Heart Failure in 2021

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Agenda

• Stages of HF
• HFrEF (systolic HF)
  • Diagnostic update
  • Management update
  • Advanced Therapies
• HFpEF (diastolic HF)
  • Diagnostic update
  • Management update
  • Coming attractions …
At Risk for Heart Failure

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Stage D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural Heart Disease</strong></td>
<td><strong>Development of Symptoms of HF</strong></td>
<td><strong>Refractory Symptoms of HF at rest</strong></td>
<td><strong>Refractory HF requiring specialized interventions</strong></td>
</tr>
<tr>
<td>At high risk for HF, but without structural heart disease or symptoms or HF</td>
<td>Structural heart disease, but without signs or symptoms of HF</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
<td></td>
</tr>
<tr>
<td>e.g. Patients with: • Hypertension • Atherosclerotic disease • Diabetes • Obesity • Metabolic syndrome OR • Using cardiotoxins • With FHx CM</td>
<td>e.g. Patients with: • Previous MI • LV remodeling • Including LVH and low EF • Asymptomatic valvular disease</td>
<td>e.g. Patients with: • Known structural heart disease And • Shortness of breath and fatigue, reduced exercise tolerance</td>
<td>e.g. Patients who have marked symptoms at rest despite maximal medical therapy (e.g. those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)</td>
</tr>
</tbody>
</table>

**Therapy Goals**

- • Treat hypertension
- • Encourage smoking cessation
- • Treat lipid disorder
- • Encourage regular exercise
- • Discourage alcohol intake, illicit drug use
- • Control metabolic syndrome
- • ACEI or ARB in appropriate patients for vascular disease or diabetes

**DRUGS**

- • ACEI or ARB in appropriate patients
- • Beta-blockers in appropriate patients

**Therapy Goals**

- • All measures under stage A

**Drugs for Routine Use**

- • Diuretics for fluid retention
- • ACEI, Beta Blockers

**Drugs in Selected Patients**

- • Aldosterone antagonists, ARBs, Digitalis, Hydralazine/nitrates

**Devices in Selected Patients**

- • Biventricular pacing
- • Implantable defibrillators

**Therapy Goals**

- • All measures under stage A and B
- • Dietary salt restriction
- • Extraordinary measures
  - • Heart transplant
  - • Chronic inotropes
  - • Permanent mechanical support
  - • Experimental surgery or drugs

**Drugs for Routine Use**

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- • Appropriate measures under stages A, B and C
- • Decision re: Appropriate level of care
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HFrEF

• Definition
  • Systolic heart failure
  • Ejection fraction ≤40% on echocardiogram
  • 4-chamber view
Causes of a Low EF

- Ischemic
- Nonischemic
  - Idiopathic
  - Infiltrative
  - Viral
  - Valvular
  - Tachymediated
  - Genetic
  - Exposures/Toxins
  - Deficiencies
  - Autoimmune disease
  - Iron storage disease
  - Stress/Takotsubo’s
  - Etc. etc. etc.
Evaluating for an Ischemic Etiology

• Modalities
  • Left heart catheterization
  • Cardiac MRI
  • Stress Echocardiogram
  • Nuclear Stress Test
Left Heart Catheterization

• Gold standard
• Invasive
• Radial access now the norm
• Can add RHC
  • Filling pressures (volume)
  • Cardiac output/index
Left Heart Catheterization
Key Take Away

• Often coronary disease co-occurs with other non-ischemic etiologies
  • Think: Prior myocarditis (burned out) with CAD

• In order for CAD to be the primary cause of your LOW EF
  • MultivesSEL
  • LM/LAD (Often proximal )
  • Otherwise involve a LARGE coronary territory (and almost always the anterior wall of heart)
  • In other word, the mRCA lesion – that is NOT the cause of the low EF
Cardiac MRI

• Becoming obligatory part of non-ischemic work up
• Looking for late gadolinium enhancement – pattern determines diagnosis
• Great for diagnosing infiltrative disease (amyloid, sarcoid, iron, etc.)
• In patients at low risk for ischemia, you can kill two birds with one stone if you do a stress cardiac MRI (not available everywhere)
• People have to be able to tolerate the test
• Devices must be MRI compatible AND always get one before you put a device in – artifact is real!
• Helps (a lot) if they’re in NSR and have a HR <70bpm
Cardiac MRI
Stress Echo

• Two ways to do any “stress test”
  • Actual exercise
  • Inotrope/chronotrope to “simulate exercise”
Stress Echo

• Looking for wall motion abnormalities (WMA)
• Which means you need a pretty significant/proximal stenosis to cause an observable WMA
• Makes it a good test for cardiomyopathy work up
• But, in full disclosure, I rarely use this modality….  
• No intervention capability → almost always leads to cath
• People with low EF’s often can’t exercise enough to reach 80% MPHR
• People with low EF’s can have arrhythmias when we “simulate” exercise with dobutamine
Nuclear Stress Test

- Again, you can do this with real exercise or more commonly, something that “simulates” exercise (vasodilator in this case)
- Use a radiotracer to create a “heat map” of perfusion
- Rest/stress images (like echo)
- Can distinguish ischemia vs. infarction
- Worry A LOT about balanced ischemia in this population
Evaluating for an Ischemic Etiology

- Modalities
  - Left heart catheterization – good
  - Cardiac MRI – good
  - Stress Echocardiogram - fair
  - Nuclear Stress Test - bad

Low EF

Ischemic
  - Revascularize
  - No Revasc.

Non-Ischemic
Revascularization?

- STICH Trial, 2011
  - 1212 patients with iCMP and EF <35%
  - CABG + GDMT vs. GDMT

**Table 2. Study Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Medical Therapy (N=602)</th>
<th>CABG (N=610)</th>
<th>Hazard Ratio with CABG (95% CI)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: rate of death from any cause</td>
<td>244 (41)</td>
<td>218 (36)</td>
<td>0.86 (0.72–1.04)</td>
<td>0.12</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause within 30 days after randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic-regression model</td>
<td>7 (1)</td>
<td>22 (4)</td>
<td>3.19 (1.35–7.52)‡</td>
<td>0.008</td>
</tr>
<tr>
<td>Cox proportional-hazards model</td>
<td>7 (1)</td>
<td>22 (4)</td>
<td>3.12 (1.33–7.31)</td>
<td>0.006</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>201 (33)</td>
<td>168 (28)</td>
<td>0.81 (0.66–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Death from any cause or hospitalization for heart failure</td>
<td>324 (54)</td>
<td>290 (48)</td>
<td>0.84 (0.71–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from any cause or hospitalization for cardiovascular causes</td>
<td>411 (68)</td>
<td>351 (58)</td>
<td>0.74 (0.64–0.85) &lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause or hospitalization for any cause</td>
<td>442 (73)</td>
<td>399 (65)</td>
<td>0.81 (0.71–0.93)</td>
<td>0.003</td>
</tr>
<tr>
<td>Death from any cause or revascularization with the use of PCI or CABG</td>
<td>333 (55)</td>
<td>237 (39)</td>
<td>0.60 (0.51–0.71)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Viability Testing?

- STITCH, 2019
  - 601 patients with iCMP EF <35%
  - Randomized to viability testing (PET/echo) and then randomized to CABG+medical therapy vs. Medical therapy alone

![Interaction between Treatment Assignment and Myocardial Viability Status](image)

Options for Viability Testing

- PET scan
- Cardiac MRI
- Dobutamine echocardiogram

Goal of testing:
- Distinguish ischemia (viable) from infarction (not viable)
- Revascularizing ischemia is probably a good idea
- Revascularizing infarction is a lot of risk and little (if any) benefit
Nonischemic Cardiomyopathy

- Low EF
  - Ischemic
    - Viability Testing
      - Revascularize
  - Non-Ischemic
    - Really common
    - Kinda common
    - Not so common
    - No Revasc.

Depends on the patient … look for other “clues”
Really Common niCMP

• Familial, genetic – take a good family history, including for SCD
  • Genetic testing
• Viral – “burned out” myocarditis
  • MRI
• Valvular – often primary valve (MS, MR, AS, AI) disease that goes untreated for a LONG time (not secondary valve disease)
  • TTE, MRI
• Tachymediated/LBBB – Afib is the enemy
  • EKG, Zio, Loop
• Stress Cardiomyopathy “Takotsubo’s”
  • TTE/MRI
Less Common niCMP

- Infiltrative disease (“burned out”)
  - Hypertrophic cardiomyopathy (HCM vs. HOCM)
    - TTE, MRI, genetic testing
  - Sarcoidosis
    - Concurrent lung disease, blocks/tachys, LAD, PET scan, MRI
  - Amyloidosis (AL vs. TTR)
    - TTE (strain!) or MRI
- LV Noncompaction (“burned out”)
  - MRI
- ARVC
  - Concurrent arrhythmias (VT), RV>LV disease
- Chemotherapy/Toxic Exposure
  - History, TTE with strain
- Hypothyroidism (profound) other endocrine “wonkiness”
Pretty Uncommon niCMP

- Selenium/carnitine deficiency
  - Levels, seen in this country in people with ostomies/short gut
- Autoimmune disease
  - ESR/CRP, h/o autoimmune disease OR the treatment (hydroxychloroquine)
- Iron storage disease
  - MRI, genetic (heterozygous vs. homozygous)
- Muscular dystrophies/carriers
  - Family history, genetics
- Fabry’s Disease
  - Enzyme testing, genetics
- Other infectious disease – HIV, Hepatitis
  - VERY rare!
The need for cardiac biopsy in a stable outpatient undergoing a work up for cardiomyopathy is extremely rare.

Cardiac MRI is frequently an safer/acceptable alternative

- Sarcoid (patchy)
- Amyloid (biopsy something else if you need to)
- Myocarditis (only in the acute setting)

Once you rule our ischemia – look carefully at your patient, their “internal medicine” history will often by the key to their diagnosis.
Cardiomyopathy Diagnostic Work Up

Low EF

Ischemic
- Viability Testing
  - Revascularize
  - No Revasc.

Non-Ischemic
- Cardiac MRI, Genetics, Labs, etc.
- Diagnosed Cause vs. Idiopathic
Cardiomyopathy Treatment

• Unique to Cause
• Guideline Directed Medical Therapy

• Recovery or not?
• Devices and if so, what kind…
## Unique to Cause

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia (with viability)</td>
<td>Revascularization</td>
</tr>
<tr>
<td>Valvular</td>
<td>Valve intervention (if possible)</td>
</tr>
<tr>
<td>Tachymediated</td>
<td>Sinus rhythm (often by any means necessary)</td>
</tr>
<tr>
<td>LBBB</td>
<td>CRT</td>
</tr>
<tr>
<td>HOCM</td>
<td>Negative inotropes, myectomy, ASA</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Immunosuppression (MTX, steroids, rituximab)</td>
</tr>
<tr>
<td>Amyloid</td>
<td>AL: chemo; TTR: Tafamadis</td>
</tr>
<tr>
<td>Selenium/Carnitine deficiency</td>
<td>Replacement</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>Treat underlying inflammation</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Phlebotomy, chelation</td>
</tr>
</tbody>
</table>
Guideline Directed Medical Therapy

- Beta-blockers
  - Metoprolol succinate
  - Carvedilol
  - Bisoprolol

- RASi
  - ACEi
  - ARB
  - ARNI

- MRA
  - Spiro
  - Eplerenone

- SGLT2i
  - Dapagliflozin
  - Empagliflozin
Mechanism of Action

Beta Blockers

- ↓Contractility
- ↓CO
- ↓Arterial blood volume
  - ↑Renin release
  - ↑Angiotensin II
  - ↑Aldosterone secretion
  - ↑Tubular reabsorption of Na and H₂O
- ↑Venous pressure
- ↑Sympathetic nervous outflow
- ↓GFR
- ↓Urinary output Na and H₂O
- ↑Total body Na and H₂O
  - → Oedema
Beta-Blockers

• CIBIS-II, *Lancet* 1999 (Bisoprolol) - when added to standard therapy, bisoprolol resulted in reduced all-cause mortality and morbidity
  • Most B1 selective, best in reactive airway disease or bad COPD
• MERIT-HF, *Lancet* 1999 (Metoprolol) - when added to standard therapy, long-acting metoprolol resulted in reduced all-cause mortality and morbidity
  • Less BP lowering than carvedilol, more BP room for other GDMT or higher doses for more arrhythmia suppression
• COPERNICUS, *Circulation* 2002 (Carvedilol) - in symptomatic HF patients, the addition of carvedilol to conventional therapy reduces mortality and morbidity
  • More BP lowering, best for people with higher BP’s
  • Some data (based on COMET published in Lancet, 2003) that it’s better than metoprolol
# Beta Blocker Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25mg QD</td>
<td>10mg QD</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125mg BID</td>
<td>25mg BID</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>12.5mg QD</td>
<td>200mg QD*</td>
</tr>
</tbody>
</table>
Key Take Away

• BB are negative inotropes – do not, do NOT, DO NOT use them in decompensated HF

• Fix your volume first! Giving a BB to someone with too much volume on board is flirting with danger

• In very marginal patients, this is the last one I add and the first one I take away

• People do NOT like taking beta-blockers

• Young men REALLY do not like taking beta-blockers
Mechanism of Action
RASi (ACEi)

• CONSENSUS, *NEJM 1987* - In patients with severe CHF, enalapril improves mortality and is well tolerated.

• SOLVD, *NEJM 1991* - Enalapril reduces mortality and HF hospitalizations when added to conventional therapy in patients with HFrEF.

The results from both CONSENSUS and SOLVD resulted in ACE-inhibitors quickly becoming standard of care in HFrEF patients.
RASi (ARB)

• Val-HeFT, *NEJM 2001* - valsartan in addition to standard therapy was not shown to improve survival but did reduce the incidence of a composite endpoint of morbidity and mortality; combination with an ACE-inhibitor plus beta blocker was associated with significantly worse outcomes.

• CHARM, *Lancet 2003* - candesartan in patients intolerant to ACE-inhibitors was well tolerated and reduced cardiovascular mortality and hospitalization for heart failure.
RASi (ARNi)

- PARADIGM-HF, NEJM 2014 - treatment with sacubitril/valsartan was shown to reduce CV mortality or heart failure hospitalizations when compared to enalapril

Sacubitril/Valsartan (ARNi)

- 24/26mg BID
- 49/51mg BID
- 97/103mg BID

- Valsartan is TWICE as bioavailable when combined with sacubitril
- In other words, if you can tolerate valsartan 40mg BID, you can tolerated sacubitril/valsartan 24/26mg BID
- The naturesis is real
- The hypotension is real
- DECREASE the diuretics first!
Sacubitril/Valsartan

Sacubitril

Nepriyisin

Inactive fragments

Natriuretic Peptides
Adrenomedullin
Substance P
Bradykinin
Angiotensin II
Others

Vasoconstriction, higher blood pressure, increased sympathetic tone, increased fibrosis, ventricular hypertrophy

Vasodilation, natriuresis, diuresis, lower blood pressure, decreased sympathetic tone, decreases RAAS

Valsartan

RAAS
## RASi Dosing

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<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Captopril</td>
<td>6.25mg TID</td>
<td>50mg TID</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5mg BID</td>
<td>20mg BID</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5mg QD</td>
<td>40mg QD</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25mg QD</td>
<td>10mg QD</td>
</tr>
<tr>
<td>Candesartan</td>
<td>4mg QD</td>
<td>32mg QD</td>
</tr>
<tr>
<td>Losartan</td>
<td>25mg QD (12.5mg QD)</td>
<td>100mg QD</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40mg BID (20mg BID)</td>
<td>160mg BID</td>
</tr>
<tr>
<td>Sacubitril/Valsartan</td>
<td>24/26mg BID*</td>
<td>97/103mg BID</td>
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Key Take Away

- ACEi/ARB are great
- ARNI are better
- ARNI do lower BP more
- When converting from ACEi, need 48 hours “washout” (not for ARB)
- If hypotensive with ARNi, decrease diuretics first
Mineralocorticoid Receptor Antagonist (MRA)

• RALES, NEJM 1999 - In patients with HFrEF, spironolactone led to a reduction in all-cause mortality

• EPHESUS, NEJM 2003 – The addition of eplerenone to optimal medical therapy reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure
Mechanism of Action

- ↓ Contractility → ↓ CO → ↓ Arterial blood volume → ↑ Renin release → ↑ Angiotensin II → ↑ Aldosterone secretion → ↑ Tubular reabsorption of Na and H₂O → ↓ GFR → ↓ Urinary output Na and H₂O → ↓ Total body Na and H₂O → ↑ Sympathetic nervous outflow → ↑ Venous pressure → ↑ Renal vasoconstriction → Maintains blood pressure → ↓ Renin release → ↑ Angiotensin II → ↑ Aldosterone secretion → ↑ Tubular reabsorption of Na and H₂O → ↓ GFR → ↓ Urinary output Na and H₂O → ↓ Total body Na and H₂O → Oedema
# MRA Dosing

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<th>Target</th>
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</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>25mg QD (12.5mg QD)</td>
<td>50mg QD</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25mg QD</td>
<td>50mg QD</td>
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</tbody>
</table>
Key Take Away

• MRA is what you can get on board when often you can’t get anything else on – they really don’t lower BP that much

• Anyone with a h/o arrhythmia needs a K>4, use this!

• Watch the renal function carefully – especially in older folks and those with suboptimal renal function

• Gynecomastia is real

• Eplerenone is about ½ as “potent” as Spiro
SGLT-2 Inhibitors

• DAPA-HF, NEJM 2019 - among patients with HFrEF, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of diabetic status

• EMPEROR-REDUCED, NEJM 2000 - among patients receiving recommended therapy for HFrEF, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless diabetes
*PCT – proximal convoluted tubule
** ATP – Adenosine tri-phosphate
***GLUT – glucose transporter

Increased urinary Na+ and Glucose excretion

- Reduced ATP consumption in PCT and relative hypoxia in renal cortex
- Reversion of myofibroblasts to Erythropoietin producing fibroblasts
- Increase in haematocrit
- Weight loss
- Improved ventricular loading conditions

Diuresis

- Increased glucagon vs insulin ratio
- Reduced plasma volume and improved endothelial function
- Reduction in blood pressure and afterload
- Reduction in ventricular preload

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DAPA-HF

• 4,744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo

• Median follow up 18.2 months

• Primary outcome: composite of worsening heart failure (hospitalization or an urgent visit resulting in IV for heart failure) or cardiovascular death
Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.\(^c\)

<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</td>
<td>events/100 patient-yr</td>
<td>values</td>
<td>events/100 patient-yr</td>
</tr>
<tr>
<td>Efficacy outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary composite outcome — no. (%)(^f)</td>
<td>386 (16.3)</td>
<td>11.6</td>
<td>502 (21.2)</td>
<td>15.6</td>
</tr>
<tr>
<td>Hospitalization or an urgent visit for heart failure</td>
<td>237 (10.0)</td>
<td>7.1</td>
<td>326 (13.7)</td>
<td>10.1</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>231 (9.7)</td>
<td>6.9</td>
<td>318 (13.4)</td>
<td>9.8</td>
</tr>
<tr>
<td>Urgent heart-failure visit</td>
<td>10 (0.4)</td>
<td>0.3</td>
<td>23 (1.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>227 (9.6)</td>
<td>6.5</td>
<td>273 (11.5)</td>
<td>7.9</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death or heart-failure hospitalization — no. (%)</td>
<td>382 (16.1)</td>
<td>11.4</td>
<td>495 (20.9)</td>
<td>15.3</td>
</tr>
<tr>
<td>Total no. of hospitalizations for heart failure and cardiovascular deaths(^a)</td>
<td>567</td>
<td>—</td>
<td>742</td>
<td>—</td>
</tr>
<tr>
<td>Change in KCCQ total symptom score at 8 mo(^g)</td>
<td>6.1±18.6</td>
<td>—</td>
<td>3.3±19.2</td>
<td>—</td>
</tr>
<tr>
<td>Worsening renal function — no. (%)(^h)</td>
<td>28 (1.2)</td>
<td>0.8</td>
<td>39 (1.6)</td>
<td>1.2</td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>276 (11.6)</td>
<td>7.9</td>
<td>329 (13.9)</td>
<td>9.5</td>
</tr>
</tbody>
</table>

A Primary Outcome

Hazard ratio, 0.74 (95% CI, 0.65–0.85)
P = 0.001

B Hospitalization for Heart Failure

Hazard ratio, 0.70 (95% CI, 0.59–0.83)

C Death from Cardiovascular Causes

Hazard ratio, 0.82 (95% CI, 0.69–0.98)

D Death from Any Cause

Hazard ratio, 0.83 (95% CI, 0.71–0.97)

EMPEROR-REDUCED

• 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy

• Median Follow Up: 16 months

• Primary outcome: composite of cardiovascular death or hospitalization for worsening heart failure
# EMPEROR-REDUCED

**Table 2. Primary and Secondary Cardiovascular Outcomes.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Empagliflozin (N=1863)</th>
<th>Placebo (N=1867)</th>
<th>Hazard Ratio or Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite outcome — no. (%)</strong></td>
<td>361 (19.4)</td>
<td>462 (24.7)</td>
<td>0.75 (0.65 to 0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>246 (13.2)</td>
<td>342 (18.3)</td>
<td>0.69 (0.59 to 0.81)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>187 (10.0)</td>
<td>202 (10.8)</td>
<td>0.92 (0.75 to 1.12)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes specified in hierarchical testing procedure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of hospitalizations for heart failure</td>
<td>388</td>
<td>553</td>
<td>0.70 (0.58 to 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean slope of change in eGFR — ml/min/1.73 m² per year</td>
<td>-0.55±0.23</td>
<td>-2.28±0.23</td>
<td>1.73 (1.10 to 2.37)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Backward stepwise logistic regression multivariable model to predict any serious ventricular arrhythmia, resuscitated cardiac arrest or sudden death

<table>
<thead>
<tr>
<th>Predictor Variable*</th>
<th>Odds Ratio (95% CI)</th>
<th>p Value**</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-transformed NT-proBNP (per 1 unit increase)</td>
<td>1.54 (1.34 – 1.77)</td>
<td>&lt;0.001</td>
<td>36.0</td>
</tr>
<tr>
<td>Previous Ventricular Arrhythmia</td>
<td>1.93 (1.41 – 2.64)</td>
<td>&lt;0.001</td>
<td>16.8</td>
</tr>
<tr>
<td>LVEF (per 5% increase)</td>
<td>0.86 (0.78 – 0.94)</td>
<td>0.001</td>
<td>11.9</td>
</tr>
<tr>
<td>Systolic BP (per 10mmHg)</td>
<td>0.88 (0.81 – 0.96)</td>
<td>0.004</td>
<td>8.1</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.42 (1.11 – 1.82)</td>
<td>0.005</td>
<td>7.8</td>
</tr>
<tr>
<td>Sex: male</td>
<td>1.53 (1.10 – 2.12)</td>
<td>0.012</td>
<td>6.3</td>
</tr>
<tr>
<td>BMI (per 1 kg/m² increase)</td>
<td>1.03 (1.00 – 1.05)</td>
<td>0.020</td>
<td>5.4</td>
</tr>
<tr>
<td>Sodium (per 1 mmol/L increase)</td>
<td>0.96 (0.92 – 0.99)</td>
<td>0.039</td>
<td>4.3</td>
</tr>
<tr>
<td>Non-white race</td>
<td>0.85 (0.72 – 0.99)</td>
<td>0.038</td>
<td>4.3</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>0.80 (0.63 – 1.02)</td>
<td>0.067</td>
<td>3.4</td>
</tr>
<tr>
<td>Cardiac Resynchronization Therapy</td>
<td>0.64 (0.39 – 1.04)</td>
<td>0.070</td>
<td>3.3</td>
</tr>
<tr>
<td>Previous HF hospitalization</td>
<td>0.99 (0.78 – 1.27)</td>
<td>0.985</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Randomized treatment and history of heart failure hospitalization were fixed factors in the model. **The p-value threshold was set at p<0.1

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Key Take Away

• SGLT-2 are super promising! Still much to learn…
• Can’t use in DM1
• Can use in folks without diabetes
• Most common side effect is UTI/yeast infection
• Well tolerated, can be expensive
• The arrhythmia data really bolsters the argument that these drugs impact remodeling (in a good way) over and above all other drugs
GDRT Summary

• BB, RASi, MRA and SGLT-2i
• A little of all is better than a lot of 1 or 2
• Be aggressive!
• Use the hospitalization as a chance to do this FAST and SAFE
• Q2 weeks x4 is another great solution
• You don’t have to all this by yourself
• When someone “fails” figure out why
• Needing to “wean/stop” GDMT means they need to see me
HFpEF

• Definition
  • Diastolic heart failure
  • Ejection fraction >40% on echocardiogram
    • Enlarged atria
    • Left ventricular hypertrophy
    • Often normal sized LV
Causes of HFpEF

- Myocardial
  - Microvascular ischemia
  - Myocyte hypertrophy
  - Scarring/infarction
- Infiltrative disease
- Pericardial
  - Constriction
- Restrictive Disease
  - Hypertensive heart disease
  - Diffuse fibrosis
Clinical Phenotypes of HFpEF

• Middle aged, metabolic disease
• Older, often thin/frail, heavy vascular calcification
• Infiltrative disease*
  • Middle aged: AL
  • Older (men): TTR
Diagnosis

• S/sx of HF
• Preserved EF
• Evidence of diastolic dysfunction on echocardiogram?

Doppler echocardiographic criteria for classification of diastolic function

<table>
<thead>
<tr>
<th>Left atrial pressure</th>
<th>Normal</th>
<th>Low or normal</th>
<th>Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal diastolic function</td>
<td>Normal diastolic dysfunction</td>
<td>Mild diastolic dysfunction</td>
<td>Moderate diastolic dysfunction</td>
</tr>
<tr>
<td>Impaired relaxation</td>
<td>Pseudonormal</td>
<td>Reversible restrictive</td>
<td>Fixed restrictive</td>
</tr>
</tbody>
</table>
HFpEF Diagnostic Work Up

HFpEF

Specific Cause
1. Hypertensive Heart Disease
2. Hypertrophic Cardiomyopathy
3. LV Noncompaction
4. Amyloid
5. Prior chemo/radiation (fibrosis)
6. Constriction

Non-Specific Cause
HCM Treatment

• TTE/MRI/Genetics
• HOCM – negative inotropes/myectomy/ASA
• SCD prevention
  • Prior cardiac arrest or sustained ventricular arrhythmias
  • Family history of first-degree or close relative with SCD
  • Personal h/o syncope
  • Massive LVH (>3cm) or LV aneurysm
  • EF <50%
  • Also consider NSVT or % scar on MRI
LV Noncompaction

• TTE/MRI
• Genetics
• Arrhythmias
  • Genetics is helpful here!
• Stroke risk
  • LOW threshold for AC
Cardiac Amyloidosis

• TTE/MRI/Occasionally genetic testing
• AL – treated with MM chemotherapy
  • Serum free light chains
  • SPEP
• TTR – treated with tafamadis
  • PYP scan
ATTR-ACT Study

• NEJM, 2018

• 441 patients with transthyretin amyloid cardiomyopathy in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo

• Median follow up: 30 months

• Primary outcome: Hierarchical assessment of all-cause mortality, followed by frequency of cardiovascular-related hospitalizations
### Primary Analysis, with Finkelstein–Schoenfeld Method

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>P Value from Finkelstein–Schoenfeld Method</th>
<th>Win Ratio (95% CI)</th>
<th>Patients Alive at Mo 30 no. (%)</th>
<th>Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 per patient per yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled Tafamidis</td>
<td>264</td>
<td>&lt;0.001</td>
<td>1.70 (1.26–2.29)</td>
<td>186 (70.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Placebo</td>
<td>177</td>
<td></td>
<td></td>
<td>101 (57.1)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

### Analysis of All-Cause Mortality

![Graph showing survival rates and hazard ratio](image)

Hazard ratio, 0.70 (95% CI, 0.51–0.96)

<table>
<thead>
<tr>
<th>No. at Risk (cumulative no. of events)</th>
<th>Pooled tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>264 (0)</td>
<td>177 (0)</td>
</tr>
<tr>
<td></td>
<td>259 (5)</td>
<td>173 (4)</td>
</tr>
<tr>
<td></td>
<td>252 (12)</td>
<td>171 (6)</td>
</tr>
<tr>
<td></td>
<td>244 (20)</td>
<td>163 (14)</td>
</tr>
<tr>
<td></td>
<td>235 (29)</td>
<td>161 (16)</td>
</tr>
<tr>
<td></td>
<td>222 (42)</td>
<td>150 (27)</td>
</tr>
<tr>
<td></td>
<td>216 (48)</td>
<td>141 (36)</td>
</tr>
<tr>
<td></td>
<td>209 (55)</td>
<td>131 (46)</td>
</tr>
<tr>
<td></td>
<td>200 (64)</td>
<td>118 (59)</td>
</tr>
<tr>
<td></td>
<td>193 (71)</td>
<td>113 (64)</td>
</tr>
<tr>
<td></td>
<td>99 (78)</td>
<td>51 (75)</td>
</tr>
<tr>
<td></td>
<td>0 (78)</td>
<td>0 (76)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>P Value from Finkelstein-Schoenfeld Method</th>
<th>Survival Analysis Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
<th>Cardiovascular Hospitalization Relative Risk Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall — pooled tafamidis vs. placebo</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTR genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTRm</td>
<td>0.30</td>
<td>0.22</td>
<td>0.79</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>ATTRwt</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I or II</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>0.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg vs. placebo</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg vs. placebo</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CardioOncology

- Prior chemotherapy exposure
  - Dose matters
  - Drug matters
  - EF before matters
- Radiation
  - Dose matters
  - Field/zone matters
  - Coronaries matter
- Use global longitudinal strain on TTE
- Stage B HF: Low threshold for BB/ACEi
Promising Future for Everyone Else?

- **EMPEROR-PRESERVED, NEJM 2021**
- 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy
- Median Follow Up: 26.2 months
- Primary outcome was a composite of cardiovascular death or hospitalization for heart failure
# EMPEROR-PRESERVED

<table>
<thead>
<tr>
<th>Variable</th>
<th>Empagliflozin (N=2997)</th>
<th>Placebo (N=2991)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td>415 (13.8)</td>
<td>511 (17.1)</td>
<td>0.79 (0.69–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>259 (8.6)</td>
<td>352 (11.8)</td>
<td>0.71 (0.60–0.83)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>219 (7.3)</td>
<td>244 (8.2)</td>
<td>0.91 (0.76–1.09)</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary outcomes specified in hierarchical testing procedure**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Empagliflozin (N=2997)</th>
<th>Placebo (N=2991)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of hospitalizations for heart failure</td>
<td>407</td>
<td>541</td>
<td>0.73 (0.61–0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (CKD-EPI) mean slope change per year — ml/min/1.73 m²/yr</td>
<td>-1.25±0.11</td>
<td>-2.62±0.11</td>
<td>1.36 (1.06–1.66)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Anker, et al. NEJM, 2021.*
EMPEROR-PRESERVED

Hazard ratio, 0.79 (95% CI, 0.69–0.90)
P<0.001

When to Refer to Cardiology/HF?

• HFrEF
  • Diagnostic work up
  • Unable to get all GDMT on board
  • Need to downtitrare GDMT
  • Refractory hospitalizations
  • Advanced therapy candidate?

• HFpEF
  • Diagnostic work up
  • Specific HFpEF treatment
  • Refractory hospitalizations
Questions?

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