Treating HFrEf, what comes after the Big Four?

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Disclosures

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Objectives

- How to approach patients with persistent symptoms after foundational therapy has been optimized
- Evidence for medical therapy “after the big four”
- Recommendations from the 2021 heart failure guidelines: after foundational therapy
Vignette 1

- 72 F, admitted with acute on chronic HF without clear precipitant
  - Remote Anterior wall MI
  - Prior HF admission 2 months ago, compliant with meds and diet, no clear precipitant
  - LVEF 20% at baseline
  - Remote CRT-D

- PMHx
  - HTN

- Meds
  - Sacubitril-Valsartan 96-103mg PO BID
  - Spironolactone 25mg/d
  - Bisoprolol 10mg/d
  - Empagliflozin 10mg/d
  - Furosemide 40mg/d
  - Atorvastatin 80mg/d
  - ASA

- BP 110/75, HR 62 bpm (2 days post-admission)
- JVP 10 cm, bibasilar crepitations at presentation, now chest is clear
- ECG: CRT paced 62bpm (98% pacing)
- Creat 128mmol/L, K 5.0 mmol/L

- Decongested with IV furosemide x 48h

- So now what?
  a) DC home on same meds?
  b) Add a new medication?
HFrEF: LVEF ≤ 40% AND SYMPTOMS

Initiate Standard Therapies

- ARNI or ACEI/ARB then substitute ARNI
- BETA BLOCKER
- MRA
- SGLT2 INHIBITOR

Assess Clinical Factors for Additional Interventions

- HR >70 bpm and sinus rhythm
  - Consider labradine®
- Recent HF hospitalization
  - Consider verapamil®
- Black patients on optimal GDMT, or patients unable to tolerate ARNI/ACEI/ARB
  - Consider combination hydralazine-nitrates
- Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT
  - Consider digoxin

Initiate standard therapies as soon as possible and titrate every 2-4 weeks to target or maximally tolerated dose over 3-6 months.

Reassess LVEF, Symptoms, Clinical Risk

- NYHA III/IV, Advanced HF or High-Risk Markers
  - CONSIDER
    - Referral for advanced HF therapy (mechanical circulatory support/transplant)
    - Referral for supportive/palliative care

- LVEF < 35% and NYHA III/IV (ambulatory)
  - Refer to CCS CRT/ICD recommendations

- LVEF > 35%, NYHA I, and Low Risk
  - Continue present management, reassess as needed

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Personalizing therapy

- Elevated HR in Sinus rhythm
- Recurrent hospitalizations
- Renal failure
- Black patient
- A fib
- Persistent symptoms on maximally tolerated GDMT
Evidence on therapy

<table>
<thead>
<tr>
<th>HFrEF drug therapy</th>
<th>Chronic ambulatory HF</th>
<th>New-onset HF</th>
<th>HF hospitalization*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacubitril-valsartan</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>High</td>
<td>High</td>
<td>High†</td>
</tr>
<tr>
<td>β-blockers</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>MRAs</td>
<td>High</td>
<td>High</td>
<td>High†</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>High</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>High</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Vericiguat</td>
<td>Moderate</td>
<td>N/A</td>
<td>NA</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>H-ISDN</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Quality of evidence supporting recommendation
†Clinical setting not specified
‡N/A indicates not available
HFrEF: LVEF ≤ 40% AND SYMPTOMS

Initiate Standard Therapies

- ARNI or ACEIARB then substitute ARNI
- BETA BLOCKER
- MRA
- SGLT2 INHIBITOR

Assess Clinical Factors for Additional Interventions

- HR > 70 bpm and sinus rhythm
  - Consider Verapamil
- Recent HF hospitalization
  - Consider Venetoclax
- Black patients on optimal GDMT, or patients unable to tolerate ARNIACEI/ARB
  - Consider combination hydralazine-nitrates
- Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT
  - Consider digoxin

initiate standard therapies as soon as possible and titrate every 2-4 weeks to target or maximally tolerated dose over 3-6 months

Reassess LVEF, Symptoms, Clinical Risk

- NYHA III/IV, Advanced HF or High-Risk Markers
- LVEF < 35% and NYHA I-II (ambulatory)
- LVEF > 35%, NYHA I, and Low Risk

CONSIDER
- Referral for advanced HF therapy (mechanical circulatory support/transplant)
- Referral for supportive/palliative care

Refer to CCS CRT/ICD recommendations

Continue present management, reassess as needed
Soluble guanylate cyclase stimulators (sGCs), such as vericiguat, directly enhance cyclic GMP production and also enhance endogenous sGC sensitivity to nitric oxide. This results in a cascade of adaptive effects on the heart, blood vessels and kidneys providing the physiological rationale for their use in patients with HF.
**VICTORIA Trial:** Vericiguat, a soluble guanylate cyclase stimulator

### “Chronic HF”
- NYHA class II–IV
- LVEF < 45%
- Guideline based HF therapies

### “Worsening event”
- Recent hospitalization or IV diuretic use
- With elevated natriuretic peptides
  - BNP ≥ 300 & pro-BNP ≥ 1000 pg/ml NSR
  - BNP ≥ 500 & pro-BNP ≥ 1600pg/ml AF

- 5050 high-risk patients randomized to vericiguat vs placebo
- Primary outcome: composite of CV death or first HF hospitalization
- Median f/u 10.8 months

*Armstrong et al. JACC Heart Fail. 2018*
VICTORIA TRIAL OBJECTIVES

• To assess whether vericiguat reduces the primary composite outcome of cardiovascular (CV) death or first HF hospitalization

• Secondary outcomes were:
  – Components of the primary composite endpoint
  – Total HF hospitalizations; first and recurrent
  – Composite of all-cause mortality or first HF hospitalization
  – All-cause mortality

• To evaluate the safety and tolerability of vericiguat in this high-risk population with HF with reduced EF (HFrEF)
<table>
<thead>
<tr>
<th>Index event — no. (%)</th>
<th>1673 (66.2)</th>
<th>1705 (67.6)</th>
<th>3378 (66.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for heart failure in previous 3 mo</td>
<td>1673 (66.2)</td>
<td>1705 (67.6)</td>
<td>3378 (66.9)</td>
</tr>
<tr>
<td>Hospitalization for heart failure in previous 3–6 mo</td>
<td>454 (18.0)</td>
<td>417 (16.5)</td>
<td>871 (17.2)</td>
</tr>
<tr>
<td>Intravenous diuretic for heart failure (without hospitalization) in previous 3 mo</td>
<td>399 (15.8)</td>
<td>402 (15.9)</td>
<td>801 (15.9)</td>
</tr>
<tr>
<td>Mean body-mass index‡</td>
<td>27.7±5.8</td>
<td>27.9±6.1</td>
<td>27.8±5.9</td>
</tr>
<tr>
<td>Mean ejection fraction at screening — %</td>
<td>29.0±8.3</td>
<td>28.8±8.3</td>
<td>28.9±8.3</td>
</tr>
<tr>
<td>Ejection fraction &lt;40% — no. (%)</td>
<td>2158 (85.8)</td>
<td>2158 (85.6)</td>
<td>4316 (85.7)</td>
</tr>
<tr>
<td>NYHA class — no./total no. (%)</td>
<td>I</td>
<td>2/2523 (0.1)</td>
<td>2/5046 (&lt;0.1)</td>
</tr>
<tr>
<td>II</td>
<td>1478/2523 (58.6)</td>
<td>1497/2523 (59.3)</td>
<td>2975/5046 (59.0)</td>
</tr>
<tr>
<td>III</td>
<td>1010/2523 (40.0)</td>
<td>993/2523 (39.4)</td>
<td>2003/5046 (39.7)</td>
</tr>
<tr>
<td>IV</td>
<td>35/2523 (1.4)</td>
<td>31/2523 (1.2)</td>
<td>66/5046 (1.3)</td>
</tr>
<tr>
<td>Mean time from initial diagnosis of heart failure with reduced ejection fraction to randomization — yr</td>
<td>4.7±5.5</td>
<td>4.8±5.4</td>
<td>4.8±5.4</td>
</tr>
</tbody>
</table>
# VICTORIA: Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Vericiguat (N=2526)</th>
<th>Placebo (N=2524)</th>
<th>Treatment Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Events/100 Pt-Yrs</td>
<td>%</td>
</tr>
<tr>
<td><strong>PRIMARY COMPOSITE OUTCOME</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>35.5</td>
<td>33.6</td>
<td>38.5</td>
</tr>
<tr>
<td>Cardiovascular death‡</td>
<td>27.4</td>
<td>29.6</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>SECONDARY OUTCOMES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>16.4</td>
<td>12.9</td>
<td>17.5</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>27.4</td>
<td>25.9</td>
<td>29.6</td>
</tr>
<tr>
<td>Total HF hospitalizations</td>
<td>38.3</td>
<td>42.4</td>
<td>40.9</td>
</tr>
<tr>
<td>Secondary composite outcome</td>
<td>37.9</td>
<td>35.9</td>
<td>40.9</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>27.4</td>
<td>29.6</td>
<td>10.5</td>
</tr>
</tbody>
</table>

### Patients with Adverse Events of Clinical Interest

<table>
<thead>
<tr>
<th></th>
<th>Vericiguat</th>
<th>Placebo</th>
<th>Difference in % vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>Estimate (95% CI)*</td>
</tr>
<tr>
<td>Patients in population</td>
<td>2519 (9.1)</td>
<td>2515 (7.9)</td>
<td>1.2 (-0.3 to 2.8)</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>229 (9.1)</td>
<td>198 (7.9)</td>
<td>1.2 (-0.3 to 2.8)</td>
</tr>
<tr>
<td>Syncope</td>
<td>101 (4.0)</td>
<td>87 (3.5)</td>
<td>0.6 (-0.5 to 1.6)</td>
</tr>
</tbody>
</table>

*Based on the Miettinen & Nurminen method.
Note: Includes events/measurements from the day of first dose of study drug to 14 days after the last dose of study drug.
Based on data up to the primary analysis cutoff date (18 Jun 2019).
CI indicates confidence interval.
Recommendation

• We recommend that vericiguat, an oral sGC stimulator, be considered in addition to optimal HF therapies for HFrEF patients with worsening symptoms and heart failure hospitalization in the past 6 months, to reduce the risk of subsequent HF hospitalization

  *(Conditional Recommendation; Moderate-Quality Evidence)*.

• This recommendation places value on the use of an additional medication to reduce the risk of hospitalization in a **high-risk patient population** despite the relatively modest relative benefits observed in the VICTORIA trial.
**HFpEF: LVEF ≤ 40% AND SYMPTOMS**

**Initiate Standard Therapies**
- ARNI or ACEI/ARB (then substitute ARNI)
- Beta Blocker
- MRA
- SGLT2 Inhibitor

**Assess Clinical Factors for Additional Interventions**
- HR > 70 bpm and sinus rhythm
  - Consider hydralazine
- Recent HF hospitalization
  - Consider venovert
- Black patients on optimal GDMT, or patients unable to tolerate ARNI/ACEI/ARB
  - Consider combination hydralazine-nitrates
- Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT
  - Consider digoxin

**Reassess LVEF, Symptoms, Clinical Risk**
- NYHA III/IV, Advanced HF or High-Risk Markers
  - Consider
    - Referral for advanced HF therapy (mechanical circulatory support/transplant)
    - Referral for supportive/palliative care
- LVEF < 35% and NYHA I-II (ambulatory)
  - Refer to CCS CRT/ICD recommendations
- LVEF > 35%, NYHA I, and Low Risk
  - Continue present management, reassess as needed

Initiate standard therapies as soon as possible and titrate every 2-4 weeks to target or maximally tolerated dose over 3-6 months.
Ivabradine

Selective HR reduction

- Decreases myocardial O$_2$ consumption without: Effecting conduction
- Effecting contractility

- Increases coronary flow
- Improves myocardial O$_2$ supply
- Increases stroke volume & preserves cardiac output

References:
SHIFT Trial

- Randomized, double-blind, placebo-controlled trial in 6505 patients to test the hypothesis that heart rate slowing with the $I_f$ inhibitor ivabradine improves cardiovascular outcomes in patients with:
  - Moderate to severe chronic heart failure (HF)
  - Hospitalization for worsening HF within the 12 months prior to randomization
  - Left ventricular ejection fraction $\leq 35\%$
  - Sinus rhythm and heart rate $\geq 70$ bpm
  - Receiving guidelines-based background HF therapy

Lancet 376, 2010
Figure 2: Kaplan-Meier cumulative event curves for (A) the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure, (B) hospital admission for worsening heart failure, and (C) cardiovascular death.
Ivabradine

• **Recommendations:**
  
  We recommend that ivabradine be used for patients with HFrEF and symptoms despite treatment with GDMT for the prevention of cardiovascular death and HF hospitalization
  
  - a resting heart rate > 70 beats per minute (bpm)
  - sinus rhythm, for the prevention of cardiovascular death and HF hospitalization
  
  • *(Strong Recommendation; High-Quality Evidence).*

• **Practical tips:**
  
  - Ivabradine has no direct effect on BP, myocardial contractility or renal function
  - Typical reductions in resting sinus HR following treatment with b-blockers range from 10-14 bpm
Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

Anne L. Taylor, M.D., Susan Ziesche, R.N., Clyde Yancy, M.D., Peter Carson, M.D., Ralph D’Agostino, Jr., Ph.D., Keith Ferdinand, M.D., Malcolm Taylor, M.D., Kirkwood Adams, M.D., Michael Sabolinski, M.D., Manuel Worcel, M.D., and Jay N. Cohn, M.D., for the African-American Heart Failure Trial Investigators*
A-HEFT TRIAL

Figure 1. Kaplan–Meier Estimates of Overall Survival.
Hydralazine-nitrate

• We recommend the combination of hydralazine and isosorbide dinitrate (H-ISDN) be considered in patients with HFrEF who are unable to tolerate an ACEi, ARB, or ARNI because of hyperkalemia, renal dysfunction or other contraindications, in the following settings:
  • Chronic HF (Strong Recommendation, Moderate-Quality Evidence)
  • New onset HF (Weak Recommendation, Low-Quality Evidence)
  • HF hospitalization (Weak Recommendation, Low-Quality Evidence)

• We recommend the combination of hydralazine and isosorbide dinitrate (H-ISDN) be considered in addition to standard GDMT at appropriate doses for black patients with HFrEF and advanced symptoms (Strong Recommendation; Moderate-Quality Evidence).
THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

The Digitalis Investigation Group*
DIG-trial

Figure 1. Mortality in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

Figure 3. Incidence of Death or Hospitalization Due to Worsening Heart Failure in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

NEJM 336,8 1997
• We suggest digoxin be considered in patients with HFrEF and atrial fibrillation, with poor control of ventricular rate and/or persistent symptoms despite optimally tolerated β-blocker therapy (Weak Recommendation; Low-Quality Evidence).

• We suggest digoxin be considered in patients with HFrEF in sinus rhythm who continue to have moderate to severe symptoms despite GDMT to relieve symptoms and reduce hospitalizations (Weak Recommendation; Moderate-Quality Evidence).

• **Practical tip.** Serum concentrations of digoxin < 1.2 ng/mL are associated with less treatment-related morbidity.

• **Practical tip.** Digoxin can cause atrial and ventricular arrhythmias particularly in the presence of hypokalemia and/or worsening renal function and levels should be monitored accordingly.

Note: There is also a role for ablation in select patients with Afib
Key points:

- Additional clinical factors (or phenotypes) can determine what additional therapies should be considered on top of standard 4 drugs

- Every attempt should be made to titrate all indicated therapies 3-6 months following diagnosis
After titration of medications

Recommendation:

We recommend that after a diagnosis of HFrEF, standard medical therapy should be initiated and titrated to target or maximally tolerated doses with a repeat assessment of LVEF before referral for ICD or CRT

(Strong Recommendation; Moderate-Quality Evidence)
Summary for therapies

• **Values and preferences.** High value is placed on prescribing a combination of individual therapies that reduce CV mortality and HHF in well conducted randomized controlled trials.

• The complementary mechanisms of action of these agents in patients with HFrEF provides further rationale for a multidrug approach.

• The Committee acknowledges lack of evidence favouring one particular titration strategy for guideline-directed medical therapy (GDMT) over another.
Summary

- New clinical trial evidence has driven the need for HFrEF Guidelines Update

- After the foundational 4 therapies are optimized, further treatment options should be considered in patients who remain symptomatic

- Personalization of care allows for additional therapies based on clinical factors
  - ivabradine, vericiguat, H-ISDN, digoxin

- Reassessment of ejection fraction and should be done in all patients prior to device consideration
Take away slide

• In patients who remain symptomatic after optimization of foundational therapies, further medical therapy can be considered.

• This additional therapy, based on individual patient factors, includes ivabradine, vericiguat, hydralazine-nitrates and digoxin.

• Medical therapy should be optimized in the first 3-6 months post-diagnosis of heart failure.

• Reassessment of ejection fraction and should be done in all patients prior to device consideration.