Contemporary Medical Management of Heart Failure

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2/10/17
Epidemiology of Heart Failure in the US

- More deaths from heart failure than from all forms of cancer combined
- 550,000 new cases/year
- 4.7 million symptomatic patients; estimated 10 million in 2037

In the Worcester Heart Failure Study, the total death rates were high throughout the 5-year follow-up period among patients discharged after hospitalization for decompensated heart failure.
Objectives

• Ivabradine
• Sacubitril/valsartan
• Valley Transitional Care Program
Goal Directed Background Therapy
ACC/AHA/HFSA 2010 Guidelines

- ACE-I or ARB (NYHA Class I-IV) with EF ≤ 40%
- Beta blockers (NYHA Class II-IV) with EF ≤ 40%
  - Carvedilol, bisoprolol, metoprolol CR/XL
- MRAs (NYHA Class II-IV) with EF < 35%
  - < 40% after MI
- Hydralazine and isosorbide dinitrate with EF < 40% in African Americans
- Digoxin (NYHA Class II-III) if symptomatic
Ivabradine: Specific and Selective Inhibitor of the $I_f$ Ion Channel

Channel principally responsible for the SA Node Pacemaker Current

Ivabradine: pure heart rate reduction

$I_f$ inhibition reduces the diastolic depolarization slope, and thereby lowers heart rate

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Karl Swedberg, Michel Komajda, Michael Bohm, Jeffrey S Bove, Ian Ford, Ariane Dubost-Bruma, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

Summary
Background Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure.

Methods Patients were eligible for participation in this randomised, double-blind, placebo-controlled, parallel-group study if they had symptomatic heart failure and a left-ventricular ejection fraction of 35% or lower, were in sinus rhythm with heart rate 70 beats per min or higher, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a β blocker if tolerated. Patients were randomly assigned by computer-generated allocation schedule to ivabradine thrice a maximum of 7.5 mg twice daily or matching placebo. Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure. Analysis was by intention to treat. This trial is registered, number ISRCTN70429960.

Findings 6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). Data were available for analysis for 3241 patients in the ivabradine group and 3264 patients allocated placebo. Median follow-up was 22.9 (IQR 18.28) months. 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0.82, 95% CI 0.75–0.90, p<0.0001). The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo vs 514 [16%] ivabradine; HR 0.74, 0.66–0.83; p<0.0001) and deaths due to heart failure (151 [5%] vs 113 [3%]; HR 0.74, 0.58–0.94, p=0.014). Fewer serious adverse events occurred in the ivabradine group (3388 events) than in the placebo group (3847; p=0.025). 150 (5%) of ivabradine patients had symptomatic bradycardia compared with 32 (1%) of the placebo group (p<0.0001). Visual side-effects (phosphene) were reported by 89 (3%) of patients on ivabradine and 17 (1%) on placebo (p<0.0001).

Interpretation Our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder.

Funding Servier, France.

Lancet, Sept. 11, 2010
SHIFT Trial

- Randomized, double-blinded, placebo controlled
- 6,500 subjects
  - Male (76%), Caucasian (89%)
  - Class II – IV heart failure, EF<35%, HR>70bpm
  - Admission for heart failure in the previous 12 months
- On optimal medical management
  - 90% on BB, 84% on ACE/ARBs, 60% Aldo antagonists
- Ivabradine vs. placebo, followed for 22.9 months
- Primary endpoint: composite of CV death or hospital admission for heart failure
### Beta Blocker use in SHIFT

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine group (n=3241)</th>
<th>Placebo group (n=3264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at target dose of β blocker*</td>
<td>743 (26%)</td>
<td>745 (26%)</td>
</tr>
<tr>
<td>Patients at ≥50% target dose of β blocker*</td>
<td>1581 (56%)</td>
<td>1600 (56%)</td>
</tr>
<tr>
<td>Reasons for failure to reach target dose*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>933 (44%)</td>
<td>952 (45%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>676 (32%)</td>
<td>670 (32%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>284 (14%)</td>
<td>302 (14%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>267 (13%)</td>
<td>245 (12%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>134 (6%)</td>
<td>125 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>199 (9%)</td>
<td>219 (10%)</td>
</tr>
<tr>
<td>Patients not receiving β blocker</td>
<td>344 (11%)</td>
<td>341 (10%)</td>
</tr>
<tr>
<td>Reasons for non-prescription of β blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>126 (37%)</td>
<td>109 (32%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>59 (17%)</td>
<td>68 (20%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>35 (10%)</td>
<td>39 (11%)</td>
</tr>
<tr>
<td>Cardiac decompensation</td>
<td>23 (7%)</td>
<td>31 (9%)</td>
</tr>
<tr>
<td>Dizziness or bradycardia</td>
<td>24 (7%)</td>
<td>17 (5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (5%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Raynaud or peripheral arterial disease</td>
<td>16 (5%)</td>
<td>20 (6%)</td>
</tr>
</tbody>
</table>
Cardiovascular Death and Heart Failure Admissions

Graph showing the percentage of patients with primary composite endpoint (%), with two lines representing Placebo (937 events) and Ivabradine (793 events). The hazard ratio (HR) is 0.82 (95% CI 0.75-0.90), p<0.0001.
Heart Failure Admissions

Placebo (672 events)
Ivabradine (514 events)

HR 0.74 (95% CI 0.66–0.83), p<0.0001
Deaths due to Heart Failure

Placebo (151 events)
Ivabradine (113 events)

HR 0.74 (95% CI 0.58–0.94), p=0.014
What Can We Conclude from the SHIFT Trial?

• In patients with all-cause cardiomyopathy (EF<35%), and heart rates > 70bpm
  – There was no difference total cardiovascular mortality
  – Ivabradine reduces
    • Mortality due to heart failure
    • Heart failure admissions
### Recommendation for Ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
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<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF $\leq 35%$) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).</td>
</tr>
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</table>

Ivabradine is a new therapeutic agent that selectively inhibits the $I_f$ current in the sinoatrial node, providing heart rate reduction. One RCT demonstrated the efficacy of ivabradine in reducing the composite endpoint of cardiovascular death or HF hospitalization (38). The benefit of ivabradine was driven by a reduction in HF hospitalization. The study included patients with HFrEF (NYHA class II-IV, albeit with only a modest representation of NYHA class IV HF) and left ventricular ejection fraction (LVEF) $\leq 35\%$, in sinus rhythm with a resting heart rate of $\geq 70$ beats per minute. Patients enrolled included a small number with paroxysmal atrial fibrillation ($<40\%$ of the time) but otherwise in

See Online Data Supplement 4.
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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BACKGROUND

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-
**Natriuretic Peptide System**

- pro-BNP
- BNP
- NT-pro-BNP

**Renin-Angiotensin System**

- angiotensinogen (liver secretion)
- angiotensin I
- angiotensin II
- AT₁ receptor

**Heart Failure**

- LCZ696
- AHU377
- Valsartan
- LBQ657

**Inactive Fragments**

- Vasodilation
- ↓ blood pressure
- ↓ sympathetic tone
- ↓ aldosterone level
- ↓ fibrosis
- ↓ hypertrophy
- Natriuresis / Diuresis
Methods

• Randomized, multi-center, double blind trial
• 8442 patients with Class II-IV HFrEF (< 40%)
  • 71.6% NYHA Class II
• Primary outcome – composite
  • Death from cardiovascular cause, or
  • Hospitalizations for HF
Results

Trail stopped early after median f/u of 27 months b/c the boundary for an overwhelming benefit with LCZ696 had been crossed
### Table 2. Primary and Secondary Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite outcome — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary outcomes — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</td>
<td>-2.99±0.36</td>
<td>-4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function§</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
### Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (<em>Level of Evidence: A</em>) (9-14), OR ARBs (<em>Level of Evidence: A</em>) (15-18), OR ARNI (<em>Level of Evidence: B-R</em>) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
</tbody>
</table>
Valley’s heart failure program helps keep patients out of hospital

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THE RECORD
30-Day Readmission Rate HF

2014
2015
2016

National Crude
Valley Hospital
TCP

Valley Health System
In affiliation with
Cleveland Clinic
Heart and Vascular Institute
Unique Aspects to Heart Failure Program

• Multidisciplinary team
  – HF APPs
  – RNs
  – Pharmacists
  – Social Workers
  – Mobile Health
  – Home Care & Hospice
  – Post-acute Partners

• “High Touch”
When to refer to a HF Specialist

- HF hospitalization
- Difficulty up-titrating neurohormonal blockade
- Need to reduce doses of neurohormonal blockade
- Persistent NYHA Class III-IV symptoms
- Deterioration of renal/liver function
- Increasing diuretic requirements
Questions