Update on Heart Failure Therapies and Guidelines

Perminder Singh Bains MD
Abbotsford Regional Hospital

Objectives
- Review latest CCS HF guidelines
- How to best optimize patients with HF
- Understand the role and how to implement novel therapies for HFrEF

Heart Failure is the Fastest Rising Cardiovascular Condition in Canada

1. Management of Heart Failure Patients in Ontario: Recommendations from Best Practice, April 2013, Ross et al. Treating the right patient at the right time; Access to HF care, CJC 2006
3. Ross H et al. Can J Cardiol 2006; 22(9); 749-754

Heart Failure is a Progressive Condition
- With each acute event, myocardial injury may contribute to progressive LV dysfunction
- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality

Medical Therapies and HFrEF

ACEI=angiotensin converting enzyme inhibitor; ANP=atrial natriuretic peptide; ARB=angiotensin receptor blocker; HF=heart failure; MRA=mineralocorticoid receptor antagonist; NEPI=neprilysin inhibitor; NP=natriuretic peptide; OVERTURE=Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

Digitalis
Diuretics
Vasodilators
Inotropes (dobutamine)
MRA (spironolactone)
ACEIs (captopril; enalapril)
ACEIs (lisinopril)
β-blockers (bisoprolol)
β-channel inhibitor (ivabradine)
ACEIs (ramipril)
ARBs (candesartan; valsartan)
β-blockers (metoprolol)
MRA (eplerenone)
H-ISDN (hydralazine and isosorbide dinitrate)

Since the discovery of ANP in 1981, numerous agents have been adopted into clinical practice for treatment of chronic HF Despite the known potential beneficial effects of the natriuretic peptide system, enhancing this system is not exploited by any currently approved chronic HF agents

Development terminated

Approved HF agents
1981 Discovery of ANP
1990s ACEIs (captopril)
1990s Diuretics
1990s β-blockers
1990s MRA (spironolactone)
2000s ACEIs (lisinopril)
2000s β-blockers (bisoprolol)
2000s ACEIs (ramipril)
2000s ARBs (candesartan)
2000s β-blockers (metoprolol)
2010s ACEIs (enalapril)
2010s MRA (eplerenone)
2010s H-ISDN (hydralazine and isosorbide dinitrate)

1981 Discovery of ANP
1989 Omapatrilat (NEPi+ACEI)
2002 OVERTURE study
2002 LCZ696
2014 PARADIGM-HF study

With HF, >90% of people in Canada will have Heart Failure in 2030
50,000 New cases are diagnosed each year
1.4 million hospital days per year
500k with HF 2015, >750k people in Canada will have Heart Failure in 2030
2.9 billion Actual and Projected Incidence of HF in Canada

HF is a Progressive Condition with High Morbidity and Mortality

Mortality
Acute episode
Disease progression
Function & quality of life (QoL)
• With each acute event, myocardial injury may contribute to progressive LV dysfunction
• Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality

Mortality
Acute episode
Disease progression
Sudden Death Event

Mortality
Acute episode
Disease progression
Sudden Death Event

CREDENTIALS AND DISCLOSURES
- BSc Pharmacy
- Medicine UBC
- Internal Medicine UBC
- Cardiology UBC
- Advanced Heart Failure and Cardiac Transplantation
- Director Abbotsford Regional Hospital Heart Failure Program
- Servier

2016-06-06
Survival rates in chronic HF have improved with the introduction of new therapies; however, significant mortality remains.

- 50% of patients die within 5 years of diagnosis
- 24% of patients died within 1 year of diagnosis

Ace Inhibitor Therapy: Mortality and Admissions Reduction

ACE Inhibitors

Patient with LVEF <40%

- NYHA I or II (17)
- NYHA III or IV (95)

**Study**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Randomization</th>
<th>Event Rate</th>
<th>HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi</td>
<td>Low</td>
<td>0.70</td>
<td>0.59 (0.48)</td>
<td>0.39</td>
</tr>
<tr>
<td>ACEi</td>
<td>Med</td>
<td>0.79</td>
<td>0.59 (0.48)</td>
<td>0.39</td>
</tr>
<tr>
<td>ACEi</td>
<td>High</td>
<td>0.79</td>
<td>0.59 (0.48)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

**Summary**

- ACEi therapy significantly reduces mortality and hospital admissions in patients with LVEF <40%

**References**

1. Cohn et al. (2001)
3. CIBIS II (1999)
5. MERIT-HF (1999)

**HF Outcomes is Unchanged Despite Advances In Medical Therapy**

Prognosis for HF patients remains poor with only slight improvements in overall mortality.

**Table**

<table>
<thead>
<tr>
<th>Year</th>
<th>HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>1.79 (1.43)</td>
<td>0.10</td>
</tr>
<tr>
<td>2002</td>
<td>1.79 (1.43)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**Graph**

- Cumulative mortality (%)
- Number at risk
- Odds (95% CI)
- ACE, Placebo, BB, MRA

**ACE Inhibitors**

- Placebo, ACE, BB, MRA
- Mortality & Admissions Reduction

**Diagram**

- Study outcomes
- Total patients
- Mortality
- Admissions

**Conclusion**

ACE inhibitors significantly reduce mortality and hospital admissions in patients with HF.
**BB: Heart Rate Matters**

Meta-regression line for magnitude of heart rate reduction and risk ratio of all-cause mortality.

Study Conclusions:
- The magnitude of heart rate reduction is statistically significantly associated with the survival benefit of beta-blockers (BB) in heart failure, whereas the dose of BB is not.

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**Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms: EMPHASIS-HF**

Primary Endpoint: CV Mortality and HF hospitalization

- Eplerenone vs Placebo
  - Mortality: Hazard ratio, 0.77 (95% CI, 0.67 to 0.88)
  - Hospitalization: Hazard ratio, 0.63 (95% CI, 0.54 to 0.70)

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**RALES: Aldosterone Antagonist Reduces All-Cause Mortality in Chronic HF**

- Primary Endpoint: CV mortality and HF hospitalization
- Spironolactone vs Placebo
  - Mortality: Hazard ratio, 0.58 (95% CI, 0.47 to 0.70)
  - Hospitalization: Hazard ratio, 0.76 (95% CI, 0.62 to 0.90)

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**Patient selection and follow-up are important**

- In-hospital death associated with hyperkalemia: 3X
- Hospitalization associated with hyperkalemia: 3X

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**References**

Emerging Therapies: Ivabradine

- Ivabradine: Novel heart rate lowering therapy in HF patients with HFrEF specifically blocking the HCN channel responsible for the cardiac pacemaker if current.
- Main Study: Shift
  - Systolic heart failure
  - Moderate to severe chronic heart failure
  - NYHA class II–IV
  - Left ventricular ejection fraction ≤ 35%
  - Heart rate ≥ 70 bpm
  - Sino-atrial rhythm
  - Optimal standard therapy

Ivabradine dose: 7.5 mg twice daily
Median study duration: 23 months

Ivabradine: Effect on CV Mortality and Hospitalizations for Worsening HF (Primary Endpoint)

In 6505 patients with:
- Systolic heart failure
- Moderate to severe chronic heart failure
- NYHA class II–IV
- Left ventricular ejection fraction ≤ 35%
- Heart rate ≥ 70 bpm
- Sino-atrial rhythm
- Optimal standard therapy

Currently, marketed drugs target only the RAAS system
However, the NP system is counter regulatory to the RAAS system in HF

Heart Failure Is A State Of Neurohormonal Imbalance

- As HF advances, the RAAS becomes the predominantly activated neurohormonal system.
- Currently, marketed drugs target only the RAAS system.
- However, the HF system is counter regulatory to the RAAS system in HF

Ivabradine: Effect on Outcomes in Patients with HF & HFpEF

Ivabradine induced a 24% reduction in primary outcome vs. placebo.

Ivabradine: Safety and Tolerability

Safety
- Fewer adverse events in the ivabradine group (3388 events) than in the placebo group (3847; p=0.025)
- 5% (150) had symptomatic bradycardia compared with 1% (32) of the placebo group (p=0.0001)
- 3% (49) reported visual side effects reported compared to 1% (17) on placebo (p=0.0001); did not lead to more withdrawal

Tolerability
- Ivabradine dosage: 7.5 mg twice daily
- Mean dosage: 6.4 mg twice daily (28 days); 6.5 mg twice daily (1 year)
- 70% of patients are taking the 7.5 mg twice daily dosage after 1 year

LCZ696 simultaneously inhibits NEP (via LY26364) and blocks the AT1 receptor (via valsartan)
**NEP Inhibition Must be Accompanied by Simultaneous RAAS Blockade**

NEP metabolizing angiotensin I

Ang I is converted to Ang II. Inhibition of NEP is insufficient to decrease Ang II levels, counteracting the potential beneficial effects of RAAS inhibition.

NEP inhibition must be accompanied by the diuretic, mineralocorticoid receptor antagonist.

**PARADIGM-HF: The largest mortality-morbidity trial in patients with HFrEF**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>LCZ696 200 mg BID</td>
<td>4,520</td>
<td>4,490</td>
<td>4,280</td>
<td>4,910</td>
<td>5,340</td>
<td>5,500</td>
<td>5,610</td>
<td>5,690</td>
<td>5,670</td>
<td>5,670</td>
<td>5,670</td>
<td>5,670</td>
<td>5,670</td>
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<td>5,690</td>
<td>5,670</td>
<td>5,670</td>
<td>5,670</td>
<td>5,670</td>
<td>5,670</td>
</tr>
</tbody>
</table>

**PARADIGM-HF: Study Design**

- LCZ696: 200 mg BID
- Enalapril: 10 mg BID

**PARADIGM-HF: Key Inclusion Criteria**

- Chronic HFrEF NYHA FC II IV with LVEF ≤40%
- BP (or NT-proBNP) levels as follows:
  - ≥100 (or ≥400 pg/mL), or
  - ≥100 (or ≥400 pg/mL) and a hospitalization for HF within the last 12 months
- ≥4 weeks' stable treatment with an ACE inhibitor or an ARB, and a β-blocker or a mineralocorticoid receptor antagonist
- A diuretic antagonist should be considered for all patients (with treatment with a stable dose for ≥4 weeks, if given)

**PARADIGM-HF: Key exclusion criteria**

- History of angioedema
- 25% increase in LVEF between screening and randomization in phase II
- Systolic BP 90 mmHg or diastolic BP 50 mmHg at screening or at randomization,
- ≥25% decrease in eGFR between screening and end of enalapril run-in or between screening and randomization
- Absolute value for creatinine clearance <30 mL/min
- Major CV surgery, PCI, or carotid angioplasty within the 3 months prior to screening
- Ambulatory HF and LVEF ≤40% at screening or randomization,
- ≥25% decrease in eGFR between screening and end of enalapril run-in or at randomization,
- Current acute decompenated HF
- History of severe pulmonary disease
- Acute coronary syndrome, stroke, transient ischemic attack, cardiac, cerebral, or other major CV surgery, PCI, or cerebral angioplasty within the 3 months prior to screening.
Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCCEI</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72 (65, 79)</td>
<td>72 (65, 79)</td>
</tr>
<tr>
<td>Gender, n (%):</td>
<td>1,080</td>
<td>1,080</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>658</td>
<td>658</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>422</td>
<td>422</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
<td>885</td>
<td>885</td>
</tr>
<tr>
<td>NYHA class I</td>
<td>159</td>
<td>159</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>364</td>
<td>364</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>325</td>
<td>325</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>63.8</td>
<td>63.8</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n (%)</td>
<td>1,117</td>
<td>1,117</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>293</td>
<td>293</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2,312</td>
<td>2,312</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Age, years</td>
<td>540</td>
<td>540</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>280</td>
<td>280</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>260</td>
<td>260</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>1,260</td>
<td>1,260</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>540</td>
<td>540</td>
</tr>
</tbody>
</table>

Sacubitril/Valsartan Showed Consistent Benefit over Enalapril, Across all Pre-Specified Subgroups

This was observed for the primary end-point (CV death or HF hospitalization) and for death from CV causes.

The Benefit of Sacubitril/Valsartan over Enalapril was Consistent in Subgroups of Patients Receiving Different Therapies

The effect of ARB vs placebo derived from CHARM-AHF trial

The effect of ACE inhibitor vs placebo derived from SOLVD trial

The effect of Sacubitril/Valsartan vs ACE inhibitor derived from PARADIGM-HF trial

Sacubitril/Valsartan Doubles the Effect on CV Death of Current Renin-Angiotensin-Aldosterone System Inhibitors

Effect of ACE inhibitor vs placebo derived from CHARM-AHF trial

20%

Effect of Sacubitril/Valsartan vs ACE inhibitor derived from PARADIGM-HF trial

15%

17%
Sacubitril/Valsartan significantly reduced the number of sudden cardiac deaths by 40% compared with enalapril.

![Graph showing reduction in sudden cardiac deaths](image)

**HiHF patients treated with LCZ696 were less likely to be hospitalized for heart failure multiple times than HiHF patients treated with enalapril.**

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (n=4,187)</th>
<th>Enalapril (n=4,187)</th>
<th>p-value</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 admission</td>
<td>145 (3.5)</td>
<td>214 (5.1)</td>
<td>0.027</td>
<td>0.61%</td>
</tr>
<tr>
<td>2 admissions</td>
<td>72 (1.7)</td>
<td>119 (2.9)</td>
<td>0.100</td>
<td>0.59%</td>
</tr>
<tr>
<td>&gt;2 admissions</td>
<td>13 (0.3)</td>
<td>26 (0.6)</td>
<td>0.261</td>
<td>0.57%</td>
</tr>
</tbody>
</table>

Duration of hospital stay per admission was similar for LCZ696 and enalapril, but the LCZ696 group had 18% fewer stays in intensive care.

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696</th>
<th>Enalapril</th>
<th>Rate ratio (95% CI)</th>
<th>p-value</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of stays in intensive care</td>
<td>748</td>
<td>879</td>
<td>0.83 (0.72-0.96)</td>
<td>0.015</td>
<td>18%</td>
</tr>
</tbody>
</table>

Fewer LCZ696-treated HiHF patients required intravenous positive inotropic support during hospitalization compared with enalapril.

<table>
<thead>
<tr>
<th>Event</th>
<th>Sacubitril/Valsartan (n=4,187)</th>
<th>Enalapril (n=4,192)</th>
<th>p-value</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients requiring IV positive inotropic support</td>
<td>161 (3.8)</td>
<td>203 (4.9)</td>
<td>0.005</td>
<td>22%</td>
</tr>
<tr>
<td>Patients receiving vasopressors requiring inotropic support</td>
<td>44 (1.1)</td>
<td>55 (1.3)</td>
<td>0.007</td>
<td>22%</td>
</tr>
<tr>
<td>Patients requiring inotropic support for cardiac implantation or cardiac transplantation</td>
<td>34 (0.8)</td>
<td>46 (1.1)</td>
<td>0.006</td>
<td>26%</td>
</tr>
</tbody>
</table>

Sacubitril/Valsartan Efficacy was Maintained With Reduced Dose Compared to Reduced Dose of Enalapril.

<table>
<thead>
<tr>
<th>Event</th>
<th>Sacubitril</th>
<th>Enalapril</th>
<th>Rate ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>Events/100</td>
<td>Events/100</td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>1</td>
<td>4.0</td>
<td>4.0</td>
<td>1.00 (0.80-1.25)</td>
<td>0.94</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>3.0</td>
<td>1.00 (0.80-1.25)</td>
<td>0.94</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>2.0</td>
<td>1.00 (0.80-1.25)</td>
<td>0.94</td>
</tr>
</tbody>
</table>
Symptomatic Hypotension was More Common with Sacubitril/Valsartan vs Enalapril However Few of these Patients Discontinued Study Drug Because of Hypotension

Prescribing Tips
- LVEF <40% on 3 months guideline driven therapy (triple therapy), based on the potential for LVEF improvement on standard therapy
- Consider decreasing diuretic dose at time of initiation
- Reduce other antihypertensives at time of initiation
- Follow up labs in one week

Future Directions Valsartan/Sacubitril
- FortiFi Program (40 clinical trials)
- PARADIGM-HF examining the efficacy and safety of Entresto in heart failure patients with reduced ejection fraction (compared to valsartan), expected study completion in 2019
- PARADISE-MI testing the hypothesis that Entresto can reduce cardiovascular death, heart failure hospitalizations and new onset heart failure in patients at high risk for heart failure after a myocardial infarction, expected study completion in 2020
- TRANSITION comparing in-hospital initiation of Entresto to initiation after hospital discharge in heart failure patients with reduced ejection fraction (HFrEF) who have recently been hospitalized for acute decompensation, expected study completion in 2018
- PIONEER investigating the effect of in-hospital initiation of Entresto on changes in NT-proBNP (compared to enalapril) in patients with HFrEF following an acute decompensation, expected study completion in 2016
What about HFpEF

- Lack of mortality data
- ACEi or ARB in all patients (Hospitalization)
- HBA if increased HF levels
- Beta blockers if history of MI or angina
- Diuretics for symptom relief
- Treat hypertension, ischemia, atrial fibrillation, valvular heart disease etc.

TOPCAT

- Multicentre, international, randomized, double blind placebo-controlled trial
- Age >50, LVEF <45%, controlled BP, Serum K < 5.0
- Primary Endpoint: Composite of CV death, aborted cardiac arrest, hospitalizations for HF
- Secondary outcomes: Death from any cause, hospitalization for any cause, hyperkalemia, elevated Serum Cr (2x baseline)
- 3,445 patients (1,151 US, 326 Canada, 167 Brazil, 123, Argentina, 1066 Russia, 612 Georgia)
- Mean follow up 3.3 years
- 9% of patients in each group discontinued the study medication

TOPCAT – Dosage at 8 Months

<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>Spiro N=1689</th>
<th>Placebo N=1676</th>
<th>Total N=3365</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg</td>
<td>271 (16.0)</td>
<td>221 (13.2)</td>
<td>492 (14.6)</td>
</tr>
<tr>
<td>15 mg</td>
<td>277 (16.4)</td>
<td>143 (8.5)</td>
<td>420 (12.5)</td>
</tr>
<tr>
<td>30 mg</td>
<td>885 (52.6)</td>
<td>983 (58.7)</td>
<td>1872 (55.6)</td>
</tr>
<tr>
<td>65 mg</td>
<td>352 (21.9)</td>
<td>329 (19.8)</td>
<td>581 (17.3)</td>
</tr>
</tbody>
</table>

Analysis of total HF Hospitalizations:
- Spironolactone: 6.8/100 person-years
- Placebo: 8.3/100 person-years
  (P=0.03)
Lack of mortality data
- ACEi or ARB in all patients (Hospitalization)
- MRA if increased NP levels
- Beta blockers if history of MI or angina
- Diuretics for symptom relief
- Treat hypertension, ischemia, atrial fibrillation, valvular heart disease etc.

Evidence-based medications are a major cornerstone in HF treatment
- Standard therapy includes ACE (or ARB if intolerant), BB and MRA
- Appropriate titration & follow up are required for full benefit

New medications such as ivabradine and LCZ696 should be considered in eligible patients based on guideline recommendations to reduce the risk of death and hospitalization in some patients
- Consider using aldosterone antagonists in HFrEF patients with elevated natriuretic peptides.

Case 1 - 60F with Breast Cancer and Dyspnea

- Complaints of fatigue, nausea, NYHA II shortness of breath and palpitations after 4 treatments
- Exam: BP 138/74 HR 94. Exam benign
- HTN - Amlodipine 10mg
- Non smoker
- No family history of cardiac disease
- Cath 2014 for chest pain :Normal
- MUGA Feb 2016 EF 57%

Subgroup Analyses by Region

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>New Medications</th>
<th>No New Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA II</td>
<td>1.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>NYHA III</td>
<td>2.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>4.5%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Subgroup Analyses by Randomization

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>60F with Breast Cancer</th>
<th>No Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA II</td>
<td>1.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>NYHA III</td>
<td>2.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>4.5%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>
**BRAJACTT What?**

- 4 cycles of doxorubicin/cyclophosphamide
- 4 cycles of trastuzumab/paclitaxel
- 13 cycles of trastuzumab

- What type of complications can these combinations of therapies cause?

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**Case continued**

- What tests do you order? Do you start any therapies until the tests are back?

  - Na 131, K 4.2 Cr 89, BNP: 12
  - CXR: Normal
  - Urgent Echo: Normal LVEF (58% Simpson). No significant valvular abnormality

- She has googled these drugs and is worried about the potential cardiotoxicity

  - How should I be monitored during therapy?

  - Significant changes:
    - Drop of EF >10 or LVEF <53%
    - + Troponin
    - Global longitudinal strain drop by 15% or <LLN

  - Patient reassured symptoms are side effects from chemotherapy

  - 12 weeks later repeat MUGA 53% (initially 57%) - Troponin with infusions negative

  - How to manage patient?
**Subclinical LV dysfunction – Beta Blockers**

<table>
<thead>
<tr>
<th>Beta Blocker &amp; Calcium Channel Blocker</th>
<th>Beta Blocker</th>
<th>Calcium Channel Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Nifedipine</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Verapamil</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Diltiazem</td>
<td>Carvedilol</td>
</tr>
</tbody>
</table>

**Subclinical LV dysfunction – RAAS Inhibitors**

<table>
<thead>
<tr>
<th>RAAS Inhibitor</th>
<th>RAAS Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitor</td>
<td>ARB Inhibitor</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Candesartan</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Losartan</td>
</tr>
<tr>
<td>Enalapril</td>
<td>ValspRD</td>
</tr>
</tbody>
</table>

**Subclinical LV dysfunction – Combo neurohormonal blockade**

<table>
<thead>
<tr>
<th>Neurohormonal Blockade</th>
<th>Neurohormonal Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone Antagonist</td>
<td>Angiotensin II Receptor</td>
</tr>
<tr>
<td>Dipeptidyl Peptidase</td>
<td>Neprilysin</td>
</tr>
</tbody>
</table>

**Subclinical LV dysfunction – Statin**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Lovastatin</td>
</tr>
</tbody>
</table>

**Asymptomatic LV dysfunction**

<table>
<thead>
<tr>
<th>Asymptomatic LV Dysfunction</th>
<th>Asymptomatic LV Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Ventricular Ejection</td>
<td>Left Ventricular Ejection</td>
</tr>
<tr>
<td>Fraction</td>
<td>Fraction</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Reduced</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

- Relationship of LVEF to LLN
  - Absolute
    - Decrease of less than 10 points from baseline
    - Absolute decrease of greater than or equal to 10 points from baseline

- Relationship of LVEF to LLN
  - Within Normal Limits
    - Continue
  - Less than or equal to 5 points below LLN
    - Continue
  - Greater than or equal to 6 points below LLN
    - Hold

- Repeat LVEF assessment after 3 to 4 weeks, consider cardiac assessment
- If criteria for continuation are met – resume trastuzumab
- If 2 consecutive holds or a total of 3 holds occur, discontinue trastuzumab
Ongoing fatigue
NYHA II symptoms unchanged
15 pound weight gain
Leg swelling, occasional
Phr/orthopnea
MUGA EF 42%
How to proceed?

Hold trastuzumab
Repeat LVEF assessment in 3-4 weeks
Fluid and sodium restriction
Furosemide 40mg po daily
Bioprolol 2.5mg po daily
Ramipril 2.5mg po bid

Feels much better, almost normal
No symptoms of congestion
Weight back at baseline
Tolerating heart failure therapies
What to do with medical therapy?

BP 132/66 Hr 84 bpm
JVP 2cm
Lungs clear
Normal heart sounds
No edema

Ramipril 5mg BID
Bioprolol 5mg daily
Furosemide 20mg

MUGA 58% (Initial MUGA 57%)
What to do with trastuzumab?
Can I stop the heart failure therapies?
With addition of LV enhancement therapy on board
Completes full course of chemotherapy
NYHA I
MUGA EF ~ 54% at end of last cycle.

How to follow patients after chemotherapy?

EF remains normal. LVEF 58% on Echo
Global longitudinal strain normal
BNP 21
At patient request medications weaned off over the next year

How do we approach this patient and optimize HF therapies?

Radiation increases risk of CAD as early as 5 years
Patient had moderate disease in LAD, LCx, but significant RCA lesion stented
Degree of LVEF reduction (28%) not in keeping with CAD
- NYHA II-III
- Carvedilol 25mg bid, Ramipril 5mg daily, Spironolactone 12.5mg daily, Amiodipine 10mg, Furosemide 40mg bid, ASA 81mg daily, Clopidogrel 75mg daily.
- O/E HR 78 (reg), BP 102/68, SpO2, mild edema

How to best optimize?
When to reassess his LVEF?
Defibrillator?

NYHA I or LVEF>35%
NYHA I - III and LVEF ≤ 35%
NYHA IV

Continue present management
Refer to ICD/CRT algorithm
Consider:
- Hydralazine/nitrates
- Referral for advanced HF therapy (mechanical circulatory support/transplant)
- Advance HF referral

*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-proBNP >600 pg/ml)

Patient with LVEF <40%
NYHA I
NYHA II - IV:
- SR, HR ≥ 70 bpm*
- NYHA II - IV: SR with HR <70 bpm or AF or pacemaker

Continue triple therapy
ADD ivabradine† and SWITCH ACEi or ARB to LCZ696 for eligible patients**

SWITCH ACEi or ARB to LCZ696 for eligible patients**

Triple Therapy
- ACEi (or ARB if ACEi intolerant), BB, MRA
- Titrate to target doses or maximum tolerated evidence-based dose
- Reassess Symptoms
- Reassess Symptoms and LVEF
- Reassess every 1-3 years or with clinical status change
- Reassess as needed according to clinical status

Diuretics to Relieve Congestion
- Titrated to minimum effective dose to maintain euvolemia

Advance Care Planning and Documentation of Goals of Care
- Non-pharmacologic therapies (teaching self care, exercise)
- Consider LVEF reassessment every 1-5 years


Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction

Key Points
- Cardio-oncology is a growing discipline
- Understand the type of chemo used to anticipate problems and plan treatment
- Routine surveillance, possibly lifelong
- Use guideline directed