An Update in Heart Failure: SGLT2i, Guidelines, Implementation, and Advanced Disease

Larry A. Allen, MD, MHS
ACP Meeting, February 2022
Disclosures

• Employee: University of Colorado
• Consultant: Abbott, ACI Clinical, Amgen/Cytokinetics, Boston Scientific, Cytokinetics, Novartis
• Stockholder: None
• Research support: NIH / NHLBI, PCORI, AHA
• Honoraria: None
Objectives

1. Review emerging data on SGLT2i in heart failure.
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2. Summarize recent changes to guideline-directed management and treatment for heart failure, across ejection fraction.
3. Consider challenges and opportunities to better implement evidence-based medicine into practice.
4. Recognize advanced heart failure.
Case: 75F w/ T2DM, obesity, s/p MI 2014, LVEF 25%, AF, transfers care to you

Medications:
ASA 81 mg
- Warfarin to INR 2-3
- Atorvastatin 80 mg (LDL 95)
- Lisinopril 10 mg
- Metoprolol succinate 50 mg
- Metformin 1000 mg bid
- Glipizide 5 mg daily


Other: Getting more frail, recent fall. Refusing vaccines.

Exam: BP 129/78, HR 80 in AF, BMI 36 Euvolemic

Labs: K 4.6, Cr 1.4
HCT 31%, Ferr 220, Fe 15%
Echo severe mitral regurgitation
ECG AF, QRS 160 LBBB

https://hfsa.org/patient (image)
https://www.heart.org/en/health-topics/heart-failure
https://www.cardiosmart.org/topics/heart-failure
Intro

2004-2014

- After BB, ACEI/ARB, MRA, CRT-D...
- Inotropes/calcitropes kill people
- Nesiritide a dud
- Tolvaptan a dud
- HFpEF nothing
Intro

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2014-2021
- Sacubitril/valsartan
- SGLT2i for HFrEF, then HFpEF
- +/- Vericiguat
- +/- Omecamtiv
- +/- CardioMEMS, other remote monitoring
- Tafamidis + RNA interference drugs
- AF ablation for HFrEF
- Mevacamten
- Better genetics CM → gene therapy ATTR
Heart Failure is “new and improved”

Consensus Statement

Universal Definition and Classification of Heart Failure
A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association

BHYKEM BOZKURT, MD, PhD, Chair, ANDREW JS COATS, DM, DSC, HIROYUKI TSUTSUI, MD, Co-Chair.

Symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality

and corroborated by at least one of the following

Elevated natriuretic peptide levels

or

Objective evidence of cardiogenic pulmonary or systemic congestion

Figure 1. Universal definition of HF.
LVEF remains central to definitions … for now

**HF with reduced EF (HFrEF):**
- HF with LVEF ≤ 40%

**HF with mildly reduced EF (HFmrEF):**
- HF with LVEF 41-49%

**HF with preserved EF (HFpEF):**
- HF with LVEF > 50%

**HF with improved EF (HFimpEF):**
- HF with a baseline LVEF ≤ 40%, a ≥ 10 point increase from baseline LVEF, and a second measurement of LVEF > 40%

A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021 Mar 1
Heart Failure staging and treatment matches disease progression

**AT-RISK FOR HEART FAILURE (STAGE A)**
Patients at risk for HF but without current or prior symptoms or signs of HF and without structural, biomarker, or genetic markers of heart disease.

**PRE-HEART FAILURE (STAGE B)**
Patients without current or prior symptoms or signs of heart failure but evidence of one of the following:
- Structural Heart Disease: e.g. LVH, chamber enlargement, wall motion abnormality, myocardial tissue abnormality, valvular heart disease
- Abnormal cardiac function: e.g. reduced LV or RV ventricular systolic function, evidence of increased filling pressures or abnormal diastolic dysfunction
- Elevated natriuretic peptide levels or elevated cardiac troponin levels in the setting of exposure to cardiotoxins

**HEART FAILURE (STAGE C)**
Patients with current or prior symptoms and/or signs of HF caused by structural and/or functional cardiac abnormality

**ADVANCED HEART FAILURE (STAGE D)**
Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care

**Heart Failure in Remission**

**Persistent Heart Failure**

with GDMT and risk factor modification

1. SGLT2i

2014-2021

- Sacubitril/valsartan
- **SGLT2i for HFrEF** then HFpEF
- +/- Vericiguat
- +/- Omecamtiv
- +/- CardioMEMS, other monitoring
- Tafamidis + RNA interference drugs
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SGLT2i: A brief history

- SGLT1 discovered in intestine.
- SGLT2 predominantly in kidney: responsible for 90% of glucose reabsorption.
- Canagliflozin (Invokana), FDA approved 3/2013.
- Dapagliflozin (Farxiga), FDA approved 1/2014.
- Empagliflozin (Jardiance), FDA approved 8/2014.

- 2008, FDA required drug companies to conduct a cardiovascular outcomes trial for safety for all new T2DM drugs, in response to signal for increased MI risk with the thiazolidinedione rosiglitazone (as well as sulfonylurea tolbutamide).
SGLT2i Reduces HF in Patients with T2DM and Varying Baseline CVD

## SGLT2i in HFrEF: DAPA-HF and EMPEROR-Reduced

### DAPA-HF Primary Endpoint: CV Death, HF Hospitalization, or an Urgent HF Visit

<table>
<thead>
<tr>
<th></th>
<th>SGLT2i</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>EMPEROR-Reduced</td>
<td>249/1863 (13.4%)</td>
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<td>DAPA-HF</td>
<td>276/2373 (11.6%)</td>
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Test for overall treatment effect: *P* = 0.018

Test for heterogeneity of effect: *P* = 0.39

### CV death

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<td>EMPEROR-Reduced</td>
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<td>DAPA-HF</td>
<td>227/2373 (9.6%)</td>
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Test for overall treatment effect: *P* = 0.027

Test for heterogeneity of effect: *P* = 0.40

### First hospitalization for HF or CV death

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Test for overall treatment effect: *P* < 0.0001

Test for heterogeneity of effect: *P* = 0.89

---

SGLT2i in HFrEF: DAPA-HF and EMPEROR-Reduced

DAPA:HF Primary Endpoint: CV Death, HF Hospitalization, or an Urgent HF Visit

EMPEROR-Reduced: Primary Endpoint: Time to CV Death or HF Hospitalization

SGLT2i in HFrEF: DAPA-HF and EMPEROR-Reduced


**All-cause mortality**

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< 15% reduction in death
SGLT2i in HFrEF: DAPA-HF and EMPEROR-Reduced

**DAPA-HF Primary Endpoint: CV Death, HF Hospitalization, or an Urgent HF Visit**

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Test for overall treatment effect $P < 0.0001$
Test for heterogeneity of effect $P = 0.89$

< 25–30% reduction in HF hosp

Benefit independent of diabetes status or HbA1c

**T2DM**

- HR 0.75 (0.63–0.90)

**No T2D**

- HR 0.73 (0.60–0.88)

\[ P (\text{interaction}) = 0.80 \]

HbA1c reduction minimal $\rightarrow$ mechanisms not completely known

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest. 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dapagliflozin (N = 2373)</th>
<th>Placebo (N = 2371)</th>
<th>Hazard or Rate Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>values events/100 patient-yr</td>
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<td></td>
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</tr>
<tr>
<td>Laboratory and other measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to 8 mo§§§</td>
<td>Glycated hemoglobin — %§§§</td>
<td>0.04±1.29</td>
<td>-0.24 (-0.34 to -0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>-0.21±1.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine — mg/dl</td>
<td>0.04±0.25</td>
<td>0.02 (0.01 to 0.03)</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td></td>
<td>0.07±0.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematocrit — %</td>
<td>-0.19±3.81</td>
<td>2.41 (2.21 to 2.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2.31±3.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NT-proBNP — pg/ml</td>
<td>101±2944</td>
<td>-303 (-457 to -150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>-196±2387</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight — kg</td>
<td>0.10±4.09</td>
<td>-0.87 (-1.11 to -0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>-0.88±3.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure — mm Hg</td>
<td>-0.38±15.27</td>
<td>-1.27 (-2.09 to -0.45)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>-1.92±14.92</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The first clearly positive large RCT to show improvement in clinical outcomes from a drug used to treat HFrEF

Packer M. NEJM 2021.
Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.

The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.
Effect of Different HF Therapies in Specific Trials Aiming to Recruit HFpEF Patients (LVEF ≥50%)

Endpoint studied: First event of CV death or HHF

<table>
<thead>
<tr>
<th>Trial</th>
<th>% Reduction</th>
<th>vs</th>
<th>Event Rate (active vs control)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM-Preserved (2003)</td>
<td>5%</td>
<td>placebo</td>
<td>8.6 vs 9.1</td>
<td>0.95 (0.79, 1.14)</td>
</tr>
<tr>
<td>DIG (ancillary) (2006)</td>
<td>8%</td>
<td>placebo</td>
<td>NA</td>
<td>0.92 (0.71, 1.20)</td>
</tr>
<tr>
<td>I-PRESERVE (2008)*</td>
<td>4%</td>
<td>placebo</td>
<td>5.48 vs 5.74</td>
<td>0.96 (0.84, 1.09)</td>
</tr>
<tr>
<td>TOPCAT (2014)</td>
<td>7%</td>
<td>placebo</td>
<td>NA*** (5.9 vs 6.6)</td>
<td>0.93 (0.79, 1.10)</td>
</tr>
<tr>
<td>PARAGON-HF (2019)**</td>
<td>6%</td>
<td>valsartan</td>
<td>12.8 vs 14.1</td>
<td>0.94 (0.82, 1.08)</td>
</tr>
<tr>
<td>EMPEROR-Preserved (2021)</td>
<td>17%</td>
<td>placebo</td>
<td>6.7 vs 8.0</td>
<td>0.83 (0.71, 0.98)</td>
</tr>
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*I-PRESERVE: patients with LVEF ≥45%. **PARAGON-HF: patients with LVEF ≥50%; event rate is for total HHF or CV death. ***event rate is for patients with LVEF ≥45%.
### Effect of DLB Aiming to

<table>
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<tr>
<th>% reduction of the composite first event of CV death</th>
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<tbody>
<tr>
<td>vs placebo</td>
<td>5%</td>
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<td>vs valsartan</td>
<td></td>
<td>17%</td>
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<tr>
<td>vs placebo</td>
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### Study Details

- **CHARM-Preserved (2003)**
- **DIG (ancillary) (2006)**
- **I-PRESERVE (2008)**
- **TOPCAT (2014)**
- **PARAGON-HF (2019)**
- **EMPEROR-Preserved (2021)**

### Event Rate

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**HR (95% CI)**

<p>| | | | | |</p>
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<td>0.95</td>
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<td>0.93</td>
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<td>(0.79, 1.14)</td>
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* **I-PRESERVE**: patients with LVEF ≥45%.
* **PARAGON-HF**: patients with LVEF >50%; event rate is for total HHF or CV death. *** event rate is for patients with LVEF ≥45%.

### Additional Data

- **EMPEROR-Preserved**
  - **HFpEF (≥50%)**: n=4,005
  - **HFmrEF (41–49%)**: n=1,983

<table>
<thead>
<tr>
<th>Age, years (±SD)</th>
<th>HFpEF (≥50%)</th>
<th>HFmrEF (41–49%)</th>
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<tr>
<td>Women, n (%)</td>
<td>72.8 ± 9.2</td>
<td>70.1 ± 9.7</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2019 (50)</td>
<td>657 (33)</td>
</tr>
<tr>
<td>Ischaemic HF, n (%)</td>
<td>1913 (48)</td>
<td>1025 (52)</td>
</tr>
<tr>
<td>NYHA functional class II, n (%)</td>
<td>1134 (28)</td>
<td>983 (50)</td>
</tr>
<tr>
<td>NT-proBNP (median, IQR), pg/mL</td>
<td>3255 (81)</td>
<td>1628 (82)</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter, n (%)</td>
<td>946 (482, 1677)</td>
<td>1025 (550, 1882)</td>
</tr>
<tr>
<td>Baseline eGFR (mL/min/1.73 m²)</td>
<td>2224 (56)</td>
<td>911 (46)</td>
</tr>
<tr>
<td>Baseline eGFR (mL/min/1.73 m²)</td>
<td>59.4 ± 19.5</td>
<td>63.0 ± 20.3</td>
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**Co-medications of interest, n (%)**

- **ACE inhibitors/ARBs/ARNi**: 3149 (79) vs 1690 (85)
- **Beta blocker**: 3375 (84) vs 1792 (90)
- **MRA**: 1320 (33) vs 924 (47)
- **Diuretics**: 3246 (81) vs 1563 (79)

*ACE inhibitors/ARBs/ARNi*
## SGLT2i Safety: Outpatient initiation

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<th>Event, %</th>
<th>T2DM</th>
<th>No DM</th>
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<tr>
<td></td>
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<td>Dapagliflozin 10 mg + Usual Care</td>
<td>Placebo + Usual Care</td>
</tr>
<tr>
<td>Any serious AE¹,‡</td>
<td>41.7</td>
<td>48.3</td>
<td>34.6</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>4.0</td>
<td>5.4</td>
<td>5.3</td>
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<tr>
<td>AE of interest¹</td>
<td></td>
<td></td>
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<tr>
<td>Volume depletion</td>
<td>7.8</td>
<td>7.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Renal AE</td>
<td>8.5</td>
<td>8.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Fracture</td>
<td>2.1</td>
<td>2.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Amputation</td>
<td>1.1</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Major hypoglycemia§</td>
<td>0.4</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Diabetic ketoacidosisǁ</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

---

**SERIOUS ADVERSE EVENTS**

- **Empagliflozin**
  - 47.9%
- **Placebo**
  - 51.6%

**EMPEROR-Preserved**
SGLT2i Summary

1. SGLT2i beneficial in multiple settings
   • T2DM
   • All HF, regardless of LVEF, regardless of DM status
   • CKD +/- DM
   • *Exception: GLP1ra in vascular disease and obesity - use both?*

2. Minimal side effects
   • Other than vaginal candida infections (maybe UTI)

3. Easy to use
   • Single dose, no titration
   • Hypotension and renal dysfunction limited

4. $$
   • Canagliflozin to go generic 2025?
Case: 75F w/ T2DM, obesity, s/p MI 2014, LVEF 25%, AF, transfers care to you

Medications:
- ASA 81 mg
- Warfarin to INR 2-3
- Atorvastatin 80 mg (LDL 95)
- Lisinopril 10 mg
- Metoprolol succinate 50 mg
- Metformin 1000 mg bid
- Glipizide 5 mg daily


Other: Getting more frail, recent fall. Refusing vaccine.

Exam: BP 129/78, HR 80 in AF, BMI 36 Euvolemic

Labs: K 4.6, Cr 1.4
- HCT 31%, Ferr 220, Fe 15%
- Echo severe mitral regurgitation
- ECG AF, QRS 160 LBBB

https://hfsa.org/patient (image)
https://www.heart.org/en/health-topics/heart-failure
https://www.cardiosmart.org/topics/heart-failure
ARS: You consider adding an SGLT2i. What is involved in doing this?

A) Assess anticipated out-of-pocket costs for SGLT2i.
B) Start dapagliflozin 10 mg daily or start empagliflozin 10 mg daily.
C) Closer monitoring of fasting sugars after initiation.
D) Continue or stop glipizide depending on baseline HbA1c, future HbA1c, and any episodes hypoglycemia.
E) Warn patient of chance of vaginal yeast infection.
F) All of the above.
You consider adding an SGLT2i. What is involved in doing this?

Assess anticipated out-of-pocket costs for SGLT2i.  
Start dapagliflozin 10 mg daily or start empagliflozin 10 mg daily.  
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E) Warn patient of chance of vaginal yeast infection.
F) All of the above.
Putting it together: HF Guidelines!
Lots of “evidence”: large RCTs, only 20 years, only HFrEF

Piotr Ponikowski et al.
The Effects of Adding One GDMT to Another in HFrEF Appear to be Additive

Subtractive
1 + 1 = 0.5

Redundant
1 + 1 = 1.0

Partially Additive
1 + 1 = 1.5

Fully Additive
1 + 1 = 2.0

Synergistic
1 + 1 = 2.5

GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction.
“High-Value” Rx = “Quad Therapy”, “Four Pillars”

**Improved Health Outcomes**

<table>
<thead>
<tr>
<th>ARNi</th>
<th>Beta-Blocker</th>
<th>MRA</th>
<th>SGLT2i</th>
<th>Loop Diuretic</th>
</tr>
</thead>
</table>
| 30%-35% RRR in **death** and hospitalization
due to heart failure (HF) and/or worsening HF | Cumulative risk reduction in all-cause mortality if all four evidence-based medical therapies are used RRR 73%; ARR: 26%; NNT=3.9 over 24 months |

**Additional HF Clinical Trials**

- Hydral-ISDN (A-HeFT)
- Ivabradine? (SHIFT)
- Vericiguat? (VICTORIA)
- Devices (GUIDE-HF, COAPT, RAFT, SCD-HeFT)

• AHA/ACC Heart Failure Guidelines:
  ➢ Last full 2013.
  ➢ New full guideline due out 4/2022
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra ©* (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans
ESC 2021:
Central Figure for HFrEF
Except for $$
In-hospital starts

To reduce mortality - for all patients

- ACE-I/ARNI
- BB
- MRA
- SGLT2i

PIOISTER, IMPACT-HF, ATHENA-HF, EMPULSE
ESC 2021
AF ablation in HFrEF?

**AF-CHF: Amiodarone in HFrEF**

- **Composite Outcome**
  - Hazard ratio, 0.90 (95% CI, 0.77–1.06)
  - P=0.20
  - No. at Risk:
    - Rhythm control: 518, 432, 303, 169, 60
    - Rate control: 502, 412, 281, 162, 53

**CASTLE-AF: PVI in HFrEF**

- **Death or Hospitalization for Worsening Heart Failure**
  - Hazard ratio, 0.62 (95% CI, 0.43–0.87)
  - P=0.007 by Cox regression
  - P=0.006 by log-rank test
  - Repeat ablation 24%


ESC 2021
ESC 2021

Management of HFrEF

To reduce mortality - for all patients
- ACE-I/ARNI
- BB
- MRA
- SGLT2i

To reduce HF hospitalization/mortality - for selected patients

Volume overload
- Diuretics

- SR with LVEF ≥ 35%
  - CRT/PDI
- SR with LVEF 13–49% or non-LBBB ≥ 350 ms
  - CRT/PDI

To reduce HF hospitalization and improve QOL - for all patients

- Exercise rehabilitation
- Multi-professional disease management
- CR?
- PT/Strength?
Sequencing? “Expert” Consensus Decision Pathway (ECDP)

HFrEF Stage C Treatment

ARNI/ACEI/ARB (ARNI preferred*) AND evidence-based beta-blocker† with diuretic agent as needed

For patients with eGFR ≥ 30 mL/min/1.73 m² or creatinine ≤ 2.5 mg/dL in males or ≤ 2.0 mg/dL in females or K+ ≤ 5.0 mEq/L, NYHA class II-IV

Add

Aldosterone antagonist

For patients meeting eGFR criteria, NYHA class II-IV

Add

SGLT2i

For patients with persistent volume overload, NYHA class II-IV

Titrate

Diuretic agent

For persistently symptomatic Black patients despite ARNI/beta-blocker/aldosterone antagonist/SGLT2 inhibitor, NYHA class III-IV

Add

Hydralazine + isosorbide dinitrate

For patients with resting HR ≥ 70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III

Add

Ivabradine

"Best" option depends on the patient...

Guidelines for HfPEF?

- **SGLT2i:**
  - EMPEROR studies: benefits mostly preserved by LVEF.

- **ARNI (sacubitril/valsartan):**
  - PARAGON: The closer to LVEF 40%, more benefit
  - Better value in HFmrEF?

- **MRA:**
  - HFrEF: RALES, EPHESEUS, EMPHASIS → ~30% RRR
  - HfPEF: TOPCAT → minimal 7%

- **Treat comorbidities**
  - HTN, DM, AS, CAD, Obesity, etc
  - AF control? EAST-AFNET

---

**Figure 3.** Treatment effects of sacubitril/valsartan vs active comparator (either enalapril or valsartan) across a range of ejection fraction for the composite of total heart failure hospitalization and cardiovascular death. Estimated rate ratios and 95% confidence intervals obtained from negative binomial regression models with ejection fraction expressed via restricted cubic spline. RAS indicates renin-angiotensin-aldosterone-system inhibitor.
Early AF control? EAST-AFNET 4

- AF <12 months
- High risk
- Stable HF 29%


Hospitalization with worsening of heart failure
139/6620 (2.1) 169/6558 (2.6) 0.81 (0.65 to 1.02)‡

Figure 2. Aalen-Johansen Cumulative-Incidence Curves for the First Primary Outcome.
The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.
Case: 75F w/ T2DM, obesity, s/p MI 2014, LVEF 25%, AF, transfers care to you

Medications:
- ASA 81 mg
- Warfarin to INR 2-3
- Atorvastatin 80 mg (LDL 95)
- Lisinopril 10 mg
- Metoprolol succinate 50 mg
- Metformin 1000 mg bid
- Glipizide 5 mg daily


Other: Getting more frail, recent fall. Refusing vaccine.

Exam: BP 129/78, HR 80 in AF, BMI 36 Euvolemic

Labs: K 4.6, Cr 1.4
- HCT 31%, Ferr 220, Fe 15%
- Echo severe mitral regurgitation
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https://hfsa.org/patient (image)
https://www.heart.org/en/health-topics/heart-failure
https://www.cardiosmart.org/topics/heart-failure
ARS: What intervention is likely of value to this patient?

A) Start dapagliflozin 10 mg daily.
B) Double dose of metoprolol succinate.
C) Switch lisinopril to sacubitril/valsartan 24/26 mg bid.
D) Start spironolactone 25 mg daily.
E) All of the above (and more, but not all at once).
What intervention is likely of value to this patient?

A. Start dapagliflozin 10 mg daily.
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- Lisinopril 10 mg
- Metoprolol succinate 50 mg
- Metformin 1000 mg bid
- Glipizide 5 mg daily

SH: Lives alone, daughter in town.
Medicare A, B, D, supplement.

Other: Getting more frail, recent fall.
Refusing vaccine.

Exam: BP 129/78, HR 80 in AF
Euvolemic

Labs: K 4.6, Cr 1.4
HCT 31%, Ferr 220, Fe 15%
Echo severe mitral regurgitation
ECG AF, QRS 160 LBBB

**GUIDELINE-CONCORDANT CARE**

Medications:
- **Apixaban** 5 mg bid
- **Atorvastatin** 40-80 mg
- **Alirocumab** 75 mg SC q2w
- **Sacubitril/valsartan** 97/103 mg bid
- Metoprolol succinate **200 mg** daily
- **Spironolactone** 25 mg daily
- **Empagliflozin** 10 mg daily
- **Liraglutide** 1.2 mg SC qd

Other
- Mitraclip
- CRT-D
- **AF ablation**
- Cardiac rehab 36 sessions v. PT
- mRNA Covid, flu, and other age-appropriate **vaccinations**
- More…
3 Implementation

INERTIA
GDMT underuse in HFrEF: lack of initiation and intensification

The majority of eligible patients are not prescribed guideline-directed medical therapies (GDMT)

<table>
<thead>
<tr>
<th></th>
<th>Percent of Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB 1.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ARNI 12.8%</td>
<td>12.8%</td>
</tr>
<tr>
<td>ACEI/ARB/ARNI 26.2%</td>
<td>26.2%</td>
</tr>
<tr>
<td>Beta-Blocker 32.9%</td>
<td>32.9%</td>
</tr>
<tr>
<td>MRA 65.9%</td>
<td>65.9%</td>
</tr>
<tr>
<td>SGLT2i? 2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

When prescribed, the majority of doses are <50% of target

Greene et al. CHAMP registry. JACC 2018.
MRA underuse in HFrEF despite consistent data in 3x RCT

<table>
<thead>
<tr>
<th>s/p MI</th>
<th>NYHA I-II</th>
<th>NYHA IIIb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eplerenone</td>
<td>EMPHASIS-HF (2010)</td>
</tr>
<tr>
<td>Patients</td>
<td>n=6632</td>
<td>n=2737</td>
</tr>
<tr>
<td>Included</td>
<td>• 3-14 days post-MI</td>
<td>• Age ≥55 y</td>
</tr>
<tr>
<td></td>
<td>• LVEF ≤40% after the MI</td>
<td>• HF with NYHA class 2</td>
</tr>
<tr>
<td></td>
<td>• Plus either:</td>
<td>• LVEF ≤30% (or ≤35% + GFR &gt;130 msec)</td>
</tr>
<tr>
<td></td>
<td>o Clinical signs of HF, or</td>
<td>• Receiving an ACE inhibitor/ARB + beta-blocker</td>
</tr>
<tr>
<td></td>
<td>o Diabetes</td>
<td>• Plus either: CV hospitalization within 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>months, or BNP &gt;250 pg/mL</td>
</tr>
<tr>
<td>Excluded</td>
<td>• Serum creatinine &gt;220 umol/L</td>
<td>• Eligible for MRA based on EPHESUS or RALES</td>
</tr>
<tr>
<td></td>
<td>• Serum potassium &gt;5.0 mmol/L</td>
<td>• eGFR &lt;30 ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serum potassium &gt;5.0 mmol/L</td>
</tr>
</tbody>
</table>

### Death

<table>
<thead>
<tr>
<th></th>
<th>MRA (%)</th>
<th>Control (%)</th>
<th>RR/HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS</td>
<td>14.4</td>
<td>16.7</td>
<td>0.85 (0.75-0.96)</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>12.5</td>
<td>15.5</td>
<td>0.78 (0.64-0.95)</td>
</tr>
<tr>
<td>RALES</td>
<td>35</td>
<td>46</td>
<td>0.70 (0.60-0.82)</td>
</tr>
</tbody>
</table>

#### Intervention

- **Eplerenone** (initially 25 mg/d, then increased as tolerated to target dose of 50 mg/d)
  - EPHESUS: Mean dose 43 mg/d (i.e. most achieved target dose)
  - Spironolactone (25 mg/d x 8 weeks, then increased as tolerated to 50 mg/d; could decrease to 25 mg q2 days if hyperkalemia)

#### Control

- Placebo

#### Follow-up

- Mean 1.3 years
- Mean 1.8 years
- Mean 2 years
MRA underuse may reflect hyperkalemia concerns?

<table>
<thead>
<tr>
<th>Hyperkalemia</th>
<th>EPHESUS ≥6 mmol/L</th>
<th>EMPHASIS-HF</th>
<th>RALES serious only</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS ≥6 mmol/L</td>
<td>5.5</td>
<td>3.9</td>
<td>p=0.002</td>
<td></td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>8</td>
<td>3.7</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>RALES serious only</td>
<td>2</td>
<td>1</td>
<td>p=0.42</td>
<td></td>
</tr>
</tbody>
</table>
ARNI underuse in HFrEF likely includes cost concerns
OOP cost is tricky to get and convey

• Depends on:
  ➢ Health insurance product, of which there are thousands
  ➢ Pre-authorization
  ➢ Other drugs expenses that push patients into different copay categories during the year

A DECISION AID FOR
RENIN-ANGIOTENSIN INHIBITOR DRUG OPTIONS FOR
PATIENTS WITH HEART FAILURE

LET'S TALK COST

You may be wondering, "How do I find out how much an ARNI will cost ME?"
There are two options to find out:

**Option 1: Call your insurance company.**
On the back of your insurance card, call the member services number and ask the representative the following:
"My clinician is considering prescribing the ARNI sacubitril/valsartan for me. Would you please tell me how much it would cost on my plan for a month of this medicine?" (60 tablets of 49/51 mg a month)

**Option 2: Call your pharmacy.**
Your clinician can begin a plan to switch you to an ARNI and write a prescription. You'll be able to see the cost before you finalize the plan, and decide whether you'd like to move forward. If you feel the cost is too high, you may leave the prescription unfilled; however, it's important you then get in touch with your clinician and work together to find a plan that will work better for you.

Interventions to Improve GDMT

Provider decision support for prescribing

Activated Patient

Shared Decision Making

Patient education for adherence

Clinical Inertia

Disempowered
EPIC-HF trial

Patients “activated” prior to a clinic appointment will be more likely to engage their clinician around their medication plan, which will prompt greater HFrEF prescribing.

3-minute video (URL link) + 1-page checklist (PDF)
**Primary Endpoint: GDMT Intensification at 30 days**

19.3% increase in GDMT with EPIC-HF activation tool (p=0.001)

Figure 1. Patient priorities-aligned decision making for older adults with multiple chronic conditions.

- Are disease-specific evidence-based guidelines applicable?
  - Yes:
    - >10 y life expectancy
    - Few conditions
    - Fit and functional
    - Disease-based guidelines as consistent with patient preferences
  - Uncertain:
    - 2-10 y life expectancy
    - Increasing number/severity of conditions
    - Impaired function
    - Health Priorities-Aligned Care: Current Care Planning
  - No:
    - <1-2 y life expectancy
    - Advanced/end-stage disease (e.g., dementia, cancer, and heart failure)
    - Deescalate treatments
    - Palliative care
    - Symptom management

Figure 2. Decision making and care of older adults with multiple chronic conditions. The Multiple Chronic Conditions Action Steps facilitate decision making in the face of uncertainty of disease guideline-driven decision making for the large segment of older adults with increasing numbers of chronic conditions and functional limitations.
Case: 75F w/ T2DM, obesity, s/p MI 2014, LVEF 25%, AF, transfers care to you

Medications:
- ASA 81 mg
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https://hfsa.org/patient (image)
https://www.heart.org/en/health-topics/heart-failure
https://www.cardiosmart.org/topics/heart-failure
ARS: There are many options. What should you start with?

A) It depends on what therapy is likely to give the greatest absolute improvement in survival and quality of life.
B) It depends on anticipated side effects, and how concerned the patient is about those side effects.
C) It depends on the patient’s ability to do laboratory follow up.
D) It depends on expected patient out-of-pocket costs and her ability and willingness to pay those costs.
E) All of the above.
There are many options. What should you start with?

It depends on what therapy is likely to give the greatest absolute improvement in survival and quality of life.

A

It depends on anticipated side effects, and how concerned the patient is about those side effects.

B

It depends on the patient’s ability to do laboratory follow up.

C

It depends on expected patient out-of-pocket costs and her ability and willingness to pay those costs.

D

All of the above.

E
ARS: There are many options. What should you start with?

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**GUIDEINE-CONCORDANT CARE**

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- Apixaban 5 mg bid
- Atorvastatin 40 mg
- Alirocumab 75 mg SC q2w
- Sacubitril/valsartan 97/103 mg bid
- Metoprolol succinate 200 mg daily
- Spironolactone 25 mg daily
- Empagliflozin 10 mg daily
- Liraglutide 1.2 mg SC qd

Other
- Mitraclip
- CRT-D
- AF ablation
- Cardiac rehab 36 sessions v. PT
- mRNA Covid, flu, and other age-appropriate vaccinations
- More…

**HEALTH-PRIORITES ALIGNED CARE**

Medications:
- OOP Cost?
- Polypharmacy?
- Her significant side effects?
- Relative value?

Other
- Life expectancy?
- Complications of procedures?
- Values, goals, preferences
• HF is often *progressive* despite best medical and device therapy.

• The only medical specialty that truly owns “failure”.

## Criteria for advanced heart failure

All the following criteria must be present despite optimal medical treatment:

1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].

2. Severe cardiac dysfunction defined by at least one of the following:
   - LVEF $\leq$30%
   - Isolated RV failure (e.g., ARVC)
   - Non-operable severe valve abnormalities
   - Non-operable severe congenital abnormalities
   - Persistently high (or increasing) BNP or NT-proBNP values and severe LV diastolic dysfunction or structural abnormalities (according to the definitions of HFpEF).

3. Episodes of pulmonary or systemic congestion requiring high-dose i.v. diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing $\geq$1 unplanned visit or hospitalization in the last 12 months.

4. Severe impairment of exercise capacity with inability to exercise or low 6MWT distance ($<300$ m) or $pVO_2 <12$ mL/kg/min or $<50\%$ predicted value, estimated to be of cardiac origin.

6MWT = 6-minute walk test; ARVC = arrhythmogenic right ventricular cardiomyopathy; BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; i.v. = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; $pVO_2$ = peak oxygen consumption; RV = right ventricular. Modified from 376.

Warning Signs of Advanced Heart Failure ("events" or "milestones")

**I**
- IV inotropes

**N**
- NYHA IIIB/IV or persistently elevated NPs
- End-organ dysfunction

**E**
- Ejection fraction < 35%

**D**
- Defibrillator shocks

**H**
- Hospitalizations > 1
- Edema despite escalating diuretics
- Low blood pressure, high heart rate

**E**
- Prognostic medication – progressive intolerance or down-titration of GDMT

Outcomes for HF are poor, regardless of LVEF

- Average age of a patient hospitalized with HF in the US is **79 years old**.
- Average number of major **comorbidities** is ~5.
- Outcomes relatively similar across LVEF. 

Dunlay SM, et al. JACC-HF. Oct 2021
Heart Failure tends to be progressive

**AHA Scientific Statement**
Guidance for Timely and Appropriate Referral of Patients With Advanced Heart Failure
A Scientific Statement From the American Heart Association
Endorsed by the Heart Failure Society of America

Alanna A. Morris, MD, MSc, FAHA, Chair; Prateek Khazanie, MD, MPH, Vice Chair; Mark H. Drazner, MD, MSc, Vice Chair; Nancy M. Albert, PhD, Khaoljah Breshette, ND, MS, FAHA; Lauren B. Cooper, MD, MHS; Howard J. Eisen, MD;

- NYHA I-II symptoms
- Tolerating GDMT
- No hospitalizations
- No evidence of end-organ dysfunction

- NYHA III-IV symptoms
- Downtitration of or inability to tolerate GDMT
- Frequent hospitalizations
- Recurrent arrhythmias or ICD shocks
- Worsening renal function

- Multiorgan failure
- Severe malnutrition/cardiac cachexia unresponsive to supplementation
Referral for Advanced Therapies: ~40% “too sick” at initial contact

Fig. 3. Primary reason cited to not offer advanced heart failure therapies: summary of reported primary reasons not to offer AHF therapies by therapy. The most common reasons cited were patients’ being too ill to benefit from the therapy and prohibitive psychosocial reasons.
TAKE HOME!

- SGLT2i prescribing should be in your wheelhouse
TAKE HOME!

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• Patient OOP cost is challenging
• If patients are failing GDMT, get HELP! Cardiology and/or palliative care