New and Experimental Therapies for Heart Failure

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Director of Heart Improvement Program
at Bryan Heart
Adjunct Professor in the Department of Nutrition and Health Sciences at UNL

Disclosure
Currently on the speaker bureau’s for the following companies related to this talk:

Colanor – Amgen
Entresto – Novartis

All honoraria to Big Heart Initiative charitable fund

New Therapies
I.) Recently Released Drugs
   A. Colanor – Ivabradine
   B. LCZ696 - Entresto
II.) Update Old Studies
   A. Respicardia
   B. FIX
   C. INNOVATE
   D. CardioMEMs
III.) New Studies
   A. Baroreceptor Stimulation
   B. Paragon - LCZ 696 - Entresto
   C. Genetic AF - Bucindolol
IV.) Conclusion
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Ivabradine or Colanor

Heart Rate vs Hospitalization Rate
Higher HR associated with ↑ HF Hospitalization

Castagno JACC 2012
Ivabradine or Corlanor

Mortality + Morbidity
Directly Related to Heart Rate

(CHARM study & Others)

Higher Baseline Heart Rates Have Been Associated with Greater Rates of HF Hospitalization

Baseline Patient Characteristics from CHARM

- The purpose of this retrospective analysis of the CHARM study was to determine the relationship between baseline resting heart rate and outcomes. Of the 7,560 patients with HF, those who were randomized to the lower rate arm had lower mortality.

<table>
<thead>
<tr>
<th>HEART RATE GROUP AT BASELINE</th>
<th>REDUCED LEFT VENTRICULAR EJECTION FRACTION PATIENTS (LVEF ≤ 40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1,414</td>
</tr>
<tr>
<td>Median baseline heart rate</td>
<td>60</td>
</tr>
<tr>
<td>Interquartile range (bpm)</td>
<td>(54–64)</td>
</tr>
<tr>
<td>Hospital admission for HF, [n]</td>
<td>69.4%</td>
</tr>
<tr>
<td></td>
<td>(1,186)</td>
</tr>
<tr>
<td>P value for trend</td>
<td></td>
</tr>
</tbody>
</table>

- Greater percentages of patients in the highest heart rate tertiles had been previously admitted to the hospital because of HF decompensation.

Corlanor® Is a First-in-Class, HCN Channel Blocker That Lowers Heart Rate

- The first new treatment for chronic heart failure since 2006.
- Blocks a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker.
- Lowers heart rate with no effect on ventricular repolarization or myocardial contractility (no negative inotropic effect).
- At recommended doses, heart rate reduction with Corlanor® is approximately 10 bpm at rest and during exercise.
- Corlanor® causes a dose-dependent reduction in heart rate.
- The size of the effect of Corlanor® is dependent on baseline heart rate.
Ivabradine or Corlanor + Effect on:
1.) NYHA
2.) KCHF
3.) EQ5D
4.) LV End Systolic Size  65 → 58
5.) Stroke Volume     59 → 67
6.) Exercise Duration - Better than Carvedilol
7.) NT BNP
8.) Peak VO₂
9.) EF               ≈ 2.7%
Ivabradine or Corlanor

At best if HR > 77
Target HR 50-60

Corlanor® Has an Established Safety Profile

<table>
<thead>
<tr>
<th>MOST COMMON ADVERSE EVENTS</th>
<th>Corlanor® (N = 3,260)</th>
<th>Placebo (N = 3,278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>10%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Hypertension, blood pressure increased</td>
<td>8.9%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>8.3%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Phosphenes, visual brightness</td>
<td>2.8%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

> Phosphenes (Luminous Phenomena) are transient enhanced brightness in a targeted area of visual field, usually triggered by sudden variations in light intensity.
> - Often reported to be of mild to moderate intensity and lead to treatment discontinuation in <1% of patients

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Phrenic Nerve Pacer for CSA

Status: Enrollment over
Study: In progress

SLEEP DISORDERED BREATHING
Cycle of CSA Intertwined with Cycle of Heart Failure

- Cycle of CSA
- Cycle of Heart Failure
- Hypoperfusion
- Hypoxemia
- Hypercapnia

- Cycle of CSA
- Cycle of Heart Failure
- Hypoperfusion
- Hypoxemia
- Hypercapnia

CSA Increases Mortality in Heart Failure Patients

- The relationship of increased mortality and CSA was constant across all levels of severity of CSA.
- Mortality increases with increased AHI.
- Mortality remains high even with optimal current therapies.

Procedure Similar to Other Cardiac Device Implants

- Procedure occurs in the EP lab.
- Device implanted in right pectoral region.
- Similar lead implant approach, just different target vessels.
- Procedure length approx. 2-3 hrs.
- Hospitalization similar to pacemaker/ICD.
Cardiac Concepts’ Approach for Heart Failure & CSA
The RespiCardia™ System

- Unilateral transvenous lead placed in the left pericardiophrenic vein for phrenic nerve stimulation (alternatively right brachiocephalic vein, when lead available)
- Optional sensing lead placed in the azygos vein
- Implantable pulse generator with proprietary algorithm designed to restore natural breathing patterns & decrease hypoxia episodes

TherapyEliminated Respiratory Instability & Improved Oxygenation

Clinical Results
Therapy shows improvement in indices of sleep apnea

- Central Apnea Index
- Central Apnea Index
- Central Apnea Index
- Arousal Index
- Oxygen Desaturation Index
- Arousal Index
- Apnea Hypopnea Index

- 12 / 13 patients had >70% reduction in CAI
- % change = -91.0 p<0.0001*
- % change = -49.0 p=0.0006*
- % change = -55.0 p=0.001*
- % change = -51.0 p=0.0005*
- % change = -55.0 p=0.001*
- % change = -49.0 p=0.0006*
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Optimizer for CHF Narrow Complex
Status: Enrollment ongoing
Preliminary Data: EF ↑

Regional to Global Effects

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seconds</td>
<td>Hours</td>
<td>Months</td>
</tr>
<tr>
<td>CCM signals directly reach the myocardium in an ellipsoid area ~4x7cm by electronic conduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate effects on activity of key regulatory proteins (Phospholamban)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>This rapid effect allows for immediate local change in contractile function and acute improvement in contractile function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies show up-regulation and down-regulation of genes consistent with reversal of fetal gene program to normal adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local changes result in unloading of remote areas and normalization of gene expression in these remote areas via improved regional electronic coupling between cells increasing the area of direct signal effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over time, reduced mechanical stresses interrupt the &quot;remodeling cascade&quot; and induce global reverse remodeling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy studies show remote effects by 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D Echo human studies &amp; ventriculography studies in animals demonstrate reverse remodeling</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Randomized Controlled Studies

**FIX-CHF-4**
- **Europe**
- n=164
- Randomized Controlled Double-Blind
- IMPROVED Exercise Tolerance & QoL

**FIX-HF-5 I**
- **US**
- n=50
- Feasibility Randomized Controlled Double-Blind
- IMPROVED Exercise Tolerance & QoL

**FIX-HF-5 II**
- **US**
- n=428
- Pivotal Multicenter Randomized Controlled
- IMPROVED Exercise Tolerance & QoL

**FIX-HF-5 II Subgroup Analysis – Results**

**FIX-HF-5 II Subgroup Analysis – Results**
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Vagas Nerve Stimulator

Status: Enrollment ongoing
Preliminary Data: EF ↑, HF ↓
Increased Exercise Capacity

P-values are versus paired baseline

Improved Quality of Life

P-values are versus paired baseline

Left Ventricular Ejection Fraction Increase

P-values are versus paired baseline
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Agenda

- Company Overview
- Background and Rationale
- HF Pressure Measurement System
- Review of Feasibility Study
- CHAMPION Study Plan

Heart Sensor Placement in Pulmonary Artery

Implant can be EASILY placed in cath lab

Patient Data Viewed on Secure Web

- Real-time
- Daily access
- Easy-to-read
- Physician Alerts
- Home transmissions
- Over 3000 readings
CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III heart failure patients

Protocol Review

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Barostim neo System Technology Platform

Programmable Barostim neo Platform

- Single electrode placed outside the Carotid Artery
- Implantable Pulse Generator (IPG) Implantable under the skin

The system includes three components:

1. Implantable Pulse Generator (IPG): Implantable under collar bone and provides control and delivery of electrical energy through Carotid Artery
2. Carotid Artery Lead: Single lead wire placed in either Carotid Artery and connected to IPG
3. Programmer System: External device used to program and adjust the therapy non-invasively

The system is minimally invasive and highly adaptable:

- Single-side access
- Non-invasive insertion and controlled at physician’s office
- Therapy can be adjusted to meet each patient’s individual needs as they change over time, providing personalized treatment and evolving results of non-surgical therapy
The Baroreflex as a Therapeutic Target

Carotid Baroreceptor Stimulation

Integrated Autonomic Nervous System Response

- Inhibits Sympathetic Activity
- Enhances Parasympathetic Activity

Mechanisms of Barostim in the Treatment of Heart Failure

<table>
<thead>
<tr>
<th>Managing Objective</th>
<th>Adequately Meets Barostim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce cardiac, lung, coronary &amp; systemic pressures</td>
<td>Reversal of dilated &amp; hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Reduce heart rate and promote vagal cardiac arrhythmia</td>
<td>Reduced sympathetic tone</td>
</tr>
<tr>
<td>Initiate activation of PAM and sympathetic nervous system</td>
<td>Reduced motor neuron-mediated nerve secretion</td>
</tr>
<tr>
<td>Reduce venous congestion &amp; filling pressures</td>
<td>Increased venous capacitance</td>
</tr>
<tr>
<td>Reduce myocardial ischemia</td>
<td>Coronary artery vasodilation</td>
</tr>
<tr>
<td>Increase exercise tolerance</td>
<td>Increased muscle sympathetic nerve activity</td>
</tr>
<tr>
<td>Reduce obstructive sleep apnea</td>
<td>Reduced sympathetic tone</td>
</tr>
<tr>
<td></td>
<td>Reduced upper airway smooth muscle tension</td>
</tr>
</tbody>
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Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction

William Abraham, MD1, Michael Zile, MD2, Fred Weaver, MD3, Christian Butter, MD4, Anique Ducharme, MD5, Marcel Hallbach, MD6, Didier Klug, MD7, Eric Lovett, PhD8, Jochen Müller-Ehmsen, MD9, Jill Schafer, MS10, Michele Senni, MD11, Vijay Swanarup, MD12, Rolf Wachter, MD13, William Little, MD14; on behalf of the BAT for HFrEF Study Group

1Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA; 2Department of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA; 3Division of Cardiology, University of California, San Francisco, CA, USA; 4Department of Medicine, University of California, San Francisco, CA, USA; 5Cardiovascular Division, University of Wisconsin, Madison, WI, USA; 6Division of Cardiology, University of Florida, Gainesville, FL, USA; 7Division of Cardiology, University of Utah, Salt Lake City, UT, USA; 8Department of Cardiology, University of California, Los Angeles, CA, USA; 9Department of Cardiology, University of Florida, Gainesville, FL, USA; 10Division of Cardiology, University of Miami, Miami, FL, USA; 11Division of Cardiology, University of Miami, Miami, FL, USA; 12Division of Cardiology, University of Miami, Miami, FL, USA; 13Division of Cardiology, University of Miami, Miami, FL, USA; 14Division of Cardiology, University of Miami, Miami, FL, USA.
BAT Significantly Improves NYHA Class

- Improvement in NYHA class with BAT treatment compared to baseline.
- Significant difference observed with p-values provided for each comparison.

BAT Significantly Improves Quality of Life Score

- Bar graph showing improvement in Quality of Life Score with BAT treatment.
- Significant difference observed with p-values provided.

BAT Significantly Improves 6-MHW Distance

- Bar graph showing improvement in 6-Minute Walking Distance with BAT treatment.
- Significant difference observed with p-values provided.
Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction: Safety and Efficacy in Patients With and Without Cardiac Resynchronization Therapy

Michael Zile, MD, William Abraham, MD, Fred Weaver, MD, Christian Butter, MD, Anique Ducharme, MD, Marcel Halbach, MD, Didier Klug, MD, Eric Lovett, PhD, Jochen Müller-Ehmsen, MD, Jill Schafer, MS, Michele Senni, MD, Vijay Swarup, MD, Rolf Wachter, MD, William Little, MD; on behalf of the BAT for HFrEF Study Group
MLWHF QoL Score

6-MHW Distance

NT-proBNP
Summary

Baroreflex Activation Therapy is safe in HFrEF.

BAT significantly improves quality of life score, exercise capacity, NT-proBNP, and possibly the burden of HF hospitalizations.

Results were most pronounced and statistically significant in No-CRT patients.

Each of these observations should be confirmed in an adequately powered, prospective, randomized clinical outcome trial.
Fully Approved US Pivotal Clinical Trial

2015

Pivotal Heart Failure Clinical Trial – Key Enrollment Criteria

Key Inclusion Criteria

- NYHA Class III
- Left ventricular ejection fraction ≤ 35%
- Heart failure defined as:
  - HF hospitalization within 12 prior months, BNP ≥ 100 or NT-proBNP ≥ 400, OR
  - BNP ≥ 400 or NT-proBNP ≥ 1600
- On optimal, guideline-directed, stable HF therapy for at least 4 weeks prior to enrollment
  - ≤ 100% increase or 50% decrease in dose of any medication other than a diuretic

Key Exclusion Criterion

- Patients with a CRT(D) implant or indication for CRT.

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**LCZ696 Angiotensin Receptor Neprilysin Inhibitor (ARNI)**

LCZ696 is a new compound with a complex molecular structure.

LCZ696 is the first in a new class of compounds called angiotensin receptor neprilysin inhibitor (ARNIs).

![Molecular structure of LCZ696](image)

**System while Simultaneously Blocking the RAAS Restoring the Neurohumoral Balance in HF**

![Diagram showing LCZ696's role in the RAAS system](image)

**LCZ696 Mechanism of Action**

- Activation of the RAAS can lead to long-term harmful effects in HF.

- LCZ696 targets the RAAS to restore neurohumoral balance.

- Pathologic effects:
  - Hypertension
  - Proteinuria
  - Heart failure

- Physiologic response:
  - Vasodilation
  - Decreased sodium and water retention
  - Improved cardiac output and renal perfusion
PARADIGM

LCZ696 vs Enalapril (High dose)
for Heart Failure (EF<35)

Endpoint - Death or HF Hospitalization

N = 8458

STOP RULES

Stop rules made so conservative ... mathematically almost impossible to stop trial early - Milton Packer

Stopped Early for Marked Improvement in LCZ group

There has not been this much anticipation in the field in 20 years - Clyde Yancy 2014

Figure A
Time to First Occurrence of CV Death or Heart Failure Hospitalizations in PARADIGM-HF

p=0.0001
HR (95%CI): 0.80 (0.73, 0.87)

No. at risk
ENTRESTO: 4,181, 3,822, 3,663, 3,518, 3,273, 3,022, 2,773, 2,523, 2,276
Enalapril: 4,212, 3,852, 3,693, 3,548, 3,403, 3,258, 3,113, 2,968, 2,823

Bryan
PARAMOUNT-HF

LCZ696 Entresto vs Valsartan

For Diastolic Heart Failure
PARAMOUNT Trial

Reduction in NT-proBNP from baseline to Week 12 was significantly greater with LCZ696 compared with valsartan (P = 0.005)

<table>
<thead>
<tr>
<th>NT-proBNP</th>
<th>LCZ696 (n=134)</th>
<th>Valsartan (n=132)</th>
<th>LCZ696 vs valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, pg/mL (95% CI)</td>
<td>703 (670, 914)</td>
<td>662 (733, 1,012)</td>
<td>0.77 (0.94, 1.52) P = 0.005</td>
</tr>
<tr>
<td>Week 12, pg/mL (95% CI)</td>
<td>605 (112, 714)</td>
<td>835 (710, 981)</td>
<td></td>
</tr>
</tbody>
</table>

*7.7% trend of the change from baseline treatment effect between LCZ696 and valsartan. LCZ696 reduced NT-proBNP 23% more than valsartan with a p-value of 0.005.

Reference: [Journal Name], 2015; 98: 591-598.
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Genetic AF Trial
Bucindolol vs Placebo
All-Cause Mortality after new onset AF (Group 1), compared to No AF (Group 2) and chronic/established AF (HFrEF, BEST trial)

HF Outcome by AF and LVEF

No approved heart failure (β-blocker) has shown efficacy for reducing major morbidity and mortality in HFrEF patients with permanent AF (Steenstra M et al. JACC-HF 1:21-28, 2013).

"However, all is not so original at the intersection of AF and HFrEF, which occurs commonly (2) due to overlap in their underlying pathophysiologic 20, 21."
I. Current State of Rhythm Control in CHF
AMIODARONE

GOOD NEWS-BAD NEWS

Approximately 15% of patients taking amiodarone will experience an adverse event within the first year of use. 50% will experience an adverse event with long term use. 16% have to stop the drug by the end of five years for a serious adverse event. **

** CHF stat trial

Table 1. Incidence (%) of adverse effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Amiodarone</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>2</td>
<td>2</td>
<td>0.40</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15-30</td>
<td>&lt;3</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypothyroidal</td>
<td>3-6</td>
<td>0-1</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2.3</td>
<td>0.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sinus</td>
<td>0.6</td>
<td>0.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>2-10</td>
<td>&lt;10</td>
<td>0.20</td>
</tr>
<tr>
<td>Skin</td>
<td>1.3</td>
<td>0.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Optical nerve</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

** CHF stat trial

Adverse Events Associated with Discontinuation of Amiodarone

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Amiodarone</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypothyroidal</td>
<td>1.2</td>
<td>0.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2.5</td>
<td>0.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>3-6</td>
<td>&lt;10</td>
<td>0.20</td>
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<td>Optical nerve</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0001</td>
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</tbody>
</table>
II. Bucindolol in CHF
Anti-adrenergic Agents with Phase 2 or 3 Heart Failure Clinical Trial Data

<table>
<thead>
<tr>
<th>Compound</th>
<th>β₂-AR blockade</th>
<th>β₁-AR blockade</th>
<th>α₁-AR blockade</th>
<th>α₂-AR blockade</th>
<th>MS blocking</th>
<th>NS blocking</th>
<th>RA blocking</th>
<th>β₂-AR selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>++ + + + + + + + +</td>
<td>+ + + + + + + +</td>
<td>+ + + + + + + +</td>
<td>+ + + + + + + +</td>
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<td>+ + + + + + + +</td>
<td>+ + + + + + + +</td>
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<tr>
<td>Metoprolol</td>
<td>+ + + + + + + +</td>
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<td>+ + + + + + + +</td>
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<tr>
<td>Bisoprolol</td>
<td>+ + + + + + + +</td>
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</tr>
<tr>
<td>Carvedilol</td>
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<td>+ + + + + + + +</td>
<td>+ + + + + + + +</td>
<td>+ + + + + + + +</td>
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</tbody>
</table>

A TRIAL OF THE BETA-BLOCKER BUCINDOLOL IN PATIENTS WITH ADVANCED CHRONIC HEART FAILURE

**Abstract**

Background: Although beta-adrenergic– receptor antagonists reduce mortality and morbidity in patients with trials to moderate chronic heart failure, their effect on survival in patients with more advanced heart failure is unknown. We conducted a randomized, double-blind, placebo-controlled trial of bucindolol (a beta-blocker and a left ventricular ejection fraction (LVEF) undergoing a beta-blocker Investigators: The BUCINDOLOL in Advanced CHRONIC HEART FAILURE (BUCINDOL) trial enrolled 728 patients with heart failure designated as New York Heart Association (NYHA) functional class III or IV, severe LVEF (≤35%) and a left ventricular ejection fraction (LVEF) undergoing a beta-blocker (BUCINDOL) trial enrolled 728 patients with heart failure designated as New York Heart Association (NYHA) functional class III or IV, severe LVEF (≤35%) and a left ventricular ejection fraction (LVEF) undergoing a beta-blocker (BUCINDOL). All patients were randomized to bucindolol or placebo, enrolled a total of 728 patients, and followed for the primary and safety endpoints for any reason.

Results: The data and safety monitoring board recommended stopping the trial after the seventh interim analysis at 214 (placebo) and 176 (bucindolol) patients. There was no difference in treatment effect between the two groups (primary outcome).

4/1/2015
Beta-1 Adrenergic Receptor Polymorphisms
(26 total & 13 NS SNPs (1.8%/2.7% nt/a. variation)

\[ \beta_1 \, 389 \, \text{Arg/cGT Gly:} \]
- 3-4 x higher signal Tx capacity
- More R*T
- Higher binding affinity for NE

Mason DA et al JBC 1999; Taylor M, Britton MR, Cong Heart Failure 2004;
Lappet et al PNAS 2006; Walsh et al J Cardiac failure 2008; O'Connor et al PLOS ONE, 2012
III. Bucindolol in AF

No evidence that approved heart failure β-blockers lower mortality in AF/HFREF

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<table>
<thead>
<tr>
<th>Beta-Blocker</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td></td>
<td>1.04 (1.00 - 1.08)</td>
<td>0.05</td>
</tr>
<tr>
<td>Nebivolol</td>
<td></td>
<td>1.02 (0.97 - 1.08)</td>
<td>0.49</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td></td>
<td>1.01 (0.97 - 1.06)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Combined All-Cause Mortality Risk

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β-blockers do not decrease HF endpoints in HF/EF patients in “permanent” AF (exception is bucindolol in β-389 Arg/Arg genotype)

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ACM = all cause mortality
HFRI = Heart failure hospitalization
COP = cardiovascular mortality
ṣe = means of subject

IV. Genetic AF Trial
Who to refer

1. Afib -- symptoms or duration more than 5 min in last 120 days
2. EF less than 50%
3. Any Symptoms

New Therapies
I.) Recently Released Drugs
   A. Colanor – Ivabradine
   B. LCZ696 - Entresto
II.) Update Old Studies
   A. Respicardia
   B. FIX
   C. INNOVATE
   D. CardioMEMs
III.) New Studies
   A. Baroreceptor Stimulation
   B. Paragon – LCZ 696 - Entresto
   C. Genetic AF - Bucindolol
IV.) Conclusion
Conclusions

1. New important drugs
   1. Entresto
   2. Colanor
2. Multiple experimental therapies
   look promising ... results pending...
   available soon
3. BHIP now starting to evaluate several
   exciting NEW therapies