TIME TO TREATMENT IN HF: THE TIME IS NOW
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Speaker Disclosure
Dr. Jonathan Howlett

• Relationships with commercial interests:
  – Grants/Research Support: AstraZeneca, Merck, Servier, Pfizer, Novartis, CVRx, Medtronic
  – Speakers Bureau/Honoraria: Otsuka, Bayer, Forrest.
  – Consulting Fees: General Electric, Government of Canada, Alberta
  – Other: Nil

I ALWAYS TALK ABOUT OFF LABEL USE OF MEDS ESPECIALLY TODAY!!
Speaker Disclosure
Dr. Martin Cowie

- Research grants administered by Imperial College London from Bayer, Boston Scientific, St Jude Medical, and ResMed

- Consultancy and speaker fees from ResMed, Servier, Novartis, Pfizer, Bayer, Medtronic, Boston Scientific, St Jude Medical, Alere, Daiichi-Sankyo, Bristol Myers Squibb, Roche, Amgen, MSD, Respocardia, Sorin

- Non-Executive Director of the National Institute for Health and Care Excellence (NICE) in England but opinions are my own
Speaker Disclosure
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 Disclosure
Dr. Peter Liu

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

• **Clinical Trials:** Roche

• **Speaker Fees:**

• **Other:**
Disclosure of Commercial Support

Specific details of relationship:

– This program has received financial support from Servier Canada in the form of an educational grant
– This program has received in-kind support from Canadian Heart Failure Society in the form of logistical support

Potential for conflict(s) of interest:

– Speakers have received honoraria from Canadian Heart Failure Society
– Servier Canada is the manufacturer of ivabradine
Mitigating Potential Bias

Potential biases are acknowledged and are mitigated by presenting data supported by national and international guidelines, and as follows:

• Information presented is evidence-based
• Material has been developed and reviewed by a Planning Committee

Off-label uses of drugs will be discussed and identified as such by the speaker
Learning Objectives

• Review updated Canadian guidelines for the timely and effective use of evidence-based medications for patients with HFrEF

• Recognize real-world strategies for accelerating the uptake of novel treatments for HFrEF

• Explore the relationship between myocyte metabolism and heart rate
Accreditation

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Canadian Cardiovascular Society. You may claim a maximum of 1 hour.
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:05-12:10 pm</td>
<td>Welcome and introduction</td>
<td>Jonathan Howlett, MD</td>
</tr>
<tr>
<td>12:10-12:20 pm</td>
<td>Myocyte metabolism and HR</td>
<td>Jonathan Howlett, MD</td>
</tr>
<tr>
<td>12:20-12:35 pm</td>
<td>Impact of the latest therapies</td>
<td>Peter Liu, MD</td>
</tr>
<tr>
<td>12:35-12:45 pm</td>
<td>HFrEF: what is the urgency?</td>
<td>Nadia Giannetti, MD</td>
</tr>
<tr>
<td>12:45-1:00 pm</td>
<td>Lessons learned from the Optimize HF Program</td>
<td>Martin Cowie, MD</td>
</tr>
<tr>
<td>1:00-1:05 pm</td>
<td>Reconciling the guidelines with reality</td>
<td>Jonathan Howlett, MD</td>
</tr>
<tr>
<td>1:05-1:15 pm</td>
<td>Questions and answers: panel discussion</td>
<td>Jonathan Howlett, MD</td>
</tr>
<tr>
<td>1:15-1:20 pm</td>
<td>Audience polling system: basic science questions for the future</td>
<td>ALL</td>
</tr>
<tr>
<td>1:20 pm</td>
<td>Closing remarks and evaluations</td>
<td>Jonathan Howlett, MD</td>
</tr>
</tbody>
</table>
Housekeeping Details

• Please turn your phones to silent mode

• Please remember to complete your evaluation forms at the end of the session, by texting EVALUATION to (647) 696-5222

• Audience polling via text message... let’s try it out!
Audience Polling - Interact with us today!

1. Using your mobile phone, text **HFUPDATE** to **37607** one time.

2. When polls are shown, text the answer to the code **37607** to vote in each poll

*Let’s test it out!*
Audience Polling
Which picture should Dr. Howlett submit to land a role in the new CBC police drama?

A.  

B.  

C.  

D.  

Text answer to 37607
The Burden of Heart Failure

Heart Failure is a growing epidemic

- Heart Failure is on the rise in Canada.
- 600,000 Canadians are living with Heart Failure.
- 50,000 Canadians are diagnosed each year with Heart Failure.
- 1.2 Canadians has been touched by Heart Failure.
- Heart Failure costs more than $2.8 billion per year.

Heart Failure costs everyone

- Heart Failure patients have long and frequent hospital stays.
- There is no cure for Heart Failure.
- Heart Failure patients are complex, often managing other conditions.
- Heart Failure patients experience shortness of breath, exhaustion and swelling.
- Heart Failure caregivers are often overwhelmed and stressed.
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

REASSESS SYMPTOMS

- 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

Nonpharmacologic therapies (teaching self-care, exercise)

Advance Care Planning and Documentation of Goals of Care
Myocyte Metabolism and HR

Jonathan Howlett, MD, FRCPC, FACC
Clinical Professor of Medicine
Libin Cardiovascular Institute of Alberta
University of Calgary
Past President CHFS
Calgary, AB
Audience Polling

Which statement most closely outlines your beliefs regarding *elevated* sinus heart rate in patients with decompensated heart failure:

A) Heart rate reduction improves mortality in the chronic setting but not the acute setting

B) Sinus tachycardia in acute heart failure is a physiologic response and the treatment should be directed against the underlying condition rather than heart rate directly

C) Heart rate directly impacts systolic function and should be reduced in acute settings

D) It would be dangerous to directly reduce a heart rate to less than 120 in cardiogenic shock setting

E) Only Beta blockers have been proven in acute heart failure
Heart Rate as a Mechanism of Benefit in Systolic HF

1. Heart rate can be a maladaptive response in HF
2. Early effects of HR reduction and beta blockade are not identical
3. There are supportive data for early reduction of HR
Early Benefit of Treatment on Hospitalization for Heart Failure

No change in outcome first 3 months
Why is this?
Force Frequency Relation

• Initially described by Bowditch (Bowditch-Treppe phenomenon in 1871)

• Refers to increased contractility of isolated muscle strips with increased rate stimulation
  – Now refers to both *in vitro* or *in vivo* models

• May be measured via:
  – Fibre/cell shortening in myocytes
  – Static force in papillary muscles
  – Rate of pressure rise in intact hearts

• Nearly always coupled with relaxation
Normal heart increasing HR

Increased Ca++ efflux
With CaMKIIδ activation

**Increased** Ca++ clearance

Increased Ca++ flux
Increased systolic Ca++
Unchanged diastolic Ca++

**Increased** contractile force

Eisner, D. Circ Res. 2017;121:181-195. DOI: 10.1161/CIRCRESAHA.117.310230
Normal Human Papillary Muscle: Ca++ Level and Tone
DCM Human Papillary Muscle: Ca++ Level and Tone
This is Confirmed in Explanted Muscle Strips

[Graph showing force and [Na] over frequency for nonfailing and DCM+ICM muscle strips]
Myocyte Performance Increases With Overexpression of SERCA and Decreases With Overexpression of Phospholamban

Influence of the force–frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy

G. Hasenfuss, C. Holubarsch, H.-P. Hermann, K. Astheimer, B. Pieske and H. Just

Medizinische Klinik III, Universität Freiburg, Germany
Effect of HR: Normal vs. Failing LV

- Ejection fraction (%)
- Cardiac index (l.min⁻¹.m⁻²)
- Heart rate (min⁻¹)

Control vs. DCM comparison.
Acute Effects of Heart Rate Reduction With Beta Blockade

Reduction of LV performance acutely
Improvement chronically

Beta Blockers Exert Several Simultaneous Effects on Myocyte

Direct negative inotropy with beta blockade
Ivabradine Selectively Inhibits the If Current Leading to Effective Heart Rate Reduction in Sinus Rhythm

![Graph showing the effects of Ivabradine on heart rate and wall stress](image)

- **Left ventricle wall stress (g/cm²)**
  - Contraction
  - Relaxation

- **Time (ms)**
  - 0, 100, 200, 300, 400

- **Heart rate reduction**

- **Systolic time**

- **Diastolic time**

- **Ivabradine**

- **Atenolol**

Ivabradine Improved LV Function Within 24 hrs
Decreased heart rate, improved SV but preserved CI

10 patients with advanced HF, LVEF <35%, HR ≥80 bpm and max tolerated BB dose

- Heart rate (bpm) and stroke volume (ml)
- Cardiac index (l/min/m²)

Ivabradine i.v.

De Ferrari, Eur J Heart Fail. 2008;10:550-555
During hospitalization

- **Beta-blockers**
  
  on BBs: not stop after admission, with reduction in doses if necessary (based on clinical and hemodynamic condition of patients). BBs were uptitrated every 48 h in both groups
  
  No BBs before admission: BBs were started at low doses (carv: 3,125 mg/12 h or 6.25 mg/12 h, bisop: 1.25 to 2.5 mg/day) once the patient was stabilized, in both groups.
  
  - **Ivabradine**: added to BBs at initial dose of 5 mg bid after and uptitrated every 48 h until a dose of 7.5 mg bid based on HR

After discharge

- **BBs**: uptitration continued at the 14 and 28 days visits in both groups
  
  - **Ivabradine**: uptitration to target dose of 7,5 mg bid at 14 days
Effect of early treatment of ivabradine with BBs vs BB alone in patients hospitalized for WHF: randomized ETHIC study

Effect of early treatment of ivabradine with BBs vs BB alone in patients hospitalized for WHF: randomized ETHIC study

n = 71 patients hospitalized for WHF

Better reduction in BNP

Effect of early treatment of ivabradine with BBs vs BB alone in patients hospitalized for WHF: randomized ETHIC study

n = 71 patients hospitalized for WHF

Better HR control

# Selective HR Reduction in Advanced HF: Single Centre Series

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n=7)</th>
<th>Day 0, 6-12 hours (n=7)</th>
<th>24 hour post IVA (n=7)</th>
<th>48 hour post IVA (n=7)</th>
<th>Pre-discharge (n=7)</th>
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</thead>
<tbody>
<tr>
<td>Ivabradine</td>
<td>----</td>
<td>2.5 bid</td>
<td>2.5 bid</td>
<td>5.0 bid</td>
<td>5.5 bid</td>
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<tr>
<td>Milrinone</td>
<td>6/7</td>
<td>6/7</td>
<td>3/7</td>
<td>1/7</td>
<td>0/7</td>
</tr>
<tr>
<td>Pressor</td>
<td>3/7</td>
<td>1/7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Beta blocker?</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6/7</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>0</td>
<td>2/7</td>
<td>4/7</td>
<td>6/7</td>
<td>7/7</td>
</tr>
<tr>
<td>HR</td>
<td>105</td>
<td>95</td>
<td>93</td>
<td>90</td>
<td>80</td>
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<tr>
<td>MAP</td>
<td>72</td>
<td>70</td>
<td>74</td>
<td>74</td>
<td>72</td>
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<tr>
<td>RAP</td>
<td>16</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td></td>
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<tr>
<td>MVO2</td>
<td>45</td>
<td>60</td>
<td>61</td>
<td>65</td>
<td>---</td>
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<tr>
<td>PAOP</td>
<td>33</td>
<td>23</td>
<td>22</td>
<td>20</td>
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<tr>
<td>CI</td>
<td>1.8</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
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<tr>
<td>SVi</td>
<td>22</td>
<td>31</td>
<td>35</td>
<td></td>
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<td>eGFR</td>
<td>29</td>
<td>33</td>
<td>39</td>
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<td>41</td>
</tr>
</tbody>
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Heart Rate as a Mechanism of Benefit in Systolic HF

1. Heart rate can be a maladaptive response in HF
2. Early effects of HR reduction and beta blockade are not identical
3. There are supportive data for early reduction of HR
Impact of the Latest Therapies

Peter Liu, MD, FRCPC
Chief Scientific Officer &
Vice President, Research
University of Ottawa Heart Institute
Professor of Medicine, University of Ottawa
Ottawa, ON
Biomarkers such as NTproBNP are excellent predictors of outcome for patients with heart failure...

Do newer treatments for heart failure with reduced ejection fraction (HFrEF), such as Ivabradine or Sacubitril/Valsartan impact at all on NTproBNP levels in patients (hence prognosis)?

A. Reduce NTproBNP somewhat, but rather slowly (e.g. over one year)
B. Reduce NTproBNP significantly (>30%), but do so relatively slowly
C. Reduce NTproBNP somewhat, but do so rapidly (<1 month)
D. Reduce NTproBNP significantly, and do so rapidly (<1 month)
E. Have no consistent impact on NTproBNP over time
Early Impact of Recent Evidence-based Therapies
Acute Heart Failure Results From Loss of Homeostasis Amongst Interconnected Systems

The reserve for interconnected systems to rebalance following perturbation is limited, thus prone to decompensation.

- Activation of stress response, including heart rate increase & immune activation
- Tissue Congestion & Decrease in Vital Organ Perfusion
- Increase in Peripheral Vasohormones
- Decrease in Renal Clearance

Felker et al. Circ Heart Fail 2010;3(2):314–25
All-cause Mortality After Each Subsequent Hospitalization for HF

CHF

1\(^{st}\) Admission (n = 14,374)
2\(^{nd}\) Admission (n = 3,358)
3\(^{rd}\) admission (n = 1,123)
4\(^{th}\) Admission (n = 417)

1\(^{st}\) hospitalization: 30 d mortality = 12%; 1 yr = 34%
All-cause Mortality and HF Rehospitalization in the Vulnerable Phase

Stress Biomarkers (e.g. NTproBNP or hsTn) Are Highly Prognostic in ADHF

Change in BNP as Px Marker

## Evidence-based Rx on HFrEF Outcomes

<table>
<thead>
<tr>
<th>Rx Mode</th>
<th>Mortality</th>
<th>HF Progr’n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi/ARB</td>
<td>✓ ✓</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>β-blocker</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>MRA</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>ARNI (Sacubitril/Val)</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Ivabradine (HR&gt;77/min)</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
</tr>
</tbody>
</table>
Brad always believed in Democracy – Vote Early & Vote Often
Network Meta-analysis of HFrEF Rx

Burnett H, Cope S, et al., Circ Heart Failure 2017; 10:e003529
<table>
<thead>
<tr>
<th></th>
<th>Post-MI</th>
<th>Class II</th>
<th>Class III-IV HF</th>
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<tr>
<td><strong>Trial</strong></td>
<td>EPHESUS</td>
<td>EMPHASIS</td>
<td>RALES</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>6632</td>
<td>2737</td>
<td>1663</td>
</tr>
<tr>
<td><strong>Baseline Mortality</strong></td>
<td>12% / yr</td>
<td>9% / yr</td>
<td>23% / yr</td>
</tr>
<tr>
<td><strong>Reduction in Mortality</strong></td>
<td>↓ 15%</td>
<td>↓ 24%</td>
<td>↓ 30%</td>
</tr>
<tr>
<td><strong>NNT/year to save 1 life</strong></td>
<td>59</td>
<td>51</td>
<td>14</td>
</tr>
</tbody>
</table>
Sacubitril/Valsartan Simultaneously Enhances the Beneficial Effects of the NP System While Blocking Detrimental Effects of the RAAS

peptide; NPR=natriuretic peptide receptor; RAAS=renin-angiotensin-aldosterone ANP=atrial natriuretic peptide; Ang=angiotensin; AT1 = angiotensin II type 1; BNP=B-type natriuretic peptide; cGMP=cyclic guanosine monophosphate; GTP=guanosine triphosphate; NEP=neprilysin; NP=natriuretic system

Sacubitril/Valsartan Benefits Both Sudden & HF Deaths

NT-proBNP ↓ Rapidly With Sacubitril/Valsartan Rx

NT-proBNP remains an accurate measure of severity of HF in the setting of treatment with LCZ696 but BNP will not be reliable!

Influence of Sacubitril/Valsalrtan on NT-proBNP Reduction and Influence on Outcomes

Risk of Primary Endpoint After 1 month

- Did Not Achieve NT-proBNP < 1000
- Achieved NT-proBNP < 1000

Patients Achieving NT-proBNP < 1000

- 1 Month
- 8 Months
- Sustained

- LCZ696
- Enalapril

P < 0.001

P < 0.001

P < 0.001
### Effect of Effective Rx on HFrEF Outcomes

<table>
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<tr>
<td>Ivabradine (HR&gt;77/min)</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
</tr>
</tbody>
</table>
Ivabradine Significantly Reduced Mortality

The higher the HR at baseline, the greater the benefits

- Patients with baseline HR ≥ 70 and ≥ 77 bpm

<table>
<thead>
<tr>
<th></th>
<th>≥ 70 bpm</th>
<th>≥ 77 bpm</th>
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<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
<td></td>
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<tr>
<td>CV death or hospital admission for worsening HF</td>
<td>18% (p&lt;0.0001)</td>
<td>25% (p&lt;0.0001)</td>
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<tr>
<td><strong>Mortality endpoints</strong></td>
<td></td>
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<tr>
<td>All-cause mortality</td>
<td>10% (p = 0.092)</td>
<td>19% (p=0.0074)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>9% (p = 0.128)</td>
<td>19% (p=0.0137)</td>
</tr>
<tr>
<td>Death from HF</td>
<td>26% (p=0.014)</td>
<td>39% (p=0.0017)</td>
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<tr>
<td><strong>Other endpoints</strong></td>
<td></td>
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<tr>
<td>All-cause hospital admission</td>
<td>11% (p=0.003)</td>
<td>18% (p=0.0002)</td>
</tr>
<tr>
<td>Any CV hospital admission</td>
<td>15% (p=0.0002)</td>
<td>21% (p&lt;0.0001)</td>
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<tr>
<td>Hospital admission for worsening of HF</td>
<td>26% (p&lt;0.0001)</td>
<td>31% (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

Effect of Ivabradine on Primary Outcome in Patients With High HR (≥ 77 bpm)

**CV death or hospitalization for HF**

HR = 0.75 (0.67–0.85)
p < 0.0001

Graph showing cumulative frequency over time from randomization (months) with standard therapy and standard therapy & ivabradine. The graph indicates a 25% decrease in CV death or hospitalization for HF with ivabradine.

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ivabradine</th>
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<tbody>
<tr>
<td>0</td>
<td>1,700</td>
<td>1,657</td>
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<tr>
<td>6</td>
<td>1,436</td>
<td>1,472</td>
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<td>12</td>
<td>1,210</td>
<td>1,291</td>
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<td>18</td>
<td>970</td>
<td>1,054</td>
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<td>24</td>
<td>518</td>
<td>566</td>
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<tr>
<td>30</td>
<td>208</td>
<td>211</td>
</tr>
<tr>
<td>36</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Effect of Ivabradine on Total HF Hospitalizations

Cumulative incidence of HF hospitalizations (first and repeated)

IRR (95% CI), 0.75 (0.65;0.87)

\[ P=0.0002 \]

- 25%
Recurrence of HF Hospitalization
Total-time Approach

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First hospitalization</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>0.75</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Second hospitalization</td>
<td>189 (6%)</td>
<td>283 (9%)</td>
<td>0.66</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Third hospitalization</td>
<td>90 (3%)</td>
<td>128 (4%)</td>
<td>0.71</td>
<td>p=0.012</td>
</tr>
</tbody>
</table>

Favours ivabradine
Favours placebo

## Effect of Ivabradine on CV and HF Hospitalizations Over the 3 Months After a First HF Hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Cumulative number of events</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ivabradine (N=514)</td>
<td>Placebo (N=672)</td>
</tr>
<tr>
<td>Cardiovascular hospitalizations</td>
<td></td>
<td>(adjusted for prognostic factors)</td>
</tr>
<tr>
<td>1 month</td>
<td>38</td>
<td>76</td>
</tr>
<tr>
<td>2 months</td>
<td>90</td>
<td>155</td>
</tr>
<tr>
<td>3 months</td>
<td>131</td>
<td>221</td>
</tr>
<tr>
<td>Heart failure hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>2 months</td>
<td>56</td>
<td>97</td>
</tr>
<tr>
<td>3 months</td>
<td>86</td>
<td>148</td>
</tr>
</tbody>
</table>
Ivabradine Decreased NT-proBNP, a Predictor of HF Prognosis

- Patients with systolic HF in sinus rhythm, HR > 70 bpm and on optimized medical therapy (80% on ACE inhibitor, 56% on spironolactone and 88% on BB)
- Patient treated with ivabradine for 3 months (5 mg BID, uptitrated to 7.5 mg BID after 2 weeks based on HR)

The decrease in NT-proBNP correlated closely with the degree of HR reduction (p=0.027)

Impact of Lowering HR on Prognosis

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

Patients with CV death or HF hospitalization, %

<table>
<thead>
<tr>
<th>HR Range</th>
<th>Outcome Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 75 bpm</td>
<td>50</td>
</tr>
<tr>
<td>70 - &lt; 75 bpm</td>
<td>40</td>
</tr>
<tr>
<td>60 - &lt; 65 bpm</td>
<td>30</td>
</tr>
<tr>
<td>65 - &lt; 70 bpm</td>
<td>20</td>
</tr>
<tr>
<td>&lt; 60 bpm</td>
<td>10</td>
</tr>
</tbody>
</table>

p<0.0001

<table>
<thead>
<tr>
<th>Medication</th>
<th>Control</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>BP, Cr, K⁺, Na⁺</td>
<td>All patients without contraindication</td>
</tr>
<tr>
<td>ARB</td>
<td>BP, Cr, K⁺, Na⁺</td>
<td>Alternative to ACEI</td>
</tr>
<tr>
<td>BB</td>
<td>BP, HR</td>
<td>All patients without contraindication</td>
</tr>
<tr>
<td>MRA</td>
<td>BP, Cr, K⁺, Na⁺</td>
<td>All patients without contraindication</td>
</tr>
<tr>
<td>ARNI</td>
<td>BP, Cr, K⁺, Na⁺</td>
<td>Replacement for ACEI or ARB in patients with stable chronic HF with reduced left ventricular ejection fraction NYHA Class II or III</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>HR</td>
<td>Patients with stable chronic HF with reduced left ventricular ejection fraction (≤ 35%) NYHA Class II or III in SR and HR ≥ 77 bpm</td>
</tr>
</tbody>
</table>
Conclusions

- Acute heart failure is a state of multi-system decompensation, with high mortality, elevated NTproBNP and repeat hospitalization.
- Only way to impact on outcome is early initiation of evidence-based therapies known to improve patient outcome.
- ARNI (Sacubitril/Valsartan) has effect on HF outcomes early (Sudden death & hospitalization), and reduces NTproBNP within 1 month.
- If channel blockade (Ivabradine) is associated with rapid risk reduction with mortality/hospitalization benefit seen at one month (esp HR>77).
- Ivabradine reduces NTproBNP < 3 months and is very well tolerated.
HFrEF: What is the Urgency?

Nadia Giannetti, MD, FRCPC
Associate Professor, Department of Medicine
Medical Director,
Heart Failure and Heart Transplant Program
Chief, Division of Cardiology
McGill University Health Centre
Montreal, QC
What is the 30-day mortality after a heart failure hospitalization?

A. 1%
B. 5%
C. 10%
D. 15%
The burden of HF in Canada

PREVALENCE/INCIDENCE
- 600,000 HF patients in Canada
- 50,000 new cases per year

MORTALITY
- 1-year mortality rate: 25%
- 30-day mortality rate after HF hospitalization: 16%
- Median life expectancy: 5 years (all patients); 29 months (after hospitalization)

HOSPITALIZATIONS
- 30-day readmission rate: 21%
- 2nd highest cause of hospitalization in persons over 65 years of age
- LOS approximately 8 days, $10,000/hospitalization

BURDEN ON THE HEALTH CARE SYSTEM
- Cost of $2.8 billion per year
Mortality is Particularly High in the Early Phase After Hospitalization

All-cause mortality after discharge for HF is high during the 1st month

Several factors affect early outcome after a heart failure hospitalization
For patients discharged from an HF hospitalization, within 1 year:

- 42% will see a specialist and a GP
- 1% will only see a specialist
- 24% will only see a GP
- 34% won’t see any physicians

Mortality within 1 year: Ezekowitz, CMAJ, 2005, 172, 189
Survival After Admission to Hospital by Input From Heart Failure Team

[Graph showing survival rates over time with two lines: one for HF team and one for No HF team.]
Medical Therapy at Discharge

National HF Audit annual report 2014-2015, UK

http://www.bsh.org.uk/resources/national-heart-failure-audit/
Relationship between baseline adherence and outcomes at 18 Months

**All-cause death**

- Good (Adherence score = 1)
- Moderate (0.5 < Adherence score < 1)
- Poor (Adherence score ≤ 0.5)

**CV death**

- Good (Adherence score = 1)
- Moderate (0.5 < Adherence score < 1)
- Poor (Adherence score ≤ 0.5)
EARLY Impact of High HR at Discharge

- Elevated HR at discharge is associated with increased **30-day mortality** and higher readmission rates in HF patients
- Average discharge HR 76 bpm

9097 patients discharged from an HF hospitalization in Ontario (1999-2001 and 2004-2005)

<table>
<thead>
<tr>
<th>Heart rate at discharge (bpm)</th>
<th>40-60</th>
<th>61-70</th>
<th>71-80</th>
<th>81-90</th>
<th>&gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio for <strong>30-day mortality</strong></td>
<td>1.06</td>
<td>Referent</td>
<td>1.21</td>
<td>1.70</td>
<td>1.88</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.720</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.185</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

61.5% of patients with HR ≥ 70 bpm
Elevated Heart Rate at Hospital Discharge Predicts One-year Mortality


Survival (%)

41% increase in one-year mortality

\[ P = 0.01 \]

N=1658 (170 hospitals); Mean HR at discharge: 71 bpm; 1 year mortality: 33%
Early Benefit of Treatment on Hospitalization for Heart Failure

- The curves begin to diverge at 3 months, and the difference is statistically significant at 6 months.

**Endpoint- hospitalization for HF:**

- HR 0.60 (95% CI: 0.38–0.94)
- p=0.027

Days after randomization

- Early treatment with IVA reduces readmission for HF in SHIFT trial
- The curves begin to diverge at 2 weeks for those hospitalized for HF

Packer et al. Circulation 2015; 131:54-61

Komajda, EJHF, 2016, 18, 1182
Effect of Ivabradine on All-cause Hospitalizations Over the 3 Months After a First Hospital Admission for HF

Cumulative incidence of all-cause hospitalizations following first hospitalization for heart failure

Time (months) after hospital admission for heart failure

Ivabradine/Placebo

Patients at risk

Number of events

0.5

0.4

0.3

0.2

0.1

0.5

0.4

0.3

0.2

0.1

0

Ivabradine
Placebo

IRR=0.70
P<0.05

IRR=0.75
P=0.03

IRR=0.79
P=0.04

514/672
454/590
424/551
398/524

0/0
54/102
115/201
166/278

Komajda Eur J Heart failure 2016
Early Co-administration of Ivabradine and β-blockers During Hospitalization May Reduce Mortality

N=414 patients hospitalized due to worsening HF who were in sinus rhythm, NYHA Class II-IV, and LVEF <40%. Physicians were free to choose the strategy of co-administration of BBs and ivabradine (37.2%) or with BBs alone (62.8%). Lopatin et al. AHA 2017

Probability of survival

HR=0.41 (95% CI, 0.29-0.57)   P<0.0001
The Best Evidence for Improvement in Therapy is Shown in HOSPITALIZED Patients

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

![Diagram showing patients treated with evidence-based drug at admission and discharge across different studies.](image)

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

Hospitalization is the Key Moment to Optimize Treatment

Conclusions, Why it is Urgent to Act

- Mortality and readmission are high after discharge for HF
- Better adherence to guidelines recommended therapies improve outcomes
- Hospitalization is the key moment to optimize treatment
- Effective therapies are available, they need to be used!
Lessons Learned from the OPTIMIZE-HF Program

Martin R Cowie
Professor of Cardiology
National Heart & Lung Institute
Imperial College London (Royal Brompton Hospital Campus)
m.cowie@imperial.ac.uk
@ProfMartinCowie
Consecutive phases of AHF management

Immediate:
- Improve organ perfusion & haemodynamics
- Restore oxygenation
- Alleviate symptoms
- Limit cardiac & renal damage
- Prevent thromboembolism
- Minimize ICU length of stay

Intermediate:
- Identify aetiology and relevant co-morbidities
- Titrate therapy to control symptoms and congestion and optimize blood pressure
- Initiate and up-titrated disease-modifying pharmacological therapy
- Consider device therapy in appropriate patients

Pre-discharge and long-term management:
- Develop a careful plan that provides:
  a. schedule for up-titrating and monitoring of pharmacological therapy
  b. need and timing for review for device therapy
  c. who will see the patient and when
- Enrol in disease management programme, educate, initiate lifestyle adjustments
- Prevent early readmission
- Improve symptoms, QoL and survival

Goals of Treatment in Acute Heart Failure
Pre-discharge and Longer-term Management

Develop a careful plan that provides:

- who will see the patient and when
- a schedule for up-titrating and monitoring of drug therapy
- need and timing for review for device therapy

Patients should be:

- enrolled in a disease management program
- seen by their general practitioner within 1 week of discharge
- seen by the hospital cardiology team within 2 weeks of discharge (if feasible)
Statement 6

• Adults with Acute Heart Failure have a follow-up clinical assessment by a member of the community- or hospital-based specialist heart failure team within 2 weeks of hospital discharge.
Cardiology Follow-up After Discharge From NHS hospitals in England (2009-11)

THE REALITY

Bottle A et al. BMJ Open 2016; 6: e010669
Hospitalization is the Key Moment to Optimize Treatment

2013 ACCF/AHA guidelines for HF


Recommendations for Hospital Discharge

<table>
<thead>
<tr>
<th>Recommendations or Indications</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance improvement systems in the hospital and early postdischarge outpatient setting to identify HF for GDMT</td>
<td>I</td>
<td>B</td>
<td>82, 365, 706, 792–796</td>
</tr>
<tr>
<td>Before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Initiation of GDMT if not done or contraindicated;</td>
<td>I</td>
<td>B</td>
<td>204, 795, 797–799</td>
</tr>
<tr>
<td>b. Causes of HF, barriers to care, and limitations in support;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Assessment of volume status and blood pressure with adjustment of HF therapy;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Optimization of chronic oral HF therapy;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Renal function and electrolytes;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Management of comorbid conditions;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. HF education, self-care, emergency plans, and adherence;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Palliative or hospice care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended</td>
<td>I</td>
<td>B</td>
<td>82, 800–802</td>
</tr>
<tr>
<td>A follow-up visit within 7 to 14 d and/or a telephone follow-up within 3 d of hospital discharge are reasonable</td>
<td>Ila</td>
<td>B</td>
<td>101, 803</td>
</tr>
<tr>
<td>Use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients are reasonable</td>
<td>Ila</td>
<td>B</td>
<td>215</td>
</tr>
</tbody>
</table>

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.
How Do We Improve Quality?

TOTAL QUALITY MANAGEMENT
Enter your sub headline here

Lean / Six Sigma

- Quality
- Cost
- Safety
- Employee Satisfaction / Engagement
- Service / Patient Satisfaction

TQM

- Training
- Total Employee Commitment
- Continuous Improvement
- Strategic and Systematic Approach
- Decisions Based on Fact
- Integrated System
- Effective Communication
- Customer Satisfaction
- Lean Work and Quality Chain

SMART

- Specific
- Measurable
- Attainable
- Relevant
- Time Bounded
What is the care “pathway”? What needs to happen and when? And by whom?
>45 national initiatives

Optimize heart failure care from hospital discharge to patient follow-up

1. Optimize before discharge
   - A USB key including slide sets and interviews endorsing the rationale of the concept and tools for pharmacological optimization.
   - Examples of protocols for hospital discharge and patient follow-up.

2. Pre- & post-hospital discharge checklist
   - A pre- and post-hospital discharge checklist to complete at discharge and at the 2 early post-discharge follow-up visits as well.
   - Summary checklist sticker.

3. Patient education & follow-up
   - Two educational and follow-up tools are available for the patient:
     - MyHF smartphone application and the paper version.
     - My Heart Failure Passport.
Optimize heart failure care from hospital discharge to patient follow-up
Pre- & Post-hospital Discharge Checklist

**Pre- & post hospital discharge checklist**

Monitor the key aspects of heart failure at the next 3 visits right before discharge and at the 2 early post-discharge visits to monitor the progression of the disease and treatment optimization.

Optimize heart failure care from hospital discharge to patient follow-up

**A summarized checklist sticker**

- [Image of a summarized checklist sticker]
My Heart Failure Passport widely adopted
A practical follow-up for the patient

- **My daily tips**
  To improve your knowledge of heart failure

- **My results**
  To monitor the course of your disease

- **My treatment**
  To remind you to take your medication at specified times
MyHF is available worldwide for free on the stores.

12 languages are available: Brazilian, Czech, English, French, German, Korean, Italian, Portuguese, Russian, Slovakian, Slovenian, Spanish.
Heart Failure Care: Keys to Success

National tour & awareness campaign

Protocols & guidelines

Registries & Publications on improvement of the quality of care

Educational tools

Heart failure patient passport
MyHF smartphone application
What Has Been the Impact?

• https://www.optimize-hf.com/en/bibliography/
• Design paper: Int J Cardiol 2017; 236: 340-44

• Multiple abstracts at scientific congresses from many countries
• Results from Russian-speaking countries: Int J Cardiol 2018; 260: 113-7

• Manuscripts in preparation for Colombia, Brazil and Vietnam
Data From 8 Post-Soviet Countries

Optimization of heart rate lowering therapy in hospitalized patients with heart failure: Insights from the Optimize Heart Failure Care Program

Yuri M. Lopatin a,⁎, Martin K. Cowie a,⁎, Anna A. Orenbelskaya a,⁎, Iryna M. Pugava a,⁎, Naimet G. Haiyparova b,⁎, Timur A. Abdaliev b,⁎, Lenora G. Vorotnikova b,⁎, Anna I. Chumilnova a,⁎, Mira I. Turukina a,⁎, Rostislav I. Tatarinovskaya b,⁎, Galina M. Dimadatova b,⁎, Salim I. Berkinbaev b,⁎, Maria G. Grieser a,⁎, Natalia A. Kozikova a,⁎, Armina G. Rakhsheva b,⁎, Zviad V. Kipiani c,⁎, Alena K. Karyusmava a,⁎

⁎ Corresponding authors.

Abstract
Background: Hospitalization due to heart failure (HF) is an opportunity to optimize HF care in the hospital setting. As hospitalization for secondary prevention and symptom management is a commonly used treatment strategy, optimal treatment for patients with HF exacerbation is essential. This study aimed to explore the impact of heart rate lowering therapy (BBlocking Drugs, BBs; and intravenous BBs alone) in short and long-term outcomes in patients with HF exacerbation.

Methods and materials: A retrospective analysis was performed in 728 hospitalized HF patients with heart rate > 70 bpm (54% BBs and 46% intravenous BBs) admitted to the University Hospital “Almazov National Research Medical Center” in St. Petersburg, Russia, from October 2015 to April 2016. Results: In the study, 3 months, 6 months, and 12 months, there were fewer deaths for HF hospitalizations and hospitalizations for HF exacerbation in patients in the BB group compared to the control group. After 1 year, more patients in the BB group were alive compared to the control group. For patients with heart rate > 110 bpm, BB therapy reduced the risk of hospitalization and mortality. A significant difference in cumulative survival rates for the first year of follow-up was observed between patients with heart rate > 110 bpm (p < 0.001). A significant improvement was observed in quality of life (p < 0.001). A total of 52 patients were enrolled in the study. The primary endpoint was hospitalization for HF exacerbation (p = 0.001). The secondary endpoint was hospitalization for HF exacerbation (p < 0.001).

Conclusion: Heart rate lowering therapy with BBs compared to intravenous BBs in hospitalized patients with heart rate > 70 bpm is associated with reduced overall mortality and rehospitalization over the 12-month follow-up period. A prospective randomized trial is needed to confirm the advantages of this strategy.

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KM cumulative survival for all-cause mortality and HF hospitalisation in the OPTIMIZE program, adjusted for age, gender, heart rate, systolic blood pressure, serum creatinine and NYHA class.

Lopatin YM et al. Int J Cardiol 2018; 260: 113-117
Effect of Ivabradine in the Vulnerable Phase: Results from the Optimize Colombia Project

**TABLE 1**
30 days outcomes

<table>
<thead>
<tr>
<th></th>
<th>With ivabradine n = 131</th>
<th>Without ivabradine n = 137</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in LV ejection fraction</td>
<td>5%</td>
<td>0%</td>
<td>0.005</td>
</tr>
<tr>
<td>Improvement in at least one NYHA class</td>
<td>42%</td>
<td>12%</td>
<td>0.000</td>
</tr>
<tr>
<td>Decompensation+ hospitalization</td>
<td>1.53%</td>
<td>8.57%</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Optimize Brazil Initiative

Optimization of HF treatment improves clinical outcomes: an analysis of a multidisciplinary initiative in a retrospective multicenter Brazilian cohort of HF patients

219 patients, 5 Brazilian centers, 414 days of follow-up

Conclusions

• The Optimize Program is multi-pronged and acts to improve inpatient/clinic management and education of patients and their healthcare teams
• Now active in 45 countries
• Easily adaptable to local circumstances
• Low cost
• Many lessons learned as to how to maximise program effectiveness
• Perhaps something for Canada to consider?

https://www.optimize-hf.com
Reconciling the guidelines with reality

Jonathan Howlett, MD, FRCPC, FACC
Clinical Professor of Medicine
Libin Cardiovascular Institute of Alberta
University of Calgary
Past President CHFS
Calgary, AB
Audience Polling
What intervention do you think will make the biggest difference to increase integration of EBMT for people with HFrEF?

A. Increase the number of heart failure clinics

B. Increase efforts to implore care providers to titrate/add/switch medications more often

C. Start heart failure clinics in the primary care setting

D. Increase initiation of EBMT for patients while in hospital

E. Get real - nothing will work!
The Desired State...

- Titration might take several weeks to months depending on disease severity.

- The entire triple therapy titration to maximal tolerated or target doses should be completed within 4 to 6 months.
Figure 1. Patients who survived first HF hospitalization and claimed a prescription of RASi, β-blockers, or spironolactone within 90 days or statin within 180 days from discharge.

Majority <50% of target dose with little dose escalation over time

www.ccs.ca  Heart Failure Guidelines
57% of the Patients Will not See a Specialist After an HF Hospitalization

For patients discharged from an HF hospitalization, within 1 year

- 42% will see a specialist and a GP
- 1% will only see a specialist
- 24% will only see a GP
- 34% won’t see any physicians

Mortality within 1 year
Hospitalization is the Key Moment to Optimize Treatment

The Time to Treat is Now:

- Heart failure outcomes continue at a high rate
- The hospitalization period represents both a major risk and an opportunity
- Multiple maladaptive mechanisms (including HR) are active in HF patients
- Evidence-based therapy works quickly to reduce stress and adverse outcomes
- Re-emphasizing the hospital as locus for initiation of EBMT
- Organized programs can positively impact outcomes in those with HF
Please visit our website for more information and download our CCS guideline Apps

www.ccsguidelineprograms.ca
Questions?

Panel Discussion
REFLECTIVE LEARNING:
New Treatment Options in HFrEF

PARTICIPATE IN A NEW SECTION 3 MOC ACCREDITED SELF-ASSESSMENT PROGRAM

- Reflective Learning: New Treatment Options in HFrEF
  - Accredited by the Canadian Cardiovascular Society (CCS)
  - Endorsed by the Canadian Heart Failure Society (CHFS) and the Canadian Council of Cardiovascular Nurses (CCCN)
  - Valuable resource to help you optimize treatment decisions related to the management of patients with HFrEF within your practice
  - Earn up to 12 of the minimum 25 mandatory section 3 MOC credits required for the renewal of Fellowship in the Royal College

WWW.REFLECTIVELEARNING-HFREF.COM
Audience polling system: basic science questions for the future

Jonathan Howlett, MD, FRCPC, FACC
Clinical Professor of Medicine
Libin Cardiovascular Institute of Alberta
University of Calgary
Past President CHFS
Calgary, AB
• What one research question about HF do you think needs to be addressed?
Thank you!

Please fill out the evaluation form by texting EVALUATION to (647) 696-5222