<table>
<thead>
<tr>
<th>Topic</th>
<th>Lead</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction: Definitions and Diagnosis of HF</td>
<td>Elizabeth Swiggum</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Optimal medical therapy and new therapies</td>
<td>Serge Lepage</td>
<td>15 min + Q&amp;A</td>
</tr>
<tr>
<td>Non-Cardiovascular Comorbidities: Diabetes, renal failure, etc</td>
<td>Kim Connelly</td>
<td>15 min + Q&amp;A</td>
</tr>
<tr>
<td>End-Stage HF: Goals of therapy, options</td>
<td>Elizabeth and Serge</td>
<td>15 min + Q&amp;A</td>
</tr>
<tr>
<td>Conclusions and Final Questions</td>
<td>All</td>
<td>15 minutes</td>
</tr>
</tbody>
</table>
Disclosures

• Kim Connelly
  • Advisory / Honoraria/ Research support: Bristol-Myers Squibb, Novartis, Servier, BI, Merck, Lilly, Janssen
  • Clinical Trials: AMGEN, Boehringer Ingelheim

• Serge Lepage
  • Advisory / Honoraria: Novartis, Servier, Sanofi
  • Clinical Trials: Amgen, Novartis, Merck

• Elizabeth Swiggum
  • Advisory / Honoraria: Novartis, Servier, Boehringer Ingelheim
  • Clinical Trials: Novartis, Boehringer Ingelheim, InVentiv Health Clinical
Introduction: Definitions and Diagnosis of HF

Dr. Elizabeth Swiggum
Victoria, BC
Case: Code Blue

- 27 year old female, previously well
- Fever 3 weeks ago now presents to the ER with SOB, unable to lay flat
- Afebrile, HR 110 BPM in sinus, SBP 80 mmHg, passing out in the ER
- CXR – “bilat opacities consistent with infiltrate”
- Diagnosis – Bilateral pneumonia – sent home
- Rx: Antibiotics, inhalers, follow up primary care
What is heart failure?

- Chronic Heart Failure (CHF):
  - Heart failure is a complex syndrome in which abnormal heart function results in, or increases the subsequent risk of, clinical symptoms and signs of low cardiac output and/or pulmonary or systemic congestion.

- Acute Heart Failure Syndrome (AHF):
  - “gradual or rapid change in heart failure signs and symptoms resulting in the need for urgent therapy”
Before acute decompensation

**Disease Progression Pathway For Heart Failure**

**Stage A**
At high risk for HF but without structural heart disease or symptoms of HF

**Stage B**
Structural heart disease but without signs or symptoms of HF

**Stage C**
Structural heart disease with prior or current symptoms of HF

**Stage D**
Refractory HF requiring specialized interventions

**STAGES COMPLEMENT, DO NOT REPLACE NYHA CLASSES**

NYHA Classes - shift back/forth in individual patient

Stages - progress in one direction due to cardiac remodelling

Diagnosis of Heart Failure

TIME COURSE OF DECOMPENSATION

Physiologic Markers of Acute Decompensation

Time Preceding Hospitalization (Days)

HEMODYNAMICALLY STABLE

PRESYMPOTOMATIC CONGESTION

DECOMPENSATION

Filling Pressure Increase

Autonomic Adaptation

Intrathoracic Impedance Changes

Symptoms

Weight Change

Hospitalization

# Reliability of Weight in Assessing Decompensation

Weight changes have low sensitivity for decompensation

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 kg weight gain over 48-72 hrs&lt;sup&gt;1&lt;/sup&gt;</td>
<td>9%</td>
<td>97%</td>
</tr>
<tr>
<td>2% weight gain over 48-72 hrs&lt;sup&gt;1&lt;/sup&gt;</td>
<td>17%</td>
<td>94%</td>
</tr>
<tr>
<td>3 lbs in 1 day or 5 lbs in 3 days&lt;sup&gt;2&lt;/sup&gt;</td>
<td>22.5%</td>
<td></td>
</tr>
</tbody>
</table>

Lewin, 2005. N = 77<sup>1</sup>
Abraham, 2011. N = 156<sup>2</sup>
Classification of AHF

- **Hypertensive AHF**: high BP, +/- preserved LV systolic function; increased sympathetic tone with ↑HR, vasoconstriction; may be euvoalaemic or only mildly hypervolemic, and frequently with signs of pulmonary or systemic congestion.

- **Acutely Decompensated Chronic HF**: usually a hx of prog. worsening of known chronic HF on Rx, and evidence of systemic/pulmonary congestion.

- **PULMONARY OEDEMA**: Severe respiratory distress, ↑RR, orthopnea, rales. O2 sats <90% RA prior to O2

- **ACS and HF**: Clinical and lab evidence of an ACS; ~15% of patients with an ACS have signs and symptoms of HF. Episodes of AHF are frequently assoc w/ or precipitated by arrhythmia (bradycardia, AF, VT).

- **Cardiogenic shock**: Usually sys BP <90 mmHg or drop in MAP >30 mmHg and absent/low urine output. Organ hypoperfusion and pulmonary congestion develop rapidly.

- **Right HF**: low output in absence of pulmonary congestion with increased JVP, w/ or w/out HSM, and low LV filling pressures.

ESC 2008
Looking for the cause.....Key Culprits for HF Decompensation

- Medication non-compliance
- Excessive NaCl intake
- Tachyarrhythmia/ loss of NSR
- Hypertension
- Gradual volume retention
- Acute infection
- Cardiac ischemia

M → Myocardial ischemia/infarction
A → arrhythmia
D → drugs
H → hypertension
A → anaemia
T → thyroid overactive
E → temp i.e. infection
R → pulmonary embolus
R → renal failure
How confident are you in making a diagnosis of AHF??

OPPORTUNITY
## HF scoring

- **Boston criteria**
  - "definite" = 8 to 12
  - "possible" = 5 to 7
  - "unlikely" <5

<table>
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<tr>
<td>Dyspnea at rest</td>
<td>4</td>
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<tr>
<td>DOE on level ground</td>
<td>2</td>
</tr>
<tr>
<td>DOE on climbing</td>
<td>1</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>4</td>
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<tr>
<td>PND</td>
<td>3</td>
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<table>
<thead>
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<th>Physical exam</th>
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<tbody>
<tr>
<td>HR &gt; 110</td>
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</tr>
<tr>
<td>JVP &gt;6 cmH2O</td>
<td>2</td>
</tr>
<tr>
<td>JVP &gt;6 cmH2O +HM or LEE</td>
<td>3</td>
</tr>
<tr>
<td>Crackles – basilar</td>
<td>1</td>
</tr>
<tr>
<td>Crackles - &gt; basilar</td>
<td>2</td>
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<tr>
<td>Wheeze</td>
<td>3</td>
</tr>
<tr>
<td>S3</td>
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<table>
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<th>CXR</th>
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<td>alveolar pulmonary edema</td>
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<tr>
<td>Interstitial pulmonary edema</td>
<td>3</td>
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<tr>
<td>Bilateral pleural effusions</td>
<td>3</td>
</tr>
<tr>
<td>Incr CMW &gt;0.5</td>
<td>3</td>
</tr>
<tr>
<td>Incr upper flow resdistribution</td>
<td>2</td>
</tr>
</tbody>
</table>
Patient case at time of presentation

- History – Orthopnea 4
- Physical – HR >110, JVP ?, 2
- CXR – Bilat “pneumonia” (0) 4

- Total 10 (Definite)
We recommend the use of a validated diagnostic scoring system for patients in whom the diagnosis of AHF is being considered

(Strong Recommendation, Moderate Quality Evidence).

e.g. PRIDE score, Boston criteria

This recommendation places a relatively high value on evaluating the constellation of clinical findings in a patient with suspected AHF and less value on an individual physical examination finding, presenting symptom or investigation.
**CCS Guidelines**

- We recommend that in the clinical scenario when the clinical diagnosis of AHF is of *intermediate pre-test probability*, NP level be obtained to **rule-out or rule-in** AHF as the cause for the presenting symptoms suspicious of AHF

**Strong Recommendation, Moderate Quality Evidence**

<table>
<thead>
<tr>
<th>BNP (point-of-care assay)</th>
<th>Age (years)</th>
<th>Heart failure is unlikely</th>
<th>Heart failure possible but other diagnoses must be considered</th>
<th>Heart failure is very likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>&lt;100 pg/mL</td>
<td>100–500 pg/mL</td>
<td>&gt;500 pg/mL</td>
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<tr>
<td>NT-proBNP</td>
<td>&lt;50</td>
<td>&lt;300 pg/mL</td>
<td>300–450 pg/mL</td>
<td>&gt;450 pg/mL</td>
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<tr>
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<td>50–75</td>
<td>&lt;300 pg/mL</td>
<td>450–900 pg/mL</td>
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<td>&gt;75</td>
<td>&lt;300 pg/mL</td>
<td>900–1800 pg/mL</td>
<td>&gt;1800 pg/mL</td>
</tr>
</tbody>
</table>
Presenters prerogative
What about scores in Ambulatory, Non- Acute Heart Failure?

- Current diagnostic algorithms perform poorly in the outpatient setting
  - (AUC from 0.6- 0.7)
- Clinical findings are less obvious
  - Primary care accuracy 60%
  - Specialist accuracy 70%
  - Addition of ECHO or NPs up to 80%
- Newer imaging modalities, primarily ECHO under evaluation, especially for HFpEF
  - Elevated E/E’, LV Mass and LA volume index
- Other guidelines use normal BNP levels as rule out
  - Not prospectively tested
Resources to help your patient and family manage

- Heart and Stroke  Heart Failure
- BC Heart Failure Network
  - Multiple languages
  - Patient and family co-management resources
  - www.bcheartfailure.ca
Prognosis Following HF Hospitalization in Canada

Median Survival (Years)

1st Hosp. (N=14374) - 2.4 years
2nd Hosp. (N=3358) - 1.4 years
3rd Hosp. (N=1123) - 1.0 years
4th Hosp. (N=417) - 0.6 years

Setoguchi S et al., Am Heart J, 154(2), 203-205
BC Results: All Cause Mortality Cases and Rate

- Age-adjusted Mortality
- Crude Mortality

Fiscal Year:
- 2001: 134.3
- 2002: 12500
- 2003: 11517
- 2004: 107.7
- 2005: 29%
- 2006: 28.12
- 2007: -42.4%
- 2008: -19.8%

# of Cases
- 8,931
- 48.78

Rate per 1000
- 25
- 50
Is Ejection Fraction important??
Distribution of EF in Hospitalized Patients with Heart Failure

OPTIMIZE-HF Registry, N=41,267

Documented LVEF Measured Prior to or During Hospitalization

EF ≤ 40 %

EF 40-50 %

EF ≥ 50 %

Fonarow G et al. JACC. 2007; 50:768-777
Medical therapy in HF

Dr Serge Lepage
U de Sherbrooke
Incremental benefit in HF treatment

**Figure 4.** Cumulative percent reduction in odds of death at 24 months associated with sequential treatments compared with no treatment. Analysis includes only patients eligible for all 4 therapies (N=368). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.
Therapy in HFrEF

- Benefits of drugs and devices in HFrEF
  - ACEi/ARB
  - Beta blockers
  - Mineralocorticoid receptor inhibitors
  - Cardiac resynchronization therapy
  - Implanted cardioverter/defibrillator

However, 5 yr mortality remains ~50%
Medications in HF: Patients

“Medications don’t work in patients who don’t take them”

- C. Everett Koop
Impact of Collaborative Care
Survival Post ER Discharge

10 599 patients in Ontario 2004-2007 within 30 days ER visit

Lee D et al, Circulation 2010
Follow-up Cardiovascular Care

- Importance of Follow-up Care:
  - A study of 3,136 patients in Alberta with Heart Failure found those who received regular cardiovascular follow-up visits with a family physician had better outcomes.

Kaplan–Meier Survival Curves For Care Received, by Ambulatory Specialty

- Combined care (both specialist and family physician)
- Care by family physician only
- No follow-up care

CCS HF Algorithm: Therapeutic Approach To Patients With HF And Reduced Ejection Fraction

**PATIENT WITH LVEF < 40%**

**Triple Therapy**
ACEi (or ARB if ACEi intolerant), BB, MRA
Titrated 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 Sacubitril/valsartan for eligible patients

**REASSESS SYMPTOMS AND LVEF**

**NYHA I or LVEF < 35%**
Continue present management
Reassess every 1-3 years or with clinical status change

**NYHA I-III and LVEF ≤ 35%**
Refer to ICD/CRT algorithm
Consider LVEF reassessment every 1-5 years

**NYHA IV**
Consider:
- Hydralazine/nitrates
- Referral for advanced HF therapy (mechanical circulatory support/transplant)
- Advance HF referral
Reassess as needed according to clinical status

How quickly can you get to target/max tolerated Rx?

- ACE trials:
  - SOLVD: 6 weeks to get to 10 mg BID
- BB trials: on ACE/ARB already
  - CIBIS II: 12 weeks to 10 mg daily
- MRA trials: on ACE/ARB and BB already
  - EMPHASIS: 4 weeks to 50 mg daily
- CCS HF guidelines consensus: 6 months long enough… so get to it!

Frequency of follow up

Heart Failure Care

High Risk Individual
- NYHA IIIb or IV symptoms
- Recent HF hospitalization
- During titration of HF medications
- New onset heart failure
- Complications of HF therapy (rising creatinine, hypotension)
- Need to down-titrate or discontinue beta-blockers or ACEi/ARB
- Severe concomitant and active illness (e.g. COPD, frailty)
- Frequent ICD firings (1 month)

Intermediate Risk Individual
- No clear features of high or low risk.

Low Risk Individual
- NYHA I or II
- No hospitalizations in past year
- No recent changes in medications
- Receiving optimal medical/device HF therapies

Follow-up Frequency
- Visit frequency may increase during medication titration
- Follow-up every 1-4 weeks or as clinically indicated (remote monitoring possible for some titrations)
- Follow-up every 1-6 months
- Follow-up every 6-12 months

Make inactive or consider for discharge from HF clinic if a minimum of 2 of the following characteristics are present:
Causes of clinical inertia

- My patient is “stable” on current therapy
- Why should I change anything?
- He/she has “mild heart failure”
- It is inconvenient for him/her
- (It is more work for me)

A major threat to patients!
Inertia

- **Noun**
  - A tendency to do nothing or to remain unchanged

- **Synonyms:** inactivity, inaction, inactiveness, inertness, passivity
All-cause mortality (%) after a first event (or in patients with no event)

- No event (993/6853): 14.4%
- Intensification of therapy (116/361): 32.1%
- Emergency department visit (24/78): 30.8%
- Heart failure hospitalization (413/1107): 37.3%
HF is a Progressive Condition

Optimize medical and device therapy patiently and aggressively

Phase 1
Initial symptoms of HF develop and HF treatment is initiated

Phase 2
Plateau of variable length reached with initial medical management, or following mechanical support or heart transplant

Phase 3
Functional status decline with variable slope, intermittent exacerbations of HF that respond to rescue efforts

Phase 4
Stage D HF, with refractory symptoms and limited function

Phase 5
End of life

Dotted lines represent sudden cardiac death that can occur anytime during the trajectory

Newer therapies: Ivabradine

Sinus node
The pacemaker of the heart

Ivabradine selectively inhibits the &k; current in the sinus node

Na⁺
K⁺

Ivabradine

f-channel

Heart rate reduction

Ivabradine reduces the slow diastolic depolarization phase

0 mV
-40 mV
-70 mV
Newer therapies: Ivabradine

7,411 screened

6,558 randomized

3,268 to ivabradine
3,290 to placebo

Excluded: 27

Excluded: 26

3,241 analysed
2 lost to follow-up

3,264 analysed
1 lost to follow-up

Median study duration: 22.9 months; maximum: 41.7 months

### Demographic characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ivabradine group</th>
<th>Placebo group</th>
<th>HR (95% CI)</th>
<th>Test for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years (n=2424)</td>
<td>410 (20.6%)</td>
<td>527 (25.6%)</td>
<td>0.76 (0.67-0.87)</td>
<td>0.039</td>
</tr>
<tr>
<td>≥65 years (n=2474)</td>
<td>386 (20.5%)</td>
<td>410 (33.9%)</td>
<td>0.89 (0.77-1.02)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male (n=4270)</td>
<td>624 (35.4%)</td>
<td>725 (28.0%)</td>
<td>0.84 (0.76-0.94)</td>
<td>0.026</td>
</tr>
<tr>
<td>Female (n=1535)</td>
<td>169 (21.7%)</td>
<td>212 (28.3%)</td>
<td>0.74 (0.60-0.91)</td>
<td></td>
</tr>
<tr>
<td>β blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No β blocker intake at randomisation (n=685)</td>
<td>101 (29.4%)</td>
<td>134 (39.3%)</td>
<td>0.68 (0.57-0.88)</td>
<td>0.041</td>
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<tr>
<td>β blocker intake at randomisation (n=5820)</td>
<td>692 (23.9%)</td>
<td>803 (27.5%)</td>
<td>0.85 (0.76-0.94)</td>
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<tr>
<td>Cause of heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-Ischaemic (n=2087)</td>
<td>218 (21.3%)</td>
<td>296 (27.3%)</td>
<td>0.72 (0.60-0.85)</td>
<td>0.059</td>
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<tr>
<td>Ischaemic (n=4410)</td>
<td>575 (26.0%)</td>
<td>641 (29.1%)</td>
<td>0.87 (0.78-0.97)</td>
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<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NYHA class II (n=3169)</td>
<td>300 (18.9%)</td>
<td>356 (22.5%)</td>
<td>0.81 (0.69-0.94)</td>
<td>0.073</td>
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<tr>
<td>NYHA class III or N (n=3334)</td>
<td>493 (79.8%)</td>
<td>580 (34.5%)</td>
<td>0.83 (0.74-0.94)</td>
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<tr>
<td>Diabetes</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>No history of diabetes (n=4526)</td>
<td>516 (23.2%)</td>
<td>613 (27.3%)</td>
<td>0.82 (0.74-0.92)</td>
<td>0.081</td>
</tr>
<tr>
<td>History of diabetes (n=1879)</td>
<td>268 (27.5%)</td>
<td>326 (27.7%)</td>
<td>0.81 (0.69-0.95)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
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<tr>
<td>No history of hypertension (n=2191)</td>
<td>274 (25.4%)</td>
<td>330 (28.7%)</td>
<td>0.81 (0.69-0.95)</td>
<td>0.079</td>
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<tr>
<td>History of hypertension (n=4914)</td>
<td>513 (24.0%)</td>
<td>607 (28.2%)</td>
<td>0.93 (0.78-0.96)</td>
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</table>

### Baseline heart rate

<table>
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<th>HR and Test for interaction</th>
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</thead>
<tbody>
<tr>
<td>&lt;77 bpm (n=3144)</td>
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<tr>
<td>≥77 bpm (n=3357)</td>
</tr>
</tbody>
</table>
**Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
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<tbody>
<tr>
<td>CRT</td>
<td>292 (7.0)</td>
<td>282 (6.7)</td>
</tr>
<tr>
<td>ICD</td>
<td>623 (14.9)</td>
<td>620 (14.7)</td>
</tr>
</tbody>
</table>

**Panel A: Primary End Point**

Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001

**Panel B: Death from Cardiovascular Causes**

Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P<0.001
Prespecified subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696 n.</th>
<th>Enalapril n.</th>
<th>Primary End Point</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value for interaction</th>
</tr>
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<tbody>
<tr>
<td>All patients</td>
<td>4187</td>
<td>4212</td>
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<tr>
<td>Age &lt;65 yr</td>
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<td>2168</td>
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<tr>
<td>Age ≥65 yr</td>
<td>2076</td>
<td>2044</td>
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<td>Age &lt;75 yr</td>
<td>3403</td>
<td>3433</td>
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<tr>
<td>Age ≥75 yr</td>
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<td>779</td>
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<td>Sex Female</td>
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<td>Race White</td>
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<td>Race Other</td>
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Co-morbidity in HF

Dr Kim Connelly
Major comorbidities in Heart Failure

- Chronic Lung Disease
- Sleep disordered breathing
- Diabetes Mellitus
- Renal disease
- Cognitive Dysfunction and Depression
- Anemia and Iron Deficiency
- Other:
  - Osteoarthritis, Osteoporosis. Cancer. Chronic inflammatory disease, etc.
In Canada, People with Diabetes Account For...

- 1/3 of all heart attacks & strokes
- 2/5 of all heart failure admissions
- 2/3 of all non-traumatic amputations
- 1/2 all patients starting dialysis

Booth et al.; Hux et al; and Oliver et al., *Diabetes in Ontario: An ICES Practice Atlas*. 2003. [www.ices.on.ca](http://www.ices.on.ca)
1.0 kg weight gain associated with 7.1% relative increase in

Urinary Glucose Excretion with SGLT2 Inhibition

↑Filtered glucose load > 180 g/day

SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis.

*Loss of ~ 60-80 g of glucose/day (~ 240 cal/day).

EMPA-REG OUTCOME

Primary outcome: CV death, non-fatal MI or non-fatal stroke

Empagliflozin (pooled)
HR 0.86
(95.02% CI 0.74, 0.99)
*p=0.04* for superiority

Placebo

Empagliflozin

Empagliflozin 10 mg
HR 0.85 (95% CI 0.72, 1.01), *p=0.07*

Empagliflozin 25 mg
HR 0.86 (95% CI 0.73, 1.02), *p=0.09*

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.

* Two-sided tests for superiority were conducted (statistical significance was indicated if *p*≤0.0498)

All-cause mortality

Empagliflozin 10 mg
HR 0.70
(95% CI 0.56, 0.87)
p=0.0013

Empagliflozin 25 mg
HR 0.67
(95% CI 0.54, 0.83)
p=0.0003

Placebo

Kaplan-Meier estimate. CI, confidence interval; HR, hazard ratio.
Early and Sustained Reduction of Heart failure Hospitalisation and Cardiovascular Mortality

HR: 0.66
(95% CI: 0.55–0.79)
\( P < 0.001 \)

<table>
<thead>
<tr>
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<th>Empagliflozin</th>
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<td>No. of patients</td>
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<td>1634</td>
<td>775</td>
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<td></td>
<td>395</td>
<td>168</td>
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</table>

Censoring relative to randomisation (days)
Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease

HR 0.54
(95% CI 0.40, 0.75)
p<0.001

Kaplan-Meier estimate in patients treated with ≥1 dose of study drug. Hazard ratios are based on Cox regression analyses.
*Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m².
Outcomes in the LEADER Trial with the GLP-1 Agonist Liraglutide

F Hospitalization for Heart Failure

Hazard ratio, 0.87 (95% CI, 0.73–1.05)
P=0.14

Patients with an Event (%) vs. Months since Randomization

No. at Risk
Liraglutide: 4668, 4612, 4550, 4483, 4414, 4337, 4258, 4185, 1662, 467
Placebo: 4672, 4612, 4540, 4464, 4372, 4288, 4187, 4107, 1647, 442

N ENGL J MED 375;4  NEJM.ORG  JULY 28, 2016
Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial

Kenneth B. Margulies, MD; Adrian F. Hernandez, MD, MHS; Margaret M. Redfield, MD; Michael M. Givertz, MD; Guilherme H. Oliveira, MD; Robert Cole, MD; Douglas L. Mann, MD; David J. Whellan, MD, MHS; Michael S. Kiernan, MD, MS; G. Michael Felker, MD, MHS; Steven E. McNulty, MS; Kevin J. Anstrom, PhD; Mansour R. Shah, MD, MSc; Eugene Roumigui, MD; Thomas D. Cowie, MD; for the NHLBI Heart Failure Clinical Research Network

Figure 3. Prespecified Subgroup Analysis of Patients Who Died or Experienced Rehospitalization for Heart Failure by Type 2 Diabetes Status

(A) Patients with diabetes

HR: 1.54 (95% CI: 0.97-2.46); log-rank P=.07

(B) Patients without diabetes

HR: 1.02 (95% CI: 0.60-1.72); log-rank P=.94

No. at risk
Liraglutide 91 86 77 69 63 60 58 53 51 46 43 41 24
Placebo 87 80 75 73 72 66 64 58 57 56 52 50 50

No. at risk
Liraglutide 63 60 51 46 44 42 40 36 34 32 31 29 16
Placebo 59 55 49 44 41 40 40 36 33 31 29 28 16
Diabetes Canada recommendation

In adults with type 2 diabetes with clinical cardiovascular disease in whom glycemic targets are not met, an antihyperglycemic agent with demonstrated cardiovascular outcome benefit should be added to reduce the risk of major cardiovascular events (Grade 1, Level 1A for empagliflozin (2); Grade 1, Level 1A for liraglutide if age ≥50 years (3); Grade D, Consensus for liraglutide if age <50 years).
Algorithm for managing concomitant diuretics when initiating a SGLT2i

1) What is the volume status?
   - Hypervolemia
     - Continue diuretic and monitor BP/lytes/Cr/weight, assuming not hypotensive
     - Caution with multiple diuretics
   - Euvolemia
   - Volume Contraction
     - Stop diuretic and monitor
     - Initiate SGLT2i when euvolemic

2) What is the blood pressure?
   - Hypertensive
     - Continue diuretic therapy and monitor BP/lytes/Cr/weight
   - Normotensive
     - Thiazides
     - Continue therapy and monitor
     - Loop diuretics
     - Consider reducing dose by 50% and monitor BP/weight
       - If stable, continue therapy
       - If increasing, reinstitute diuresis
       - If decreasing, stop diuretic
   - Hypotensive
     - Caution, hold or reduce diuretic and re-institute if required

*References*

Renal Dysfunction

- **REC**: We recommend that heart failure patients with stable, chronic mild-to-moderate renal insufficiency (GFR>30) should receive standard therapy with an ACEi or ARB and a mineralocorticoid receptor antagonist (MRA).
- Changes in GFR after commencing therapy are not necessarily associated with worsening outcome.
- As a general rule, the serum creatinine can rise as much as 30% from baseline before it becomes necessary to stop or reduce the dose of the ACEi’s, ARB’s or MRA’s.
CKD: Drugs and Follow-up

- Measure K+, urea, creat 5-7 after
  - intensification/addition of diuretics
- Measure K+, urea, creat 7-10 days after
  - intensification/addition of RAAS
- inhibitors
- If kayexalate used, control K+, urea, creat
  - 1-2 days later
- Measure K+, urea, creat during
- intercurrent illness that can affect volume

Table 4: Independent predictors of worsening moderate to severe renal impairment

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>Wald $\chi^2$</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>eGFR (per 10 mL/min decrease)</td>
<td>1.20 (1.10-1.30)</td>
<td>14.7</td>
<td>&lt;0.001</td>
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<tr>
<td>Candesartan use</td>
<td>2.54 (1.60-4.05)</td>
<td>15.4</td>
<td>&lt;0.001</td>
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<tr>
<td>Systolic BP (per 10 mmHg increase)</td>
<td>1.16 (1.04-1.29)</td>
<td>6.5</td>
<td>0.011</td>
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<tr>
<td>ACE inhibitor use</td>
<td>1.68 (1.06-2.67)</td>
<td>4.8</td>
<td>0.029</td>
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</table>

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

End Stage HF: Goals and Options
Goals of HF Treatment

Must be discussed with patients

- Reduce mortality
- Prevent hospital admission
- Improve clinical well-being
- Improve functional capacity and quality of life

“It is now recognized that preventing HF hospitalization and improving functional capacity are important benefits to be considered if a mortality excess is ruled out.”

What is advanced Heart Failure?

- ADHF is not Advanced HF
- Patients can go NYHA IV to NYHA I-II
- No one feature identifies advanced HF
  - Combination of clinical, imaging, hemodynamic, functional and biomarker data
- Risk scores may be an effective tool to facilitate integration
7 years later
NYHA II gradually worsened to NYHA III with escalating doses of diuretic
Still working as professor but with energy conservation strategies
SBP 75 - 80 HR 75 BPM
Carvedilol 12.5 mg BID, Candesartan 4mg BID (previously 16 mg BID), spironolactone 50 mg, furosemide 120/80, warfarin, citalopram 20 mg
EF 20%, severe MR
Mitral Clip - improved MR but no improvement in symptoms

8 years later
Hospitalized for inotrope therapy twice
LVAD implanted - HeartWare - 7 mo complicated by upper GI bleed
Transplant Oct 2014
Continuous flow LVADs

- HeartMate 3 and HeartWare devices
Candidates for MCS:

Patients with advanced HF, including those, despite optimal treatment, continuing to exhibit NYHA IIIb or IV HF symptoms AND accompanied by MORE THAN ONE OF the following:

- HFrEF and, if measured, peak exercise oxygen consumption <14 mL/kg/min
- Evidence of progressive end organ dysfunction due to reduced perfusion not due to inadequate ventricular filling pressures
- Recurrent HF hospitalizations (> 2 in 1 year) not due to reversible cause
- Estimated 1 year mortality > 20-25%
- Need to progressively reduce or eliminate evidence-based HF therapies
- Requirement for inotropic support
- No psychosocial or cognitive issues precluding usage of the therapy

Care preferences and goals of care should be regularly discussed with patients and documented, with emphasis shifting from quantity to quality of life. As heart failure advances, preferences and wishes for end-of-life care should be reviewed, and a palliative care referral considered.
Patient Reference

Age 37
Gender Female
Diabetes No
COPD No
Heart failure diagnosed within the last 18 months No
Current smoker No
NYHA class 3
Receives beta blockers Yes
Receives ACEI/ARB Yes
BMI 33.5
Systolic blood pressure 75
Creatinine 82
Ejection fraction 20

Integer score: 10
Risk of dying within 1 year: 9.3%
Risk of dying within 3 years: 22.7%
The patient is in the 3rd to 4th decile of risk in a heart failure population.
Advanced to end-stage heart failure

- Advance directives
- Palliative care
- Transplant
- Mechanical Circulatory Support
What outcomes matter to HF patients?

“The outcomes that matter most to persons with heart failure”
Thank you!