Disruptive Treatment in HF: Combination Therapies for the Home Run
May 10, 2019
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University of Calgary
Past President CHFS
Calgary, AB

John Klein
Montreal, QC
Speaker Disclosures
Dr. Nadia Giannetti

• **Consulting Fees/Honoraria:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer Alliance, Novartis, Servier

• **Clinical Trials:** Amgen, Boehringer Ingelheim, Merck, Novartis, Pfizer, Servier

• **Speaker Fees:**

• **Other:**
Speaker Disclosures
Dr. Peter Liu

• **Consulting Fees/Honoraria:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Roche, Sanofi, Servier

• **Clinical Trials:** Roche

• **Speaker Fees:**

• **Other:**
Speaker Disclosures
Dr. Kim Connelly

• Received honoraria, advisory board and/or grant support from Merck, AstraZeneca, Boehringer Ingelheim, Janssen, Servier, Eli Lilly, Ferring and Novo Nordisk

• Holds patent for linagliptin and HF
Speaker Disclosure
Dr. Jonathan Howlett

- Relationships with commercial interests:
  - Grants/Research Support: AstraZeneca, Merck, Servier, Pfizer, Novartis, Medtronic, Bayer
  - Speakers Bureau/Honoraria: Bayer, Servier, Boehringer Ingleheim, Novartis
  - Consulting Fees: General Electric, Government of Canada and Alberta, Novo Nordisk, AstraZeneca, Merck, Servier, Pfizer, Novartis, St. Jude, Bayer
  - Medical Advisory Board: Cardiol
Speaker Disclosures
Mr. John Klein

• Relationships with commercial interests:
  • Grants/Research Support:
  • Speakers Bureau/Honoraria: Servier
  • Consulting Fees:
  • Other:
Learning Objectives

• Reinforce the importance of in-hospital initiation of evidence-based therapies

• Highlight the early impact of HR lowering on heart function

• Recognize the benefits to patients of early optimization of evidence-based therapies in HF
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:55 am - 12:00 pm</td>
<td>Welcome and Introduction</td>
<td>Nadia Giannetti, MD</td>
</tr>
<tr>
<td>12:00 - 12:05 pm</td>
<td>Call to Action</td>
<td>John Klein</td>
</tr>
<tr>
<td>12:05 - 12:20 pm</td>
<td>Optimizing HF Therapies as Early as Possible</td>
<td>Jonathan Howlett, MD</td>
</tr>
<tr>
<td>12:20 - 12:25 pm</td>
<td>Panel Discussion</td>
<td>Nadia Giannetti, MD</td>
</tr>
<tr>
<td>12:25 - 12:45 pm</td>
<td>Imaging the Heart: Early Impact of Lowering HR on Heart Function</td>
<td>Kim Connelly, MD</td>
</tr>
<tr>
<td>12:45 - 12:50 pm</td>
<td>Panel Discussion</td>
<td>Nadia Giannetti, MD</td>
</tr>
<tr>
<td>12:50 - 12:55 pm</td>
<td>Tying it all Together</td>
<td>Peter Liu, MD</td>
</tr>
<tr>
<td>12:55 - 1:10 pm</td>
<td>Questions and Answers</td>
<td>ALL</td>
</tr>
<tr>
<td>1:10 pm</td>
<td>Closing Remarks and Evaluations</td>
<td>Peter Liu, MD</td>
</tr>
</tbody>
</table>
Question 1: Which of the following medical therapies have been shown to improve survival in patients with heart failure?

1. ACE-inhibitors
2. Beta-blockers
3. MRAs
4. ARNIs
5. Ivabradine
6. All of the above
7. 1,2,3
8. 1,2,3,4
Question 2: Which of the following is/are independent predictors of mortality?

1. NYHA class
2. Systolic BP
3. Creatinine
4. LVEF
5. Heart rate
6. All of the above
7. 1,2,3
8. 1,2,3,4
Question 3: What can be said that is true about recovery of LVEF in patients with HFrEF following ACE/BB/MRA?

1) Almost half exhibit some degree of improvement in LVEF
2) 30% will normalize EF
3) More than 70% will still have HFrEF even if they improve EF
4) Men have better EF recovery than women
5) EF improvement does not improve prognosis during the first year
Question 4: What statement best describes your understanding of initiation of in-hospital therapies for HFrEF (assume eligible for all therapies)?

1) Triple therapy should be optimized prior to initiation of any 'new' therapies such as ARNi or SNI
2) Patients should be started on ARNi while in hospital but not SNI
3) Patients should be started on both ARNi and SNI while in hospital
4) New therapies should only be started in outpatient population
Call to Action
John Klein
Optimizing HF Therapies as Early as Possible

or Why can’t HF treatment be more like cancer treatment?

Jonathan Howlett
MD, FRCPC, FACC
Libin Cardiovascular Institute
Survival of New Onset HF in UK
Crude CHF Deaths in Canada
Angiotensin Neprilysin Inhibition with LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System
Primary composite endpoint and components in patients with HR ≥ 77 bpm at baseline (N=3357)

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine (N=1657)</th>
<th>Placebo (N=1700)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPY  n  %  PY</td>
<td>NPY  n  %  PY</td>
<td>E  95% CI  p-value</td>
</tr>
<tr>
<td>Primary composite endpoint</td>
<td>2709  454  27.40  16.76</td>
<td>2602  581  34.18  22.33</td>
<td>0.75 [0.67;0.85] 0.000006</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hospitalisation for</td>
<td>2709  298  17.98  11.00</td>
<td>2602  418  24.59  16.07</td>
<td>0.69 [0.59;0.80] 0.000008</td>
</tr>
<tr>
<td>worsening heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cardiovascular death</td>
<td>2984  255  15.39  8.54</td>
<td>2984  312  18.35  10.46</td>
<td>0.81 [0.69;0.96] 0.0137</td>
</tr>
<tr>
<td>- Death from any cause</td>
<td>2984  285  17.20  9.55</td>
<td>2984  350  20.59  11.73</td>
<td>0.81 [0.69;0.94] 0.0074</td>
</tr>
<tr>
<td>- Death from heart failure</td>
<td>2984  67   4.04   2.23</td>
<td>2984  107  6.29   5.39</td>
<td>0.61 [0.45;0.83] 0.0017</td>
</tr>
</tbody>
</table>

One year NNT is 18
One year NNT is 46
Therapeutic Approach to Patients With HFrEF

Patient with LVEF ≤ 40% and Symptoms

- Triple therapy ACEi (or ARB if ACEi intolerant), BB, MRA
  - Titrate to target doses or maximum tolerated evidence-based dose

Most of our panelists (55%) felt the entire triple therapy titration to maximal tolerated or target doses should be completed within 4 months, and 93% felt this should be completed within 6 months. Titration of ACEi and beta-blocker only would be slightly less than this duration.

- REASSESS SYMPTOMS AND LVEF

- Diuretics for eligible patients
- Management of self-care, exercise
- Nonpharmacologic planning and documentation
- Advance care planning and documentation

Titrate
Diuretics
for Congestion
Close to maintain euolemia
Chronic Underdosing of Medications Following HF Discharge

<table>
<thead>
<tr>
<th>Medication</th>
<th>0 to 30 d</th>
<th>31 to 180 d</th>
<th>181 to 360 d</th>
<th>3 to 5 y</th>
<th>Target Dosage, mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol‡</td>
<td>75 (50 to 125)</td>
<td>75 (50 to 100)</td>
<td>75 (50 to 100)</td>
<td>75 (50 to 100)</td>
<td>200</td>
</tr>
<tr>
<td>carvedilol</td>
<td>12.5 (6.25 to 25)</td>
<td>18.75 (10.37 to 37.5)</td>
<td>25 (12.5 to 50)</td>
<td>25 (12.5 to 50)</td>
<td>50</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>5 (3.75 to 10)</td>
<td>5 (2.5 to 7.5)</td>
<td>5 (5 to 10)</td>
<td>5 (5 to 10)</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>RASi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>24.8%</td>
<td>2 (1 to 4)</td>
<td>2 (1 to 3)</td>
<td>2 (1 to 4)</td>
<td>2 (2 to 4)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>19.8%</td>
<td>5 (3.125 to 7.5)</td>
<td>5 (2.5 to 10)</td>
<td>5 (3.125 to 10)</td>
<td>5 (3.75 to 10)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>16.0%</td>
<td>10 (7.5 to 20)</td>
<td>10 (5 to 20)</td>
<td>10 (5 to 20)</td>
<td>10 (7.5 to 20)</td>
</tr>
<tr>
<td>Captopril</td>
<td>11.7%</td>
<td>37.5 (25 to 62.5)</td>
<td>37.5 (25 to 62.5)</td>
<td>37.5 (25 to 62.5)</td>
<td>50 (25 to 62.5)</td>
</tr>
<tr>
<td>Losartan</td>
<td>9.6%</td>
<td>50 (25 to 75)</td>
<td>50 (25 to 75)</td>
<td>50 (50 to 75)</td>
<td>50 (50 to 75)</td>
</tr>
<tr>
<td>Candesartan</td>
<td>1.5%</td>
<td>8 (6 to 16)</td>
<td>8 (6 to 16)</td>
<td>8 (8 to 16)</td>
<td>8 (8 to 16)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>0.6%</td>
<td>120 (80 to 160)</td>
<td>120 (80 to 160)</td>
<td>120 (80 to 160)</td>
<td>80 (80 to 160)</td>
</tr>
<tr>
<td>Other</td>
<td>16.0%</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
In Contemporary Clinical Practice, Only 15–30% of Patients Are Able to Reach the BB Target Dose

<table>
<thead>
<tr>
<th>Source/Study</th>
<th>Patients</th>
<th>Years</th>
<th>Patients on</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BB</td>
<td>BB ≥ 50% target dose</td>
</tr>
<tr>
<td>CHFN (Canada)</td>
<td>17790</td>
<td>1999-2010</td>
<td>74.6%</td>
<td>-</td>
</tr>
<tr>
<td>ESC-HF (Europe)</td>
<td>3226</td>
<td>2009-2010</td>
<td>87%</td>
<td>-</td>
</tr>
<tr>
<td>IMPROVE-HF (US)</td>
<td>13381</td>
<td>2005-2007</td>
<td>86%</td>
<td>-</td>
</tr>
<tr>
<td>IMPACT-RECO (France)</td>
<td>1919</td>
<td>2005</td>
<td>65%</td>
<td>47%</td>
</tr>
<tr>
<td>OPTIMIZE-HF (US)</td>
<td>2373</td>
<td>2003-2004</td>
<td>83.5%</td>
<td>-</td>
</tr>
<tr>
<td>Shift (worldwide)</td>
<td>6505</td>
<td>2006-2010</td>
<td>89% ¥</td>
<td>56%</td>
</tr>
<tr>
<td>EMPHASIS-HF (Worldwide)</td>
<td>2737</td>
<td>2006-2010</td>
<td>87% ¥</td>
<td>39.5%</td>
</tr>
<tr>
<td>PARADIGM-HF (Worldwide)</td>
<td>8442</td>
<td>2009-2013</td>
<td>98%</td>
<td>-</td>
</tr>
</tbody>
</table>

Target dose as defined by landmark BB clinical trials

¥ as background therapy
Target Doses of EBMT in the CHECK HF Registry

Overall Cohort

39
87
34

% treated with agent
% not treated with agent

mended by guidelines. Furthermore, the more recently introduced If-channel inhibition has hardly been adopted. There is ample room for improvement of HFrEF therapy, even more than 25 years after convincing evidence that HFrEF treatment leads to better outcome. (J Am Coll Cardiol HF 2019;7:13–21) © 2019 by the American College of Cardiology Foundation.

<table>
<thead>
<tr>
<th>% Target Dose</th>
<th>ACEI/ARB</th>
<th>ARNI</th>
<th>BB</th>
<th>ACEI/ARB</th>
<th>ARNI</th>
<th>BB</th>
<th>ACEI/ARB</th>
<th>ARNI</th>
<th>BB</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>50 - &lt;100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥100</td>
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</tbody>
</table>

ACEI = angiotensin converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; ARB = angiotensin receptor blocker; BB = beta blockers; SBP = systolic blood pressure.
Heart Rate Remains Relatively High in Recent Heart Failure Trials and Heart Failure Registries

Recent Heart Failure Registries
- STAMINA (US)
- OPTIMIZE Hospital Cohort (US)
- OPTIMIZE Follow-up Cohort (US)
- IMPROVE-HF (US)
- EuroHeart Failure (Europe)
- ESC-HF (W. Europe)
- ESC-HF (E. Europe)

Recent Heart Failure Clinical Trials
- SHIFT (Ivabradine)
- EVEREST (Tolvaptan)
- PROTECT (Rolofylline)
- EMPHASIS (Eplerenone)
- ASTRONAUT (Aliskiren)
- RED-HF (Darbepoetin alfa)
- PARADIGM-HF (LCZ696)

Heart rate, bpm (mean/median)

- 60
- 65
- 70
- 75
- 80
- 85
- 90

- Median
- Mean
• Hosp. represents failure of Rx
• Bests evidence for rapid med change in hospital
• Give decongesting drug when congested
• Give HR lowering drug when HR elevated

Vs.

• There is no evidence
• It is not safe
• It will prolong hospitalization
• The old ways are best
• We have time after hospitalization to do this
UK HF Audit: Risk of Death or Hospitalization Starting at Discharge
Early Benefit of Treatment on Hospitalization for Heart Failure

Endpoint – hospitalization for HF

Hospitalization for HF begins to diverge as quickly as 2 weeks.

Early treatment with IVA reduces readmission for HF in SHIFT trial. The curves begin to diverge at 2 weeks for those hospitalized for HF.
Early Co-administration of Ivabradine and β-blockers During Hospitalization May Reduce Mortality

A retrospective analysis on 370 hospitalized HF patients with heart rate ≥70 bpm (150 BB + ivabradine, 220 BB alone) in the Optimize Heart Failure Care Program from 8 countries (2015-2016)

Probability of survival

HR=0.41 (95% CI, 0.29-0.57)  P<0.0001
**PIioneer-HF**

**Exploratory Serious Clinical Composite Endpoint**

Composite of death, HF re-hospitalization, LVAD, listing for transplant

**KM estimate of event rate (%)**

- **Sacubitril/valsartan**
  - N = 440
- **Enalapril**
  - N = 441

- **HR = 0.54; 95% CI 0.37-0.79**
- **P = 0.001**
- **NNT = 13**

Days since randomization:

- 0 7 14 21 28 35 42 49 56

*Exploratory Serious Clinical Composite endpoint was driven by the reduction of risk of death and HF re-hospitalizations*

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851
“de novo” HF can be as old as 3 years

ORIGINAL RESEARCH ARTICLE

Adherence to guidelines in management of symptoms suggestive of heart failure in primary care

Benedict Hayhoe,¹ Dani Kim,¹,² Paul P Aylin,¹,² F Azeem Majeed,¹ Martin R Cowie,³ Alex Bottle¹,²

Time taken from first symptom to NICE elements and diagnosis

Hospitalization Provides an Opportunity for HF Treatment Optimization

Significant increase in the prescription of evidence-based disease-modifying therapies at discharge compared to pre-hospitalization\(^1\)–\(^7\)

\[\text{At admission} \quad \text{At discharge}\]

- ACEi/ARB
- Beta-blocker
- MRA

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

This is a 16% absolute increase over 20 years which is 50% more than HF increase in similar time.
Therapeutic Approach to Patients with HFrEF

**Patient with LVEF ≤ 40% and Symptoms**

**Triple therapy ACEI (or ARB if ACEI intolerant), BB, MRA**
Titrate to target doses or maximum tolerated dose

Over 50% of our HF panelists estimated the MEDIAN
Time to full medication titration was 9-12 months!!
Several clinics estimated > 1 year

**NYHA I**
Continue triple therapy

**NYHA II–IV: SR, HR ≥ 70 bpm**
Add ivabradine and switch ACEi or ARB to ARNI* for eligible patients

**NYHA II–IV: SR with HR < 70 bpm or AF or pacemaker**
SWITCH ACEi or ARB to ARNI* for eligible patients

**REASSESS SYMPTOMS AND LVEF**
Breast Cancer vs. Heart Failure

**Similarities:**
- Common
- Life threatening
- Poor quality of life
- Early treatment improves mortality
- Improving mortality rates
- Highest long term risk for mortality in those surviving 2 yrs is CV death

**Differences:**
- Malignant vs. degenerative
- Well organized advocacy groups
- Combination therapy upfront
- Early access to treatment
- National reporting strategy
- Dedicated formulary committee
Stardate 8130.3: "THE NEEDS OF THE MANY OUTWEIGHT THE NEEDS OF THE FEW"
LVEF Trends Following Initial Diagnosis of HF
Median Time to Maximal EF Change 14 Months

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline LVEF (%)</th>
<th>Median Time to Maximal EF Change (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HFpEF</td>
<td>61%</td>
<td>1.32 (1.03-1.70)</td>
</tr>
<tr>
<td>Baseline HFmrEF</td>
<td>38%</td>
<td>1.40 (1.13-1.75)</td>
</tr>
<tr>
<td>Baseline HFrEF</td>
<td>18%</td>
<td>1.46 (1.15-1.85)</td>
</tr>
</tbody>
</table>

**THE MANY**
Nearly 75% will need consideration of new therapies when finished titration, however long it takes.

**THE FEW**
Only 25% possibly could have avoided ARNi and SNI.
Early Survival Benefit
How well would this go over?

• You have breast cancer
• We will start with some old drugs and see how you do.
  • We will see you every couple of months
  • We may have to try several times to ensure you are on the highest drug dose of each
• If THAT does not work, we will have to make sure we have done everything we can about you being on all of the other drugs at their optimal levels.
• If you do not respond well to this, we will see if you qualify for 1 or both of 2 newer drugs.
• Once that is done, we will see about getting another drug, but we need to do 3 separate visits first while on the older drugs to see if you qualify.
• If you are hospitalized in the meantime, we might have to start over again as someone might stop one or more of your older drugs...
Time for a Disruption in HF Treatment: Cluster Titration (CT) for HFrEF

Cluster A: Diuretic & SGLT\text{i}  Cluster B: ARNi & MRA  Cluster C: BB & SNI

**Encounter 1**
- Start 1st Med Cluster A
- Start 1st med Cluster B
- Start 1st med Cluster C

**Encounter 2 (whenever feasible)**
- Start 2nd med Cluster A
- Start 2nd med Cluster B
- Start 2nd med Cluster B

**Encounter 3 & ongoing (whenever feasible)**
- Diuretic titration
- Easiest cluster B titration
- Alternate Cluster C titration
Three Disruptions for the Treatment of Acute HF

**Problem:**

1) SLOW uptake and use of EBMT
2) LONG titration even when it happens leaving complications in its wake
3) HIGH hospital readmission and poor patient experience

**Disruption:**

a) STOP ACE, GET BNP and LVEF on admission
b) Start ALL medical therapies upfront with Cluster titration
   Pragmatic, easiest titration
c) EARLY follow up with PCP and specialist – 7 days (one or the other)
Let the Hospital be Your Friend…
Imaging the Heart: Early Impact of Lowering HR on Heart Function

Kim Connelly
MBBS, FRACP, PhD
Objectives

• Discuss HR as an independent risk factor for adverse CV outcomes
• Review impact of HR modulation upon cardiac functional outcomes
• Discuss potential mechanism behind beneficial effects
Heart Rate is Independently Linked to a Significant Increase in All-cause Mortality

Modifiable risk factors out of the top ten factors associated with increased mortality

Lowering Heart Rate Impacts on Prognosis

Outcomes based on the HR achieved after 28 days of treatment with ivabradine

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>0 D28</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
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</thead>
<tbody>
<tr>
<td>≥ 75 bpm</td>
<td>527</td>
<td>451</td>
<td>376</td>
<td>291</td>
<td>141</td>
<td>47</td>
</tr>
<tr>
<td>70 to &lt; 75 bpm</td>
<td>344</td>
<td>314</td>
<td>276</td>
<td>221</td>
<td>116</td>
<td>41</td>
</tr>
<tr>
<td>65 to &lt; 70 bpm</td>
<td>444</td>
<td>404</td>
<td>358</td>
<td>287</td>
<td>149</td>
<td>62</td>
</tr>
<tr>
<td>60 to &lt; 65 bpm</td>
<td>605</td>
<td>556</td>
<td>488</td>
<td>407</td>
<td>176</td>
<td>59</td>
</tr>
<tr>
<td>&lt; 60 bpm</td>
<td>1,192</td>
<td>1,132</td>
<td>1,004</td>
<td>842</td>
<td>414</td>
<td>162</td>
</tr>
</tbody>
</table>

p<0.0001
## Independent Risk Factor: Prognostic of Heart Rate from the PARADIGM-HF Study

8399 patients from Paradigm-HF

- Baseline HR: 72bpm
- End of study HR: 72bpm

<table>
<thead>
<tr>
<th></th>
<th>Adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1- Reference</td>
</tr>
<tr>
<td></td>
<td>Group (≤ 66 bpm)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2 (67-76 bpm)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3 (≥ 77 bpm)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CV Death</strong></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart failure hospitalizations</strong></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause Mortality</strong></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

McMurray, NEJM, 2014, 371, 993-1004
Ivabradine: Heart Rate Reduction and Benefits on Mortality/Morbidity
Ivabradine MOA and Physiological Effect
Background

• Cardiac remodeling is central to the pathophysiology of heart failure (HF) and is a prognostic factor in patients with HF

• Left ventricular (LV) enlargement and reduced ejection fraction are powerful predictors of outcomes in heart failure

• Therapeutic effects of drugs and devices on LV remodeling are associated with their longer-term effects on mortality
Sub-study Population

611 patients included from 89 centers in 21 countries

304 patients Ivabradine

Excluded (N=96)
52: Poor quality of echo recording
19: No baseline and/or 8-month recording
8: Non-matching biplane or 4-chamber views
13: Withdrawn due to death
4: Consent withdrawn

307 patients Placebo

Excluded (N=104)
52: Poor quality of echo recording
15: No baseline and/or 8-month recording
1: Non-matching biplane or 4-chamber views
23: Withdrawn due to death
13: Consent withdrawn

208 patients Ivabradine

203 patients Placebo

Median follow-up after 8-month echocardiogram: 16.1 months
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine N=304</th>
<th>Placebo N=307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Male, %</td>
<td>80</td>
<td>82</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Mean HF duration, years</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>HF ischaemic cause, %</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>NYHA class II, %</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>NYHA class III, %</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Mean HR, bpm</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg</td>
<td>121</td>
<td>119</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>


www.shift-study.com
## Baseline Background Treatment

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Ivabradine N=304</th>
<th>Placebo N=307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker, %</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>ARB, %</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Diuretic (excludes antialdo), %</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Aldosterone antagonist, %</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>Digitalis, %</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>Devices, %</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
LV End-systolic Volume Index and Outcome in the Placebo Group

Patients with primary composite endpoint, %

HR 1.62, p=0.04

LVESVI ≥ 59 mL/m²

LVESVI < 59 mL/m²

www.shift-study.com
Primary Endpoint: Change in LVESVI from Baseline to 8 Months

Left ventricular end-systolic volume index

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine (n=208)</td>
<td>65.2±29.1</td>
<td>58.2±28.3</td>
</tr>
<tr>
<td>Placebo (n=203)</td>
<td>63.6±30.1</td>
<td>62.8±28.7</td>
</tr>
</tbody>
</table>

Δ -5.8, P<0.001

www.shift-study.com
Secondary Endpoint: Change in LVEDVI from Baseline to 8 Months

Left ventricular end-diastolic volume index

- **Ivabradine** (n=204)
  - Baseline: 93.9 ± 32.8 mL/m²
  - 8 months: 85.9 ± 30.9 mL/m²
  - Change: Δ -7.9 ± 18.9 mL/m², \( P=0.002 \)

- **Placebo** (n=199)
  - Baseline: 90.8 ± 33.1 mL/m²
  - 8 months: 89.0 ± 31.6 mL/m²
  - Change: Δ -1.8 ± 19.0 mL/m²


www.shift-study.com
Secondary Endpoint: Change in LVEF from Baseline to 8 Months

Left ventricular ejection fraction

Δ + 2.7, P<0.001

Δ 2.4 ± 7.7

32.3±9.1  34.7±10.2

Baseline  8 months

Ivabradine (n=204)

Δ - 0.1 ± 8.0

31.6 ±9.3  31.5±10.0

Baseline  8 months

Placebo (n=199)
Summary of Changes in HR, LV End-Systolic/End-Diastolic Volume Indexes

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine n=304</th>
<th>Placebo n=307</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in resting HR at 8 months, bpm</td>
<td>-14.7</td>
<td>-5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in LVESVI at 8 month, mL/m²</td>
<td>-7.0</td>
<td>-0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in LVEDVI at 8 month, mL/m²</td>
<td>-7.9</td>
<td>-1.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>

www.shift-study.com
SHIFT Compared to Prior Echo HF Studies

Δ ESVI (ml/m²) vs. placebo

PHARMACOLOGICAL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Δ ESVI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVABRADINE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEAUTIFUL*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHIFT</td>
<td>-5.8</td>
<td>422</td>
</tr>
<tr>
<td></td>
<td>-2.6</td>
<td>426</td>
</tr>
<tr>
<td>EPLERENONE</td>
<td>-2.1</td>
<td>226</td>
</tr>
<tr>
<td>METOPROLOL</td>
<td>-10.8</td>
<td>149</td>
</tr>
<tr>
<td>SUCC.</td>
<td>-12.9</td>
<td>66</td>
</tr>
<tr>
<td>NEBIVOLOL</td>
<td>-14.5</td>
<td>33</td>
</tr>
<tr>
<td>CARVEDILOL</td>
<td>-1.0</td>
<td>572</td>
</tr>
<tr>
<td>ENALAPRIL</td>
<td>-3.0</td>
<td></td>
</tr>
<tr>
<td>CARMEN**</td>
<td>-6.2</td>
<td></td>
</tr>
</tbody>
</table>

CRT

<table>
<thead>
<tr>
<th>Study</th>
<th>Δ ESVI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVERSE*</td>
<td>-17.1</td>
<td>610</td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>-19.6</td>
<td>1372</td>
</tr>
</tbody>
</table>

* stable CAD and LVSD, HR>60
** estimate (LVESV2)
*** estimate from Fig. 3 of publication, Δvs. baseline, not vs. placebo

Udelson JE et al, Circulation Heart Fail 2010 (Eplerenone); Colucci WS et al, Circulation 2007 (REVERT);
Hole T et al, Echocardiography 2004 (MERIT-HF); Ghio S et al, Eur Heart J 2006 (SENIORS); Remme WJ et al, Cardiovasc Drugs Ther 2003; St John Sutton M et al, Circulation 2003 (REVERSE); Solomon SD et al, Circulation 2010 (MADIT-CRT)
## Impact of Evidence-based Therapies on LVEF

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of Studies (n)</th>
<th>$\Delta$EF (IC 95%)</th>
<th>Mean Follow-up (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1 (28)</td>
<td>12,0 (4,4-19,6)</td>
<td>52</td>
</tr>
<tr>
<td>Metoprolol CR</td>
<td>4 (587)</td>
<td>4,5 (1,8-7,1)</td>
<td>25,5</td>
</tr>
<tr>
<td>Enalapril</td>
<td>6 (431)</td>
<td>3,7 (1,5-5,9)</td>
<td>24</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>3 (185)</td>
<td>3,0 (1,9-4,1)</td>
<td>25,7</td>
</tr>
<tr>
<td>CRT</td>
<td>4 (1052)</td>
<td>2,7 (1,9-3,5)</td>
<td>21</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>1 (411)</td>
<td>2.7 (1.3-4.2)</td>
<td>35</td>
</tr>
</tbody>
</table>
Conclusions

- Heart rate reduction with ivabradine reverses left ventricular remodeling in patients with heart failure and LV systolic dysfunction:
  - Marked reductions of LV volumes
  - Significant improvement of LV ejection fraction

- These results suggest that ivabradine modifies disease progression in patients with HF receiving background therapy.
But what about mechanism?
Better Filling Increases Contractility

• Afterload has two principal components:
  • Fixed component: total peripheral resistance = \( P_{am}/Q_c \)
  • Pulsatile component: arterial compliance
As Heart Rate Increases, Arterial Compliance Decreases

![Graph showing the relationship between heart rate and arterial compliance.](image-url)
Cross-Over Study in Permanently Paced Systolic Heart Failure Patients

Table 1  Baseline characteristics of the 12 patients who completed the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>Male/female</td>
<td>11/1</td>
</tr>
<tr>
<td>NYHA class (II/III)</td>
<td>7/5</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23 ± 10</td>
</tr>
<tr>
<td>Ischaemic/non-ischaemic</td>
<td>7/5</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARA2, n (%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Beta-blocker, n (%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Furosemide³ (mg/day)</td>
<td>72 ± 16</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Pacing heart rate (b.p.m.)</td>
<td>62.9 ± 5.0</td>
</tr>
</tbody>
</table>

³All patients received furosemide.
Figure 1 Left ventricular ejection fraction (LVEF) at the end of the two 3-month periods, according to the tested pacing rate. Box-plots show median, 50th and 75th percentiles.

Figure 2 Blood B-type natriuretic peptide (BNP) levels at the end of the two 3-month periods, according to the tested pacing rate. Box-plots show median, 50th and 75th percentiles.

Table 2 Systolic blood pressure and echographic results at the end of the two 3-month periods

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure (mmHg)</th>
<th>LV end-diastolic diameter (mm)</th>
<th>LV end-systolic diameter (mm)</th>
<th>Stroke volume (mL)</th>
<th>Cardiac index (L/min/m²)</th>
<th>Doppler, E/Eₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 b.p.m.</td>
<td>112.5 ± 17.1</td>
<td>70.0 ± 6.2</td>
<td>63.0 ± 6.9</td>
<td>67 ± 28</td>
<td>2.03 ± 0.33</td>
<td>11.9 ± 3.3</td>
</tr>
<tr>
<td>75 b.p.m.</td>
<td>110.0 ± 15.7</td>
<td>69.4 ± 6.2</td>
<td>61.6 ± 7.1</td>
<td>49 ± 21</td>
<td>1.93 ± 0.34</td>
<td>13.2 ± 3.2</td>
</tr>
<tr>
<td>Delta 55–75 b.p.m.</td>
<td>+2.5 ± 4.9</td>
<td>+0.6 ± 2.3</td>
<td>−1.4 ± 1.9</td>
<td>+18 ± 15</td>
<td>+0.10 ± 0.24</td>
<td>−1.3 ± 2.3</td>
</tr>
<tr>
<td>P-value</td>
<td>0.10</td>
<td>0.19</td>
<td>0.03</td>
<td>0.001</td>
<td>0.17</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Ivabradine

- Improved myocardial perfusion
- Decreased post-systolic contraction
- Better LV filling
- Decreased afterload
- Force-frequency relationship
- Maintained contractility

Reverse remodelling

- Increased SV
- Improved renal and peripheral perfusion
- Decrease in deleterious hormone release

Catecholamines, ACE
How could reducing heart rate improve arterial elastance?

**Placebo**
- ↑ number of contraction/relaxation cycles
- ↑ muscle tone (↓ elasticity)
- ↑ afterload
- ↓ stroke volume

**Ivabradine**
- ↓ number of contraction/relaxation cycles
- ↓ muscle tone (↑ elasticity)
- ↓ afterload
- ↑ stroke volume
Ivabradine Infusion Leads to an Immediate Increase in Stroke Volume

10 severe heart failure patients (NYHA III), with advanced systolic dysfunction (Mean LVEF 21%) and HR ≥ 80 bpm treated with ACE I and beta-blockers

→ In severe systolic heart failure patients IV administration of ivabradine leads to a significant 51% increase in stroke volume.
Acute Effects: 9 Days Post-IVA Administration...

26% increase in SV

SV= 46ml

SV= 58ml
Immediate Effects on Stroke Volume

Beta-blocker: HR and inotropic reduction

Ivabradine: Pure HR reduction

Immediate Effects on Stroke Volume
Beta-blocker Infusion Has No Effect on Stroke Volume

24 patients with heart failure (FEVG < 40%), beta-blocker infusion IV

### Table 5. Hemodynamic Response to Metoprolol Versus Propranolol in Patients With Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol (n=12)</th>
<th>Propranolol (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>91 ± 3</td>
<td>85 ± 3</td>
</tr>
<tr>
<td>Post</td>
<td>73 ± 2*</td>
<td>72 ± 2*</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>20 ± 2</td>
<td>27 ± 2†</td>
</tr>
<tr>
<td>Post</td>
<td>24 ± 3*†</td>
<td>27 ± 3</td>
</tr>
</tbody>
</table>

### Table 5. Continued

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol (n=12)</th>
<th>Propranolol (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>136 ± 10</td>
<td>143 ± 9</td>
</tr>
<tr>
<td>Post</td>
<td>120 ± 7*</td>
<td>131 ± 9*</td>
</tr>
<tr>
<td>SVI, mL/M²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>26 ± 2</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>Post</td>
<td>29 ± 3</td>
<td>31 ± 2</td>
</tr>
</tbody>
</table>

SVI: Stroke Volume Index (Volume d'éjection systolique)
Haber HL et al. *Circulation* 1993
Increased Stroke Volume Persists Over the Long Term

Echocardiography study in 275 heart failure patients from the SHIFT trial (Baseline to 8 months).

Table 3: Influence of Selective Heart Rate Reduction With Ivabradine on Hemodynamic Parameters After 8 Months of Treatment Compared With Placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ivabradine (n = 143)</th>
<th>Placebo (n = 132)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>71 ± 12</td>
<td>71 ± 11.0</td>
<td>0.71</td>
</tr>
<tr>
<td>At 8 months</td>
<td>60 ± 10</td>
<td>68 ± 12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change from baseline to 8 months</td>
<td>−11 ± 13</td>
<td>−2 ± 12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p Value vs. baseline</td>
<td>&lt;0.0001</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>47 ± 12</td>
<td>45 ± 11</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Stroke volume, ml

- At baseline: 59 ± 16 (Ivabradine), 59 ± 16 (Placebo), p = 0.80
- At 8 months: 67 ± 16 (Ivabradine), 58 ± 16 (Placebo), p < 0.0001
- Change from baseline to 8 months: 9 ± 17 (Ivabradine), −1 ± 16 (Placebo), p < 0.0001

Stroke volume, ml

- At baseline: 59 ± 16 (Ivabradine), 59 ± 16 (Placebo), p = 0.80
- At 8 months: 67 ± 16 (Ivabradine), 58 ± 16 (Placebo), p < 0.0001
- Change from baseline to 8 months: 9 ± 17 (Ivabradine), −1 ± 16 (Placebo), p < 0.0001

Reil J-C al. JACC 2013
Conclusions

- Elevated HR is an adverse prognostic factor
- Pure HR reduction improves outcomes
- Reducing HR results in reverse remodeling
- Effects are independent of and additive to neurohormonal blockade
- Ivabradine is safe and well tolerated
- Ivabradine is indicated by CCS guidelines for HFrEF patients in SR
High Mortality in Hospitalized HF Patient – the “Vulnerable Paradox”
High Mortality in Hospitalized HF Patient – the “Vulnerable Paradox”

Acute HFrEF Rx: Reproducing History of Medicine

- Diuretics [1962], ACEi [1980], Beta Blocker [1990]

"Any family history of cancer, heart disease, diabetes, extinction..."
NT-proBNP Levels During & Post Discharge for ADHF

Recurrent Hospitalization

Improvement as Outpatient

Diuretic
Modern evidence-based therapy

Days Since Admission
Benefits of Combinatorial Rx for HFrEF

All-cause Mortality

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>HR (95% Credible Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNI+BB+MRA vs Placebo</td>
<td>0.38 (0.2;0.65)</td>
</tr>
<tr>
<td>ACEI+BB+MRA+IVA vs Placebo</td>
<td>0.41 (0.21;0.7)</td>
</tr>
<tr>
<td>ACEI+BB+MRA vs Placebo</td>
<td>0.44 (0.27;0.67)</td>
</tr>
<tr>
<td>ARB+BB vs Placebo</td>
<td>0.48 (0.24;0.86)</td>
</tr>
<tr>
<td>ACEI+ARB+BB vs Placebo</td>
<td>0.52 (0.32;0.8)</td>
</tr>
<tr>
<td>BB vs Placebo</td>
<td>0.58 (0.34;0.95)</td>
</tr>
<tr>
<td>ACEI+MRA vs Placebo</td>
<td>0.58 (0.36;0.9)</td>
</tr>
<tr>
<td>ACEI+BB vs Placebo</td>
<td>0.58 (0.42;0.73)</td>
</tr>
<tr>
<td>ACEI+ARB vs Placebo</td>
<td>0.83 (0.52;1.23)</td>
</tr>
<tr>
<td>ACEI vs Placebo</td>
<td>0.94 (0.67;1.01)</td>
</tr>
<tr>
<td>ARB vs Placebo</td>
<td>0.99 (0.61;1.27)</td>
</tr>
</tbody>
</table>

Cardiovascular Mortality

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>HR (95% Credible Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNI+BB+MRA vs Placebo</td>
<td>0.38 (0.16;0.71)</td>
</tr>
<tr>
<td>ACEI+BB+MRA+IVA vs Placebo</td>
<td>0.41 (0.19;0.82)</td>
</tr>
<tr>
<td>ACEI+BB+MRA vs Placebo</td>
<td>0.45 (0.25;0.75)</td>
</tr>
<tr>
<td>ACEI+ARB+BB vs Placebo</td>
<td>0.47 (0.24;0.82)</td>
</tr>
<tr>
<td>ARB+BB vs Placebo</td>
<td>0.5 (0.19;1.12)</td>
</tr>
<tr>
<td>ACEI+MRA vs Placebo</td>
<td>0.56 (0.31;0.95)</td>
</tr>
<tr>
<td>ACEI+BB vs Placebo</td>
<td>0.56 (0.37;0.75)</td>
</tr>
<tr>
<td>BB vs Placebo</td>
<td>0.62 (0.27;1.32)</td>
</tr>
<tr>
<td>ACEI+ARB vs Placebo</td>
<td>0.8 (0.43;1.33)</td>
</tr>
<tr>
<td>ACEI vs Placebo</td>
<td>0.81 (0.6;1.04)</td>
</tr>
<tr>
<td>ARB vs Placebo</td>
<td>0.85 (0.51;1.28)</td>
</tr>
</tbody>
</table>

• Komajda M, et al. Eur J Heart Fail 2018
Complementarity Between the HF Treatments
Neurohormonal + Physiological, Rapid + Chronic

Decline in systolic function

Activation of three major neurohormonal systems

Natriuretic peptide system
Renin angiotensin aldosterone system
Sympathetic nervous system

Direct determinant of heart function

Heart rate

NEUROHORMONAL
CHRONIC

PHYSIOLOGICAL
RAPID + CHRONIC
Time for a Disruption in HF Treatment: Cluster Titration (CT) for HFrEF

Cluster A: Diuretic & SGLT2
Cluster B: ARNi & MRA
Cluster C: BB & SNI

**Encounter 1**
- Start 1st Med Cluster A
- Start 1st med Cluster B
- Start 1st med Cluster C

**Encounter 2 (whenever feasible)**
- Start 2nd med Cluster A
- Start 2nd med Cluster B
- Start 2nd med Cluster B

**Encounter 3 & ongoing (whenever feasible)**
- Diuretic titration
- Easiest cluster B titration
- Alternate Cluster C titration
Ivabradine in Hospitalized HF Patients

• Effect of ivabradine on stroke volume in failing heart is immediate
• Effect of ivabradine on the failing heart in HFrEF is sustained:
  • Decreases LV volumes
  • Improves LV ejection fraction
  • Reduces NTproBNP over time
  • Reduces mortality
• Combines well with other treatment “clusters” in HFrEF
For the Patient Admitted with HFrEF

• Rapid symptom relief and volume optimization
• Assess patient risk for rehospitalization
• Hold ACEi and consider sacubitril/valsartan if no contraindication (BP, Creatinine)
• If HR>77/minute, consider adding ivabradine to beta blockade
• Patient education, community/family support
• Timely follow-up as outpatient
Question 5: What statement best describes your understanding of initiation of in-hospital therapies for HFrEF (assume eligible for all therapies)?

1) Triple therapy should be optimized prior to initiation of any 'new' therapies such as ARNi or SNI
2) Patients should be started on ARNi while in hospital but not SNI
3) Patients should be started on both ARNi and SNI while in hospital
4) New therapies should only be started in outpatient population
Thank you!

Please remember to complete the online evaluation.