Management of Heart Failure: Bridging the Gap Between Evidence and Clinical Practice

Gregg C. Fonarow, MD, FACC, FAHA, FHFSF

Eliot Corday Professor of Cardiovascular Medicine and Science
Director, Ahmanson-UCLA Cardiomyopathy Center
Co-director, UCLA Preventative Cardiology Program
Chief (Interim), UCLA Division of Cardiology

Disclosures: Consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Eli Lilly, Janssen, Medtronic, Merck, Novartis, and Pfizer
Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures globally. Two-thirds of patients with HF in the US have atherosclerotic coronary artery disease/ischemic cardiomyopathy. Despite treatment advances, a large number of eligible patients are not receiving one or more evidence-based, guideline-recommended HF therapies.

American Heart Association. 2023 Heart and Stroke Statistical Update. Dallas, Tex: American Heart Association; 2023
<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>Relative Risk Reduction in Mortality</th>
<th>Number Needed to Treat for Mortality</th>
<th>NNT for Mortality (standardized to 36 months)</th>
<th>Relative Risk Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17%</td>
<td>22 over 42 months</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>ARNI*</td>
<td>16%</td>
<td>36 over 27 months</td>
<td>27</td>
<td>21%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>28 over 12 months</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>30%</td>
<td>9 over 24 months</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>SGLT2 Inhibitor</td>
<td>17%</td>
<td>43 over 18 months</td>
<td>22</td>
<td>30%</td>
</tr>
<tr>
<td>Hydralazine/Nitrate**</td>
<td>43%</td>
<td>25 over 10 months</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>CRT</td>
<td>36%</td>
<td>12 over 24 months</td>
<td>8</td>
<td>52%</td>
</tr>
<tr>
<td>ICD</td>
<td>23%</td>
<td>14 over 60 months</td>
<td>23</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Incremental to ACEI/ARB  ** Self Identified African Americans
Mortality Among Patients Diagnosed with HF is High

Survival Rates for People With New Onset HF by Year of Diagnosis

Despite the availability of therapies with established efficacy in HFrEF, morbidity and mortality rates remain high.

Primary care data in the United Kingdom for 55,959 patients aged 45 years and older with a new diagnosis of HF and 278,679 age- and sex-matched controls.

Use and Dosing of GDMT for HFrEF in the US CHAMP-HF Registry 2016-2018

Most receiving ACEI/ARB and BB

ARNI use 13% in eligible patients
MRA use 33% in eligible patients

When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%).

Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA.

3,518 patients from 150 primary care and cardiology practices
Reasons for Underutilization of Evidence-Based Therapies

- Gaps in knowledge and awareness
- Lack of systems
- Therapeutic inertia
- RCTs study patient populations perceived as too narrow in scope
- Uncertainty regarding “effectiveness”
- Concerns about side effects
- Questions regarding: drug/device safety
- Bias (age, sex, race/ethnicity, socioeconomic)
- Concerns about access, costs, and value
Longitudinal Use/Dosing of GDMT for HFrEF: CHAMP HF Registry Therapeutic Inertia

Contextualizing Risk Among Patients with Heart Failure

What is the Effect of Adding One GDMT to Another in HFrEF?

• Subtractive $1 + 1 = 0.5$
• Redundant $1 + 1 = 1.0$
• Partially Additive $1 + 1 = 1.5$
• Fully Additive $1 + 1 = 2.0$
• Synergistic $1 + 1 = 2.5$
ACE Inhibitors

Mortality Benefit in HF with Reduced EF

CONSENSUS\(^1\)

- Placebo
- Enalapril

\(P<0.001\)

\(n = 253\)

Mortality: ↓34%

SOLVD\(^2\)

- Placebo
- Enalapril

\(P<0.0036\)

\(n = 2569\)

Mortality: ↓16%

SAVE\(^3\)

- Placebo
- Captopril

\(P=0.019\)

\(n = 2231\)

Mortality: ↓19%

CONSENSUS = Cooperative New Scandinavian Enalapril Survival Study

SOLVD = Study of Left Ventricular Dysfunction

SAVE = Survival and Ventricular Enlargement

Beta Blockers in HFrEF

**U.S. Carvedilol Study**
- Carvedilol (n=696)
- Placebo (n=398)
- Risk reduction=65%
- \( p < 0.001 \)

**MERIT-HF**
- Metoprolol CR/XL (n=1990)
- Placebo (n=2001)
- Risk reduction=34%
- \( p = 0.0062 \)

**CIBIS II**
- Bisoprolol (n=1327)
- Placebo (n=1320)
- Risk reduction=34%
- \( p < 0.0001 \)

**COPERNICUS**
- Carvedilol (n=1156)
- Placebo (n=1133)
- Risk reduction=35%
- \( p = 0.0014 \)

**ACEI 95%**

**ACEI/ARB 95%**

**ACEI 96%**

**ACEI/ARB 97%**

CIBIS II, Cardiac Insufficiency Bisoprolol Study II; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure.

Aldosterone Antagonists in HFrEF

**RALES**¹
(Severe HFrEF)
30% Risk reduction

**EMPHASIS-HF**³
(Mild HFrEF)
24% Risk reduction

**Placebo**  
**Spironolactone**  
**Eplerenone**

ACEI/ARB 94%  
BB 10%

ACEI/ARB 94%  
BB 87%

EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; RALES, Randomized Aldactone Evaluation Study; RR, risk ratio.

Sacubitril/Valsartan vs ACEI Outcomes in HFrEF
PARADIGM-HF - Significant Reduction in Primary Endpoint, CV Death and All-Cause Mortality

Primary Endpoint (CV death and HF hospitalization)

HR = 0.80 (0.73-0.87)
P = 0.0000004
Number needed to treat = 21

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sacubitril/Valsartan</td>
</tr>
<tr>
<td></td>
<td>4187</td>
</tr>
</tbody>
</table>

CV Death

HR = 0.80 (0.71-0.89)
P = 0.00008
Number needed to treat = 32

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sacubitril/Valsartan</td>
</tr>
<tr>
<td></td>
<td>4187</td>
</tr>
</tbody>
</table>

All-cause Mortality

HR = 0.84 (0.76-0.93)
P < 0.0001

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sacubitril/Valsartan</td>
</tr>
<tr>
<td></td>
<td>4187</td>
</tr>
</tbody>
</table>


BB 93%, MRA 56%
Meta-analysis of EMPEROR-Reduced and DAPA-HF Trials Highlight the Benefit of SGLT2is in HFrEF

### All-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Number with event/number of patients (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>249/1863 (13.4%)</td>
<td>0.92 (0.77–1.10)</td>
</tr>
<tr>
<td>DAPA-HF</td>
<td>279/2373 (11.6%)</td>
<td>0.83 (0.71–0.97)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.87 (0.77–0.98)</td>
</tr>
<tr>
<td>Test for overall treatment effect</td>
<td>P = 0.016</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity of effect</td>
<td>P = 0.39</td>
<td></td>
</tr>
</tbody>
</table>

### CV death

<table>
<thead>
<tr>
<th></th>
<th>Number with event/number of patients (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>187/1863 (10.0%)</td>
<td>0.92 (0.75–1.12)</td>
</tr>
<tr>
<td>DAPA-HF</td>
<td>227/2373 (9.6%)</td>
<td>0.82 (0.69–0.98)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.86 (0.76–0.98)</td>
</tr>
<tr>
<td>Test for overall treatment effect</td>
<td>P = 0.027</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity of effect</td>
<td>P = 0.40</td>
<td></td>
</tr>
</tbody>
</table>

### First hospitalization for HF or CV death

<table>
<thead>
<tr>
<th></th>
<th>Number with event/number of patients (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPEROR-Reduced</td>
<td>361/1863 (19.4%)</td>
<td>0.75 (0.65–0.86)</td>
</tr>
<tr>
<td>DAPA-HF</td>
<td>396/2373 (16.3%)</td>
<td>0.74 (0.65–0.85)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.74 (0.68–0.82)</td>
</tr>
<tr>
<td>Test for overall treatment effect</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity of effect</td>
<td>P = 0.89</td>
<td></td>
</tr>
</tbody>
</table>

**Similar benefit with and without type 2 diabetes**

---

CI, confidence interval; CV, cardiovascular; DAPA, dapagliflozin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

### Cumulative Impact of Evidence-Based Heart Failure with Reduced EF Medical Therapies

<table>
<thead>
<tr>
<th>Relative-risk</th>
<th>2 yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- -</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>↓ 23%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>↓ 35%</td>
</tr>
<tr>
<td>Aldosterone Ant</td>
<td>↓ 30%</td>
</tr>
<tr>
<td>ARNI (replacing ACEI/ARB)</td>
<td>↓ 16%</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>↓ 17%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction if all evidence-based medical therapies are used: Relative risk reduction 74.0%, Absolute risk reduction: 25.9%, NNT = 3.9

Sequencing of GDMT: Serial Strategy

- Dx: 2-4 weeks, 2-4 more weeks, 2-4 more weeks
- ACEI starting dose: titration, titration, titration
  - 2-4 more weeks, 2-4 more weeks, 2-4 more weeks
- BB starting dose: titration, titration, titration
  - 2-4 more weeks, 2-4 more weeks, 2-4 more weeks
- MRA starting dose: titration, titration
  - 2-4 more weeks, 2-4 more weeks, 2-4 more weeks
- ANRI starting dose: titration, titration
  - 2-4 more weeks, 2-4 more weeks, 2-4 more weeks
- SGLT2i starting dose

28-56 weeks till GDMT fully implemented
Timing of GDMT Benefits in HFrEF

Significant Clinically Relevant Benefits within 30 Days of Initiation for Each Rx

- >75% Relative Risk Reduction in CV death/HF hospitalization with all 4

- BB
- MRA
- ANRI
- SGLT2i
# GDMT: Simultaneous/Rapid Sequence Strategy

**Quadruple Foundational Guideline Directed Medical Therapy from Day 1**

**Hospitalized or outpatient**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7-14</th>
<th>Day 14-28</th>
<th>Day 21-42</th>
<th>Beyond</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNI</td>
<td></td>
<td>(Titrate, as tolerated)</td>
<td>Titrate, as tolerated</td>
<td>• Maintenance / further optimization of foundational therapies</td>
</tr>
<tr>
<td>BB</td>
<td>Titrate, as tolerated</td>
<td>Titrate, as tolerated</td>
<td>Titrate, as tolerated</td>
<td>• Consideration of EP device therapies/Mitraclip</td>
</tr>
<tr>
<td>MRA</td>
<td></td>
<td>Titrate, as tolerated</td>
<td></td>
<td>• Consideration of add-on therapies or advanced therapies, if refractory</td>
</tr>
<tr>
<td>SGLT2i</td>
<td></td>
<td></td>
<td></td>
<td>• Manage comorbidities</td>
</tr>
</tbody>
</table>

**Low starting doses**
- Prioritize beta-blocker titration

**Benefits of each Rx demonstrated within 30 days of initiation**
- Cumulative benefits within 30 days (>75% relative risk reduction)

**Focus on complete set of GDMT being implemented**

Modeling of Ordering of GDMT and Accelerated Up-Titration Schedule
Benefits of Simultaneous or Rapid Initiation of ARNi, BB, MRA, and SGLT2i for HFrEF Are Multifaceted

Benefits of Initiating ARNi+BB+MRA+SGLT2i as First-line Treatment for HFrEF Versus Drawn-out Historical Sequencing

- Rapid improvement in health status (within 1 to 8 weeks)*
- Rapid reduction in HF hospitalizations (within 2 to 4 weeks)*
- Rapid reduction in mortality (within 2 to 4 weeks)*
- Rapid improvement in LVEF (within 12 weeks)²
- Rapid reduction in HF rehospitalizations (within 2 to 4 weeks)³
- Improved use, adherence, persistence, overcoming inertia⁴,*

ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

GDMT: SBP Lowering and Symptomatic Hypotension

GDMT Four Pillars Effects on SBP

**ARNI (PIONEER-HF)**

![Graph showing the effect of ARNI on SBP](image1)

**BB (COPERNICUS)**

![Graph showing the effect of BB on SBP](image2)

**MRA (RALES and EMPHASIS-HF)**

![Graph showing the effect of MRA on SBP](image3)

**SGLT2i (DAPA-HF and EMPULSE)**

![Graph showing the effect of SGLT2i on SBP](image4)

**EMPULSE: Adverse Events of Special Interest**

<table>
<thead>
<tr>
<th>Adverse event category</th>
<th>Empagliflozin (n=336)</th>
<th>Placebo (n=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal failure</td>
<td>20 (6.0%)</td>
<td>22 (6.6%)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>105 (31.6%)</td>
<td>108 (32.3%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>14 (4.2%)</td>
<td>10 (3.0%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>13 (3.9%)</td>
<td>12 (3.6%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>27 (8.1%)</td>
<td>27 (8.1%)</td>
</tr>
</tbody>
</table>

*No cases of ketoacidosis were reported*
HF Patients in Clinical Practice: Safety and Tolerability in Older Patients

GDMT Four Pillars in Older Patients with HFrEF: Benefits >>> Risks

**In Randomized Clinical Trials:**

Serious adverse events occur at similar or greater frequency with placebo compared with study medication added to background medications.

**In RCTs and Clinical Practice:**

Use of GDMT in HFrEF patients age 75 years and above associated with substantially reduced hospitalization and mortality.
In-Hospital Initiation of GDMT vs Post-Discharge Initiation at Clinician Discretion

Go Slow = Rarely Initiate

- More likely to be treated
- More likely to tolerate
- More likely to fill Rx
- More likely to adhere
- More likely to persist
- More likely to feel better
- More likely to be home
- More likely to survive
**HF therapy:** combining ACEi/ARB/ARNi & BB & MRA

**Safety** = clinical exam & biology (NT-proBNP, K, Creat, hemoglobin)

**High intensity care**
- Introduction of Half optimal doses of HF therapy

**Usual care**
- Randomise 1:1; n = 1800

**Hospital discharge**
- Week 1 Safety
- Half optimal doses of HF therapy

**Follow-up and therapy adjustments per physicians usual practice**

**Primary endpoint**
- 180-day HF readmission or all-cause mortality
- 90-day follow-up

For patients randomly assigned to the high-intensity care group, Rx followed an algorithm combining optimization of oral HF therapies and frequent visits, including NT-proBNP measures, to assess congestion.

**Study design**
- Week 2 Safety
- Up-titration to Full optimal doses of HF therapy

**Study terminated 23d Sept 2022 by DSMB (n=1069 pt)**
- larger than expected difference in primary endpoint
- unethical to keep patients in usual care

**Main inclusion criteria**
- AHF pt ready to be discharged
- No or sub-optimal dose of HF therapies
- Pre-DC NT-proBNP >1500 pg/ml
Oral HF therapies prescribed in high intensity and usual care

Full optimal dose of HF therapy

ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BB, beta blockers; MRA, mineralocorticoid receptor antagonists; Pre-Rand, pre-randomization
### Vital signs and symptoms of HF

#### Improvement in hemodynamics, Day 90

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted Treatment Effect (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>-5.8 (-7.3, -4.3)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>-5.4 (-7.2, -3.5)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>0.15 (0.09, 0.21)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>-0.35 (-2.22, 1.52)*</td>
<td>0.71</td>
</tr>
</tbody>
</table>

#### Improvement in the parameters of congestion at Day 90

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted Treatment Effect (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>-1.36 (-1.91, 0.80)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Respiratory Rate, breaths/min</td>
<td>-0.4 (-0.7, -0.1)*</td>
<td>0.0028</td>
</tr>
<tr>
<td>Peripheral edema, grade</td>
<td>1.30 (1.17, 1.44)†</td>
<td>0.0002</td>
</tr>
<tr>
<td>Jugular venous pressure, cm</td>
<td>1.13 (1.05, 1.21)†</td>
<td>0.015</td>
</tr>
<tr>
<td>NYHA, class</td>
<td>1.36 (1.22, 1.53)†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL*</td>
<td>0.77 (0.67, 0.89)‡</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

* Least squares mean difference (95% CI) based on an ANCOVA model with fixed terms for treatment, LVEF (<=40>/40), geographical region, and baseline value
† Mann-Whitney odds stratified by LVEF (<=40>/40), geographical region, and baseline value; p-value from van Elteren's test. A Mann-Whitney odds value of >1.0 favors high-intensity care.
‡ Treatment effect represents the ratio of the adjusted geometric mean ratios in the two treatment groups adjusted for the specific covariates. Adjusted geometric mean ratio within each treatment group is the ratio of the post-baseline value over the baseline value from an ANCOVA model with fixed terms for treatment, LVEF <40>/40, region and baseline log-transformed NT-proBNP value.

CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.
Primary endpoint:
180-Day Readmission for HF or All-Cause Death

Secondary endpoints:
Change from Baseline to Day 90 in EQ-5D VAS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>High Intensity</th>
<th>Usual Care</th>
<th>Treatment effect</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D VAS</td>
<td>10.7 (0.9)</td>
<td>7.2 (0.9)</td>
<td>3.5 (1.7 to 5.2)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Risk Ratio 0.66 [95% CI 0.50–0.86]
Tips for Optimal Titration of GDMT

- Very close attention to volume status and diuretic dosing
- Check orthostatic vital signs during visits
- Stagger dosing of ARNI (ACEI/ARB) and beta blockers
- Recognize rises in creatinine and decreases of eGFR are expected and usually represents intra-renal hemodynamic shifts rather than AKI
- Attempt to distinguish symptoms that represent HF and comorbidities vs actual medication side effects
- Emphasis on the benefits of medication adherence, address cost barriers
- Each additional therapy improves heart function/prognosis, not an indicator of patient getting “worse”
Strategies to Help Facilitate GDMT Initiation

1. Start all 4 classes of medication at diagnosis
2. In-hospital initiation for hospitalized patients
3. Performance improvement systems (GWTG-HF, IMPROVE-HF)
4. Multidisciplinary heart failure disease management programs
5. Navigators or pharmacists to guide GDMT

Performance Improvement Systems to Facilitate GDMT Initiation

GWTG-HF: Hospital Setting

642 Participating Hospitals and 883,000 HF patient hospitalizations

IMPROVE-HF: Outpatient Setting

167 practices, 34,810 heart failure patients enrolled
Electronic Health Record Nudges for GDMT Initiation: PROMPT-HF

Central Illustration: Electronic Health Record-Based Alerting Led to Significantly Higher Rates of Guideline-Directed Medical Therapy

- Vitals
- Labs
- LVEF
- Tailored GDMT

Provider Sees Alert
N = 685

Patient seen in outpatient PCP or Cardiology Clinic and meets following criteria:
- Age > 18 years
- LVEF ≤ 40%
- Not on Quadruple Therapy

Provider Sees No Alert
(usual care arm)
N = 625

Proportion of Patients With Increase in GDMT After 30 Days

*P = 0.03 Primary Endpoint

Compared to ACEI/ARB + BB:
1. Switch to ARNI
2. Start MRA
3. Start SGLT2i

**Survival free from All Cause Mortality**

Compared to ACEI/ARB+BB:
- Comprehensive Rx including ARNI+BB+MRA+SGLT2i
  - HR 0.38 CV Death/HF Hospitalization
  - HR 0.50 CV Death
  - HR 0.32 HF Hospitalization
  - HR 0.53 Mortality

Extend Your HFrEF Patient’s Life by 6.3 Years
**Cumulative Impact of Evidence-Based HFrEF Medical Therapies on All Cause Mortality**

<table>
<thead>
<tr>
<th>Medical Therapy</th>
<th>Relative Risk to None</th>
<th>2 Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- -</td>
<td>35.0%</td>
</tr>
<tr>
<td>ARNI (vs imputed placebo)</td>
<td>↓ 28%</td>
<td>25.2%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>↓ 35%</td>
<td>16.4%</td>
</tr>
<tr>
<td>Aldosterone Ant</td>
<td>↓ 30%</td>
<td>11.5%</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>↓ 17%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction in mortality if all evidence-based medical therapies are used:
Relative risk reduction 72.9%, Absolute risk reduction: 25.5%, NNT = 4

Value Statements for GDMT for HFrEF in AHA/ACC/HFSA HF Guidelines

**Take Home Point:** An important aspect of HF care, Class 1 recommended medical therapies for HFrEF have very high value (low cost).

### In patients:

- **With chronic symptomatic HFrEF, tx with an ARNi instead of an ACEi provides high economic value.**
- **With HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value.**
  
  **Value Statement:**
  
  High Value (A)

- **With HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value.**

  **Value Statement:**
  
  High Value (A)

- **With symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.**

  **Value Statement:**
  
  Intermediate Value (A)

---

**Abbreviations:**
- ACEi indicates angiotensin-converting enzyme inhibitor
- ARB, angiotensin receptor blocker
- ARNi, angiotensin receptor-neprilysin inhibitor
- HFrEF, heart failure with reduced ejection fraction
- MRA, mineralocorticoid receptor antagonist
- SGLT2i, non-randomized; sodium-glucose co-transporter 2 inhibitor
- tx, treatment

Potential Impact of Optimal Implementation of Evidence-Based HFrEF Therapies on Mortality

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>HF Patient Population Eligible for Treatment, n*</th>
<th>Current HF Population Eligible and Untreated, n (%)</th>
<th>Potential Lives Saved per Year</th>
<th>Potential Lives Saved per Year (Sensitivity Range*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNI (replacing ACEI/ARB)</td>
<td>2,287,296</td>
<td>2,287,296 (100)</td>
<td>28,484</td>
<td>(18,230-41,017)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2,512,560</td>
<td>361,809 (14.4)</td>
<td>12,922</td>
<td>(6616-22,329)</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>603,014</td>
<td>385,326 (63.9)</td>
<td>21,407</td>
<td>(10,960-36,991)</td>
</tr>
<tr>
<td>SGLT2 Inhibitor</td>
<td>2,132,800</td>
<td>2,132,800 (100)</td>
<td>34,125</td>
<td>(21,840-49,140)</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>-</td>
<td>96,938</td>
<td>(57,646-149,477)</td>
</tr>
</tbody>
</table>

The benefits of HFrEF medications are additive/incremental and provide similar benefit to those with ischemic and non-ischemic etiologies.

No substantial overlap has been demonstrated for the 4 key evidence-based therapies for HFrEF: ARNI, beta blockers, MRA, and SGLT2i.

The optimal approach is to utilize each medication demonstrated to reduce all-cause mortality in combination, so long as not contraindicated or not tolerated, and start all without delay.

A serial or selective approach leads to delays and HF hospitalizations / deaths which could have been prevented with earlier use of GDMT.

ARNI+BB+MRA+ SGLT2i each provide high economic and clinical value.