HEART FAILURE UPDATE 2017

Nursing: Initiation & titration of HF medications

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May 12, 2018
OBJECTIVES

After this workshop, participants will be able to:

• Interpret the evidence-based pharmacological management of chronic heart failure
• Discuss strategies for promoting patient adherence to medications
• Employ practical tips for creating a patient-centered approach to medication optimization
Case - Mr. Scott

- 76 year old male with hx CAD, MI
- CABG- 8 years ago- no new blockages- medical management
- Hx of chronic renal insufficiency, hypothyroidism, heart failure and dyslipidemia
- Admitted to hospital with worsening SOB, orthopnea, PND for 7 days.
- ECG- atrial fibrillation (new)
- Echo: ejection fraction 15-20%
- Diuresis, digoxin (Afib), coumadin and referred for follow up.
Case - Mrs. Tetley

- 78 year old female with a hx of diabetes, hypertension, asthma, arthritis, and heart failure.
- Diffuse CAD - not amendable to revascularization. No history of MI.
- Admitted to hospital with pneumonia and developed worsening symptoms of heart failure consisting of SOB, orthopnea, and PND.
- Echo: ejection fraction 65%
- Diuresis - (15 pounds)
- Discharged home
A condition where the heart is unable to pump enough blood to meet the metabolic demands of the body

* Chronic condition vs. disease

* prefer to use the term ‘heart failure’ versus ‘congestive heart failure’
Causes of Heart Failure

- Coronary Artery Disease
- Hypertension
- Diabetes
- Valvular Disease
- Smoking
- Family History
- Excessive Alcohol Use
- Viral
- Idiopathic
- Chemotherapy
Heart failure - ‘Typical’ patient population

- Older
- Multiple co-morbidities

Characteristics of patients hospitalized with a new diagnosis of heart failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1997 (n=20,039)</th>
<th>2007 (n=17,262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>Age (median) years</td>
<td>76</td>
<td>78</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>54%</td>
<td>44%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36%</td>
<td>47%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26%</td>
<td>35%</td>
</tr>
<tr>
<td>COPD</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>23%</td>
<td>30%</td>
</tr>
<tr>
<td>Charlson-Deyo Comorbidity Index Score ≥ 3</td>
<td>28%</td>
<td>39%</td>
</tr>
</tbody>
</table>

The case of heart failure …

ED visit/hospitalization

Death

Medical Complexity and Frailty
Symptom burden and need for symptom palliation

Optimization of therapy, including device therapy

Terminal phase

Independent community living

Rehabilitative / community support services

Institutionalization / Hospice palliative care

Heckman et al, Reviews in Clinical Gerontology 2014
Why do Mr. Scott and Mrs. Tetley have heart failure?

AND

Why did their heart failure symptoms get worse? (the trigger)
LV ejection fraction - the % of blood pumped out of the left ventricle with each beat.

- **Normal ejection fraction: >55%**
- **HF with reduced EF**: LVEF ≤ 40% (‘HF-rEF’)
- **HF with preserved EF**: LVEF >50% (‘HF-pEF’)

The ‘different faces’ of ejection fraction!

HF-rEF: Well established guidelines on how to manage

HF-mEF: Wants attention- poking through- what do you do with me?

HF-pEF: We are still trying to figure out what best to do!

<table>
<thead>
<tr>
<th>HF-rEF</th>
<th>HF-mEF</th>
<th>HF-pEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40%</td>
<td>41-49%</td>
<td>≥ 50%</td>
</tr>
</tbody>
</table>
Ejection Fraction and NYHA

**There is no relationship between ejection fraction and symptom burden**

New York Heart Association Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1     | No limitation of physical activity  
      | Physical activity does not cause fatigue, palpitations, or SOB               |
| 2     | Slight limitation of physical activity  
      | Mild symptoms (SOB, angina) during normal physical activity                |
| 3     | Limitations of physical activity  
      | Comfortable at rest, but normal activity causes fatigue, palpitations       |
|       | or SOB                                                                           |
| 4     | Unable to carry out physical activity without discomfort  
      | Symptoms of HF at rest                                                        |

SOB-Shortness of Breath
Mr. Scott: HFrEF due to CAD (ischemic cardiomyopathy)

Mrs. Tetley: HFpEF due to diabetes, hypertension, mild CAD
What can we do for Mr. Scott and Mrs. Tetley?

Find and treat/manage the ‘trigger’

Optimize therapy to:
- Help avoid further hospitalization
- Improve quality of life
- Decrease mortality

Medications

Education- self-care

Goals of care discussions

Disease management programs

Device therapy- ICD/CRT
PHARMACOLOGICAL MANAGEMENT OF CHRONIC HEART FAILURE
HF and Preserved EF

- Control blood pressure (CHEP guidelines)
- Heart rate control (esp if afib)
- Control underlying risk factors and comorbidities
- Careful diuresis to avoid renal injury

**Recommendation 46:** We suggest candesartan be considered to reduce heart failure hospitalizations in patients with HFpEF (Weak Recommendation, Moderate Quality Evidence).

**Recommendation 47:** We recommend systolic/diastolic hypertension be controlled according to current CHEP hypertension guidelines (2017) to prevent and treat HFpEF (Strong Recommendation, High Quality Evidence).

**Recommendation 49:** We suggest that in individuals with HFpEF, serum potassium < 5.0 mmol/L, and an estimated glomerular filtration rate (eGFR) > 30 mL/min, a MRA like spironolactone should be considered, with close surveillance of serum potassium and creatinine (Weak Recommendation, Moderate Quality Evidence).

[www.ccs.ca](http://www.ccs.ca) 2017 HF guidelines
Case studies- Mr. Scott

- 76 year old male with hx CAD, MI
- CABG- 8 years ago- no new blockages- medical treatment
- Hx of chronic renal insufficiency, hypothyroidism, dyslipidemia, heart failure
- Admitted to hospital with worsening SOB, orthopnea, PND for 7 days
- Echo: EF <20%

Trigger- new atrial fibrillation
Started digoxin, coumadin, diuresis (increased Lasix)

**** caution with digoxin****
HF with reduced ejection fraction

www.ccs.ca
2017 HF guidelines
HF with reduced ejection fraction

Patient with LVEF $\leq$ 40% and Symptoms

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 $\geq$ 70 bpm
ADD hydralazine 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

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)
- Palliative Care referral

* ARNi: angiotensin II receptor blocker neprilysin inhibitor (sacubitril/valsartan)
† Refer to Table 5

Advance Care Planning and Documentation of Goals of Care

www.ccs.ca
2017 HF guidelines
Body’s reaction to inadequate cardiac output

**Low Blood Pressure/Flow**
- Activate the Renin-Angiotensin-Aldosterone System (RAAS) and Sympathetic Nervous System
- Increase heart rate
- Vasoconstriction
- Save water
  - *thirsty*

**Bigger heart size**

**Fluid retention, very tired heart**

Sensors

http://www.irasenthil.com/2013_09_01_archive.html
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Activate the Renin-Angiotensin-Aldosterone System (RAAS) and Sympathetic Nervous System

Increase heart rate

Vasoconstriction

Sensors

Save water

*thirsty

Bigger heart size

Improved HF symptoms, improved cardiac function

http://www.irasenthil.com/2013_09_01_archive.html
Evidence-based medications and oral doses shown in large clinical trials (LVEF ≤ 40%)
Target RAAS

Angiotensin Converting Enzyme Inhibitors (ACE-inhibitors)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Start dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>1.25-2.5 mg BID</td>
<td>10 mg BID</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5 mg daily</td>
<td>20-35 mg daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2-4 mg daily</td>
<td>4-8 mg daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg BID</td>
<td>5 mg BID</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1-2 mg daily</td>
<td>4 mg daily</td>
</tr>
</tbody>
</table>

Angiotensin Receptor Blocker (ARB)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Start dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4-8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg BID</td>
<td>160 mg BID</td>
</tr>
</tbody>
</table>

(Source: CCS HF guidelines, 2017)
Mineralocorticoid Receptor Antagonists (MRA)
Target- Aldosterone part of RAAS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Start Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldactone (Spironolactone)</td>
<td>12.5 mg daily</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Inspra (Eplerenone)</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
</tr>
</tbody>
</table>

Tips:
Aldactone- if worried about renal, potassium- try starting at 12.5 mg Mon-Wed-Fri.
Inspra – no gynecomastia
Alternatives to ACE Inhibitors or ARB

Use when renal impairment and ACE inhibitor or ARB are contraindicated- potassium too high, poor renal function

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<thead>
<tr>
<th>Medication</th>
<th>Start dose</th>
<th>Target dose</th>
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<tbody>
<tr>
<td>Hydralazine</td>
<td>37.5 mg TID</td>
<td>75 mg TID</td>
</tr>
<tr>
<td>Isorbide Dinitrate</td>
<td>20 mg BID</td>
<td>40 mg TID</td>
</tr>
</tbody>
</table>

Tip- if unsure of patient tolerance, start with even smaller doses and titrate slowly, one medication at a time.

Recommendation 35: We recommend the combination of H-ISDN in addition to standard GDMT at appropriate doses for black patients with HF-rEF and advanced symptoms. (Strong Recommendation, Moderate Quality Evidence) (2017)

Recommendation 36: We recommend that H-ISDN be considered in patients with HF-rEF who are unable to tolerate ACE inhibitor, ARB or ARNi because of hyperkalemia, or renal dysfunction. (Strong Recommendation, Low Quality Evidence) (2017)
## Block Sympathetic Nervous System: Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Start Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg BID</td>
<td>25 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg BID*</td>
</tr>
<tr>
<td>Metoprolol CR/XL</td>
<td>* Not available in Canada</td>
<td></td>
</tr>
</tbody>
</table>

* If weight >85 Kg

* Not available in Canada
# Block Sympathetic Nervous System: Beta Blockers

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* If weight >85 Kg

Hold off titration until fluid status stable
May experience slight increase in fluid retention within the first 2 weeks following up titration- try to manage with short term increase in diuretics.

If people have low bp:
- Prefer bisoprolol- more Beta selective
- Stagger timing with ACE inhibitor/ARB
- Take with meals- slows absorption
- Take in the evening rather than morning dose
- Consider decreasing diuretic
Mr. Scott
1 week post hospital discharge....

- Very tired, lightheaded when standing up
- SOB when bending over or walking up a few stairs. Denies orthopnea or PND
- Weight-lost 7 pounds over the past week

- Weight 165 pounds
- BP- 104/60 mm Hg sitting, 92/50 mm Hg standing
- Pulse- Irregular, rate 72
- No edema
- Lungs- clear
- Heart sounds- systolic murmur (not new), no gallop
- JVP- unable to see it in the chair or at 45 degrees

Ramipril 5 mg daily
Coreg 25 mg BID
ASA 81 mg daily
Crestor 5 mg daily
Nitrospray prn
Lasix 120 mg daily
New:
Digoxin 0.0625 mg daily
Coumadin
Mr. Scott

• What is his NYHA Class? (I,II,III,IV)

• Does he feel same/better/worse?

• What is his fluid status? (wet/dry/just right (euvolemic))

<table>
<thead>
<tr>
<th>Choice</th>
<th>Fluid status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Wet-volume overload</td>
</tr>
<tr>
<td>B</td>
<td>Dry- circulating volume low</td>
</tr>
<tr>
<td>C</td>
<td>Euvolemic- at his ‘dry weight’</td>
</tr>
<tr>
<td>D</td>
<td>I am not sure and need more information before I decide</td>
</tr>
</tbody>
</table>

Why has it changed? (trigger)
What is the plan for Mr. Scott?

- 104/60 mm Hg sitting,
- 92/50 mm Hg standing
- Pulse- Irregular, rate 72
- Weight 165 pounds

- Ramipril 5.0 mg daily
- Coreg 25 mg BID
- ASA 81 mg daily
- Lasix 120 mg daily
- Crestor 5 mg daily
- Nitrospray prn
- Digoxin 0.0625 mg daily
- Coumadin (new)

<table>
<thead>
<tr>
<th>Choice</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Increase fluid and sodium intake</td>
</tr>
<tr>
<td>B</td>
<td>Decrease diuretics</td>
</tr>
<tr>
<td>C</td>
<td>Decrease ACE inhibitor</td>
</tr>
<tr>
<td>D</td>
<td>Decrease Beta Blocker</td>
</tr>
<tr>
<td>E</td>
<td>Change Beta Blocker</td>
</tr>
<tr>
<td>F</td>
<td>Combination of the above</td>
</tr>
</tbody>
</table>
1 week later….

- Still tired- nodding off when reading the paper in the morning, nap in afternoon
- SOB when bending over or walking 1 flight of stairs. Denies orthopnea or PND
- Weight-gained 4 pounds over the past week

• 106/62 mm Hg sitting and not postural drop
• Pulse- Irregular, rate 72
• Weight 169 pounds
• Lungs clear
• No pitting edema
• Heart sounds unchanged
• JVP 3 cm at 45 degrees

<table>
<thead>
<tr>
<th>Choice</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Start MRA</td>
</tr>
<tr>
<td>B</td>
<td>Decrease diuretics</td>
</tr>
<tr>
<td>C</td>
<td>Decrease ACE inhibitor</td>
</tr>
<tr>
<td>D</td>
<td>Decrease Beta Blocker</td>
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</tbody>
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- Ramipril 5.0 mg daily
- Coreg 25 mg BID
- ASA 81 mg daily
- Lasix 80 mg daily
- Crestor 5 mg daily
- Nitrospray prn
- Digoxin 0.0625 mg daily
- Coumadin
Low blood pressure
Tips for optimizing medications

• Stagger dose of ACE inhibitor/ARB and Beta Blocker (at least 2 hours between medications)
• Consider splitting daily dose to BID
• Start with low doses and increase slowly to help reduce side effects (monthly vs every 2 weeks)
• When trying to titrate ACE Inhibitor, ARB or Beta Blocker, consider only increasing the PM dose. If tolerated, then increase the AM dose at the next visit
• Use Bisoprolol rather than Carvedilol (more Beta 1 selective)
• Give beta blocker with meals (slows absorption)
• Consider decreasing diuretic
• Consider volume depletion, or other meds (cardiovascular or other) that can contribute to hypotension or orthostatic hypotension (e.g. alpha-blocker)
Mr. Scott- optimization
Triple therapy possible?

**Factors to consider:**
- Blood pressure
- Heart rate
- Renal function
- Potassium
- Fluid status
- Timing- Mr. Scott’s events/holidays-impact on monitoring of side effects and response to treatment
HF with reduced ejection fraction

www.ccs.ca
2017 HF guidelines
Decline in Systolic Function Leads to Activation of Three Major Neurohormonal Systems

**Sympathetic nervous system**
- Epinephrine
- Norepinephrine
- \(\alpha_1, \beta_1, \beta_2\) receptors
- Vasoconstriction
  - RAAS activity \(\uparrow\)
  - Vasopressin \(\uparrow\)
  - Heart rate \(\uparrow\)
  - Contractility \(\uparrow\)

**Natriuretic peptide system**
- NPRs \(\leftrightarrow\) NPs
- Vasodilation
  - Blood pressure \(\downarrow\)
  - Sympathetic tone \(\downarrow\)
  - Natriuresis/diuresis
  - Vasopressin
  - Aldosterone
  - Fibrosis
  - Hypertrophy

**Renin angiotensin aldosterone system**
- Ang II \(\rightarrow\) AT\(_1\)R
- Vasoconstriction
  - Blood pressure \(\uparrow\)
  - Sympathetic tone \(\uparrow\)
  - Aldosterone \(\uparrow\)
  - Hypertrophy \(\uparrow\)
  - Fibrosis

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Kemp & Conte. Cardiovascular Pathology 2012;21:55–71;
Decline in Systolic Function Leads to Activation of Three Major Neurohormonal Systems

**Sympathetic nervous system**
- Epinephrine
- Norepinephrine
- $\alpha_1, \beta_1, \beta_2$ receptors

**Renin-angiotensin-aldosterone system**
- Ang II
- AT$_1$R
- Vasoconstriction
- Blood pressure
- Ang II
- Hypertrophy

**Natriuretic peptide system**
- NPRs
- NP receptors
- Vasodilation
- Blood pressure
- Sympathetic tone
- Natriuresis/diuresis
- Vasopressin
- Aldosterone
- Fibrosis
- Hypertrophy

Ang=angiotensin; AT$_1$R=angiotensin II type 1 receptor; HF=heart failure; NP=natriuretic peptides; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system

---

Decline in Systolic Function Leads to Activation of Three Major Neurohormonal Systems

**Sympathetic nervous system**
- Epinephrine
- Norepinephrine
- $\alpha_1$, $\beta_1$, $\beta_2$ receptors
- Beta blockader
- Contraction

**Renin angiotensin aldosterone system**
- Ang II
- AT$_1$R
- Vasoconstriction
- Blood pressure
- Sympathetic
- Aldosterone
- Hypertrophy

**Natriuretic peptide system**
- NPRs ↔ NP's
- Vasodilation
- Blood pressure
- Sympathetic tone
- Natriuresis/diuresis
- Vasopressin
- Aldosterone
- Fibrosis
- Hypertrophy

Ang=angiotensin, AT=angiotensin II type 1 receptor, HF=heart failure, NP=natriuretic peptide, NPR=natriuretic peptide receptors, RAAS=renin-angiotensin-aldosterone system.

Increase NP levels

Block the body from breaking down NP

Physiological response

Naturetic Peptidies

Vasodilation
  Blood pressure
  Sympathetic tone
  Aldosterone
  Fibrosis
  Hypertrophy
  Natriuresis/diuresis

NP system

Nepriysen

Inactive fragments

Heart failure symptoms/ progression

References:
Increase NP levels

Block the body from breaking down NP

Physiological response

Naturetic Pepetides

NEP inhibitor: sacubitril

Vasodilation
  Blood pressure
  Sympathetic tone
  Aldosterone
  Fibrosis
  Hypertrophy
  Natriuresis/diuresis

Block RAAS- Valsartan

Heart failure symptoms/ progression

Paradigm-HF Study

Randomized controlled trial (n=8442)
Enalapril 10 mg BID vs Sacubitril/Valsartan BID

EF <40% (amendment ≤ 35%)
Chronic symptomatic heart failure
Stable therapy for 1 month
Previously treated with ACE inhibitor or ARB
Median follow up 27 months
PARADIGM-HF: Key Inclusion Criteria

- Chronic HF NYHA FC II–IV with LVEF ≤ 40%*
- BNP (or NT-proBNP) levels as follows:
  - ≥150 (or ≥600 pg/mL), or
  - ≥100 (or ≥400 pg/mL) and a hospitalization for HFrEF within the last 12 months
- ≥4 weeks’ stable treatment with an ACEI or an ARB†, and a β-blocker
- Aldosterone antagonist should be considered for all patients (with treatment with a stable dose for ≥4 weeks, if given)

*The ejection fraction entry criteria was lowered to ≤35% in a protocol amendment
†Dosage equivalent to enalapril ≥10 mg/day
PARADIGM-HF: Key Exclusion Criteria

- History of angioedema

- eGFR < 30 mL/min/1.73 m² at screening, end of enalapril run-in or randomization, or a > 35% decrease in eGFR between screening and end of enalapril run-in or between screening and randomization

- Serum potassium > 5.2 mmol/L at screening OR >5.4 mmol/L at the end of the enalapril run-in or end of the LCZ696 run-in

- Requirement for treatment with both ACEI and ARBs

- Symptomatic hypotension, SBP <100 mmHg at screening, OR SBP <95 mmHg at end of enalapril run-in or at randomization

- Current acute decompensated HF

- History of severe pulmonary disease

- Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid, or other major CV surgery, PCI, or carotid angioplasty within the 3 months prior to screening

Who was in the study?

Mean age 64 years
Male 79%
BP 122/73 mm Hg

NYHA II (70%)
LVEF 30%
Ischemic cardiomyopathy 60%
Afib 36%
Hypertension 70%
Diabetes 35%
Hospitalized for HF in the past year 62%

ACE inhibitor 78%
ARB 22%
Beta Blocker 93%
MRA 54-57%

McMurray et al, NEJM, 2014
Primary Endpoint: Death from CV Causes or First Hospitalization for HF

Hazard ratio = 0.80
(95% CI: 0.73–0.87)
p<0.001

NNT to prevent one primary event: 21

HR: 20% difference favoring LCZ696

Cumulative probability

Days since randomization

Enalapril

LCZ696

No. at risk

*The numbers of patients who would need to have been treated (NNT) to prevent one primary event was evaluated over the duration of the trial McMurray et al. N Engl J Med 2014;371 (11):993–1004.
## Prospectively Defined Safety Events

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (n=4,187)</th>
<th>Enalapril (n=4,212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with SBP &lt;90 mmHg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Elevated serum creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 2.5$ mg/dL</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>$\geq 3.0$ mg/dL</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Elevated serum potassium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&gt;5.5$ mmol/L</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>$&gt;6.0$ mmol/L</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Angioedema</strong> (adjudicated by a blinded expert committee)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Sacubitril/Valsartan (Entresto)

1. Chronic symptomatic HF (NYHA II, III)
2. EF ≤ 35%
3. Systolic blood pressure ≥100 mg Hg
4. eGFR >30 ml/min
5. K+ < 5.2 mmol/L
6. No history of angioedema
LCZ 696 (Sacubitril/Valsartan) (Entresto)

3 doses:

50 mg: 24.3 mg sacubitril / 25.7 mg valsartan
100 mg: 48.6 mg sacubitril / 51.4 mg valsartan
200 mg: 97.2 mg sacubitril / 102.8 mg valsartan

** if taking an ACEi prior to starting Entresto - must wait at least 36 hours between stopping ACEi and starting Entresto – risk of angioedema

** watch for hypotension, extra diuresis

Tips

ACEi ‘washout’

Watch low bp

Decrease diuretics

Monitor renal (ARB)
IVABRADINE: Novel HR-lowering therapy in the management of HF patients
**Action** - Sinus node

Must be in sinus rhythm to be effective

Slows heart rate

Unlike beta blockers:

No effect on blood pressure or contractility
Systolic Heart failure treatment with the If inhibitor ivabradine Trial

In 6505 patients with

- Systolic HF
- Moderate to severe chronic HF
  - NYHA class II-IV
- Left ventricular ejection fraction $\leq 35\%$
- HR $\geq 70$ bpm
- Sinus rhythm
- Optimal standard therapy

**Ivabradine dose:** 7.5 mg twice daily
**Median study duration:** 23 months
**Median HR:** 77 bpm

To evaluate the effect of HR reduction by ivabradine added to guidelines-based treatment in patients with HF and systolic dysfunction, including:

- CV outcomes
- Symptoms
- Quality of life

Ivabradine versus placebo
Who was in the study?

Age: 69 years
Male: 76%
NYHA III 50%
BP 122/76 mm Hg
Pulse 80

Ischemic cardiomyopathy 68%
Hypertension 67%
Diabetes 30%

ACE inhibitor 79%
ARB 14%
Beta Blocker 90%
MRA 60%
Ivabradine decreased HR on top of recommended therapy

No excessive bradycardia: the higher the HR at baseline, the greater the reduction

- On top of guidelines-recommended therapy, including BB

- Baseline HR at rest

-23 bpm
-16 bpm
-14 bpm
-13 bpm
-11 bpm

$\approx 60-65$ bpm


Symptomatic and asymptomatic bradycardia and phosphenes were more frequent in the ivabradine group compared with the placebo group.

<table>
<thead>
<tr>
<th>Patients with an adverse event</th>
<th>Ivabradine n=3 232</th>
<th>Placebo n=3 260</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>2 439 (75%)</td>
<td>2 423 (74%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3%)</td>
<td>17 (1%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>17 (1%)</td>
<td>7 (&lt; 1%)</td>
<td>0.042</td>
</tr>
</tbody>
</table>
Decrease in cardiovascular mortality
Decrease in hospitalizations

HF mortality benefits

No. at risk
Placebo
Ivabradine
2,660
2,660
2,061
2,061
1,089
1,089
439
439
HR = 0.74 (0.58–0.94)
p = 0.014

Cumulative frequency, %
Early

HF hospitalization benefits

No. at risk
Placebo
Ivabradine
2,660
2,660
2,061
2,061
1,089
1,089
439
439
HR = 0.74 (0.66–0.83)
p < 0.0001

Cumulative frequency, %
Early

- The curves for ivabradine and placebo begin to diverge at 3 months, and the difference is statistically significant at 6 months
Reduction of the primary endpoints with ivabradine was consistent in all prespecified subgroups except for HR.

### CV death or hospitalization for HF

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard Ratio</th>
<th>Test for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Etiology of heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Ischemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline heart rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 77 bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 77 bpm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.029*
Take with food
Do not take with grapefruit juice (>2 fold Lancora™ exposure)
Older (age 75+) caution for side effects
Interaction with other medications:
- CYP3A4 pathway
- Slow heart rate, prolong QT
If channel in eyes - may get phosphenes - seeing flashes of lights of halos (<5% of people)
Lancora™ (Ivabradine)

1. Stable and symptomatic HF, and
2. EF ≤ 35%, and
3. SR and resting heart rate of ≥77 beats per minute who:
   - Cannot tolerate a beta blocker; OR
   - Who cannot tolerate the full strength of a beta blocker due to side effects; OR
   - Who are taking the full strength of a beta blocker but continue to have a resting heart rate ≥77 beats per minute.
Case-Mr. C.

62 year old man- 4 week history of increasing SOB. No orthopnea or PND or edema.
- PMHx- viral cardiomyopathy (8 yrs ago) (EF 35%-now 20%)
- Hypertension, family history CAD, non-smoker, rare ETOH, no diabetes, lipids normal

NYHA class I symptoms until the last month
Medications: Ramipril 10 mg daily, Metoprolol 25 mg BID
(not taking these regularly)
Mr. C.- Why is he worse?

- Angiogram- no coronary artery disease
- No arrhythmias noted (no afib– yet)
- ACE and Beta Blocker not at optimal doses.
- Hypertension, sleep apnea

Self-care issues?
- Medication side effects (itchy, cough)
**What is the plan?**

Hospital discharge:
- Candesartan 32 mg OD
- Bisoprolol 5.0 mg OD
- Lasix 40 mg OD

Weight: 103.7 Kg
bp 149/96 mm Hg, pulse 82 regular
Lab: Creatinine 110, urea 9.2, K⁺ 4.3, Na 140

NYHA II, euvoletic

---

<table>
<thead>
<tr>
<th>Choice</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Increase Bisoprolol</td>
</tr>
<tr>
<td>B</td>
<td>Decrease diuretics</td>
</tr>
<tr>
<td>C</td>
<td>Change Bisoprolol to Carvedilol</td>
</tr>
<tr>
<td>D</td>
<td>Try MRA again</td>
</tr>
<tr>
<td>E</td>
<td>Try Entresto</td>
</tr>
<tr>
<td>F</td>
<td>Try Lancora</td>
</tr>
<tr>
<td>G</td>
<td>No change</td>
</tr>
</tbody>
</table>

Cardiac rehab
Sleep study
Coaching/negotiation (meds)

MRA-persistent hyperkalemia
ACE- cough
STRATEGIES FOR PROMOTING MEDICATION ADHERENCE
• Based on your experience, what proportion of patients do you think are adherent to taking medications as prescribed?

(Adherent- taking the medication as prescribed at least 80% of the time)

<50%
50%
60%
70%
80%
90%
Based on your experience, what proportion of patients do you think are adherent to taking medications as prescribed?

(Adherent - taking the medication as prescribed at least 80% of the time)

- <50%
- 50%
- 60%
- 70%
- 80%
- 90%

USA - discharged with HF Apr 2006-Oct 2012, Age 65+ years, n=9878
At 90 days, medication adherence:
- Beta Blocker 58%
- ACE/ARB 48%
- MRA 48%

1 year (n= 6615)
- Beta Blocker 53%
- ACE/ARB 48%
- MRA 36%

Chang et al, J Am Heart Assoc, 2018 Epub
Medication adherence- part of adapting to living with HF

- Patients view self-care as an ‘adaptation’—maintain independence and quality of life
- A number of emotion-based and action-based strategies
- Learning over time from experience- planned and intentional strategies
- Fluctuations in routine often pose additional challenges- adhoc approach to irregular or unexpected situations
- Medication non-adherence was a strategy employed when life goals conflicted with medication adherence.

Harkness et al., E J Cardiovasc Nurs 2015
Mickelson & Holden, E J Cardiovasc Nurse, 2017
Past experience…….

“I have a basket of prescriptions and I set the basket down, and I start with one and go around it and take them…used this method for years, and it just seems to work and that’s why I continue it”

“I don’t take my Lasix when I am going our somewhere, I can’t always get to a bathroom quick enough……I had an accident when I was out a few months ago and I was so embarrassed I could have died”

Harkness et al., E J Cardiovasc Nurse, 2015
One patient described her strategy to improve her tolerance to a medication based on a past experience of symptomatic hypotension that prevented her from going to work. She stopped the medication for a few days, reintroduced the medication at ½ the prescribed dose and then slowly titrated the medication depending on how she felt getting out of bed in the morning.

At the same time, she did not report this to her physician and actually “lied to him about the dose” she was taking, as she was too embarrassed to disclose her own approach to titrating the medication.

Adaptation- action strategies by patients

• Simplify the process
• Pill boxes, consolidating the task (weekly vs daily), 90-day refills
• Memory aids- usual routine, physical spaces, create tools/charts
• Recruit help (caregiver), pharmacy delivery,

“We have one of our members (church) is a med student so she made that chart for him so that helps a lot….its been a ,a team effort to keep him, to get him stable.”

Mickelson & Holden, E J Cardiovasc Nurse, 2017
Medication Adherence - Implications for practice

- Understand patient and caregiver beliefs about HF their expectations and aspirations for daily life.
- Appreciate that medication management is a challenging process
- Simplify where ever possible
- Harness cues in patients' home environments and routines to increase adherence patterns.
- Consider organizational supports for medication management/leverage digital tools?
- Plan ahead using a problem-solving approach that for supporting safe medication management when usual activities or life situations are altered.
- Involve caregivers- key source of support.
Any questions??