Cytokinetics

ABOUT

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 for blood and oxygen. The leading causes of heart failure are diseases that damage the heart muscle function, including coronary heart disease and high blood pressure.

The normal, healthy heart is a muscular organ that pumps blood continuously throughout the body. The right side of the heart pumps oxygen-depleted blood from the veins into the lungs. The left side of the heart pumps oxygen-rich blood from the lungs out through the arteries to the rest of the body. When the heart muscle contracts (called systole) blood is pumped out of the heart, and when the heart muscle relaxes (called diastole) blood enters the heart.

Heart failure can affect the right side of the heart only, or both sides of the heart. Right-side heart failure occurs when the heart can't pump enough blood to the lungs, resulting in fluid buildup in the feet, ankles, legs, liver, abdomen, and the veins in the neck. Left-side heart failure occurs when the heart can't pump enough oxygen-rich blood to the rest of the body, and as a consequence, blood may back up into the lungs. Both left and right-sided heart failure may occur together and can lead to shortness of breath and fatigue.[1]

PREVALENCE OF HEART FAILURE

Almost 6 million people in the United States have heart failure[1], resulting in nearly one million hospitalizations[2] and almost 300,000 deaths each year[1]. For people over 65, the incidence of heart failure approaches 10 per 1000.[3] The annual cost of heart failure to the U.S. health care system is estimated to be $32 billion, which includes the cost of health care services, medications to treat heart failure and missed days of work.[4]

Heart failure is more common in:[1]

- **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 more 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, which can lead to heart failure.
- **People who have had a heart attack.** Heart attacks can cause damage that weakens the heart.
- **Males.** Men have been shown to have a higher rate of heart failure than women.

SYMPTOMS OF HEART FAILURE

The most common signs and symptoms of heart failure are shortness of breath, leg swelling, fatigue, persistent cough or wheezing, confusion or impaired thinking, increased heart rate and lack of appetite or nausea.[5]

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. As the heart muscle grows weaker, symptoms may get worse. 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 down[1].

DIAGNOSING HEART FAILURE

Heart failure is diagnosed based on medical and family histories, a physical examination and test results. No single test can diagnose heart failure, so a physician may recommend one or more of the following tests and refer the patient to a cardiologist: exercise stress test, blood tests, chest X-ray, electrocardiogram (EKG) coronary angiography, echocardiography or radionuclide ventriculography or multiple-gated acquisition scanning (MUGA).[5]

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 Classifications. This system relates symptoms to everyday activities and the patient's quality of life.[5]

NYHA FUNCTIONAL CLASSIFICATION	
CLASS	**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.

PROGRESSION OF HEART FAILURE

Initially, the heart compensates by:

- **Enlarging.** When the heart 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.

These temporary measures initially mask the problem. However, heart failure often worsens until these compensation mechanisms cannot address the diminished contractile function of the heart, and the patient may experience symptoms that prompt medical consultation. This explains why some people may not be aware of their condition until years after the heart muscle begins its decline.[5]

TREATING HEART FAILURE

The goals for heart failure treatment include treating the underlying cause, reducing symptoms, preventing the heart failure from worsening and improving quality of life.[1]

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. Heart failure patients often require multiple medications to treat different symptoms or contributing factors. Common medications to treat heart failure are diuretics, beta blockers, ACE inhibitors, aldosterone antagonists, digoxin, angiotensin receptor blockers and isosorbide dinitrate/hydralazine hydrochloride.[1]

Despite currently available therapies, readmission rates for heart failure patients remain high. It is estimated that approximately 25% of patients admitted to the hospital for heart failure will be readmitted within 30 days.[6] Mortality rates over the five-year period following a diagnosis of heart failure are approximately 60% in men and 40% in women.[3] 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.

ABOUT *OMECAMTIV MECARBIL*

In collaboration with Amgen, Cytokinetics is developing *omecamtiv mecarbil*, a novel cardiac muscle activator. It is an investigational drug candidate designed to increase the duration of cardiac muscle contractility and improve cardiac muscle performance, potentially helping patients preserve cardiac function and quality of life, avoid hospitalizations, and decrease the risk of mortality due to heart failure.

Omecamtiv mecarbil has been studied across nine Phase 1 clinical trials, which enrolled over 200 healthy volunteers. In addition, more than 1,300 people with heart failure have been enrolled in four Phase 2 clinical trials, including COSMIC-HF. COSMIC-HF was a Phase 2 double-blind, randomized, placebo-controlled, multicenter, dose escalation study, designed to evaluate the pharmacokinetics and tolerability of orally-administered *omecamtiv mecarbil* in approximately 450 patients. The trial met its primary pharmacokinetic objective and demonstrated statistically significant improvements in all pre-specified secondary measures of cardiac function in the treatment group employing pharmacokinetic-based dose titration. Adverse events (AEs), including serious AEs, in patients on *omecamtiv mecarbil* were comparable to placebo. It is currently the subject of GALACTIC-HF, a Phase 3 trial investigating the effects of *omecamtiv mecarbil* versus placebo on cardiovascular outcomes in 8,000 patients, which is being conducted by Amgen in collaboration with Cytokinetics.

Cytokinetics

Cytokinetics, Inc.
280 East Grand Avenue
South San Francisco, CA 94080
650 624 3000
cytokinetics.com

References

1. National Heart, Lung and Blood Institute. What is Heart Failure?. Available at: http://www.nhlbi.nih.gov/health/dci/Diseases/Hf/HF_WhatIs.html. Last revised: November 6, 2015. Accessed March 5, 2016.
2. Hall, MJ, et al. National hospital discharge survey: 2007 summary. *Natl Health Stat Report.* 2011; 29(29), 1-20.
3. Roger, VL, et al. Heart disease and stroke statistics—2011 update a report from the American Heart Association. *Circulation.* 2011; 123(4), e18-e209.
4. Centers for Disease Control and Prevention. Heart Failure Fact Sheet. Available at: http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_failure.htm. Last revised November 30, 2015. Accessed March 5, 2016.
5. American Heart Association. About Heart Failure. Available at: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/About-Heart-Failure_UCM_002044_Article.jsp.Last revised April 6, 2015. Accessed March 5, 2016.
6. Krumholz, HM, et al. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. *Circulation: Cardiovascular Quality and Outcomes.* 2009; 2(5), 407-413.