

# Heart Failure Compendium

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## New Heart Failure Guidelines Could Boost Entresto

Mary Caffrey

A new drug to treat heart failure (HF)—an angiotensin receptor-neprilysin inhibitor (ARNI)—should replace current therapies for certain patients with mild to moderate HF, according to an updated recommendation from the leading professional medical groups in the United States and Europe.

The American College of Cardiology (ACC), the American Heart Association, and the Heart Failure Society of America published an update in the *Journal of the American College of Cardiology (JACC)*. The update was timed to coordinate with similar guidance from the European Society of Cardiology. An editorial in *JACC* said the coordinated effort is designed “to promote optimal care for all patients with all forms of cardiovascular (CV) disease, to improve outcomes and enhance quality of life around the world.”<sup>1,2</sup>

Novartis’ Entresto, a combination of valsartan and sacubitril, is expected to get a sales boost based on the recommendation. The key recommendation called for ARNIs to replace angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers to treat patients with stable HF, adequate blood pressure, and good drug tolerance. ARNIs should not be given alongside an ACE inhibitor or to patients with a history of angioedema. In HF, the heart muscle weakens, causing inadequate pumping of blood through the body. Patients with this condition experience shortness of breath, chronic coughing, and loss of appetite; they also can experience cognitive symptoms.

The societies gave Entresto a “Class I” recommendation, the highest available, based on evidence from the 2014 PARADIGM trial, which found a 20% reduction in the composite endpoint of CV death or HF hospitalization. In anticipation of the news, Novartis announced increased investment in a global program of 4 clinical trials over the next 5 years, which will evaluate the long-

“Not every patient is a good candidate for every drug; these guidelines can help physicians decide who best fits which treatment,” said Clyde W. Yancy, MD, MSc, MACC, who chairs the guideline writing committee. “This document details the benefits and risks of these new therapies so that patients at high risk can be directed toward alternative therapies.”

term safety and efficacy of Entresto.

The recommendations also said that Amgen’s Corlanor (ivabradine) “may be beneficial in reducing HF hospitalizations in patients with symptomatic stable chronic HF with reduced ejection fraction,” who are being treated according to guidelines and met other clinical benchmarks, according to a statement from ACC. The committee rated the evidence for ivabradine Class IIa.

“Not every patient is a good candidate for every drug; these guidelines can help physicians decide who best fits which treatment,” said Clyde W. Yancy, MD, MSc, MACC, who chairs the guideline writing committee. “This document details the benefits and risks of these new therapies so that patients at high risk can be directed toward alternative therapies.”

For coverage of the recent 65th Scientific Sessions of the ACC, see [AJMC.com](http://AJMC.com).

### References

1. Yancy CW, Jessup M, Bozkurt B, et al. Report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Failure Society of America [published May 20, 2016]. *J Am Coll Cardiol*. 2016; doi: 10.1016/j.jacc.2016.05.011.
2. Antman EM, Bax J, Chazal RA. Updated clinical practice guidelines on heart failure: an international alignment [published online May 20, 2016]. *J Am Coll Cardiol*. 2016; doi: 10.1016/j.jacc.2016.05.012. ●

# Researchers Discover New Mechanism Related to Heart Failure

Brenna Diaz

**D**iscovery of a previously unknown heart muscle protein and how it affects mechanisms related to heart failure (HF) may lead to additional treatments for cardiovascular disease, according to a study published in *Nature Communications*.

Cardiologists Dr Matthias Eden and Professor Norbert Frey, from the University of Kiel in Germany, recently discovered the Myoscape/FAM40B/STRIP2 protein and how it directly affects the L-type calcium channel (LTCC). Specifically, the Myoscape protein influences calcium metabolism and the pumping ability of the heart muscle cells.

“In the absence of Myoscape, heart

muscle cells in the model system develop a serious impairment of calcium channel metabolism, ultimately leading to progressive heart failure,” Frey said in a statement.

Combined with the protein actinin 2, Myoscape stabilizes the LTCC in the heart muscle cells at the necessary position within the cell membrane. Using Myoscape-depleted morphant zebrafish and Myoscape knockout mice, the researchers noted that without the Myoscape protein, the calcium channel metabolism of the heart muscle cells became impaired and progressed to advanced HF. The mice, for example, depicted a reduction in LTCC currents, cell

capacity, and calcium current densities.

When artificially increasing the levels of Myoscape, the researchers saw that the calcium channel currents increased as well. As such, Myoscape seems to restore previously decreased calcium currents in failing heart muscle cells.

“Since patients with severe heart failure also exhibit reduced levels of Myoscape protein in the heart, we believe that we have here discovered a critical new mechanism for the genesis of heart failure,” Frey said.

With this dual discovery, it is possible that innovative new treatments will follow. ●

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## High Rates of Heart Failure Among Hispanics/Latinos Go Unrecognized

Brenna Diaz

**A**ccording to recent research, although Latino Americans have high rates of cardiac dysfunction with a high prevalence of diastolic dysfunction, these issues are overwhelmingly unrecognized.

The Latino/Hispanic population has high rates of diabetes, obesity, and high blood pressure, all of which may lead to cardiac dysfunction and, ultimately, heart failure (HF). However, few studies have focused on this group, and the only other large study of cardiac dysfunction within the United States looked at older, largely non-Hispanic white adults and, perhaps due to this oversight, Latino/Hispanics have often been considered at low risk for cardiac dysfunction.

The Echocardiographic Study of Latinos (ECHO-SOL), published in *Circulation: Heart Failure*, evaluated 1818 adults of Hispanic/Latino origin aged 45 to 74 years from the Bronx, Chicago, Miami, and San Diego. Many of those at risk for cardiac dysfunction were obese, had high blood

pressure, had diabetes, and/or reported low levels of physical activity. Approximately 20% were current smokers.

The project identified 2 types of cardiac dysfunction: left ventricular systolic dysfunction (LVSD) and left ventricular diastolic dysfunction (LVDD). In LVSD, the left ventricle does not push blood as forcibly as it should; in LVDD, the left ventricle is too stiff in between beats and cannot gather enough blood.

About 49.7% of adults evaluated had LVSD, LVDD, or both. The prevalence of LVSD was 3.6%, while the prevalence of LVDD was 50.3%. The prevalence of clinical HF with LVSD was 7.3%, and for those with LVDD, 3.6%; clinical HF was self-reported.

Those with LVSD were more frequently male and current smokers. Those with LVDD were more frequently female, had hypertension, had diabetes, had a higher body mass index, and had renal dysfunction. Rates of LVDD were higher among

Latino Americans with Central American and Cuban backgrounds. However, 96.1% of adults with cardiac dysfunction did not realize that they had this problem.

Carlos J. Rodriguez, MD, MPH, senior study author and associate professor of medicine and epidemiology at Wake Forest Baptist Medical Center in Winston-Salem, North Carolina, said that health professionals should have a high level of vigilance when monitoring patients of Hispanic/Latino origins and a low threshold for intensifying preventative therapies in order to avoid future HF.

Due to lack of previous research, there are no reliable estimates for how many patients with cardiac dysfunction will develop HF. Researchers plan to continue tracking ECHO-SOL participants. “Given that Hispanics/Latinos are the largest ethnic minority in the United States, with over 51 million people, they are likely to have a big impact on the heart failure epidemic,” Dr Rodriguez said in a statement. ●

## Diabetes Drug to Be Tested in Heart Failure

AJMC Staff

A diabetes drug may have benefits for individuals with chronic heart failure (HF). Boehringer Ingelheim and Eli Lilly and Company have announced plans to investigate the use of the diabetes medicine Jardiance for HF.

There are plans for 2 outcome trials, targeted to begin within the next 12 months. The trials will enroll patients with chronic HF, with and without type 2 diabetes. Jardiance has demonstrated a reduction in the risk of cardiovascular death in a dedicated outcomes trial for patients with type

2 diabetes who were at high risk of cardiovascular events.

“The EMPA-REG OUTCOME trial demonstrated that Jardiance reduces the risk of cardiovascular death in diabetes patients at high cardiovascular risk, and we now look forward to exploring whether Jardiance can also provide heart failure benefits,” Professor Hans-Juergen Woerle, global vice president of medicine at Boehringer Ingelheim, said in a statement.

The EMPA-REG OUTCOME trial found that Jardiance reduced cardiovas-

cular death by 38% and reduced the risk of hospitalization for HF in the participants by 35%. Patients with diabetes are 2 to 3 times more likely to develop HF. Overall, 5.7 million individuals in the United States have chronic HF.

“One in two people with heart failure die within 5 years of diagnosis, so there is currently a compelling need for an effective therapy to treat those suffering from this condition,” said Javed Butler, MD, MPH, of Stony Brook University Hospital. ●

## Risk of Heart Failure Increases After Myocardial Infarction

Priyam Vora

A new study published in *JAMA Cardiology* finds a strong association between coronary artery disease (CAD) and the occurrence of heart failure (HF) after myocardial infarction (MI). Put simply, a first heart attack is more likely to lead to HF in patients when the burden of CAD increases.

To understand this association, Yariv Gerber, PhD, and fellow researchers evaluated angiographic CAD and subsequent HFs in a well-defined community of patients who have suffered a first heart attack. They conducted a population-based cohort study among 1922 participants. All the participants had an incident MI diagnosed from 1990 through 2010, and they had no prior history of HF. Certain medical factors—such as cardiovascular risks, comorbid conditions, MI characteristics, and acute interventions at the time of incident MI—were also determined. Other lifestyle factors considered were smoking habits, body mass index, hypertension, diabetes, and hyperlipidemia.

Out of the total participants, the mean age was 64 and 65% were men. After following up with the participants through early 2013, the researchers found that

588 (nearly 30%) of the participants developed HF.

The investigators determined the extent of angiographic CAD at baseline and categorized the disease burden according to the number of major epicardial coronary arteries with 50% or more lumen diameter obstruction. Compared with patients with 0 or 1 blocked artery, those with 2 blocked arteries had a significantly increased risk for HF. In patients with 3 blocked arteries, the risk was much higher. This increased risk occurred independently of recurrent MI, and it did not change with HF subtypes.

### *Heart Failure After MI Often Neglected*

After following up on a study population of nearly 2000 patients who had a heart attack, no prior HF history, and a baseline angiographic assessment, it was found that at least 30% of the patients developed HF. The burden on the heart increases after incident MI. The association between angiographic CAD and incidence of HF was significant and clinically substantial.

Thus, an increasing extent of CAD, as detected by angiography at the time of the first MI, is an indicator of HF incidence

during long-term follow-up, said Dr Gerber, the lead author of the study.

In the past 20 years, the epidemiology of MI has vastly changed. Even though progress in acute treatment has improved short-term survival rates, HF remains frequent in the long-term, ultimately leading to excess mortality. It is not only important to restore vessel patency, but also to understand the contemporary mechanisms leading to its development. Understanding this is crucial to preventing the development of HF after an incident heart attack.

“Our study provides insight into the prognostic role of the extent of CAD at the time of first MI in the development of HF, as well as on the mechanisms involved,” concluded Dr Gerber. “The present findings underscore the importance of further investigations into processes taking place in the transition from the initial myocardial injury to heart failure.” ●

## Few Americans Follow All 4 Elements of a Heart-Healthy Lifestyle

Jackie Syrop

A new study finds that fewer than 3% of Americans are active enough, eat a healthy diet, are nonsmokers, and have a healthy weight and percentage of body fat—the 4 important elements of a heart-healthy lifestyle that are promoted by the American Heart Association’s Strategic Impact Goal for 2020 and Beyond. The study, published in the April 2016 issue of *Mayo Clinic Proceedings*, differs from previous studies that have examined these lifestyle characteristics separately because it examines the independent and combined effects of the 4 healthy lifestyle characteristics on markers of cardiovascular disease.

Paul D. Loprinzi, MD, and colleagues used 2003 through 2006 National Health and Nutrition Examination Survey data from a sample of 4745 Americans aged 20 to 85 years for 4 parameters: being sufficiently active (getting at least 150 minutes of moderate exercise per week), being a nonsmoker, eating a healthy diet (that includes enough vegetables and whole grains, and avoiding saturated fats), and having a recommended body fat percentage (up to 20% for men and 30% for women).

Markers of cardiovascular health included mean blood pressure in the arteries, C-reactive protein (CRP, a sign of inflammation), total cholesterol, high-density lipoprotein cholesterol (HDL-C), the ratio of total cholesterol to HDL-C, fasting low-density lipoprotein cholesterol, fasting triglycerides, fasting blood sugar, fasting insulin, and hemoglobin A1C, a measure of blood glucose over several months.

The study was conducted from August 15, 2013, through January 5, 2016. Diet information was self-reported, but the remaining data came from results of blood tests, accelerometers (to measure physical activity), and dual-energy x-ray absorptiometry (to determine percentage of body fat).

The study found that only 2.7% of all adults had all 4 healthy lifestyle characteristics and 11.1% had none. A total of 71.5% of adults do not smoke, 37.9% consumed a healthy diet, 9.6% had a normal percentage of body fat, and 46.5% were sufficiently active. Compared with men, women were more likely to not smoke and eat a healthy diet, and were less likely to be sufficiently active. Older adults and non-Hispanic

blacks had the fewest number of healthy lifestyle characteristics.

Study participants with 3 or 4 healthy lifestyle characteristics, compared with none, had more favorable levels of markers for cardiovascular disease, except for mean arterial blood pressure, fasting blood sugar, and hemoglobin A1C. Having at least 1 or 2 healthy characteristics versus no healthy lifestyle characteristics had a favorable effect on CRP, HDL-C, total cholesterol, and measures of an amino acid that is associated with a higher risk of heart attack, stroke, and blood clots.

“Although multiple healthy lifestyle characteristics are important, specific healthy lifestyle characteristics may explain much of the variation for several of the markers for heart health,” the study suggested.

More research is needed to identify strategies that work to increase the adoption of multiple healthy lifestyle characteristics among adults. ●

## Gene Transfer for Heart Failure Shows Promise

Jackie Syrop

Intracoronary gene transfer among patients suffering from heart failure (HF) increased left ventricular function beyond standard HF therapy through a single gene transfer administration, according to a new study published in *JAMA Cardiology*. Gene transfer involves introducing genes into cells so that the cells produce certain proteins—in this case, the protein adenylyl cyclase type 6 (AC6), which preliminary studies suggest may benefit heart muscle cells. The amount and function of AC6 are reduced in HF; the gene is introduced into the heart cells by an adenovirus that has

been modified (adenovirus 5). Adenoviruses are the most commonly used vectors in clinical gene transfer.

H. Kirk Hammond, MD, of the Veterans Affairs San Diego Healthcare System, and colleagues randomly assigned 56 patients (males and nonpregnant females aged 18 to 80 years) with symptomatic HF and an ejection fraction (EF; a measure of how well the left ventricle of the heart pumps with each contraction) of 40% or less to receive 1 of 5 doses of adenovirus 5, which coded for AC6, or placebo. Patients were from 7 US medical centers and were followed for up to

1 year. Patients were required to have an implanted cardiac defibrillator and at least 1 major coronary artery or graft with less than 50% obstruction.

The study’s main objective was to assess the safety of a one-time injection of adenovirus 5 in patients with HF and to identify effective doses for future trials. The investigators found that the AC6 gene transfer created a beneficial effect on cardiac function that was related to the dose administered and was deemed safe in patients with HF and reduced EF. Heart failure admission rate was 9.5% in participants who received AC6 and

28.6% in those who received placebo ( $P = .10$ ). The rates of serious adverse events were similar in both groups.

Although the 1-year mortality rate was lower in participants who received the AC6 gene transfer, the number of events was too low to draw a conclusion. The

researchers found that participants with nonischemic HF (HF not due to coronary artery disease) who received AC6 had increased EF, and they suggest targeting the gene therapy to this group of patients, who will likely have the most benefit.

The investigators concluded that AC6

gene transfer safely increased left ventricular function beyond optimal HF therapy through a single administration, and they recommend that larger trials of the gene transfer are warranted to assess the safety and efficacy of AC6 gene transfer for patients with HF. ●

## New Research on Patient and Facility Variation in Costs of VA Patients With Heart Failure

Marie Bialek

This recent cohort analysis of Veterans Affairs (VA) data suggested that there is a 4-fold variation in 1-year costs associated with heart failure (HF) among various VA treatment facilities. The study, “Patient and Facility Variation in Costs of VA Heart Failure Patients,” from *JACC: Heart Failure*, by Yoon and colleagues, evaluated costs and utilization measures such as inpatient and outpatient care, outpatient prescription drugs, and contract care; patient measures included demographics, chronic conditions, alternate health insurance, marital status, geographic region, VA facility, date of death (if applicable), and disease of disability in the case of a service-related condition.

Service networks were grouped into 5 regions (Northeast, Southeast, Mid-South, Central, and West). Of patients who received care, 2.3% ( $N = 117,870$ ) were identified as having HF. Most (56%) of the patients with HF were 70 years or older. There was a high prevalence of chronic conditions, including hyperten-

sion (76%), ischemic heart disease (53%), diabetes (46%), and renal failure (21%); the mean annual cost for the study cohort was \$30,719 per patient for inpatient care, outpatient care, and prescription drugs (half of the annual cost was due to inpatient care). The largest component of outpatient care was medical/surgical care (mean \$6614), followed by outpatient pharmacy (\$2263) and diagnostic care (\$1697).

Other factors that were associated with changes in healthcare costs included demographic factors, comorbidities, and geographic location. After adjusting for covariates, factors that were associated with significantly lower costs included old age and white race (vs black race) (both,  $P < .001$ ).

The study findings suggested that in patients 60 years or older, dual coverage that included Medicare may have caused a shift in care away from VA providers. Single marital status, higher service connection (greater disability related to their

military service), and no other insurance were associated with higher costs (all  $P < .001$ ). All comorbid conditions were associated with significantly higher costs ( $P < .001$ ) (Table). Variation in mean costs of VA healthcare ranged from \$15,983 in the lowest-cost facility to \$47,839 in the highest-cost facility.

The differences in costs were mainly explained by patient factors; however, the wide variation in costs between the low- and higher-cost facility suggests that there is some opportunity to improve resource utilization in high-cost facilities. The reasons for this discrepancy were not reported but may be related to variations in treatment patterns or provider performance. The authors reported that a deeper understanding of associated patient factors and facility costs may improve resource planning and better characterize patterns of care. ●

**TABLE.** Costliest Comorbid Conditions in VA Patients With Heart Failure in 2010

Comorbid Condition	Costs (Mean) N = 117,870
Drug use disorder	\$59,486
Other psychiatric disorders (non-depression)	\$53,536
Renal failure	\$52,385
Alcohol use disorder	\$48,401
PTSD	\$42,440
Depression	\$41,803

PTSD indicates posttraumatic stress disorder; VA, Veterans Affairs.

# Update on Intensive Management to Reduce Hospitalizations in Patients With Heart Failure

Marie Bialek

**P**atients with heart failure (HF) are at a high risk for recurrent hospitalization. About 25% of Medicare-eligible patients are readmitted within 30 days of hospitalization, and nearly 50% are readmitted within 6 months. To reduce HF readmission, effective strategies must be utilized according to the time from hospital discharge, disease severity, the burden of comorbid illnesses, and the overall goals of care. This clinical update, “Intensive Management to Reduce Hospitalizations in Patients With Heart Failure,” published in *Circulation* by Desai and colleagues, summarized the evidence-based best practices for reducing HF readmissions rates and reviewed the evolving models for outpatient HF disease management.

The recommendations were provided according to hospital discharge status (ie, prior to hospital discharge, soon after discharge, and later after discharge). To start, providers must ensure that effective treatment of HF begins during the inpatient hospital stay. Core therapeutic goals include the identification and management of factors responsible for precipitating HF decompensation because these factors serve as triggers

for recurrent readmission. Other predischarge efforts should focus on optimizing pharmaceutical care and effectively decongesting patients.

Important strategies for successful transitioning from the hospital include patient education to enhance self-care, intensive care coordination, early follow-up, and specialty support, all of which have been consistently effective in reducing readmission rates and mortality. Of note, after HF hospitalization, current treatment guidelines recommend a follow-up visit within 7 to 10 days of discharge because greater efficacy of care has been associated with the use of collaborative care that includes cardiovascular specialists rather than primary care providers alone. Fragmentation of care is a significant risk because transitional care usually relies on the use of multidisciplinary teams that include nurses, pharmacists, social workers, primary care physicians, sub-specialists, and home care providers. Patients who do not speak English and patients with cognitive impairment are at a particularly high risk for readmission and may require more individualized strategies.

Beyond the short-term period after

hospital discharge, the longitudinal surveillance of patients with HF is needed to promptly detect recurrent congestion. Remote surveillance of body weight has become a central focus of HF management using telemonitoring that also evaluates vital signs, as short-term changes in body weight correlate with fluid status. However, weight has been shown to be an insensitive marker of worsening congestion over long-term follow-up, and deterioration requiring hospitalization can occur with little to no changes in body weight. The use of implantable hemodynamic monitors may be an effective approach for selected high-risk patients.

It is also necessary to keep in mind that as HF progresses, the anticipated efficacy of ambulatory heart failure strategies predictably declines and the proportion of unavoidable hospitalizations rises. Hospice care is frequently underused or used too late in the care of patients with HF. However, the use of hospice care may be a powerful means to reduce readmission rates without increasing the rates of near-term mortality. ●

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## Looking Ahead to Target Heart Failure With Preserved Ejection Fraction

Marie Bialek

**T**he increasingly prevalent burden of heart failure (HF) is made up of 2 major types: HF with reduced ejection fraction and HF with preserved ejection fraction (HFpEF). In patients with HFpEF, abnormal diastolic function of the left ventricle and an increase in arterial stiffness lead to abnormal ventricular-arterial coupling. The diagnosis of HFpEF is made in patients with signs or symp-

toms of HF, a left ventricular ejection fraction greater than 50%, and evidence of diastolic dysfunction. Unfortunately, there are no medical or surgical therapies that improve patient survival in the setting of HFpEF, and there is even a lack of consensus on the basic pathophysiology and definition of HFpEF. The article “Targeting Heart Failure With Preserved Ejection Fraction: Current Status and Future

Prospects,” by Kanwar and colleagues, published in *Vascular Health and Risk Management*, reviewed the pathophysiology of HFpEF along with its diagnosis and treatment.

The pathophysiology of HFpEF involves multiple factors, including diastolic dysfunction, caused by increased stiffness in the extracellular matrix; increased cardiomyocyte stiffness; and

increased ventricular load as a result of ventricular-vascular uncoupling. Although there is a paucity of data from large, evidence-based trials that demonstrate morbidity and mortality benefits in patients with HFpEF, current guidelines for management of HFpEF recommend treatment of volume status, control of blood pressure, and treatment of contributing risk factors, such as sleep apnea, coronary artery disease, and valvular disease. Dietary education is also recommended for patients with HFpEF. The most important risk factor to control is, most likely, hypertension.

Guideline recommendations for treatment of comorbid conditions and symptom control are available from various groups (Table). Most data on the use of treatment are conflicting, and there are no approved therapies for patients with

HFpEF. For example, data on the use of angiotensin-converting enzyme (ACE) inhibitors are less clear in patients with HFpEF compared with patients who have HF with reduced ejection fraction; however, since angiotensin II promotes ventricular hypertrophy and fibrosis, both of which contribute to HFpEF, blocking angiotensin II can be a potential target for the treatment of HFpEF. In a similar way, angiotensin II receptor blockers (ARBs) blunt the adverse cardiovascular effects of angiotensin II, but they exert their effects further downstream compared with ACE inhibitors.

Unfortunately, trials of ACE inhibitors or ARBs in patients with HFpEF have reported conflicting results. Other trials have evaluated the use of a number of agents, including aldosterone antagonists, beta-blockers, calcium channel

blockers, nitrates, digoxin, and statins, with mixed results.

The use of a monitoring strategy that uses ongoing direct or indirect measurement of LV filling pressures holds promise. The CardioMEMS device is a wireless implanted pulmonary artery pressure monitor that has been approved in Europe and in the United States and has been shown to significantly reduce HF hospitalizations in patients with NYHA Functional Class II HF of any etiology. Despite this advance, an urgent need remains to focus on therapies and devices to treat patients with HFpEF and to better characterize mechanisms, clinical manifestations, and contribution of comorbid conditions, which may be facilitated through the collection of data using longitudinal registries. ●

**TABLE.** Guideline Recommendations for Patients With Preserved Ejection Fraction Heart Failure

Organization	Recommendations
American College of Cardiology Foundation/ American Heart Association	<ul style="list-style-type: none"> <li>• Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers for hypertension</li> <li>• Angiotensin receptor blockers to decrease hospitalization</li> </ul>
Heart Failure Society of America	<ul style="list-style-type: none"> <li>• Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for symptomatic atherosclerotic disease or diabetes plus 1 risk factor</li> <li>• Beta-blockers for patients with a history of myocardial infarction, hypertension, or atrial fibrillation</li> </ul>
European Society of Cardiology	<ul style="list-style-type: none"> <li>• Diuretics for symptom control</li> <li>• Calcium channel blockers* and other agents for hypertension, myocardial infarction, and atrial fibrillation rate control</li> </ul>

\*Contraindicated in patients with reduced ejection fraction heart failure.