Clinical Concept of Heart Failure

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FDA’s View - Treat the Disease instead of the Condition

“Heart Failure is not a disease and we should no longer approve drugs for a heterogeneous broad population, but for a well defined sub-population where we can demonstrate a marked benefit”

Dr. Stephen Grant
Deputy Director, Division of Cardiovascular Renal Products, CDER
<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk for (60 mil.) developing HF</td>
</tr>
<tr>
<td></td>
<td>HTN</td>
</tr>
<tr>
<td></td>
<td>CAD</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
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<tr>
<td>B</td>
<td>Asymptomatic HF (10 mil.)</td>
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<td></td>
<td>Previous MI</td>
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<td></td>
<td>LV systolic dysfunction</td>
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<td></td>
<td>Asymptomatic valvular disease</td>
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<tr>
<td>C</td>
<td>Symptomatic HF (5 mil.)</td>
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<tr>
<td></td>
<td>Known structural heart disease</td>
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<tr>
<td></td>
<td>Shortness of breath and fatigue</td>
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<td></td>
<td>Reduced exercise tolerance</td>
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<tr>
<td>D</td>
<td>Refractory end-stage HF (200000)</td>
</tr>
<tr>
<td></td>
<td>Marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)</td>
</tr>
</tbody>
</table>

Congestive Heart Failure

• Congestive heart failure (CHF) is a life-threatening condition in which the heart isn't able to pump enough blood to the rest of the body. The failing heart continues to work, but not as efficiently as it should. Many conditions that lead to congestive heart failure can't be reversed, but heart failure can often be treated with medications and lifestyle changes.
Case Study

• 51 year-old Electrophysiologist
• Functional Class III for 6 months
• BP 90/60 mmHg; PCWP 30 mmHg; LVEF 10%
  • Angiogram: no significant coronary disease; MRI: no hyper-enhancement (no scar tissue)
• Receiving: furosemide, digoxin, enalapril
• Started on carvedilol 3.125 mg BID that was titrated to 25 mg BID in addition to micro and macronutrients
• 6 months later:
  – EF 60%
  – Functional Class I
Over the years, I have learned that heart failure for some patients is no longer a progressive and fatal condition. Recovery may be possible when guidelines are followed. I have also learned that physicians can predict which patients are more likely to recover on the basis of “viability tests” that identify myocardium that is dysfunctional but recoverable. I have also learned that heart failure is not a disease but rather a manifestation of cardiac abnormalities for which specific therapies are available. Finally, I now know that in addition to established therapies, micronutrients and macronutrients may also play a role in patient recovery.

Bruce Handler, MD
Chicago, Illinois
31 May 2012
Congestive Heart Failure

Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: Findings from IMPROVE HF

Jane E. Wilcox, MD, a Gregg C. Fonarow, MD, b Clyde W. Yancy, MD,a Nancy M. Albert, PhD, CCNS, CCRN, FAHA, c Anne B. Curtis, MD, d J. Thomas Heywood, MD, e Patch Johnson Inge, PhD, f Mark L. McBride, MD, g Mandeep R. Mehra, MD, h Christopher M. O’Connor, MD, b Dwight Reynolds, MD, i Mary Norine Walsh, MD, j and Mihai Gheorghiade, MD k Chicago, IL; Los Angeles, and La Jolla, CA; Cleveland, OH; Buffalo, NY; Cambridge, MA; Baltimore, MD; Durham, NC; Oklahoma City, OK; and Indianapolis, IN

Background Available data suggest that improvement in left ventricular ejection fraction (LVEF) is a major predictor of improved survival in heart failure (HF). Although certain factors are associated with improvements in LVEF in select patients with HF enrolled in clinical trials, relatively little is known about such factors among patients in clinical practice. This study evaluated changes in LVEF and associated factors in outpatients with systolic HF or post-myocardial infarction with reduced LVEF during 24 months of follow-up.

Methods IMPROVE HF is a prospective evaluation of a practice-based performance improvement intervention implemented at outpatient cardiology/multispecialty practices to increase use of guideline-recommended care for eligible patients. Data were analyzed by patient groups based on absolute improvement in LVEF (<0%, 0–10%, and >10%) from baseline to 24 months and by change in LVEF as a continuous variable.

Results A total of 3,994 patients from 155 of 167 practices were eligible for analysis. The overall mean LVEF increased from 25.8% at baseline to 32.3% (+6.4%) at 24 months (P < .001), and 28.6% of patients had a >10% improvement in ejection fraction (from 24.5% to 40.2%, 92% relative improvement). Age, race, and practice setting were similar between the 3 LVEF improvement groups. Multivariate analysis revealed female sex, no prior myocardial infarction, nonischemic HF etiology, and no digoxin use were associated with >10% improvement in LVEF.

Conclusions Among patients with HF receiving care in cardiology/multispecialty practices participating in a performance measure intervention, surviving, and having repeat LVEF assessment, close to one third of patients had a >10% improvement in LVEF at 24 months. These findings indicate that HF is not always a progressive disease and that differentiation of the heterogeneous HF phenotypes may set the stage for future research and therapeutic targets. [Am Heart J 2012;163:49-56.e2.]
Improve HF

Left ventricular ejection fraction at baseline and 24 months according to tertile of LVEF improvement.
Viable but Dysfunctional Myocardium: Possibility for Recovery

Etiologic Factors

- Neurohormones (e.g. NE)
- Ischemia/Hibernation
- Cytokines (e.g. TNF α)
- Metabolic
- Hemodynamics

Myocyte
The human heart weighs between 200-425 g.

This relatively small mass uses more energy, in the form of adenosine triphosphate (ATP), than any other organ.

It pumps 5 liters of blood per minute, 7200 liters per day, and over 2.6 million liters per year.

Over 6 kilograms of ATP is hydrolyzed by the heart daily, undergo constant turnover and rebuilding.

Every 30 days, an entire heart itself is reconstructed with brand new protein components.

Soukoulis et al JACC 2010
Myocardial Damage Detected by Late Gadolinium Enhancement Cardiovascular Magnetic Resonance Is Associated With Subsequent Hospitalization for Heart Failure

Timothy C. Wong, MD, MS; Kayla M. Piehler, BS; Karolina M. Zanoba, MD; Kathie Lin, BS; Ashley Phrampton, ???; Agam Patel, BS; James C. Moon, MD; Martin Ugander, MD, PhD; Uma Valeti, MD; Jonathan E. Holtz, MD; Bo Fu, PhD; Chung-Chou H. Chang, PhD; Michael Mathier, MD; Peter Kellman, PhD; Javed Butler, MD; Mihai Gheorghiade, MD; Erik B. Schelbert, MD, MS

Background—Hospitalization for heart failure (HHF) is among the most important problems confronting medicine. Late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) robustly identifies intrinsic myocardial damage. LGE may indicate inherent vulnerability to HHF, regardless of etiology, across the spectrum of heart failure stage or left ventricular ejection fraction (LVEF).

Methods and Results—We enrolled 1068 consecutive patients referred for CMR where 448 (42%) exhibited LGE. After a median of 1.4 years (Q1 to Q3: 0.9 to 2.0 years), 57 HHF events occurred, 15 deaths followed HHF, and 43 deaths occurred without antecedent HHF (58 total deaths). Using multivariable Cox regression adjusting for LVEF, heart failure stage, and other covariates, LGE was associated with first HHF after CMR (HR: 2.70, 95% CI: 1.32 to 5.50), death (HR: 2.13, 95% CI: 1.08 to 4.21), or either death or HHF (HR: 2.52, 95% CI: 1.49 to 4.25). Quantifying LGE extent yielded similar results; more LGE equated higher risks. LGE improved model discrimination (IDI: 0.016, 95% CI: 0.005 to 0.028, P=0.002) and reclassification of individuals at risk (continuous NRI: 0.40, 95% CI: 0.05 to 0.70, P=0.024). Adjustment for competing risks of death that shares common risk factors with HHF strengthened the LGE and HHF association (HR: 4.85, 95% CI: 1.40 to 16.9).

Conclusions—The presence and extent of LGE is associated with vulnerability for HHF, including higher risks of HHF across the spectrum of heart failure stage and LVEF. Even when LVEF is severely decreased, those without LGE appear to fare reasonably well. LGE may enhance risk stratification for HHF and may enhance both clinical and research efforts to reduce HHF through targeted treatment. (Am Heart Assoc. 2013;21:e000416 doi: 10.1161/JAHA.113.000416)

Key Words: late gadolinium enhancement • magnetic resonance imaging • myocardial delayed enhancement • myocardial fibrosis • myocardial infarction
Recognizing Hospitalized Heart Failure as an Entity and Developing New Therapies to Improve Outcomes
Academics’, Clinicians’, Industry’s, Regulators’, and Payers’ Perspectives

Mihai Gheorghiade, MD,*, Ami N. Shah, MD, Muthiah Vaduganathan, MD, MPH,*, Javed Butler, MD, MPH, Robert O. Bonow, MD, MS, Giuseppe M.C. Rosano, MD, PhD, Scott Taylor, RPh, MBA, Stuart Kupfer, MD, Frank Misselwitz, MD, PhD, Arjun Sharma, MD, Gregg C. Fonarow, MD

KEYWORDS
- Hospitalized heart failure • Heart failure • Postdischarge mortality

KEY POINTS
- Hospitalized heart failure (HHF) is associated with unacceptably high postdischarge mortality and rehospitalization rates.
- This heterogeneous group of patients, however, is still treated with standard, homogeneous therapies that are not preventing their rapid deterioration.
- The costs associated with HHF have added demands from society, government, and payers to improve outcomes.
- It is important to consider that once HHF patients are stabilized by discharge, the majority of them should be considered to be in a chronic heart failure state at a significantly high risk for adverse outcomes. Delaying initiation of potentially effective therapies for weeks to months post discharge risks unabated high risk for adverse events in the meantime. Initiating therapies in patients who are stabilized in the hospital and continued long term provides a potent option to improve long-term clinical outcomes.
- With coordinated and committed efforts in the development of new therapies, improvements may be seen in outcomes for patients with HHF.
- This article summarizes concepts in developing therapies for HHF discussed during a multidisciplinary panel at the Heart Failure Society of America’s Annual Scientific Meeting, September 2012.
Chronic Heart Failure

HOSPITALIZED

• >3 million admissions in US
• Cardiac injury (+troponin)
• Rapid changes in lab values
• Mortality and rehospitalization as high as 15% and 30%, respectively, within 60-90 after d/c
• Event rate has not changed in the last decade

OUTPATIENTS

• Prevalence of 6 million (Stage C and D AHA/ACC)
• Very abnormal, but relatively stable lab values
• Mortality <5% annually in clinical trials
• Decreased morbidity and mortality in last two decades
• Death often sudden
Hospitalizations for HF

• Worsening chronic heart failure (HF): 80% of all admissions*
  *The majority managed by non cardiologist

• Acute *de novo* heart failure (diagnosed for the first time): 15%

• Advanced/end-stage/refractory HF: 5%

Gheorghiade et al. Circulation 2005
# Characteristics, Treatments, and Outcomes of Patients With Preserved Systolic Function Hospitalized for Heart Failure

A Report From the OPTIMIZE-HF Registry

Gregg C. Fonarow, MD, FACC,* Wendy Gattis Stough, PharmD,†
William T. Abraham, MD, FACC,‡ Nancy M. Albert, PhD, RN,§ Mihai Gheorghiade, MD, FACC,¶
Barry H. Greenberg, MD, FACC,¶¶ Christopher M. O’Connor, MD, FACC,¶¶ Lena Sun, MS,∗∗
Clyde W. Yancy, MD, FACC,†† James B. Young, MD, FACC,††† for the OPTIMIZE-HF
Investigators and Hospitals

Los Angeles and San Diego, California; Durham and Research Triangle Park, North Carolina;
Columbus and Cleveland, Ohio; Chicago, Illinois; and Dallas, Texas

| **Objectives** | We sought to evaluate the characteristics, treatments, and outcomes of patients with preserved and reduced systolic function heart failure (HF). |
| **Background** | Heart failure with preserved systolic function (PSF) is common but not well understood. |
| **Methods** | This analysis of the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry compared 20,118 patients with left ventricular systolic dysfunction (LVDSD) and 21,149 patients with PSF (left ventricular ejection fraction [EF] ≥40%). Sixty- to 90-day follow-up was obtained in a pre-specified 10% sample of patients. Analyses of patients with PSF defined as EF >50% were also performed for comparison. |
| **Results** | Patients with PSF (EF ≥40%) were more likely to be older, female, and Caucasian and to have a nonischemic etiology. Although length of hospital stay was the same in both groups, risk of in-hospital mortality was lower in patients with PSF (EF ≥40%) (2.9% vs. 3.9%; p < 0.0001). During 60- to 90-day post-discharge follow-up, patients with PSF (EF ≥40%) had a similar mortality risk (9.9% vs. 9.8%; p = 0.489) and rehospitalization rates (29.2% vs. 29.9%; p = 0.694) compared with patients with LVSD. Findings were comparable with those with PSF defined as EF >50%. In a risk- and propensity-adjusted model, there were no significant relationships between discharge use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker or beta-blocker and 60- to 90-day mortality and rehospitalization rates in patients with PSF. |
| **Conclusions** | Data from the OPTIMIZE-HF registry reveal a high prevalence of HF with PSF, and these patients have a similar post-discharge mortality risk and equally high rates of rehospitalization as patients with HF and LVSD. Despite the burden to patients and health care systems, data are lacking on effective management strategies for patients with HF and PSF. (Organized Program To Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure [OPTIMIZE-HF]; http://www.clinicaltrials.gov/ct/show/NCT00344513?order=1; NCT00344513) (J Am Coll Cardiol 2007;50:768-77) © 2007 by the American College of Cardiology Foundation |
Both registries and clinical trials highlight the unmet need in new therapies for patients hospitalized for heart failure.
# Clinical Characteristics of HHF Patients

Data on 200,000 US patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>75</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Hx of CAD</td>
<td>60%</td>
</tr>
<tr>
<td>Hx of Hypertension</td>
<td>70%</td>
</tr>
<tr>
<td>Hx of Diabetes</td>
<td>40%</td>
</tr>
<tr>
<td>Hx of Atrial Fibrillation</td>
<td>30%</td>
</tr>
<tr>
<td>Renal abnormalities</td>
<td>30%</td>
</tr>
<tr>
<td>SBP &gt;140 mm Hg</td>
<td>50%</td>
</tr>
<tr>
<td>SBP 90-140 mm Hg</td>
<td>45%</td>
</tr>
<tr>
<td>SBP &lt;90 mm Hg</td>
<td>5%</td>
</tr>
</tbody>
</table>

## Admission Systolic BP and Outcomes in Hospitalized Patients With HF: An OPTIMIZE-HF Analysis

<table>
<thead>
<tr>
<th>Characteristic % (SD)</th>
<th>Admission SBP mmHg</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤119 (n=12,252)</td>
<td>120-139</td>
<td>140-161</td>
<td>≥161</td>
</tr>
<tr>
<td>Mean Age, y</td>
<td>72.9 (14.0)</td>
<td>74.0 (13.5)</td>
<td>73.8 (13.6)</td>
<td>72.1 (14.6)</td>
</tr>
<tr>
<td>Mean EF (%)</td>
<td>33.3 (17.4)</td>
<td>37.8 (17.6)</td>
<td>40.9 (17.1)</td>
<td>44.4 (16.5)</td>
</tr>
<tr>
<td>Ischemic Etiology</td>
<td>50.7</td>
<td>48.8</td>
<td>44.1</td>
<td>39.2</td>
</tr>
<tr>
<td>HTN Etiology</td>
<td>13.4</td>
<td>18.1</td>
<td>25.4</td>
<td>34.8</td>
</tr>
<tr>
<td>Serum Cr&gt;2 (mg/dl)</td>
<td>20.7</td>
<td>18.0</td>
<td>18.1</td>
<td>21.5</td>
</tr>
<tr>
<td>Mean Wt change (kg)</td>
<td>-2.45 (5.00)</td>
<td>-2.68 (4.82)</td>
<td>-2.60 (4.64)</td>
<td>-2.42 (4.62)</td>
</tr>
<tr>
<td>Edema Admission</td>
<td>63.9</td>
<td>65.1</td>
<td>65.6</td>
<td>63.9</td>
</tr>
<tr>
<td>Total mortality in-hospital</td>
<td>7.2</td>
<td>3.6</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Total mortality 60-90d</td>
<td>14.0</td>
<td>8.4</td>
<td>6.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Readmission</td>
<td>30.6</td>
<td>29.9</td>
<td>30.3</td>
<td>27.6</td>
</tr>
<tr>
<td>Mean LOS, days</td>
<td>6.5 (6.6)</td>
<td>5.7 (5.3)</td>
<td>5.4 (5.0)</td>
<td>5.1 (4.8)</td>
</tr>
</tbody>
</table>

Gheorghiade M et al. JAMA. 2008;299:2656-66
In an experimental study of short-term hibernation, dobutamine infusion resulted in myocardial infarction (right) when subendocardial blood flow was further reduced from 0.17 mL/min per gram (right). With and Without indicate with and without infarction. Reproduced with kind permission of Professor Gerd Heusch, Essen, Germany.
Hospitalization for Heart Failure (HHF)

• Improving post-discharge mortality and prevention of readmissions are the most important goals for HHF patients.
Hospitalizations for Heart Failure in the United States—A Sign of Hope

Mihai Gheorghiade, MD
Eugene Braunwald, MD

Heart failure (HF) is the most common cause of hospitalization in patients older than 65 years in communities such as hypertension and renal dysfunction increased over time. Approximately 40% of these patients had diabetes and 30% had chronic obstructive pulmonary disease.

The general reduction in admission rates may reflect improvements in overall management of HF risk factors, as suggested by Gheorghiade and Braunwald.
Treat Beyond Clinical Congestion.

The main reason for admission and readmission among patients
Although this goal is often accomplished, some patients may be discharged with high left ventricular filling pressures as illustrated by high circulating natriuretic peptide levels, orthopnea, and poor exercise capacity.

A more aggressive strategy to treat “subclinical” congestion may potentially improve outcomes.
Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial

Andrew P. Ambrosy, Peter S. Pang, Sadiya Khan, Marvin A. Konstam, Gregg C. Fonarow, Brian Traver, Aldo P. Maggioni, Thomas Cook, Karl Swedberg, John C. Burnett Jr, Liliana Grinfeld, James E. Udelson, Faiez Zannad, and Mihai Gheorghiade, on behalf of the EVEREST trial investigators

Aims
Signs and symptoms of congestion are the most common cause for hospitalization for heart failure (HHF). The clinical course and prognostic value of congestion during HHF has not been systematically characterized.

Methods and results
A post hoc analysis was performed of the placebo group (n = 2061) of the EVEREST trial, which enrolled patients within 48 h of admission (median = 24 h) for worsening HF with an EF ≤ 40% and two or more signs or symptoms of fluid overload (dyspnea, edema, or jugular venous distension [JVD]) for a median follow-up of 9.9 months. Clinician-investigators assessed patients daily for dyspnea, orthopnea, fatigue, nausea, pedal edema, and JVD and rated signs and symptoms on a standardized 4-point scale ranging from 0 to 3. A modified composite congestion score (CCS) was calculated by summing the individual scores for orthopnea, JVD, and pedal edema. Endpoints were HHF, all-cause mortality (ACM), and ACM + HHF. Multivariable Cox regression models were used to evaluate the risk of CCS at discharge on outcomes at 30 days and for the entire follow-up period. The mean CCS obtained after initial therapy decreased from the mean ± SD of 4.07 ± 1.84 and the median (25th, 75th) of 4 (3.5) at baseline to 1.11 ± 1.42 and 1 (0.2) at discharge.

At discharge, nearly three-quarters of study participants had a CCS of 0 or 1 and fewer than 10% of patients had a CCS > 3. Brain natriuretic peptide (BNP) and amino terminal-proBNP, respectively, decreased from 7.24 (313, 1523) pg/mL and 4857 (2251, 9442) pg/mL at baseline to 477 (199, 1077) pg/mL, and 2834 (1218, 6675) pg/mL at discharge. Day 7. A CCS at discharge was associated with increased risk (HHF point: CCS, 9.3% C) for a subset of endpoints at 30 days (HHF: 1.06, 0.95–1.19; ACM: 1.34, 1.14–1.58; and ACM + HHF: 1.13, 1.03–1.25) and all outcomes for the overall study period (HHF: 1.07, 1.01–1.14; ACM: 1.16, 1.09–1.24; and ACM + HHF: 1.11, 1.06–1.17). Patients with a CCS of 0 at discharge experienced HHF of 2.62% and ACM of 19.1% during the follow-up period.

Conclusion
Among patients admitted for worsening signs and symptoms of HF and reduced EF, congestion improves substantially during hospitalization in response to standard therapy alone. However, patients with absent or minimal resting signs and symptoms at discharge still experienced a high mortality and readmission rate.
Adopt a Mechanistic Approach to Cardiac Abnormalities.

Heart failure is not a disease, but a manifestation of different cardiac abnormalities. Accordingly, an in-depth systematic assessment should be conducted of cardiac abnormalities (eg, valvular disease, cardiac dyssynchrony, ischemia).
**Comprehensive assessment**

<table>
<thead>
<tr>
<th>Potential targets</th>
<th>Method of assessment</th>
</tr>
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<tbody>
<tr>
<td>Congestion</td>
<td>JVP, body weight, peripheral edema</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>Blood pressure measurement</td>
</tr>
<tr>
<td>LV function, valvar disease, wall motion abnormalities, aneurysm</td>
<td>ECHO Doppler, MRI, nuclear imaging</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>Pharmacological or exercise testing with imaging</td>
</tr>
<tr>
<td>CAD</td>
<td>Cardiac catheterization and angiography</td>
</tr>
<tr>
<td>Ventricular dysynchrony (wide QRS)</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Violate but dysfunctional myocardium</td>
<td>Low-dose dobutamine ECHO, MRI</td>
</tr>
</tbody>
</table>

**Cardiac reconstruction**

(five overarching thematic targets—myocardium, coronary arteries, electrical system, pericardium, valves)

- **Myocardium**
  - LV dysfunction
    - ACE-I or ARB
    - Beta-blockers
    - Aldosterone antagonist
    - Hydralazine
    - Digoxin
    - Macronatrium
    - Micronatrium
    - Metabolic modulators

- **Coronary arteries**
  - CAD
    - Anti-platelet
    - Statins
    - Revascularization
    - Other ESC guideline recommended therapy for secondary prevention

- **Electrical system**
  - Sudden cardiac death
    - ICD
    - Beta-blockers
    - Aldosterone antagonists
  - Ventricular dysynchrony
    - CRT +/- ICD

- **Valves**
  - Surgery
  - Procedural
  - Statins
  - Per-ESC guidelines

- **Pericardium**
  - Atrial fibrillation
    - Rate control
    - Digoxin
    - Beta-blocker
    - Non-dihydropyridine calcium channel blockers
    - Warfarin
    - Rhythm control
    - MAZE procedure

**Congestion** — (salt restriction, diuretics, ultrafiltration, vasopressin antagonists)

**Hypertension** (ACE-I or ARB, beta-blockers, diuretics, others per ESC guidelines)

**Enhance Adherence** (education, disease management, performance improvement systems)
Treat Noncardiac Comorbidities.

The increasing rates of important non cardiac comorbidities, including hypertension and renal dysfunction, over the last decade, highlight the importance of targeting these conditions in the overall management of HF. In addition, diabetes, chronic obstructive pulmonary disease, and sleep apnea may also contribute to this high event rate after hospitalization.
Heart Failure With Preserved Ejection Fraction
Treat Now by Treating Comorbidities

Sanjiv J. Shah, MD
Mihai Gheorghiade, MD

Heart failure (HF) is a major public health problem, with prevalence of more than 5 million cases and an incidence of 660,000 new cases per year in the United States alone. Among patients older than 65 years, HF has become the most common discharge diagnosis and the primary cause of readmission within 60 days of discharge, resulting in estimated costs of $34.8 billion per year. Nearly half of all patients with HF have a preserved ejection fraction (HFPEF). Patients with HFPEF have a high all-cause mortality after hospitalization for HF: 2.9%, in-hospital mortality; 4%, 30- to 90-day mortality; 22% to 29%, 1-year mortality; and 65%, 5-year mortality. These data underscore the urgent need to find ways to improve outcomes for these patients.

Unlike patients with HF and reduced ejection fraction, few large randomized controlled trials have been specifically designed for patients with HFPEF. These trials have shown minimal benefit, resulting in persons concluding that there is little evidence on which to treat for patients with HFPEF. Underlying the belief is there are few evidence-based therapies for patients with HFPEF; this is the implication that adverse outcomes in these patients are driven by worsening HF, which may not necessarily be accurate. Although recent large observational studies have shown high rates of morbidity and mortality in patients with HFPEF, these studies have not documented causes of rehospitalization or death. However, data from prior observational studies and clinical trials suggest that these outcomes are driven by important comorbidities that are common in patients with HFPEF.

Patients diagnosed with HFPEF are typically elderly (mean age, 74-76 years), more often women (62%-66%), and frequently have multiple comorbidities, including hypertension (55%-77%), coronary artery disease (CAD) (36%-53%), atrial fibrillation (32%-41%), diabetes mellitus (32%-45%), chronic kidney disease (23%-26%), cerebrovascular disease (15%), as well as obesity and anemia. In the Acute Decompensated Heart Failure National Registry (ADHERE) study, 91% of patients with HFPEF had a diagnosis of hypertension, CAD, or diabetes. Secular trends demonstrate that the prevalence of comorbidities in patients with HFPEF is continuing to increase. CAD may be especially important in patients with HFPEF. Although CAD appears to be less common in patients with HFPEF than in patients with HF and reduced ejection fraction, the prevalence and severity of angiographically documented CAD in patients with HFPEF has not been well studied. In the Coronary Artery Surgery Study (CASS), in which CAD was documented by coronary angiography, the presence and extent of CAD was a major determinant of prognosis in patients with HFPEF. Similarly, in the Duke Cardiovascular Databank of patients with angiographically documented CAD, the presence of severe multivessel coronary disease has been associated with increased mortality in patients with HFPEF.

Unlike recent large outcome studies of patients with HFPEF that have primarily examined all-cause rehospitalization and all-cause mortality, prior studies have ascertained the specific causes of adverse events, which help in understanding morbidity and mortality in patients with HFPEF. Two large randomized clinical trials of patients with HFPEF and mortality data have been completed to date: the Carvedilol in Heart Failure—Preserved (CHARM-Preserved) and the Ancillary Digitalis Investigation Group (Ancillary DIG) trial, which showed that an angiotensin-receptor blocker and digoxin, respectively, did not improve survival. Although susceptible to selection bias, the CHARM-Preserved trial and Ancillary DIG trial provide important insight into the causes of morbidity and mortality in patients with HFPEF. In each trial, during approxi...
Augment Use of Underused Agents Known to Decrease Hospitalizations.

The use of digoxin is on a steep decline and mineralocorticoid antagonists are underused in patients with HF in the United States. DIG trial showed that use of digoxin reduced overall hospitalization rate by almost 30%, EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial revealed that compared with placebo, use of eplerenone reduced all-cause hospitalization by almost 25%.
Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial‡

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Aims

In the Digitalis Investigation Group (DIG) trial, digoxin reduced mortality or hospitalization due to heart failure (HF) in several pre-specified high-risk subgroups of HF patients, but data on protocol-specified 2-year outcomes were not presented. In the current study, we examined the effect of digoxin on HF death or HF hospitalization and all-cause death or all-cause hospitalization in high-risk subgroups during the protocol-specified 2 years of post-randomization follow-up.

Methods and results

In the DIG trial, 6800 ambulatory patients with chronic HF, normal sinus rhythm, and LVEF ≤45% (mean age 64 years, 26% women, 17% non-whites) were randomized to receive digoxin or placebo. The three high-risk groups were defined as NYHA class III–IV symptoms (n = 2233), LVEF <25% (n = 2256), and cardiothoracic ratio (CTR) >55% (n = 2345). In all three high-risk subgroups, compared with patients in the placebo group, those in the digoxin group had a significant reduction in the risk of the 2-year composite endpoint of HF mortality or HF hospitalization: NYHA III–IV [hazard ratio (HR) 0.65; 95% confidence interval (CI) 0.57–0.75; P < 0.001], LVEF <25% (HR 0.61; 95% CI 0.53–0.71; P < 0.001), and CTR >55% (HR 0.65; 95% CI 0.57–0.75; P < 0.001). Digoxin-associated HRs (95% CI) for 2-year all-cause mortality or all-cause hospitalization for subgroups with NYHA III–IV, LVEF <25%, and CTR >55% were 0.88 (0.80–0.97; P = 0.012), 0.94 (0.76–0.93; P = 0.001), and 0.85 (0.77–0.94; P = 0.002), respectively.

Conclusions

Digoxin improves outcomes in chronic HF patients with NYHA class III–IV, LVEF <25%, or CTR >55%, and should be considered in these patients.
### Results by high-risk patients subgroups: HF Hospitalization or HF mortality in DIG Trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>% (events/total)</th>
<th>Absolute risk difference</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NYHA class III or IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>40% (445/1105)</td>
<td>29% (329/1118)</td>
<td>– 11%</td>
<td>0.65 (0.57–0.75)</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>LVEF &lt;25%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>39% (444/1129)</td>
<td>27% (304/1127)</td>
<td>– 12%</td>
<td>0.61 (0.53–0.71)</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CTR &gt;55%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>40% (465/1170)</td>
<td>29% (336/1175)</td>
<td>– 11%</td>
<td>0.65 (0.57–0.75)</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High risk (either of the above)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>36% (783/2167)</td>
<td>26% (566/2191)</td>
<td>– 10%</td>
<td>0.66 (0.59–0.73)</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
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</tbody>
</table>

Gheorghiade et al, LBCT ESC HF Belgrade 2012
Mitochondria as a Therapeutic Target in Heart Failure

Marina Bayeva, PhD,* Mihai Gheorghiade, MD,† Hossein Ardehali, MD, PhD*

Chicago, Illinois

Heart failure is a pressing public health problem with no curative treatment currently available. The existing therapies provide symptomatic relief, but are unable to reverse molecular changes that occur in cardiomyocytes. The mechanisms of heart failure are complex and multiple, but mitochondrial dysfunction appears to be a critical factor in the development of this disease. Thus, it is important to focus research efforts on targeting mitochondrial dysfunction in the failing heart to revive the myocardium and its contractile function. This review highlights the 3 promising areas for the development of heart failure therapies, including mitochondrial biogenesis, mitochondrial oxidative stress, and mitochondrial iron handling. Moreover, the translational potential of compounds targeting these pathways is discussed. (J Am Coll Cardiol 2012;xx:xxx) © 2012 by the American College of Cardiology Foundation
Mitochondrial dysfunction is at the basis of a constellation of metabolic abnormalities that significantly contribute to Chronic conditions and diseases.
Summary

- Myocardium as a main target for therapy
- Hospitalized Heart Failure (HHF)
- Practical consideration to improve HHF outcomes