

# Advances in Heart Failure

## Minnesota's Role in the NHLBI's Heart Failure Network

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### ABSTRACT

Heart failure is a condition that affects nearly 5 million people in the United States and costs the nation an estimated \$35 billion a year. Although common, the condition presents treating clinicians with real challenges. There currently are few effective therapies for people with acute decompensated disease. As part of the National Heart Lung and Blood Institute-funded Heart Failure Network, Minnesota researchers are attempting to change this. This article describes the work of the Heart Failure Network and several Minnesota-designed protocols that are being tested, including one that's looking at 2 different treatment strategies for patients hospitalized with acute decompensated heart failure who go on to develop poor renal function and another that will evaluate the use of sildenafil (Viagra) for patients with heart failure and preserved left ventricular systolic function.

Heart failure is a chronic condition characterized by fatigue, shortness of breath, and fluid retention. Those symptoms are the result of abnormal myocardial function during the cardiac cycle. Roughly 50% of all patients with heart failure have impaired contractile function. This decrease in the heart muscle's ability to effectively pump blood is often referred to as systolic heart failure. The remaining 50% of patients suffer from heart failure with preserved systolic function, sometimes referred to as diastolic heart failure, in which normal filling of the ventricle is impaired during diastole. The clinical course of heart failure is punctuated by periods of acute worsening, which can be severe enough to require hospitalization or cause death. When properly treated, patients can recover; but they often do not achieve the functional status they had at baseline.

Heart failure affects nearly 5 million people in the United States and is more common in older individuals—1 in 10 people age 65 and older has heart failure. Episodes of acute worsening of symptoms are so common that decompensated heart failure is the most common reason patients age 65 and older are admitted to the hospital. In the United States alone, more than 1 million

patients are hospitalized each year as a result of the condition.<sup>1</sup> Largely because of the cost of these hospitalizations, the current annual economic impact of heart failure in this country is estimated at more than \$35 billion.<sup>1</sup>

Hypertension, diabetes, tobacco use, and obesity are associated with an increased risk of heart failure. Like the rest of the United States, Minnesota is experiencing an epidemic of obesity and diabetes. According to Centers for Disease Control and Prevention data, approximately 25% to 30% of Minnesotans are obese, 21% smoke, 20% have hypertension, and 3% to 4% have diabetes.<sup>2</sup> Those percentages are likely to increase over time. The increasing prevalence of these contributing conditions in addition to the aging population make it inevitable that the number of patients afflicted with heart failure will continue to increase.

### Management of Heart Failure

There are a number of effective treatments for chronic heart failure. Neurohormonal antagonists such as ACE inhibitors, beta-blockers, and aldosterone receptor antagonists improve quality of life and survival rates. In addition, the combination of hydralazine and isosorbide dinitrate increases survival among African-Americans with heart failure. Digoxin alleviates many of the symptoms associated with the disease, and devices such as cardiac defibrillators and biventricular pacemakers can improve quality of life and outcomes in carefully selected patients.

Few interventions have been shown to be effective in the management of acute decompensated heart failure, however. Inotropes such as milrinone, dopamine, dobutamine, and levosimendan have uniformly failed to improve outcomes in hospitalized patients. In fact, some of these drugs have been associated with increased mortality. Nitrates such as nitroglycerin and nitroprusside have favorable hemodynamic effects but have not been tested in randomized controlled trials to assess their impact on long-term outcomes. Other vasodilators such as nesiritide result in short-term hemodynamic and symptomatic improvements but so far have not been shown to favorably affect long-term outcomes. Novel vasodilators such as endothelin receptor antagonists are

ineffective, and hemodynamically tailored therapy using invasive pulmonary artery catheters does not improve outcomes.

It is possible that vasodilators, inotropes, and hemodynamic monitoring have failed to improve outcomes because they do not specifically address the primary problem of congestion. The vast majority of patients hospitalized with heart failure have symptoms related to fluid retention. Loop diuretics have been used for more than 40 years to address these symptoms. However, they have not been studied carefully in well-controlled clinical trials. Although these agents are used in 90% of patients hospitalized with heart failure and are effective in reducing volume overload, as many as 50% of patients are discharged from the hospital without any significant fluid removal.<sup>3</sup> Moreover, loop diuretics are associated with electrolyte depletion, sympathetic nervous system activation, and reduced renal function. These agents could directly contribute to adverse clinical outcomes in a number of patients with acute decompensated heart failure.<sup>4,5</sup> For those reasons, novel drugs such as vasopressin antagonists have been developed to remove fluid through alternative mechanisms. Unlike traditional diuretics, which increase urine output and sodium excretion, vasopressin antagonists stimulate the kidney to produce free water without an increase in sodium loss. Early trials comparing the use of traditional diuretics with a combination of diuretics plus vasopressin antagonists have shown that the addition of vasopressin antagonists can increase fluid removal early in the course of therapy.<sup>6,7</sup> However, a large randomized clinical trial investigating the use of a vasopressin antagonist for acute decompensated heart failure was unable to show any evidence of improved long-term outcomes despite small, transient improvements in volume reduction in symptoms.<sup>8</sup>

Ultrafiltration is another approach that is showing promise for the management of patients with acute decompensated heart failure and congestion. Ultrafiltration mechanically removes fluid directly from the blood vessels using intravenous catheters and a small machine that sits near the patient. Blood is removed through an IV and pumped across a semipermeable membrane that removes fluid and solutes before returning blood products to the patient. This mechanical removal of fluid has several advantages over traditional loop diuretics: It allows the physician to precisely control the rate of fluid removal. In addition, ultrafiltration does not deplete important electrolytes such as magnesium and potassium, nor does it stimulate the sympathetic nervous system, thereby preserving normal renal blood flow and physiology.

The use of ultrafiltration in patients with acute decompensated heart failure was first studied by investigators in Minnesota. This group of Twin Cities investigators showed that ultrafiltration was safe and more effective than diuretics for removing fluid.<sup>9</sup> The results of this study led to a larger one comparing ultrafiltration with use of traditional diuretics in patients hospitalized with decompensated heart failure. The second study not only confirmed the safety and effectiveness of ultrafiltration, it also showed that the use of ultrafiltration was associated with improved outcomes during 90-day follow-up in this patient population.<sup>10</sup> Ultrafiltra-

tion is the only intervention associated with improved outcomes in the acute treatment of patients with decompensated heart failure.

### Heart Failure Research in Minnesota

Minnesota has long been associated with research on the treatment of heart failure. University of Minnesota researcher Jay Cohn, M.D., was the principal investigator for the first clinical trial to demonstrate improved outcomes in patients with chronic heart failure using a combination of hydralazine and isosorbide dinitrate in the 1980s.<sup>11</sup>

Since that time, he and other local cardiologists have become leaders in the area of heart failure. In 2002, they formed the Minnesota Heart Failure Consortium, a project of the Minnesota Medical Research Foundation. The consortium includes Hennepin County Medical Center; the University of Minnesota Medical Center, Fairview; the Minneapolis Veterans Affairs Medical Center; Minnesota Heart Clinic; Metropolitan Cardiology Consultants; Park Nicollet Health Services; Central Minnesota Heart Center; Mayo Medical Center; Regions Hospital; SMDC Health System; the Minnesota Heart Institute; and the St. Paul Heart Clinic. Investigators at these institutions have designed and conducted studies that have significantly contributed to the understanding and treatment of heart failure. A list of their completed and ongoing research is available on the Minneapolis Medical Research Foundation website [www.mmrf.org/MMRF/research/MHFC/home.html](http://www.mmrf.org/MMRF/research/MHFC/home.html).

In 2005, the National Heart Lung and Blood Institute (NHLBI) selected the Minnesota Heart Failure Consortium and Mayo Clinic from more than 30 applicants to serve as regional coordinating centers for a national network that would rapidly implement novel approaches to the management of congestive heart failure. The other regional centers are Duke University, Harvard University, Baylor University, the University of Vermont, the University of Utah, Montréal Heart Institute, and Morehouse School of Medicine. Funding from the NHLBI supports the network's infrastructure and the costs associated with enrolling patients in clinical trials.

### Heart Failure Network Protocols

Minnesota has contributed significantly to the development of the first 4 research protocols approved by the Heart Failure Network. The Minnesota Heart Failure Consortium and Mayo Clinic are leading the investigative efforts for 2 of them. The Heart Failure Network protocols are designed to address important clinical questions in the area of heart failure and explore novel interventions that otherwise would be difficult to perform without NHLBI financial support.

The first protocol, CARRESS HF, was developed by the Minnesota Heart Failure Consortium. It will explore 2 different treatment strategies for patients hospitalized with acute decompensated heart failure who later go on to experience declining renal function, a condition that affects 25% of patients hospitalized with heart failure and is associated with increased complications

and death. There currently is no standard of care for the treatment of such patients. Practice patterns vary among regions and include diverse interventions such as withholding diuretics and replacing fluids, increasing the intensity of diuretic therapy, adding vasodilators or inotropes, and using ultrafiltration. The CARRESS HF study will compare ultrafiltration with a stepped-care algorithm emphasizing the use of diuretic agents. If ultrafiltration proves to be safe and effective in this clinical setting, it will become the new standard of care and positively affect tens of thousands of patients each year who are hospitalized with decompensated heart failure and go on to develop worsening renal function.

The second protocol approved by the Heart Failure Network was designed and is led by heart failure specialists at Mayo Clinic. The RELAX protocol will evaluate the use of sildenafil (Viagra) for patients with heart failure and preserved left ventricular systolic function. Heart failure with preserved systolic function disproportionately affects older individuals and women. Unfortunately, there are no treatments that are known to be effective for this condition. Sildenafil has vasodilating properties and anti-proliferative properties that could be effective in managing it. Endpoints of particular interest in this study include peak oxygen consumption during exercise stress testing, diastolic function assessed during echocardiography, and left ventricular function and mass measured during MRI imaging. If sildenafil proves effective, it will represent a major advance in the treatment and understanding of diastolic heart failure, which accounts for half of all heart failure cases.

The third Heart Failure Network trial led by Duke University Medical Center, DOSE HF, will study the use of diuretics in patients hospitalized with acute decompensated heart failure. Diuretics effectively decongest patients with fluid overload. However, they directly stimulate the sympathetic nervous system and adversely affect renal function. Because they are consistently associated in a dose-dependent fashion with excess mortality, the optimal dosing strategy of diuretics in acute decompensated heart failure has not been established. This study protocol will randomly assign patients in a 2 x 2 factorial design to receive high-dose versus low-dose intravenous diuretics. Patients will also be randomly assigned to receive their diuretics as a continuous infusion or intermittent bolus. This will be the largest and most rigorous study of the use of diuretics in acute decompensated heart failure ever performed and will significantly contribute to the understanding of how to manage this patient population.

The fourth Heart Failure Network protocol also led by Duke University Medical Center, SMMART, explores the effectiveness of surgical intervention in heart failure patients with nonischemic cardiomyopathy and moderate-to-severe mitral regurgitation. Currently, there is no approach that's clearly been identified as best for treating such patients. Optimal medical therapy and surgical intervention with repair of the mitral valve are both standard options available to patients today. Yet, there has been no randomized trial to definitively establish which approach is most effective. The SMMART trial will answer this question and assist patients and

physicians in choosing the most beneficial treatment strategy.

These and other NHLBI Heart Failure Network study protocols are addressing important questions that clinicians face every day when dealing with patients with decompensated heart failure. The results of these studies will influence treatment guidelines for years to come with respect to the appropriate use of diuretics, novel treatments such as ultrafiltration and sildenafil, and surgical interventions.

## Conclusion

As the U.S. population ages, more people will be diagnosed with and suffer from the chronic debilitating symptoms of heart failure. The cost of and resources necessary for caring for these patients will be enormous. Although there is no cure for heart failure, a number of therapeutic advances offer new options for patients with this condition, and many of these advances are emerging from studies initiated and being done by researchers in Minnesota.

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## REFERENCES

1. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol.* 2005;46(6):e1-82.
2. Hahn RA, Heath GW, Chang MH. Cardiovascular disease risk factors and preventive practices among adults—United States, 1994, A behavioral risk factor atlas. *MMWR Morbid Mortal Wkly Rep.*
3. Adhere - Acute Decompensated Heart Failure National Registry: Q1 2004 National Benchmark Report. P0305403. 2004. Ref Type: Report
4. Shlipak MG, Massie BM. The clinical challenge of cardiorenal syndrome. *Circulation.* 2004;110(12):1514-7.
5. Ahmed A, Husain A, Love TE, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J.* 2006;27(12):1431-9.
6. Gheorghide M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation.* 2003;107(21):2690-6.
7. Gheorghide M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA.* 2004;291(16):1963-71.
8. Konstam MA, Gheorghide M, Burnett JC, Jr., et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA.* 2007;297(12):1319-31.
9. Bart BA, Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J Am Coll Cardiol.* 2005;46(11):2043-6.
10. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol.* 2007;49(6):675-83.
11. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med.* 1986;314(24):1547-52.