hormone produced by the adrenal glands that increases the kidneys' retention of sodium and water. Aldosterone inhibition decreases fluid retention, diminishing blood volume and blood pressure. Stage C heart failure patients with compromised ejection fraction have been found to benefit from MRAs, such as spironolactone (Aldactone) or eplerenone (Inspra).³⁵⁶ Emerging evidence suggests spironolactone may also decrease heart failure-related hospitalizations and improve cardiac function in patients with mildly reduced (40–49%) or preserved ($\geq 50\%$) ejection fractions.^{357,358}

When using MRAs, potassium, kidney function, and diuretic dosing should be carefully monitored to reduce risk of high blood potassium levels and kidney problems, which can be life-threatening.³³¹ Spironolactone is also associated with gynecomastia, the swelling of breast tissue in males.³⁵⁶

Diuretics. Diuretics can be helpful in stage C heart failure patients with reduced ejection fraction who experience fluid retention. Diuretics work by altering the way the kidneys handle sodium or chloride, thus increasing urination. Loop diuretics like furosemide (Lasix), torsemide (Demadex), and bumetanide (Bumex) are the preferred choice for treating heart failure because of their more potent action compared with thiazide diuretics like hydrochlorothiazide (Microzide). Diuretics can improve symptoms and quality of life; however, there is uncertainty regarding their effects on outcomes in heart failure patients.³⁵⁹⁻³⁶¹ The effectiveness of diuretics diminishes with prolonged use of high doses, high sodium intake, and the use of non-steroidal anti-inflammatory drugs (NSAIDs).³⁶² Diuretics can cause electrolyte imbalance, and their use at the lowest dose needed to manage fluid retention is recommended.³³¹

Other medications. In addition to core medical treatment with individualized combinations of SGLT2 inhibitors, renin-angiotensin system inhibitors (ARN inhibitors, ACE inhibitors, or ARBs), beta blockers, and MRAs, as well as diuretics for symptom relief, the following medications may be indicated for specific patients with symptomatic heart failure:

- **Isosorbide dinitrate and hydralazine.** Isosorbide dinitrate and hydralazine (BiDil) dilate blood vessels and lower blood pressure by relaxing smooth muscles in the vascular walls. This drug combination has been found to reduce complications and death rate specifically in African American heart failure patients with reduced ejection fraction and moderate-to-severe functional limitation.^{363,364} It may also help stage C heart failure patients who are unable to tolerate first-line therapy with ARN inhibitors, ACE inhibitors, or ARBs.^{331,364} Common adverse side effects of BiDil treatment are headache, digestive upset, and low blood pressure.³⁶⁴

- **Sinoatrial current inhibitor.** Increased resting heart rate is a risk factor for heart failure-related hospitalization and death.^{331,363} Ivabradine (Corlanor), classified as a sinoatrial current inhibitor, slows the heart rhythm and has been shown to reduce heart failure-related hospitalizations and deaths in stage C heart failure patients who have reduced ejection fraction, mild-to-moderate functional limitation, a normal heart rhythm, and a resting heart rate of 70 beats per minute or higher.³⁶⁴ However, it is recommended beta blocker therapy be optimized before considering the addition of ivabradine to treatment.³³¹ Potential adverse side effects of ivabradine include arrhythmias and visual side effects.³⁶⁴
- **Vericiguat.** Vericiguat (Verquvo), as a guanylate cyclase stimulator, has a nitric oxide-like blood vessel-dilating effect. A large randomized controlled trial found vericiguat lowered the risks of heart failure-related hospitalization and cardiovascular death in patients with reduced ejection fraction and recently worsening heart failure.³⁶⁵ Its use may therefore be considered for this particular population of heart failure patients.³³¹ Low blood pressure and anemia are the main adverse side effects of vericiguat.³⁶⁶
- **Digoxin.** Digoxin (Lanoxin) is a plant-derived compound known as a cardiac glycoside that has been used to treat cardiac problems for over 200 years, but its usefulness has declined as safer and more effective medical options have become available. Digoxin functions as a positive inotrope, meaning it increases the contractile force of the heart muscle, and also lowers heart rate.³⁶⁴ Digoxin may decrease symptoms and hospitalizations in stage C heart failure patients with reduced ejection fraction, and may be beneficial in patients who remain symptomatic despite optimized treatment with core medications.^{331,367} Digoxin's benefits are countered by its potential to cause

serious heart rhythm irregularities at doses not much higher than those needed to produce a therapeutic effect.³⁶⁷

- **Omega-3 fatty acids.** Omega-3 fatty acids, in conjunction with core medical therapies, have been shown to improve cardiac function and modestly decrease risks of cardiovascular events and death in heart failure patients with reduced ejection fraction.^{368,369} The majority of trials showing cardiovascular benefits have used highly purified ethyl esters of eicosapentaenoic acid (EPA), with or without docosahexaenoic acid (DHA).^{331,370} These omega-3 fatty acids are only available by prescription, and may increase the risk of bleeding more than over-the-counter supplements. A possible link between their use and increased risk of atrial fibrillation has been reported.³⁷⁰
- **Potassium binders.** Potassium-binding medications may be recommended to patients who are otherwise unable to optimize treatment with spironolactone or other potassium-raising medications (ACE inhibitors, ARBs, and ANR inhibitors).³³¹ Sodium polystyrene sulfonate (Kayexalate) is an older potassium-binding drug that can only be used short-term due to potentially dangerous digestive toxicity; two newer drugs, patiomer (Veltassa) and sodium zirconium cyclosilicate (Lokelma), have shown promise in clinical trials.³⁷¹ Adverse side effects of patiomer include low magnesium levels and digestive problems, and sodium zirconium cyclosilicate can cause problematic edema.^{331,372,373}
- **Anticoagulants and antiplatelets.** Anticoagulants (eg, apixaban [Eliquis] and warfarin [Coumadin] and antiplatelets (eg, clopidogrel [Plavix] and aspirin) have not been found to have benefits in heart failure patients generally, and their use is only recommended for those with a co-occurring condition that increases blood clot risk, such as previous heart attack or stroke, venous thromboembolism, atrial fibrillation, and other cardiac conditions that trigger

blood clotting.³³¹ These drugs are associated with increased risk of serious bleeding, and dosing must be carefully considered.

Medical Devices

Medical devices can have an important role in improving outcomes and survival in select patients with heart failure, as a complement to optimal medical therapy.^{331,374} Implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) are examples of such devices. ICDs are similar to pacemakers, and they monitor the heart's rhythm to ensure it beats at an optimal rate. CRT is a pacemaker that sends timed electrical impulses to the heart's left and right ventricles so they pump more efficiently. For those not suited for either ICD or CRT, options available include an implantable device that stimulates pressure receptors in the carotid artery, vagus nerve stimulation, and cardiac contractility modulators that stimulate stronger ventricular function, although it is unknown whether these interventions reduce hospitalization or death rates.³³¹

Surgeries

In patients whose symptomatic heart failure is complicated by atrial fibrillation, a procedure called ablation may relieve symptoms and improve quality of life, and has been found to reduce heart failure-related hospitalizations and deaths.^{331,375} The procedure involves using a catheter to direct heating or freezing to a small region of the heart, resulting in scarring that interrupts the origination of abnormal heart beats.³⁷⁶ Coronary artery bypass graft surgery can improve survival in select heart failure patients with ejection fraction $\leq 35\%$ and advanced coronary artery disease.³³¹

Interventions for Valvular Heart Disease

Valvular heart disease is a known risk factor for heart failure. This is true for multiple types of cardiac valve disease, including aortic stenosis and mitral and tricuspid valve regurgitation.⁴⁰¹ Aortic stenosis is the most prevalent cardiac valve pathology worldwide, and heart failure is a leading cause of death in people with aortic stenosis.⁴⁰² Aortic valve replacement is the main treatment for aortic stenosis, and can be performed both through major invasive surgery as well as a much less invasive method called transcatheter aortic valve replacement (TAVR). Another term, transcatheter aortic valve implantation (TAVI), refers to the same procedure as TAVR; usage of this term is more common in Europe whereas “TAVR” is more common in the United States.^{403,404} The advent of TAVR has made valve replacement for aortic stenosis available to many more patients who would be at undue risk from major surgery. As adoption of TAVR has grown, it is now becoming increasingly available to people who have low-risk aortic stenosis as well—and is now the preferred therapy for aortic stenosis for most patients.⁴⁰⁵

TAVR’s relative low risk has made it the leading procedure for aortic stenosis, with some saying it has revolutionized the treatment of aortic stenosis.^{405,406} Deciding on TAVR or traditional surgical aortic valve replacement should be based on risk-benefit profile, shared decision-making between patient and physician, and patient-specific clinical indications.³³¹

A retrospective observational study in patients with heart failure found symptomatic improvement after TAVR, regardless of class of disease. However, patients with reduced ejection fraction experienced the least improvement.⁴⁰⁷ In a randomized controlled trial that included 178 patients (average age 77 years) who had heart failure with reduced ejection fraction and moderate aortic stenosis, TAVR was not superior to surveillance for a composite outcome of all-cause death, disabling stroke, and hospitalizations. TAVR did, however, result in an improvement in symptomatic quality of life.⁴⁰⁸ An earlier meta-analysis compared surgical aortic

valve replacement to TAVR and found a relative survival benefit at two years for TAVR overall, regardless of the specific valve device implanted or baseline surgical risk profile. The clearest benefit was in patients with femoral access TAVR and in women. In men, and when thoracic access was used, TAVR was not superior to surgery.⁴⁰⁹ A follow-up analysis confirmed the survival benefit of TAVR relative to surgery and found that stroke risk was lower with the TAVR procedure, while major vascular complications and permanent pacemaker implantations were lower with surgery.⁴¹⁰

Until recently, studies had not specifically addressed whether TAVR would provide benefits over surveillance among people with asymptomatic severe aortic stenosis. A randomized controlled trial published in late 2024 addressed this question. Among 901 patients with asymptomatic severe aortic stenosis enrolled in this study, TAVR reduced the occurrence of stroke, unplanned cardiovascular hospitalization, or death from any cause, compared with active surveillance. Moreover, TAVR resulted in markedly reduced risk of hospitalization for heart failure compared with surveillance, although this was an exploratory endpoint so needs to be replicated in other studies.⁴¹¹

Emerging evidence suggests SGLT2 inhibitors may be associated with improved TAVR outcomes. In a randomized controlled trial, 1,222 individuals with a history of heart failure and severe aortic stenosis who were undergoing TAVR were given either 10 mg of the SGLT2 inhibitor dapagliflozin daily plus standard care or standard care alone, beginning at hospital discharge, and followed for one year. All subjects also had at least one of these conditions: diabetes, left ventricular systolic dysfunction, or renal insufficiency. The primary outcome of interest was a composite of death from any cause or worsening of heart failure. Compared with placebo, the treated group was 28% less likely to experience the composite outcome, although the rate of death from any cause did not differ significantly

between the groups. Subjects in the dapagliflozin group were 37% less likely to experience a worsening of heart failure and more likely to develop genital infections or low blood pressure—known side effects of SGLT-2 inhibitors.⁴¹²

These trial results provide some confirmation for the findings of an earlier observational study in 311 patients with diabetes and severe aortic stenosis undergoing TAVR, 75 of whom were being treated with SGLT2 inhibitors. One year after the procedure, SGLT2 inhibitor users had a higher likelihood of left ventricular recovery. Remarkably, those with especially low baseline left ventricular ejection fraction ($\leq 30\%$) were particularly likely to benefit. Those not treated with SGLT2 inhibitors were more likely to develop worse extra-valvular cardiac damage, while SGLT2 inhibitor users experienced more beneficial cardiac remodeling. After two years, SGLT2 inhibitor use was associated with lower rates of major adverse cardiovascular events, all-cause death, and heart failure. These findings remained significant after results were adjusted for confounding factors.^{413,414}

Heart Failure with Mildly Reduced, Improved, or Preserved Ejection Fraction

While most heart failure research and recommendations focus on patients with reduced left ventricular ejection fraction, the 2022 guidelines made special note to address those with heart failure symptoms and mildly reduced (40–49%) or preserved ($\geq 50\%$) ejection fractions. The SGLT2 inhibitor empagliflozin in particular was found to be beneficial in heart failure patients with ejection fractions $>60\%$. Even in those with preserved ejection fractions $\geq 83.3\%$, treatment with empagliflozin improved heart failure outcomes, clinical status, and health-related quality of life.^{377,378} Importantly, empagliflozin reduced rates of heart failure hospitalizations and cardiovascular deaths in both diabetic and non-diabetic participants.

Evidence suggests treatment with other core heart failure medications (ACE inhibitor, ARB, or ARN inhibitor, plus MRA, beta blocker, and diuretics as needed for symptoms) is likely to improve outcomes in symptomatic heart failure patients with mildly reduced ejection fractions, including those whose ejection fractions have improved from reduced to mildly reduced. In addition, these medications may benefit those whose heart failure symptoms have decreased or resolved. Their usefulness appears less likely, however, in those with preserved ejection fractions, but treatment with MRAs, ARBs, or ARN inhibitors may improve outcomes in select individuals, especially those with ejection fractions at the lower end of the preserved category (closer to 50%).^{331,379}

Advanced Heart Failure (ACCF/AHA stage D)

Stage D heart failure is an advanced form of the condition that is not responsive to core heart failure medications. This stage is characterized by severe cardiac dysfunction; unplanned hospital visits within the previous year due to progressive heart failure; and severe symptoms, including unintentional weight loss, fatigue, and shortness of breath while performing daily tasks (eg, getting dressed or bathing) or at rest.³⁸⁰

Diuretics for symptom relief are a mainstay of treatment for advanced heart failure. Inotropic drugs, kidney dialysis, and the use of mechanical circulatory support may also be part of life-extending care for some patients with advanced heart failure, and heart transplant may be an option for select patients. In addition, a re-evaluation of any co-existing health problems that may be contributing to heart failure may lead to treatments that improve the clinical status of some patients with advanced heart failure. It is important to consider the individual circumstances of each stage D heart failure patient and decide whether and when end-of-life hospice care and palliative treatments are appropriate.^{331,380}

8 Novel and Emerging Therapies for Heart Failure

Stem Cell Therapy

Stem cell therapy for cardiac regeneration is an emerging and continuously evolving field. Stem cells are renewable, unspecialized precursor cells that can transform into specialized cell types.¹⁴⁴⁻¹⁴⁶ Acute myocardial infarction, chronic ischemic heart failure, cardiomyopathy, and left ventricle dysfunction are all associated with a loss of cardiomyocytes (cardiac muscle cells) that was previously considered irreversible. Adult cardiomyocytes have a limited capacity for self-repair; however, research suggests stem cells could offer a novel approach to replacing or repairing damaged cells and tissues.^{147,148} Multiple preclinical studies suggest stem cells may help reduce inflammatory response and cardiac fibrosis, and also help with the recovery of damaged cardiac tissue, yet much remains to be discovered and clarified.¹⁴⁹

Several clinical studies have been conducted with stem cells as a potential treatment for heart failure and other cardiac-related conditions. Several reviews and meta-analyses indicate that stem cell treatments appear to benefit heart failure patients, with those treated experiencing lower mortality rates and fewer cardiac events.^{147,150,151} However, the authors of these articles recommend interpreting the results with caution, as many of the studies were of lower quality and had minimal benefits. Other clinical trials have shown no benefit from stem cell treatments.^{152,153}

Some scientists pointed out that different methods of processing stem cells may have led to the contradictory clinical outcomes.¹⁵⁴ The initial hype surrounding stem cell therapy also likely led to clinical testing before the science was fully appreciated and understood, leading to inconsistent results.^{148,155} Some studies that led to the early excitement have since been discovered to be faulty, and several were retracted.¹⁵⁵ As such, the science behind whether stem cells may benefit heart

failure patients is still not clear and will require more reproducible, well-designed studies.

The use of stem cells as a therapy for heart failure is an interesting and potentially important area; however, more high-quality studies (clinical and preclinical) are needed before its usefulness can be determined and implemented as a standard treatment.

Testosterone

Testosterone is a male hormone that helps regulate bone density, fat distribution, muscle strength, red blood cell production, sperm production, and sex drive. Inadequate levels of testosterone can contribute to cardiovascular diseases, including heart failure. However, this connection is overlooked by many mainstream physicians.^{156,157} A decline in circulating testosterone may exacerbate exercise intolerance and muscle mass loss (cachexia) seen in heart failure patients.^{158,159}

An estimated 25% of men with heart failure have evidence of testosterone deficiency.¹⁶⁰ A recent study involving 167 Chinese men with chronic heart failure measured their testosterone levels and followed them for at least three years. Patients in the low testosterone group had worse cardiac function and higher mortality and hospital readmission rates.¹⁶¹ A review of eight published studies indicated testosterone replacement therapy can enhance exercise capacity and muscle strength, but not ejection fraction, blood pressure, and other markers of cardiac health. More quality research is needed to understand the association between testosterone levels and clinical outcomes in heart failure patients.¹⁶² Another study randomized 39 men with heart failure and testosterone deficiency to an exercise training, intramuscular testosterone injection, or training and testosterone group. The combination group showed the most improved muscle nerve activity, muscle wasting, and functional capacity.¹⁶³

Some evidence suggests testosterone replacement may also benefit women with heart failure. Testosterone therapy was shown to improve exercise capacity (six-minute walk test and muscle performance) and insulin resistance in a study of 36 women with stable heart failure.¹⁶⁴ Testosterone therapy may be useful in cardiovascular events such as heart failure, angina, and ischemia.¹⁶⁵

Individuals with heart failure should consider testing their testosterone levels using an inexpensive blood test. If levels are suboptimal, testosterone replacement therapy may relieve some heart failure symptoms. More randomized, controlled clinical trials are required to clarify testosterone's role in cardiac health. More information about testosterone replacement therapy is available in the [Male Hormone Restoration](#) and [Female Hormone Restoration](#) protocols.

Vagus Nerve Stimulation

Each of two vagus nerves carries signals from the brain to the heart to control heart rate as part of the parasympathetic nervous system. In chronic heart failure, vagal activity is reduced, increasing heart rate and mortality.¹⁶⁶⁻¹⁶⁸ Vagus nerve stimulation is an approved treatment for depression and epilepsy that does not respond to drug therapy, and may also be useful in the treatment of chronic heart failure. In a multi-center open-label trial, implantation of an electro-stimulator device around the right vagus nerve and chronic nerve stimulation for one year significantly improved quality of life, ejection fraction, and a six-minute walk test in 23 NYHA class II/III patients.¹⁶⁷

The INOVATE-HF (Increase of Vagal Tone in Heart Failure) trial was a multinational, randomized, controlled trial that examined 707 people with heart failure and reduced ejection fraction. The study found that vagus nerve stimulation improved 6-minute walk distance, NYHA functional classification, and quality of life scores, but did not improve risk of death or a cardiac event.¹⁶⁹ Further research is warranted

to better understand optimal delivery of this therapy, and if specific patient subgroups are more likely to benefit from this therapy.

Trimetazidine

As heart failure develops, perturbations in energy metabolism in the heart compromise its function. The failing heart muscle cells are unable to derive energy from fatty acids, the primary energy source for the healthy heart. Therefore, declining cardiac function in heart failure is compounded by inefficient fatty acid utilization.^{170,171}

The drug trimetazidine (TMZ) has garnered interest because it has been shown to help overcome impaired cardiac fatty acid metabolism. TMZ boosts glucose utilization in the heart, lessening the reliance on fatty acids for energy.^{309,310} Animal research suggests TMZ may also help mitigate cardiac fibrosis, which contributes to heart failure progression.³¹¹ Some clinical evidence suggests TMZ, along with conventional therapies, improves symptoms, cardiac function, and prognosis in some patients with heart failure.^{172,312} However, much of this evidence comes from small studies that lack rigorous design and execution, so should be viewed as preliminary until larger, well-designed trials evaluate the effects of TMZ in people with heart failure.

A meta-analysis of three randomized clinical trials involving 326 heart failure patients found that TMZ, when provided as an add-on therapy, offered a protective effect, reduced all-cause mortality, and increased survival rates.¹⁷³ Another meta-analysis of 19 randomized controlled trials involving nearly 1,000 chronic heart failure patients found TMZ treatment improved clinical symptoms and cardiac function and reduced cardiac hospitalizations and serum levels of BNP and C-reactive protein.¹⁷⁴

In a comprehensive analysis of studies including 884 subjects with chronic heart failure, TMZ reduced hospitalization for cardiac causes by 57%. Moreover, TMZ was associated with improved left ventricular ejection fraction, exercise capacity, left ventricular end-diastolic diameter, and NYHA functional classification.¹⁷⁵

In another review of published studies including data on 955 heart failure patients, TMZ was associated with improved left ventricular ejection fraction, left ventricular end-systolic volume, NYHA classification, and exercise capacity. Most impressively, TMZ use was associated with a 71% reduction in all-cause mortality and 58% reduction in cardiovascular events.¹⁷⁶

However, a randomized double-blind study in 60 patients with stable, nonischemic heart failure found 35 mg of TMZ twice daily did not result in significant changes to left ventricular ejection fraction, exercise capacity, oxygen uptake, or quality of life.¹⁷⁷ Another randomized controlled trial published in February 2019 found TMZ failed to improve exercise capacity among patients with hypertrophic cardiomyopathy whose mean age was 50 years.³¹³ A randomized trial conducted in Bangladesh during 2015–2016 found that glyceryl trinitrate outperformed TMZ in improving NYHA classification at six and 12 weeks in patients with ischemic cardiomyopathy.³¹⁴ Some evidence suggests diabetics with heart failure may benefit from TMZ, but not all studies have confirmed the benefits for this group.³¹⁵

Despite over 40 years of published studies,¹⁷⁸ TMZ has not received FDA approval. Marketed as Vastarel MR in Europe, scientific research shows TMZ has the capability to protect vulnerable, oxygen-deprived heart muscle. However, concerns about lack of long-term data on heart attack and cardiac mortality make regulatory approval difficult.

The authors of a literature review of TMZ and heart failure concluded the following³¹⁵:

“... we cannot recommend using trimetazidine in [CHF patients] as a result of the significant limitations connected with these studies—meta-analyses based on unpowered studies and the retrospective character of [a key study]. A well designed, randomized clinical study, placebo-controlled, with well selected endpoints, appropriate patient group, and follow-up duration is still needed to possibly recommend the use of trimetazidine in HF patients... There are still no answers to key questions as to the role of this drug in selected cardiovascular conditions as well as whether this drug can reduce mortality in any group of patients with cardiovascular disease.”

TMZ can cause side effects such as Parkinsonism (ie, slowed or stiff movements, speech disturbances, hand tremors, and disequilibrium), which could contribute to a fall in older populations.^{179,180} A 2019 population-based study found TMZ use was a significant predictor of new-onset Parkinsonism symptoms. The researchers called for close monitoring of patients prescribed TMZ for emergence of Parkinsonism symptoms.³¹⁶ Another study found that while TMZ often produces Parkinsonism, drug withdrawal generally results in resolution of symptoms in patients with mild, symmetrical Parkinsonism.³¹⁷

Some trials are underway,³¹⁸ and recent review articles^{319,320} suggest there is interest in continuing to explore the potential benefits of TMZ. Future trials will help clarify what role TMZ has to play in the management of heart failure and related conditions.

Other Potential Therapies

Gene therapy holds some promise for treating heart failure. Efforts are underway to enhance heart muscle sensitivity to calcium via the SERCA2a gene, a protein that pumps calcium into cardiac muscle cells. Other calcium-handling proteins may be candidates for future gene therapy work. Antagomirs are a class of drug that block

microRNA, which play a role in gene expression and protein synthesis. Preliminary research suggests antagomirs improve cardiac function.¹⁰

Another potential therapy involves *CD31 agonist peptides*. CD31, a transmembrane glycoprotein present on endothelial cells and white blood cells, may play a protective role in heart failure. In a recent randomized study, mice with both preserved and reduced ejection fractions received either 2.5 mg/kg of CD31 or placebo by subcutaneous infusion. Daily treatment with CD31 improved ejection fraction and left ventricle filling pressure. In mice with a preserved ejection fraction, it prevented diastolic left ventricle dysfunction. Researchers concluded CD31 improved heart function and may be useful in treating heart failure.¹⁸¹ *Ultrafiltration therapy* can be used for fluid reduction in patients with refractory heart failure (ie, those with advanced heart failure who experience symptoms while at rest) that are not responsive to other medical therapies, such as diuretics. Ultrafiltration removes sodium and water from the blood across a semipermeable membrane and a pressure gradient to make plasma water. It improves congestion, cardiac output, and lowers right atrial and pulmonary pressures.¹⁸²

In early 2019 the FDA approved a device to treat patients with chronic, moderate-to-severe heart failure who remain symptomatic despite receiving optimal medical therapy, and who lack other treatment options.³⁰³ The Optimizer Smart System has been shown in clinical trials to improve walking distance, decrease symptoms, improve quality of life, and improve cardiovascular outcomes.³⁰⁴⁻³⁰⁶ This device may also decrease mortality in these patients.^{304,307}

The Optimizer device is implanted in a minimally-invasive procedure under local anaesthesia,³⁰⁸ and has been associated with a low rate of complications.³⁰⁴ A trial published in 2019 found that, in patients with left ventricular ejection fraction between 25% and 45%, hospitalizations decreased by 75% compared to before

implantation of the device. In this group of patients, three-year survival did not differ from that predicted by an established model; however, among those with a left ventricular ejection fraction of 35–45%, three-year survival was significantly better than that predicted by the same model.³⁰⁵

9 Dietary and Lifestyle Consideration

Cessation of Tobacco and Excessive Alcohol Use

Intake of more than 7–8 alcoholic drinks per day for more than five years may increase the risk of cardiovascular dysfunction that can lead to heart failure. Patients with a history of alcohol overconsumption are encouraged to abstain from drinking.³ However, light-to-moderate drinking (up to one drink daily for women and two drinks daily for men) may be associated with a reduced risk of heart failure compared with those who abstain from drinking.^{32,183,184}

Smoking is a major risk factor for many medical conditions, including cardiovascular diseases. Stopping smoking was shown to provide benefits for patients with congestive heart failure similar to benefits offered by primary drugs.^{33,185} Several other studies found people who quit smoking have a lower risk of cardiovascular disease.¹⁸⁶

The DASH Diet and Mediterranean Diet

The DASH (Dietary Approaches to Stop Hypertension) eating plan, which is rich in fruits, vegetables, whole grains, and low-fat dairy products, has been shown to lower systolic blood pressure by 8–14 mmHg^{187,188} and is often recommended for people with heart failure.^{189,190} The Mediterranean diet, which is similar to the DASH diet in emphasizing fruits, vegetables, and whole grains, is also a healthy dietary pattern for those with heart failure.¹⁸⁹

Specifically restricting dietary sodium intake remains controversial in the context of heart failure.¹⁹¹⁻¹⁹⁴ However, both the DASH and Mediterranean dietary patterns generally do not contain large amounts of sodium relative to the typical Western diet. Until large, randomized, controlled trials can address the question of whether specifically restricting dietary sodium is optimal for heart failure patients, adhering to a diet rich in unprocessed plant-based foods is a good option.¹⁹⁵

Monitor Micronutrient Sufficiency

Deficiencies in micronutrients, such as potassium, calcium, magnesium, and zinc play an important role in the progression of heart failure. These nutrients help maintain the proper relaxation and contraction of heart muscle cells. A comprehensive literature review suggests micronutrients improve health outcomes in heart failure patients, including symptoms, work capacity of the heart, and left ventricular ejection fraction.¹⁹⁶

In a recent multi-center, longitudinal study, 246 heart failure patients were asked to fill out four-day food diaries. Analysis of these diaries revealed micronutrient deficiency to be a strong, independent predictor of one-year hospitalization or death rates, particularly in patients with comorbid depressive symptoms. The most common dietary deficiencies were calcium, folate, magnesium, zinc, and vitamins C, D, E, and K. These results suggest promoting a varied diet may prevent micronutrient deficiencies, and diet quality plays a role in heart failure outcomes.¹⁹⁷

The frequency of malnutrition increases with degree of heart failure severity, ranging from an estimated 22% in NYHA class II patients to 63% in class III patients.³¹ Micronutrient insufficiency is of particular concern among patients on certain heart failure medications. Further research is needed to document the effects of micronutrients on quality of life and heart failure patient survival.

Potassium and zinc. Diuretic use is associated with electrolyte depletion.

Potassium is essential for normal heart rhythm and function. Conversely, ACE inhibitors and ARBs decrease the excretion of potassium and may lead to elevated potassium levels. ACE inhibitors, ARBs, and thiazide increase urinary excretion of zinc.³¹

Magnesium. Loop diuretics increase renal excretion of magnesium and other essential minerals.³¹ In a study of 68 patients admitted to the hospital for heart failure, 38% presented with low magnesium levels at admission and 72% had excessive urinary magnesium loss.¹⁹⁸ Several clinical trials have investigated the use of magnesium in heart failure patients. A recent analysis of 40 trials including over one million participants concluded that increasing dietary magnesium intake lowered risk of stroke, diabetes, heart failure, and mortality.¹⁹⁹

B-vitamins. Chronic therapy with diuretics, which are administered to many patients with heart failure, may prevent the reabsorption of thiamine and increase its urinary excretion, contributing to thiamine deficiency. A study in 25 patients with heart failure found that furosemide use at 80 mg or more per day was associated with a 98% prevalence of thiamine deficiency.³¹ Deficiencies of several vitamins, including riboflavin, pyridoxine, folic acid, and B12 have also been documented in heart failure patients. Riboflavin, B12, and folic acid play a role in homocysteine metabolism. Homocysteine is an amino acid that can cause damage to the inner lining of blood vessels (the endothelium), and elevated homocysteine levels have been associated with a poor prognosis in heart failure patients.^{200,201}

Exercise

Exercise training is a valuable addition to other heart failure interventions. Regular exercise that provokes mild-to-moderate shortness of breath is beneficial, and best undertaken in a structured, medically-supervised program.^{202,203} In clinically stable

patients able to participate, cardiac rehabilitation improves heart-related quality of life, functional capacity, endothelial function, and reduces hospitalizations and mortality.⁴⁷ Exercise training is considered suitable for most heart failure patients in NYHA class I–III.²⁰⁴

Published studies evaluating the efficacy of exercise training in heart failure patients report improvements in skeletal muscle oxygen utilization, diastolic function, symptoms and quality of life measures; increased exercise capacity, muscle strength and endurance; and reductions in inflammatory cytokines (eg, TNF- α and IL-6), NYHA functional class, hospital stays and mortality.²⁰⁵

In addition to formal structured exercise programs that may include aerobic and resistance exercise components, lifestyle approaches that emphasize activities such as brisk walking, taking stairs, gardening, and house work are also considered valuable.²⁰⁴

Regular physical activity can also help maintain a healthy weight, which in turn promotes optimal cardiovascular health.

Maintain Healthy Blood Sugar Levels

Diabetes and insulin resistance are major risk factors for heart failure. Diabetes not only increases risk of heart failure, but also worsens the outcome of patients with existing heart failure.³ The diabetic heart is more susceptible to ischemic (low oxygen) injury, myocardial infarction, and oxidative damage.²⁰⁶ Strategies for maintaining blood sugar control are reviewed in Life Extension's **Diabetes and Glucose Control** protocol.

For those with diabetes and heart failure, the choice of diabetes medication may be complex. *Metformin* is often the first-line drug of choice for managing blood sugar in diabetics without overt heart disease. It was historically contraindicated in

patients with heart failure due to concerns over increased risk of lactic acidosis. However, accumulating evidence suggests the risk of lactic acidosis may not be as pronounced as once thought. In fact, studies suggest metformin may reduce heart failure risk in diabetic patients and improve two-year survival rates in those with heart failure.^{207,208} Metformin is now commonly prescribed to diabetics with heart failure.²⁰⁹

Emerging evidence increasingly favors another class of diabetes medication, SGLT-2 inhibitors, in the management of diabetes in people with heart failure.^{209,210} (Refer to the Novel and Emerging Therapies section for more information).

Reduce Stress

Reducing stress levels may also promote optimal heart health. Anxiety is a serious mood disorder that affects many heart failure patients. Feeling anxious can make the heart beat faster, which in turn increases breathing rates and blood pressure levels. This can exacerbate heart failure, as the heart is already struggling to meet the body's demand for oxygen-rich blood. In addition, stress may affect lifestyle behaviors that influence heart disease, such as alcohol consumption, overeating, smoking, and physical inactivity.²¹¹

In one review of six prospective cohort studies, there was a significant association between hospitalization and anxiety.²¹² Further research is needed to determine if anxiety can help predict a cardiac event or hospitalization in those with chronic heart failure. Research on meditation (focused mental practices that improve concentration and mindfulness) suggests a benefit on cardiovascular risk, especially in addition to traditional treatments.²¹³ However, randomized trials with large cohorts are needed to clarify the role this method of stress reduction plays in cardiac health.

10 Nutrients

Coenzyme Q10

Coenzyme Q10 (CoQ10) has a central role in maintaining proper cardiac function and producing cellular energy in the mitochondria. It is also a potent antioxidant that helps maintain healthy blood sugar levels, preserve cognitive function, and support optimal heart health. CoQ10 is concentrated in healthy heart muscle, and CoQ10 deficiency is associated with heart failure.^{214,215} In one randomized controlled study, patients with moderate-to-severe heart failure who received 100 mg CoQ10 three times daily in addition to standard treatment showed improved symptoms and reduced risk of major cardiovascular events.¹¹

In another trial that assessed circulating levels of CoQ10 in 257 cardiac patients, those with in-hospital mortalities had significantly lower levels of CoQ10.²¹⁶ In a recent analysis of 14 randomized controlled trials, which included over 2,000 patients with heart failure, supplementation with CoQ10 resulted in a 31% lower mortality rate and an increased exercise capacity as compared with placebo.²¹⁷

An examination of seven systematic reviews suggests CoQ10 supplementation is beneficial for heart failure patients,²¹⁸ while another systematic review of 28 trials found CoQ10 enhanced exercise capacity, improved symptoms, and lowered blood pressure levels in heart failure patients.²¹⁹ Other research indicates heart failure patients with lower CoQ10 levels have up to a two-fold risk of dying as compared to those with higher CoQ10 levels.²²⁰

As shown in several studies conducted by Life Extension Scientific Advisory Board Member Peter H. Langsjoen, MD, FACC, CoQ10 supplementation is especially important for individuals on cholesterol-lowering statin therapy (HMG CoA reductase inhibitors). Statin medications block the biosynthesis of both cholesterol and CoQ10, and they worsen heart muscle dysfunction in heart failure patients.¹²⁻¹⁵

In one study, diastolic dysfunction (heart muscle weakness) occurred in 70% of previously normal patients treated with 20 mg per day of Lipitor for six months. This heart muscle dysfunction was reversible with 100 mg of CoQ10 three times daily.¹⁵

Three comprehensive reviews have investigated 19 different clinical trials on the use of CoQ10 in heart failure.²²¹⁻²²³ The results of 13 randomized controlled trials, encompassing 395 participants, revealed that CoQ10 supplementation led to a statistically significant average net increase of 3.7% in ejection fraction. For individuals with heart failure, Life Extension suggests an optimal CoQ10 blood level of 4 µg/mL.

Pycnogenol in combination with CoQ10 (PycnoQ10) may improve exercise capacity, ejection fraction, and edema in heart failure patients. In a single-blind, 12-week observational study of patients with NYHA class II or III heart failure, PycnoQ10 was well tolerated and improved systolic and diastolic function as well as heart and respiratory rate. Further research is warranted.²²⁴

Research Validates CoQ10's Benefits

An intriguing study published in *The European Journal of Heart Failure* showed that CoQ10 supplementation significantly improves survival for even the most severe heart failure patients, while dramatically reducing incidence of hospitalization. This intriguing study, known as the *Q-SYMBIO* trial, shows CoQ10 supplementation can restore deficient CoQ10 levels in patients with moderate-to-severe heart failure, extending lifespan and improving quality of life.¹¹

The data obtained by the Q-SYMBIO investigators revealed that heart failure patients who took 100 mg of CoQ10 three times daily were significantly less likely to:

- die from heart failure;
- die from any cause; and
- have a major adverse cardiac event during the study period compared with control subjects.¹¹

After only three months of supplementation, the researchers detected reduced levels of NT-proBNP, a marker of heart failure released from over-worked heart muscle cells.^{11,225} At two years, significantly more treated patients had improved their heart failure classification than placebo recipients.¹¹

The study's main endpoint (ie, a major adverse cardiac event [defined as unplanned hospitalization for worsening heart failure, death from a cardiovascular cause, urgent heart transplantation, or artificial mechanical heart support]) was reached by only 15% in the treatment group versus 26% in the placebo group.¹¹

Hawthorn

Hawthorn (*Crataegus* spp.) is a traditional cardiovascular tonic of plant origin that has been in use since the Middle Ages. Hawthorn extracts contain dozens of biologically active molecules, including flavonoids and polyphenols. The hawthorn-derived phytochemicals most thoroughly studied in humans are oligomeric procyanidins (OPCs). A typical hawthorn dose provides between 30 and 340 mg a day of procyanidins.²²⁶⁻²²⁸

Hawthorn extracts are believed to lower blood pressure by dilating coronary and peripheral blood vessels, inhibiting ACE, anti-oxidative and anti-inflammatory effects, and mild diuretic activity.^{229,230} Hawthorn's efficacy in the treatment of heart failure has been demonstrated in over 4,000 patients, with significant reductions in subjective discomfort ratings, improved left ventricular ejection fraction, and

increased cardiac efficiency.²³¹ A recent meta-analysis of randomized clinical trials including over 600 subjects concluded that Hawthorn extract improves parameters such as maximal workload, left ventricle ejection fraction, and rate pressure product (a measure of the stress put on the cardiac muscle).²³²

The SPICE trial was a large, randomized controlled study of 2,681 NYHA class II or III patients with a left ventricular ejection fraction $\leq 35\%$. A 900 mg/day dose of a standardized extract from hawthorn leaves and flowers (providing 169 mg OPCs) significantly reduced cardiac mortality, and sudden cardiac death was significantly reduced for the subgroup of patients with a left ventricular ejection fraction $\geq 25\%$.^{233,234} In the HERB chronic heart failure trial, which was a placebo-controlled trial of 120 patients with NYHA class II or III heart failure, 900 mg/day standardized hawthorn extract improved left ventricular ejection fraction compared with the control group.²³⁵

Pyrroloquinoline quinone

Pyrroloquinoline quinone (PQQ), a cofactor for several energy-generating reactions in the mitochondria of the cell, may stimulate the production of new mitochondria (mitochondrial biogenesis) through interactions with mitochondrial regulatory genes.²³⁶ Impaired mitochondrial function has been implicated in heart failure development.²³⁷ In a controlled trial involving cell lines and animal models, formulations of nanocurcumin and PQQ helped modulate hypoxia-induced hypertrophy (enlargement) of human heart cells.²³⁸

In animal models of ischemic injury (depriving the heart muscle of oxygen), treatment or pretreatment with PQQ reduced the extent of ischemic damage and degree of lipid peroxidation. In addition, PQQ improved ventricular function and reduced arrhythmias (irregular heartbeats).^{239,240}

Omega-3 Fats

Omega-3 fatty acids from fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to reduce inflammation, oxidative stress, triglyceride levels, and thrombosis risk.^{381,382} A meta-analysis of eight studies involving nearly 317,000 individuals found that those who consumed the highest level of dietary omega-3 fats had a 16% lower risk of heart failure than those whose omega-3 consumption was lowest.³⁸³ An analysis of six studies, comprising over 17,000 participants with a median follow-up of 9.7 years, found that the highest blood levels of EPA and DHA, compared to the lowest, were associated with a 41% lower risk of heart failure.³⁸⁴

Omega-3 fatty acids may also improve the course of heart failure.³⁸³ A meta-analysis of 12 randomized placebo-controlled trials that included a total of 81,364 participants confirmed that omega-3 fish oil supplementation reduced recurrent heart failure-related hospitalizations.³⁸⁵ VITAL-HF (Vitamin D and Omega-3 Trial–Heart Failure), an analysis of study data examining fish oil supplementation and heart failure outcomes, found a significant reduction in recurrent hospitalizations for heart failure in those who received fish oil omega-3 supplementation compared with placebo.³⁸⁶ Another later analysis of the VITAL study data found that first hospitalizations for heart failure were reduced by more than 30% in people with type 2 diabetes. This protective effect was not observed in non-diabetics, and the protective benefit was greater in Black participants than in people of other racial backgrounds.³⁸⁷

A meta-analysis of findings from 12 randomized controlled trials with 2,162 participants found omega-3 fatty acid supplementation improved left ventricular ejection fraction in heart failure patients, with greater improvement in those with preserved ejection fraction ($\geq 50\%$). Daily dosages of 1,000–3,000 mg, and greater than 3,000 mg, yielded improvement in left ventricular ejection fraction, whereas doses of less than 1,000 mg did not. Longer duration of omega-3 supplementation

was associated with greater improvement.³⁸⁸ A meta-analysis of 13 randomized controlled trials found that as dosage of omega-3 fish oil increased, so did cardiovascular protection.³⁸⁹

Carnitine

L-carnitine is an amino acid that aids in transporting fatty acid into the mitochondria. In decompensated heart failure, L-carnitine metabolism is altered, and cardiac energy metabolism is compromised.²⁴⁸ Research indicates carnitine deficiency is associated with cardiomyopathy, and 1.5–6 grams of L-carnitine daily increased exercise capacity in addition to improving left ventricle ejection fraction and clinical outcomes.²¹⁴ A meta-analysis of 17 randomized controlled trials, including 1,624 patients, found supplementation with L-carnitine improved clinical systems in congestive heart failure patients, including overall cardiac efficiency, left ventricle ejection fraction, and cardiac output.²⁴⁹ A recent literature review concluded that L-carnitine helps transport fatty acids into the mitochondria, resulting in reduced oxidative stress and inflammation. Carnitine supplementation protects against ventricular dysfunction and cardiac arrhythmias, and may help reduce hypertension, diabetes mellitus, insulin resistance, and hyperlipidemia.²⁵⁰

Several studies evaluating the role of L-carnitine or its analog, propionyl-L-carnitine, in heart failure have shown statistically significant increases in exercise capacity, maximum exercise time, peak heart rate, and peak oxygen consumption.²⁵¹ A study that administered 30 mg/kg propionyl-L-carnitine supplementation to 30 heart failure patients demonstrated a reduced pulmonary artery pressure, improved exercise capacity, increased oxygen utilization, and reduced ventricular size.²⁵²

Improvements in ejection fraction (13.6% after 180 days) were observed in a 60-patient study of NYHA class II and III heart failure patients who received 1.5 grams propionyl-L-carnitine per day in addition to their conventional treatments (digitalis

and diuretics).²⁵³ Another trial, which enrolled 80 patients with NYHA class III or IV heart failure caused by dilated cardiomyopathy (heart disease in which the ventricles become enlarged and unable to adequately pump blood), demonstrated a significantly improved 3-year survival after supplementation with L-carnitine.²⁵⁴

Creatine

Creatine helps ensure the chemical energy supply to muscle tissue. Most research focusing on creatine has targeted its potential use in skeletal muscle metabolism, but a few studies have investigated its potential to improve heart muscle energetics in cardiovascular disease.²⁵⁵

A systematic review of creatine supplementation in patients with heart failure, ischemic heart disease, or acute myocardial infarction analyzed six randomized trials that collectively enrolled 1,226 patients with heart failure. Four of the trials demonstrated a significant reduction in dyspnea (breathing difficulty) in patients with heart failure receiving creatine, creatine phosphate, or phosphocreatinine.^{255,256}

In a randomized double-blind study, 100 subjects engaged in an 8-week exercise program, followed a prepared diet regimen, and received 5 grams/day of creatine monohydrate. The control group received only the diet and exercise intervention. At the end of the study, the treatment group demonstrated reduced inflammatory markers, including IL-6, and improved endothelial functioning.²⁵⁷

Taurine

Taurine, an amino acid found in the heart, may serve as a cardioprotective agent. In a double-blind, placebo-controlled, randomized study, 16 patients with heart failure received 500 mg of taurine three times daily for two weeks. Taurine supplementation enhanced physical function and improved cardiovascular functional capacity.²⁵⁸ In another randomized placebo-controlled trial, heart failure patients with an ejection fraction less than 50% were given 500 mg taurine three

times daily for two weeks. The subjects exercised before and after supplementation. Inflammatory and atherogenic (arterial plaque) markers were decreased in the treatment group, suggesting taurine is a cardioprotective agent.²⁵⁹

In a randomized placebo-controlled clinical trial that enrolled 29 NYHA class II or III heart failure patients with a left ventricular ejection fraction < 50% (average 29.27%), subjects received 500 mg taurine three times daily or placebo. After two weeks, exercise capacity increased significantly in the taurine group compared with placebo.²⁶⁰ Another study that compared taurine (3 grams/day) to low-dose CoQ10 (30 mg/day) supplementation in 17 patients with congestive heart failure (ejection fraction < 50%) revealed a significant improvement in ejection fraction in the taurine group after six weeks, as shown by echocardiography.²⁶¹

D-ribose

D-ribose, a naturally-occurring pentose sugar that is a key component in adenosine triphosphate (ATP), may aid in energy generation and functional recovery in patients with heart failure and ischemic heart disease. Multiple preclinical studies have demonstrated that supplementation with D-ribose following myocardial ischemia (when blood flow to the heart is blocked or reduced, and the heart muscle is deprived of oxygen) enhanced the regeneration of ATP.²⁶²

Research supports the use of D-ribose for optimal cardiovascular health. In a pilot study of 11 NYHA class II–IV patients, supplementation with 5 grams/dose D-ribose for six weeks led to some improvements in tissue Doppler velocity (a measure of the heart's velocity while beating) and the velocity ratio of diastolic filling to heart valve relaxation. Researchers conclude that D-ribose may be beneficial for patients in heart failure, but further research with larger cohort sizes is needed to substantiate these benefits.²⁶³

In another trial of 15 patients with NYHA class II or III heart failure and chronic coronary artery disease, the administration of D-ribose (5 grams, three times daily) improved cardiac functional parameters as assessed by echocardiography and quality of life scores.²⁶⁴ D-ribose supplementation improved respiratory parameters during exercise in 44% of patients in one study.²⁶⁵ Significant benefits of daily oral D-ribose in NYHA class II and III patients were reported in a double-blind, randomized, crossover trial. D-ribose supplementation significantly improved left atrial functional parameters, quality of life, and physical function activity scores in the treatment group.²⁶⁶

Arjuna (*Terminalia arjuna*)

The arjuna tree is native to India, where its bark has been used in Ayurvedic medicine for centuries due to the belief that it may have cardiogenic properties—that is, it may improve the efficiency and function of the heart muscle.³⁹⁶ Arjuna contains a wide variety of bioactive compounds such as triterpenoids, tannins, and flavonoids. These compounds and others in arjuna appear to offer beneficial effects that may be relevant to heart health, as demonstrated in preclinical studies, including decreasing lipid peroxidation and generation of free radicals, modulating inflammation, and protecting against fibrosis.³⁹⁷

The cardiogenic properties of arjuna have been demonstrated in healthy individuals. For instance, two randomized controlled trials in healthy people found that 400 mg daily of an arjuna extract called Oxyjun for eight weeks resulted in a 3.6–3.7% increase in left ventricular ejection fraction, representing a statistically significant improvement compared with placebo.^{394,395}

Some preliminary trials have observed that arjuna may provide small benefits for people with heart failure.^{398,399} However, as of early 2025, the totality of the evidence is mixed and inconclusive. For example, an arjuna extract was unable to increase

left ventricular ejection fraction in a study involving 100 people who had heart failure with left ventricular ejection fraction $\leq 40\%$. Participants were randomized to receive 750 mg arjuna extract or a placebo twice daily for 12 weeks. Results showed that the group receiving arjuna had no significant improvements in the primary outcome of left ventricular ejection fraction compared with placebo. Nevertheless, the arjuna group had a significant improvement in secondary outcomes compared with placebo: distance covered in the 6-minute walk test, symptom severity and stability, and oxidative stress biomarkers.⁴⁰⁰ More research is needed to determine whether arjuna can provide meaningful benefits for people with heart failure.

Vitamin D

A number of observational studies have suggested an association between low vitamin D levels and chronic heart failure,^{201,281} particularly among the elderly.²⁸² For example, in a study of 548 patients re-hospitalized with heart failure, 75% were vitamin D deficient (defined as < 20 ng/mL for this study), and for each 10 ng/mL decrease in vitamin D levels, the risk of all-cause mortality increased by 10%.²⁸³

The contribution of vitamin D deficiency to the pathology of heart failure as well as its protective effects for cardiovascular health are most likely exerted by several mechanisms, including effects on the hypertensive hormone angiotensin II, influence on vascular endothelial function, effects on systemic inflammation, and impact on the risk of cardiovascular mortality.^{201,281,284} Vitamin D may affect BNP and parathyroid hormone levels, as well as enhance heart contractility.²⁸⁵ A synthetic vitamin D analog (paricalcitol) decreased inflammation and cell death in mice following experimental heart attack, while transgenic mice that lacked the vitamin D receptor showed decreased survival following a heart attack.²⁸⁶

Intervention trials of vitamin D for heart failure have had mixed results. In a prospective study, 100 patients with heart failure (NYHA class I–III) received 50,000 IU vitamin D every week for eight weeks, followed by 50,000 IU every month for two months. At the end of the study, patients on supplemental vitamin D saw improvements in exercise capacity and reductions in NYHA heart failure scores.²⁸⁷ Another intervention showed that the administration of 2,000 IU vitamin D daily for nine months in 93 patients with heart failure had an anti-inflammatory effect.^{288,289}

In a recent randomized double-blind trial, 40 NYHA class II–III patients with vitamin D deficiency or insufficient vitamin D levels received either 10,000 IU vitamin D3 daily or a placebo for six months. Researchers found that in high doses, vitamin D3 replenished diminished vitamin stores, improved quality of life scores, and normalized BNP, parathyroid hormone, and C-reactive protein levels.²⁸⁵ More research is warranted to determine if these results occur at lower dosages.

Intervention trials using vitamin D have demonstrated modest results for lowering blood pressure. A review of 11 randomized controlled trials, including 716 subjects, found a small reduction in systolic (3.6 mmHg) and diastolic (3.1 mmHg) blood pressure at doses of 800–2,900 IU vitamin D daily in individuals with high blood pressure.²⁹⁰ In another analysis of randomized controlled studies, the effect of vitamin D replacement on heart failure was mixed. It reduced the risk of mortality in one study, but did not affect heart function, exercise capacity, or quality of life in two others.²⁰¹

Resveratrol

Resveratrol, a polyphenol found in grapes, nuts, and red wine, has potent antioxidant activity. A randomized controlled study in which rats with induced post-infarction heart failure were given 15 mg/kg body weight per day of resveratrol showed that resveratrol supplementation decreased the severity of heart failure,

improved left ventricular function, decreased collagen deposits in the myocardium, lowered oxidative stress, and attenuated inflammatory signaling pathways.²⁹¹ A recent literature review of clinical data found that resveratrol reduces inflammation, promotes endothelial function, supports healthy blood pressure levels, and helps reduce biomarkers of cardiovascular disease.²⁹²

Resveratrol may play a role in myocardial ischemia, myocarditis, cardiac hypertrophy, and heart failure. Possible mechanism of action include reducing oxidative stress and inflammation, improving calcium handling, decreasing apoptosis, and modifying inflammatory pathways.²⁹¹ Further research is warranted to fully understand resveratrol's role in heart health.

Selenium

Selenium is a cofactor necessary for a number of cellular metabolic processes. In an animal model of hypertension leading to heart failure, a selenium-free diet was associated with high mortality (70%); however, supplementation with 50 or 100 mcg/kg resulted in survival rates of 78% and 100%, respectively.²⁹³ In humans, severe selenium deficiency has been firmly linked to a reversible form of heart failure. Known as Keshan disease, the condition is potentially fatal if untreated.^{294,295} Several studies also suggest less severe selenium deficiency may be associated with heart failure.²⁹⁴

In a recent randomized, double-blind, placebo-controlled trial involving 53 patients with congestive heart failure, 200 µg selenium per day for 12 weeks reduced serum insulin levels, decreased LDL cholesterol levels, increased HDL cholesterol levels, reduced C-reactive protein levels, and elevated the plasma antioxidant capacity.²⁹⁶

Magnesium

Magnesium is a mineral found in the body that is a cofactor in over 600 enzymatic reactions,⁴¹⁵ including protein synthesis and blood pressure and blood glucose

regulation. It is also required for energy production and bone development, and plays a role in muscle contraction, nerve impulses, and maintaining a normal heart rhythm. Magnesium deficiency is common in people with congestive heart failure, and is believed to worsen clinical outcomes in this population.²⁹⁷ Recent research suggested risk factors for cardiovascular disease, including cholesterol and blood pressure levels, are associated with low serum levels and dietary intake of magnesium.²⁹⁸

A recent literature review focusing on epidemiological research suggests high magnesium intake is associated with lower risk of cardiovascular risk factors and cardiovascular disease, including coronary heart disease and stroke. A recent meta-analysis demonstrated a strong association between heart failure and increment of 100 mg/day of magnesium intake.²⁹⁹ Further randomized controlled clinical trials will help elucidate magnesium's role in heart health.

In another trial, 300 mg magnesium citrate was found to improve heart rate variability (ie, the time variation between heartbeats) after five weeks of supplementation.³⁰⁰ Magnesium oxide, at a dose of 800 mg daily for three months, improved arterial elasticity compared with placebo in individuals with chronic heart failure.³⁰¹ In another study, magnesium orotate (6,000 mg daily for one month, 3,000 mg daily for 11 months) or placebo was given to patients with severe congestive heart failure. The survival rate after one year of supplementation was 76% for the magnesium group vs. 52% for the placebo group. The authors concluded *"Magnesium orotate may be used as adjuvant therapy in patients on optimal treatment for severe congestive heart failure, increasing survival rate and improving clinical symptoms and patient's quality of life."*³⁰²

L-carnosine

L-carnosine is a dipeptide (two amino acids linked together) made in the body from the amino acids L-histidine and beta-alanine. It is abundant in skeletal muscles and the brain. Meat and fish are the main dietary sources of L-carnosine as well as beta-alanine. Preclinical evidence shows that L-carnosine may provide benefit to the heart muscles through several mechanisms, including support for calcium homeostasis, defense against oxidative stress, and detoxification of reactive molecules such as advanced glycation end products and oxidized lipids.³⁹⁰ L-carnosine precursor supplementation (ie, L-histidine and beta-alanine) combined with exercise training has shown benefits in animal models of heart failure.^{391,392}

A randomized controlled clinical trial included 50 people who had stable congestive heart failure with severe left-ventricular systolic dysfunction and were receiving standard medical treatment. The participants were randomized to either continue with the standard treatment or receive 500 mg L-carnosine per day in addition to standard treatment. The results showed that, compared to baseline, those who received L-carnosine had significant improvements in six-minute walk time and subjective rated quality of life at six months. The L-carnosine group also experienced significant improvements in exercise capacity and aerobic fitness compared to the group that continued with only standard treatment.³⁹³

Update History



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