Heart Failure: Current Management Strategies

CSHP Fall Education Session- September 30th, 2017

Carolyn MacKinnon & Tamara Matchett
BscPharm, ACPR Candidates
Objectives

1. Describe the pathophysiology & presentation of heart failure
2. Identify current management strategies for heart failure
3. Discuss heart failure treatment updates and how they may apply to practice
Patient Case

**ID**
- 68 year old male

**CC**
- Increasing SOBOE

**PMHx**
- HF-rEF x 5 years, NYHA II
- COPD

**Physical Exam**
- BP 110/60 mmHG
- HR 72 bpm
- Minimal pedal edema

**Labs**
- Na 138, K 4.2, SCr 86 mmol/l (CrCl 61 ml/min), NT-proBNP 2480 pg/ml

**Diagnostic tests**
- LVEF: 35%

**Medications:**
- Bisoprolol 10 mg daily
- Telmisartan 40 mg daily
- Spironolactone 25 mg daily
- Furosemide 40mg daily
What is your next step?

A. Start sacubitril/valsartan 24mg/26mg
B. Start ivabradine 7.5mg BID
C. Change spironolactone to eplerenone
D. Start hydralazine/nitrates
Congestive Heart Failure = Heart Failure
Epidemiology

- About 600,000 Canadians living with heart failure
- 50,000 Canadians diagnosed/year
- Risk of CV death is INCREASED after HF hospitalization
- Costs to the health care system is over $2.8 million/year
- More common in men than women before age 65
Pathophysiology

- Inability for heart to pump sufficient blood for body’s metabolic needs
- ↓ ventricular filling (diastolic) and/or ↓ contractility (systolic)
- Leading causes: heart damage from previous myocardial infarction and hypertension
Out with the Old...

<table>
<thead>
<tr>
<th>Terminology</th>
<th>LVEF</th>
</tr>
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<tbody>
<tr>
<td>Preserved EF (HF-pEF)</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Reduced EF (HF-rEF)</td>
<td>&lt;40%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Terminology</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preserved EF (HF-pEF)</td>
<td>≥ 50%</td>
</tr>
<tr>
<td>Mid-range EF (HF-mEF)</td>
<td>41-49%</td>
</tr>
<tr>
<td>Reduced EF (HF-rEF)</td>
<td>≤40%</td>
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</tbody>
</table>
Symptoms

- **Primary manifestations**: dyspnea & fatigue
- Edema
- Orthopnea
- Exercise intolerance
- Cough
- Mental status changes (confusion)
## New York Heart Association (NYHA) Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue <strong>fatigue, palpitation, dyspnea</strong></td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. Discomfort increases with physical activity.</td>
</tr>
</tbody>
</table>
Diagnosis

- Clinical history and physical exam
  - Symptoms, functional limitation, risk factors, comorbidities, vital signs, volume status
- Initial investigations
  - CXR, ECG, CBC, electrolytes, renal function
- Natriuretic peptides
  - NT-proBNP or BNP
- Ventricular function
  - Echo, LVEF
HF Management
Strategies to Date
Therapies improving survival

🚫 HF with preserved EF (HF-pef) $\geq 50$
  - No therapies improving survival

🚫 HF with mid range EF (HF-mef) 41-49%
  - No therapies improving survival

✅ HF with reduced EF (HF-ref) $\leq 40$
  - Survival benefit shown with: Beta blockers, ACE inhibitors/angiotensin receptor blockers, aldosterone antagonists, F channel inhibitors, angiotensin receptor neprilysin inhibitor
Canadian Cardiovascular Society (CCS) Guidelines
Guideline Timeline

- **2006:** Heart Failure Diagnosis and Management Guidelines
- **2007-2014:** Annual Updates
- **2015:** Heart Failure Companion: Bridging Guidelines to Your Practice
- **2017:** Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure
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

Advance Care Planning and Documentation
Angiotensin Receptor Neprilysin Inhibitor (ARNI)
Angiotensin receptor neprilysin inhibitor (ARNI)

Sacubitril (neprilysin inhibitor) + Valsartan (Ang II receptor blocker) = “LCZ696”
**Sacubitril/Valsartan (Entresto)**

**Natriuretic Peptide System**

Natriuretic peptides → Neprilysin → Sacubitril → Inactive fragments → Vasodilation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone
- ↓ Hypertrophy

**Renin Angiotensin System**

Angiotensin I → Angiotensin II → Angiotensin II Receptor → Vasoconstriction
- ↑ Blood pressure
- ↑ Sympathetic tone
- ↑ Aldosterone
- ↑ Hypertrophy

Sacubitril blocks the breakdown of neprilysin, allowing the natriuretic peptides to remain active. Valsartan blocks the angiotensin II receptor, preventing vasoconstriction and related effects.
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D.,
for the PARADIGM-HF Investigators and Committees*
**PARADIGM-HF**

<table>
<thead>
<tr>
<th>P</th>
<th>Patients with HF NYHA class II-IV with EF ≤40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>LCZ696 200 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>(Sacubitril 97mg/ Valsartan 103 mg twice daily)</td>
</tr>
<tr>
<td>C</td>
<td>Enalapril 10 mg twice daily</td>
</tr>
<tr>
<td>O</td>
<td>Composite of death from cardiovascular causes or hospitalization for heart failure</td>
</tr>
</tbody>
</table>
PARADIGM-HF

**SINGLE-BLIND RUN-IN PERIOD†**
(6 to 8 weeks)

<table>
<thead>
<tr>
<th>MEDIAN EXPOSURE:</th>
<th>MEDIAN EXPOSURE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 DAYS</td>
<td>29 DAYS</td>
</tr>
<tr>
<td>(N = 10,513)</td>
<td>(N = 9419)</td>
</tr>
</tbody>
</table>

**ENTRESTO**
97/103 mg twice daily
N = 4209

**ENTRESTO**
49/51 mg twice daily

**ENTRESTO**
97/103 mg twice daily

**DOUBBLE-BLIND PERIOD‡**
(Duration was event-driven; median follow-up duration was 27 months)

**ENTRESTO**
97/103 mg twice daily
N = 4233

**(1:1 RANDOMIZATION)**

**Enalapril**
10 mg twice daily
N = 4233
Primary outcome: CV mortality or first hospitalization for HF

ENTRESTO vs ENALAPRIL:
21.8% vs 26.5%,
p<0.001

ARR: 4.7%
NNT: 21
PARADIGM-HF: Outcomes

Efficacy

- 3.2% ARR in CV death : NNT 31
- 3% ARR in first hospitalization : NNT 33
- 2.3% ARR in death from any cause: NNT 44

All statistically significant
PARADIGM-HF: Outcomes

Safety

- Less likely to be discontinued due to adverse event (10.7% vs 12.3%, p=0.03)
- Less likely to cause cough (11.3% vs 14.3%), hyperkalemia (4.3% vs 5.6%) or renal impairment (3.3% vs 4.5%, all p<0.05)
- More likely to cause symptomatic hypotension
  - Mean SBP at 8 months 3.2 mmHg lower in Entresto group
When do we use it?
When do we use it?

CCS Guidelines:

- an ARNI should be used in place of an ACEi or ARB, in patients with HFrEF NYHA Class II to IV, who remain symptomatic despite treatment with maximum tolerated doses of ACEI/ARB + BB + MRA
Checklist

☑ Ejection fraction < 40%
☑ NYHA Class II or III
☑ BP ≥ 100 mm Hg
☑ eGFR ≥ 30 ml/min
☑ Potassium < 5.2 mmol/L
☑ ACEi/ARB, BB, MRA at max tolerated dose
## Entresto (LCZ696) - Supplied

<table>
<thead>
<tr>
<th>Low dose</th>
<th>Moderate dose</th>
<th>High (target) dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>24mg/26mg</td>
<td>49mg/51mg</td>
<td>97mg/103mg</td>
</tr>
<tr>
<td>Sacubitril/Valsartan</td>
<td>aka 50mg</td>
<td>Sacubitril/Valsartan</td>
</tr>
<tr>
<td>aka 50mg</td>
<td>aka 100mg</td>
<td>aka 200mg</td>
</tr>
</tbody>
</table>

103mg of valsartan in Entresto = 160mg of valsartan in Diovan
Entresto (LCZ696) - Dosing

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Initial Dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Higher dose of RAAS inhibitor</strong></td>
<td><strong>49/51mg BID</strong></td>
<td>Increase to target 97/103mg BID over 2-4 weeks</td>
</tr>
<tr>
<td><strong>ACEI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril $\geq$10mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril $\geq$10mg/d</td>
<td></td>
<td></td>
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<tr>
<td>Perindopril $\geq$4mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril $\geq$5 mg/d</td>
<td></td>
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<tr>
<td><strong>ARB</strong></td>
<td></td>
<td></td>
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<tr>
<td>Candesartan $\geq$16mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irbesartan $\geq$150mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan $\geq$50 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olmesartan $\geq$10 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan $\geq$40 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valsartan $\geq$160 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lower dose of RAAS inhibitor, higher risk of hypotension (low BP, &gt; 75yrs poor renal function), or moderate hepatic impairment</strong></td>
<td><strong>24/26mg BID</strong></td>
<td>Increase to target 97/103mg over 6 weeks</td>
</tr>
</tbody>
</table>

- ACEI: Angiotensin Converting Enzyme Inhibitors
- ARB: Angiotensin Receptor Blockers
Entresto (LCZ696)

Switching:

From ACEI

Stop ACEI 36 hours prior to first dose of Entresto

↑ Risk of angioedema

From ARB

Initiate Entresto at the time the next dose is due
Safety & Precautions

- **Contraindications:** hx of angioedema
- **Adverse effects:** hypotension, hyperkalemia, dizziness, renal impairment, angioedema, may increase statin levels, alzheimers?
- **Monitor:** K+, SCr, BP 1 week after initiation, after each dose increase and with each practitioner visit
Safety & Precautions

- **Drug interactions:**
  - ACE/ARB, aliskiren (RAAS), potassium sparing diuretics, trimethoprim, K supplements (↑ K), NSAIDs (↑ SCR), lithium (lithium toxicity), statins? (statin toxicity)
Safety & Precautions

- **Elevates BNP levels** - use NT pro BNP
- **Should not** be initiated in patients with acutely decompensated heart failure, or clinically-relevant ischemic events, such as acute myocardial or cerebral infarction
Coverage

- Entresto cards
  - Covers cost of prescription
Coverage

● Recently added to NB formulary: Special Authorization

● NYHA class II or III HF who meet the following criteria:
  ○ LVEF < 40%.
  ○ NYHA class II to III symptoms despite at least four weeks of treatment with a stable dose of ACEI or ARB and BB and AA
  ○ BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL.
F-Channel Inhibitors
Ivabradine (Lancora™)

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

Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, 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.

Lancet 2010; 376: 875-85
Published Online
August 29, 2010
DOI:10.1016/S0140-6736(10)61198-1
### SHIFT 2010

| **P** | Adults in sinus rhythm, with resting HR ≥70 bpm, LVEF ≤ 35%, stable symptomatic chronic HF (NYHA II-IV) for ≥ 4 wk, HF hospitalization within 12 mo, and on guideline-directed therapy (ACE/ARB, BB, +/- aldosterone antagonist) |
| **I** | Ivabradine 5 mg BID/ 7.5 mg BID/ 2.5 mg BID |
| **C** | Placebo |
| **O** | CV death or HF hospitalization |
SHIFT Study Design

- Blinding & random allocation
- Median follow up 22.9 mo
- Assessed resting heart rate at 2 weeks, then every 4 months, which guided dose adjustments.

*HR in bpm
Primary Outcome: CV mortality or HF hospitalization

Ivabradine vs placebo:
24.5% vs 28.7%, $p<0.0001$

RRR: 18%
ARR: 5%
NNT: 20
Results

2° endpoints (ivabradine vs placebo)

- 1 % ARR in CV mortality: NNT 100
- 5% ARR in Hospital Admission for HF: NNT 20
- 2 % ARR in Death from HF: NNT 50
- 4% ARR in All-cause hospital admissions: NNT 25

*HR was 8 bpm lower in ivabradine group at end of study
Subgroup Analysis

Patients receiving $\geq 50\%$ target beta blocker dose (56% in each group)

- **Primary endpoint and secondary mortality endpoints:** not significantly reduced
- **HF hospital admissions:** significantly reduced by 19\%
SHIFT

Adverse Events

- Symptomatic bradycardia (5%)
- Asymptomatic bradycardia (6%)
- Atrial Fibrillation (9%)*
- Visual changes (3%)

Fewer all serious adverse events found in study group

*not statistically significant
Ivabradine (Lancora) Safety & Precautions

- **Contraindications:** acute HF, BP <90/50, resting HR <60 bpm, hepatic impairment, pacemaker, prolonged QT

- **Adverse effects:** bradycardia, AFib, visual changes, vertigo, heart block, ventricular tachycardia*, hypotension*, ventricular fibrillation*, torsades de pointes*

- **Drug interactions:** strong and moderate CYP3A4 inhibitors, CYP3A4 inducers, QTc prolonging agents, K⁺ depleting diuretics, amiodarone, simvastatin

*Post-Market/Case Reports (<1%)
Safety & Precautions, cont’d

● No safety data for CrCl <15mL/min
● Pregnancy and breastfeedings risks cannot be ruled out
● Limited data in patients with cardiac devices (ICD or CRT). Caution and close cardiac monitoring is recommended.
When do we use it?

CCS Guidelines:

- Ivabradine should be considered in patients with HFrEF who:
  - Are symptomatic despite treatment with appropriate doses of ACEi + BB + MRA
  - Have a resting HR $> 70$ bpm,
  - Are in sinus rhythm
  - Had a prior HF hospitalization within 12 months
Administration & Dosing

- BID with meals
- Initiate at 5 mg BID. Titrate to target dose of 7.5 mg BID (max dose) as long as tolerated, and not to a specific HR
- Start ivabradine at the lowest dose in patients > 75 years of age (e.g. 2.5mg po BID).
- Discontinuation of treatment should be considered if despite use of the highest dose (7.5 mg BID) for several months, there has been no clear decrease in the patient’s resting heart rate.
Ivabradine (Lancora) Coverage

● Currently not covered by NBPDP
● Cost per day is approximately $2.50
Patient Case

**ID**
- 68 year old male

**CC**
- Increasing SOBOE

**PMHx**
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- COPD

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**Diagnostic tests**
- LVEF: 35%

**Medications:**
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- Telmisartan 80 mg daily
- Spironolactone 25 mg daily
- Furosemide 40 mg daily
What is your next step?

A. Start sacubitril/valsartan 24mg/26mg
B. Start ivabradine 7.5mg BID
C. Change spironolactone to eplerenone
D. Start hydralazine/nitrates

Option
A. Start low dose Entresto
   - BP > 100
   - K < 5.2
   - eGFR > 30ml/min
   - on stable doses on ARB, BB and MRA
Summary: Entresto and Ivabradine

Both medications should only be considered after standard triple therapy has been completed with ACEi + BB + MRB

Entresto

- Limited by BP and hyperkalemia
  - BP $\geq 100$ mmHg
  - K+ $< 5.2$
- Reduced CV death, hospitalization for HF and all cause mortality

Ivabradine

- Limited by HR
  - CCS: $> 70$ bpm
- Reduced death from HF, hospitalization for HF, and all cause-hospitalization
Thank You
References

- BC’s Heart Failure Network. Bcheartfailure.ca [Accessed September 2017]
- Canadian Cardiovascular Society Guidelines Library. ccs.ca [Accessed September 2017]
  - 2015 Heart Failure Bridging Guidelines, 2017 Guidelines
- Swedberg K., et al. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT). Eur J Heart Fail. 2010 Jan;12(1):75-81
- Truven Health 2017: Micromedex.[Accessed September 2017]
**LANCORA™ dosing recommendations**

**Recommended dose & dosage adjustment**

<table>
<thead>
<tr>
<th>Initiative and titration</th>
<th>Titration schedule designed for ease of use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>After 2 weeks:</strong></td>
<td><strong>Persistently at or above 50 bpm</strong></td>
</tr>
<tr>
<td>**Recommended</td>
<td><strong>Increase dose to the next higher dose</strong></td>
</tr>
<tr>
<td>starting dose:**</td>
<td><strong>(Maximum dose 7.5 mg BID)</strong></td>
</tr>
<tr>
<td>5 mg BID</td>
<td><strong>Maintain dose</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Persistently between 50 bpm and 60 bpm</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Decrease dose to the next lower dose</strong></td>
</tr>
<tr>
<td></td>
<td><strong>(Minimum dose 2.5 mg BID)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Persistently below 50 bpm or symptoms</strong></td>
</tr>
<tr>
<td></td>
<td><strong>related to bradycardia</strong></td>
</tr>
</tbody>
</table>

*Such as dizziness, fatigue or hypotension

*Half of the 5-mg tablet

- Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals.
- Treatment must be discontinued if heart rates below 50 bpm or symptoms of bradycardia persist. No rebound effect was observed after abrupt withdrawal of ivabradine.
Diuretics to Relieve Congestion
Titrated to minimum effective dose to maintain euwaicria

Advance care planning and documentation of goals of care

Non-pharmacologic therapies (teaching self care, exercise)

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 LCZ696 for eligible patients**

NYHA II-IV: SR with HR <70 bpm or AF or pacemaker
SWITCH ACEi or ARB to LCZ696 for eligible patients**

Reassess Symptoms and LVEF

NYHA I or LVEF >35%
Continue present management

NYHA I-III and LVEF <35%
Refer to ICD/CRT algorithm

Consider:
• Hydralazine/nitrates
• Referral for advanced HF therapy (mechanical circulatory support/transplant)
• Advanced HF referral

NYHA IV
Reassess as needed according to clinical status†

Reassess every 1-3 years or with clinical status change‡

Consider LVEF reassessment every 1-5 years

* Pending Health Canada approval
† Ivabradine may be added when available in Canada
‡ LCZ696, when available in Canada, will replace ACEi or ARB in patients with elevated NP or recent hospitalization (BNP >150 pg/ml or NT-pro-BNP >600 pg/ml)
§ Refer to Table 4
Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction

Patient with LVEF <40%

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

Reassess Symptoms

NYHA I

NYHA II-IV: SR, HR ≥70 bpm

NYHA II-IV: SR with HR <70 bpm or AF or pacemaker
Titrated to target doses or maximum tolerated evidence-based dose

Reassess Symptoms

NYHA I
Continue triple therapy

NYHA II-IV: SR, HR $\geq 70$ bpm
ADD Ivabradine* and SWITCH ACEi or ARB to LCZ696 for eligible patients**

NYHA II-IV: SR with HR <70 bpm or AF or pacemaker
SWITCH ACEi or ARB to LCZ696 for eligible patients**

Reassess Symptoms and LVEF

NYHA I or LVEF $>$35%
Continue present management

NYHA I-III and LVEF $\leq 35$
Refer to ICD/CRT algorithm

NYHA IV
Consider:
- Hydralazine/nitrates
- Referral for advanced HF therapy (mechanical circulatory support/ transplant)
- Advanced HF referral