

HEART FAILURE

DISEASE FACT SHEET AND OPPORTUNITY FOR *OMECAMTIV MECARBIL*

What is heart failure

Heart failure is a chronic, progressive condition that develops when the pumping action of the heart is inadequate to meet the body's needs. Heart failure arises from the heart's inability to deliver sufficient oxygen-rich blood to fulfill the body's requirements. The leading causes of heart failure are diseases that lead to damage of the heart muscle function, including coronary artery disease and high blood pressure.

An understanding of proper heart function is helpful to inform the consequences when the pumping function may be compromised. The heart is actually comprised of two pumps combined together. The right side of the heart pumps blood from the veins into the lungs. The left side of the heart pumps blood from the lungs out through the arteries to the rest of the body. Blood is pumped out of the heart when the heart muscle contracts (called systole) and blood enters the heart when the heart muscle relaxes (called diastole).

Systolic heart failure occurs when the contractile function of the heart muscle is compromised and becomes limited. As a consequence, blood may back up into the lungs (termed left-sided heart failure) and fluid may build up in the feet, ankles, legs, liver, abdomen, and the veins in the neck (termed right-sided heart failure). Both left and right-sided heart failure may occur together and can lead to shortness of breath and fatigue¹.

What are the symptoms of heart failure?

The most common signs and symptoms of heart failure are²:

- Shortness of breath or trouble breathing
- Swelling in the ankles, feet, legs, abdomen, and neck
- Persistent coughing or wheezing
- Confusion or impaired thinking
- Fatigue (tiredness)
- Increased heart rate
- Lack of appetite or nausea

All of these symptoms are the result of a build-up of fluid in the body or the poor delivery of blood to the tissues. Sometimes the only symptoms that are evident with patients is that they may feel tired or have shortness of breath after routine physical effort, such as climbing stairs. As the heart muscle grows weaker, symptoms may increase in their severity and frequency. In severe cases, patients may have shortness of breath even while lying flat. The build-up of fluid associated with worsening heart failure can also cause weight gain, frequent urination, and a cough that is aggravated at night and when lying down¹.

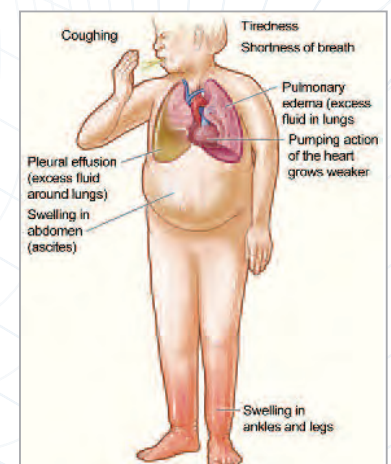
How common is heart failure?

Approximately 5.7 million people in the United States have heart failure¹, resulting in nearly one million hospitalizations³ and approximately 300,000 deaths each year¹. For people over 65 years of age, the incidence of heart failure approaches 10 per 1000 and approximately 50% of people diagnosed with heart failure will die within 5 years⁴.

Heart failure is more common in¹:

- People who are 65 years old or older. Heart failure is the most common reason for hospital admittance among Medicare patients.
- African Americans. African Americans are more likely than people of other races to have heart failure and are likely to have symptoms at a younger age, have more hospital visits due to heart failure, and eventually die from heart failure.
- People who are overweight. Being overweight increases your risk of heart disease and type 2 diabetes. These diseases can lead to heart failure.

Additionally, men have been shown to have a higher rate of heart failure than women.



How is heart failure diagnosed?

No single test can diagnose heart failure, so if a patient is showing symptoms of heart failure, a doctor may recommend one or more of the following tests and refer the patient to a cardiologist²:

- Physical examination
- Blood Tests
- Chest X-ray
- Electrocardiogram (abbreviated as EKG or ECG)
- Echocardiography
- Exercise Stress Test
- Radionuclide Ventriculography or Multiple-Gated Acquisition Scanning (abbreviated as MUGA)
- Coronary Angiography (also called Coronary Arteriography)

In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life⁵.

NYHA Classification	
Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

How does heart failure progress?

Initially, the heart compensates by:

- Enlarging. When the heart chamber enlarges, it can contract less vigorously and still pump the same amount of blood.
- Developing more muscle mass. The increase in muscle mass occurs because the contracting cells of the heart get bigger to allow the heart chamber to enlarge.
- Increasing heart rate. The pump works more often to help increase the heart's output.

Additionally, the body also tries to compensate in other ways:

- The blood vessels narrow to keep blood pressure up, trying to make up for the heart's loss of power.
- The body diverts blood away from less important tissues and organs to maintain flow to the most vital organs, the heart and brain.

These temporary measures may mask the problem of heart failure, but they do not solve it as heart failure often worsens until these substitute processes no longer work. Eventually, the heart and the body's compensation mechanisms cannot address the diminished contractile function of the heart muscle and, as a result, the patient may experience the fatigue, breathing problems or other symptoms that usually prompt medical consultation. The body's compensation mechanisms help explain why some people may not become aware of their condition until years after their heart muscle begins its decline².

How is heart failure treated?

The goals for all stages of heart failure treatment include:

- Treating the underlying cause, such as coronary heart disease or high blood pressure
- Reducing symptoms
- Stopping the heart failure from getting worse
- Increasing lifespan and improving quality of life

Currently, there is no cure to halt or reverse the progression of heart failure. However, treatments usually include lifestyle changes, medicines, and ongoing care. If the heart failure is at a severe stage, medical procedures or surgery may be necessary. Researchers continue to study new ways to treat heart failure and its complications.

Heart failure patients oftentimes require multiple medications to treat their symptoms. Each medication is aimed at treating a different symptom or contributing factor. The following medicines are commonly used to treat heart failure¹:

- Diuretics (water or fluid pills)
- ACE inhibitors
- Aldosterone antagonists
- Angiotensin receptor blockers
- Beta blockers
- Isosorbide dinitrate/hydralazine hydrochloride
- Digoxin

Despite currently available therapies, readmission rates for heart failure patients remain high. It is estimated that between 13% and 33% of patients initially admitted to the hospital for chronic heart failure will be readmitted within 12 to 15 months of the initial admission⁶. Mortality rates over the five-year period following a diagnosis of heart failure are approximately 60% in men and 45% in women⁴. The high morbidity and mortality in the setting of current therapies points to the need for novel therapeutics that offer further reductions in morbidity and mortality.

The annual cost of heart failure to the U.S. health care system is estimated to be \$39 billion. A portion of that cost is attributable to drugs used to treat each of chronic and acute heart failure. Approximately 70% of those costs are due to hospitalization, home health and physician care. New drug therapies that could reduce the number of hospitalizations could decrease the cost to the health care system.

What R&D is Cytokinetics conducting to address heart failure?

Omecamtiv mecarbil is a novel, small-molecule, direct activator of cardiac myosin, the motor protein that causes cardiac contraction. It is being evaluated as a potential treatment of heart failure in both intravenous and oral formulations with the goal of establishing a new continuum of care for patients in both the in-hospital and outpatient settings.

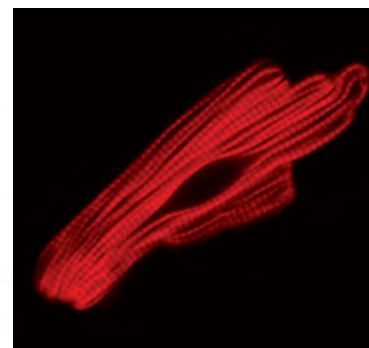
Omecamtiv mecarbil is now in a broad clinical trials program designed to evaluate the novel drug candidate in a variety of patients with heart failure. Data from the Phase IIB trial evaluating *omecmtiv mecarbil* as an intravenous formulation known as ATOMIC-AHF (**A** Trial of **O**meamtiv **M**ecarbil to **I**ncrease **C**ontractility in **A**cute **H**eart **F**ailure) were reported in 2013. This clinical trial was an international, multicenter, randomized, double-blind, placebo-controlled study in approximately 600 patients, enrolled in 3 sequential, ascending-dose cohorts. In each cohort, patients were randomized to receive *omecmtiv mecarbil* or placebo.

Oral formulations of *omecmtiv mecarbil* are currently being evaluated in a Phase II trial known as COSMIC-HF (**C**hronic **O**ral **S**tudy of **M**yosin **A**ctivation to **I**ncrease **C**ontractility in **H**eart **F**ailure). COSMIC-HF is designed to evaluate the safety and efficacy of a novel cardiac muscle myosin activator, *omecmtiv mecarbil*, in approximately 450 patients with heart failure and left ventricular systolic dysfunction. COSMIC-HF is a double-blind, randomized, placebo-controlled, multicenter, dose escalation study designed to select and evaluate an oral modified-release formulation of *omecmtiv mecarbil* in patients with heart failure and left ventricular systolic dysfunction.

Both ATOMIC-AHF and COSMIC-HF are being conducted by Amgen in collaboration with Cytokinetics. For more information regarding the ongoing and completed clinical trials, please visit www.clinicaltrials.gov

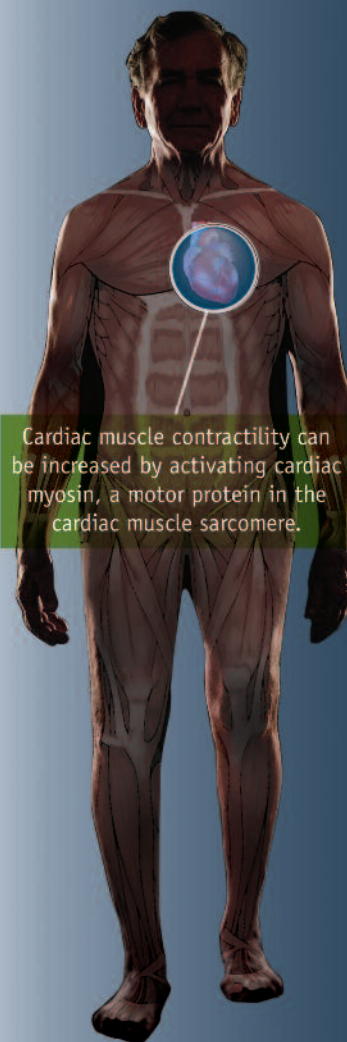
References

1. National Heart, Lung and Blood Institute. (2010). (Retrieved from http://www.nhlbi.nih.gov/health/dci/Diseases/Hf/HF_WhatIs.html)
2. American Heart Association. (2010). Retrieved from http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/About-Heart-Failure_UCM_002044_Article.jsp)
3. US Department of Health and Human Services, National Hospital Discharge Survey: 2007 Summary, P. 8 (Retrieved from <http://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf>)
4. Journal of the American Heart Association, Circulation: Heart Disease and Stroke Statistics 2011 Update. (Retrieved from <http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3182009701>)
5. (Source: HFSA Retrieved from http://www.outhf.org/questions_stages.htm)
6. Bhatia RS, 2006; Pawanant S, 2007



About Us

Cytokinetics is a clinical-stage biopharmaceutical company focused on the discovery and development of novel small molecule therapeutics that modulate muscle function for the potential treatment of serious diseases and medical conditions. Cytokinetics is developing *tirasemtiv*, a fast skeletal muscle activator, as a potential treatment for amyotrophic lateral sclerosis (ALS). *Tirasemtiv* has been granted orphan drug designation and fast track status by the U.S. Food and Drug Administration and orphan medicinal product designation by the European Medicines Agency for the potential treatment of ALS. Cytokinetics is collaborating with Amgen Inc. to develop *omecamtiv mecarbil*, a cardiac muscle activator, for the potential treatment of heart failure. Cytokinetics is collaborating with Astellas Pharma Inc. to develop CK-2127107, a skeletal muscle activator, for spinal muscular atrophy. Amgen holds an exclusive license worldwide to develop and commercialize *omecamtiv mecarbil* and Astellas holds an exclusive license worldwide to develop and commercialize CK-2127107. Both licenses are subject to Cytokinetics' specified development and commercialization participation rights. All of these drug candidates have arisen from Cytokinetics' muscle biology focused research activities and are directed towards the cytoskeleton. The cytoskeleton is a complex biological infrastructure that plays a fundamental role within every human cell. Additional information about Cytokinetics can be obtained at <http://www.cytokinetics.com/>.



Cardiac muscle contractility can be increased by activating cardiac myosin, a motor protein in the cardiac muscle sarcomere.



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