Heart Failure: New Drugs and Devices

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No relevant disclosures
HFrEF- What is *old* in drug therapy?

- Beta-blockers (Carvedilol and Metoprolol xl)
- ACE-I inhibitor (Enalapril, Ramipril etc.)
- ARBs (Losartan, Candesartan, Valsartan etc.)
- MRAs (Spironolactone and Eplerenone)

HFrEF- What is *new* in drug therapy?

1- Angiotensin Receptor Neprilysin Inhibitor (ARNI)- Sacubitril/Valsartan
2- Sodium Glucose Co-transport-2 Inhibitors (SGLT2i)- Empagliflozin and Dapagliflozin
3- Sinus node modulator (Ivabradine)
4- Soluble Guanylate Cyclase Stimulator (Vericiguat)
5- Transthyretin tetramer stabilizer (Tafamidis)
HFrEF - What is old in Device therapy?

- Cardiac Resynchronization Therapy (CRT)
  - for LVEF<=35% and prolonged QRS

HFrEF - What is new in Device therapy?

For narrow QRS and LVEF <45%
1- Cardiac Contractility Modulation (CCM)

For narrow QRS and LVEF <35%
2- Baroreflex Activation Therapy (BAT)

For moderate-severe or severe secondary Mitral Regurgitation
3- Mitraclip
HFpEF- What is *old* in drug therapy?

- MRAs (Spironolactone) COR IIb, LOE B-R, EF>=45%, elevated BNP or HF admission within 1 year, GFR>30, creatinine <2.5, K<5

HFpEF- What is *new* in drug therapy?

- Angiotensin Receptor Neprilysin Inhibitor (ARNI)- (Valsartan/Sacubitril), approved in 2021, EF 45-57%
- Sodium Glucose Co-transporter-2 Inhibitor (Empaglifozin)- published 8/27/2021
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

Potential Mechanisms of Benefit
- Vasodilation
- Sympathetic nervous system activity
- Parasympathetic nervous system activity
- Natriuresis/diuresis
- Favorable cardiac remodeling
- Cardiac fibrosis/hypertrophy
- Risk of arrhythmia

1- ARNI

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

- PARADIGM HF trial 2014
- ARNI (200 mg bid) vs enalapril (10 mg bid)
- N 8442, symptomatic HF, EF<=40%, f/u 27 m
- Primary outcome – composite of CV death or HF hospitalization
- 22% vs 27% in enalapril
- ARNI was superior to enalapril in reducing the risks of death and of hospitalization for heart failure
ARNI

- Dose - 24/26 mg bid titrate up 97/103 mg bid
- Contraindications: Pregnancy, history of angioedema, Hypotension, Severe Hepatic impairment
Sodium-Glucose Co-transporter-2 Inhibitors (SGLT2i)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Baseline</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPA-HF</td>
<td>RCT, Primary outcome-CV death or HF hosp, f/u 1.5 yrs.</td>
<td>N 4744, HFrEF, NYHA II-IV, EF &lt;40%</td>
<td>Dapagliflozin 10 mg daily vs placebo</td>
<td>16% vs 21% in placebo, 30% reduction in HF hosp</td>
</tr>
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</table>
2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment

**Indications for Use of an SGLT2 Inhibitor**

- HFrEF (EF ≤40%) with or without diabetes
- NYHA class II–IV HF
- Administered in conjunction with a background of GDMT for HF

- Dose: 10 mg po daily
- Contraindications: Type I DM, Dialysis, Lactation
- Cautions: eGFR<20 for Empa and <30 for Dapa, pregnancy, mycotic genital infection, ketoacidosis, urosepsis and pyelonephritis, Necrotizing fasciitis of perineum
Ivabradine: If-channel inhibitor

- Slows sinus node rate
- SHIFT trial
- Elevated resting heart rate is a risk factor for adverse outcome
- RCT, DB, PC, EF<=35%, in sinus >=70 bpm, HF hospitalization
- Ivabradine up to 7.5 mg bid vs placebo
- N 6558, f/u 23 m
- Primary endpoint CV death or HF hospitalization
- 24% vs. 29% in placebo, mostly HF hosp
- Approved in 2015

Swedberg K et al. Lancet 2010
Ivabradine

- Starting dose 5 mg bid for 2 weeks, Max dose 7.5 mg bid (can be started as 2.5 mg bid)

- Contraindications: acute decompensated HF, BP<90, sick sinus syndrome, advanced AV block
Endothelial dysfunction due to oxidative stress and inflammation reduces nitric oxide bioavailability leading to insufficient activation of sGC. The resulting cGMP deficiency is associated with myocardial dysfunction and impaired endothelium-dependent vasomotor regulation (orange). Vericiguat directly stimulates sGC in a NO-independent manner and by sensitizing the enzyme to endogenous NO (green). cGMP = cyclic guanosine monophosphate; HF = heart failure; NO = nitric oxide; sGC = soluble guanylate cyclase.
VERICIGUAT- novel oral soluble guanylate cyclase stimulator- enhances cGMP pathway, and sensitized soluble GC to endogenous NO

- VICTORIA Trial
- Phase 3, RCT, parallel, placebo controlled, double blind, multicenter
- Primary endpoint – combination of time to CV death or HF hospitalization
- Titrated up to 10 mg daily vs matching placebo
- N = 5,050 , HFrEF, NYHA II-IV, EF<45%, Median f/u 11 months

<table>
<thead>
<tr>
<th></th>
<th>Vericiguat</th>
<th>Placebo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>36%</td>
<td>39%</td>
<td>p=0.02</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>27%</td>
<td>30%</td>
<td>p=ns</td>
</tr>
<tr>
<td>CV death</td>
<td>16%</td>
<td>18%</td>
<td>P=ns</td>
</tr>
</tbody>
</table>
• Vericiguat (Verquvo) is indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and EF<45%.
Indicated for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.
HFrEF Stage C Treatment

ARNI/ACEI/ARB (ARNI preferred; Figures 3A and 3B)*, AND evidence-based beta-blocker† (Figure 3C) with diuretic agent (Figure 3D) 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 (Figure 3E)

For patients meeting eGFR criteria (Figure 3F), NYHA class II-IV

Add

SGLT2 inhibitor (Figure 3F)

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

Titrare

Diuretic agent (Figure 3D)

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

Add

Hydralazine + isosorbide dinitrate (Figure 3G)

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

Add

Ivabradine (Figure 3H)

*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.
†Carvedilol, metoprolol succinate, or bisoprolol.

ACE = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K⁺ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.
## Therapy for HFpEF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>TOPCAT trial 2014</td>
<td>RCT, N 3445, symptomatic HF, EF&gt;=45%</td>
<td>Spironolactone 15-45mg daily vs placebo, f/u 3.3 yrs</td>
<td>CV death, aborted arrest, HF hosp</td>
<td>18.6 % vs 20% in placebo (nonsig), But HF hosp (sig)</td>
</tr>
<tr>
<td>ARNI</td>
<td>PARAGON-HF 2019</td>
<td>RCT, N 4822, symptomatic HF, EF&gt;=45%</td>
<td>Sacubitril-valsartan 97/103 mg bid vs valsartan 160 mg bid</td>
<td>CV death and HF hosp</td>
<td>37% vs 42% (nonsig)</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>EMPEROR-Preserved 2021</td>
<td>RCT, N 5988, symptomatic HF, EF&gt;=40%, f/u 26 m</td>
<td>Empagliflozin 10 mg daily vs placebo</td>
<td>CV death or HF hosp</td>
<td>13% vs 17% (p&lt;0.001) Mainly HF hosp</td>
</tr>
</tbody>
</table>
Cardiac Resynchronization Therapy

FDA approval in 2002
For LVEF <=35%
**Prolonged QRS >120-130 ms**
NYHA functional class I-IV

Contraindicated
1- NYHA I, QRS<=150 ms, non-LBBB
2- NYHA II, QRS<=150 ms, non-LBBB

Findings from BEAT-HF Trial

FDA approval for
-NYHA II-III + LVEF <=35%
-NT-proBNP <1600 pg/ml
Cardiac Contractility Modulation (CCM)

**FIGURE 1 Clinical Implementation of CCM Treatment**

CCM Signal applied during absolute refractory period to the RV septum via standard pacing leads

- Rechargeable Implanted Pulse Generator

- Biological effects seen remotely over time

- Biological effects seen rapidly in region of signal applications

- Improved peak VO2
- MLWHFQ and NYHA;
- Reduced HF Hospitalizations

CCM signals are delivered from an implanted pulse generator connected to the heart via one atrial lead (for p-wave sensing) and two ventricular leads (for sensing timing of local electrical activation and for delivering CCM signals). CCM signals are biphasic pulses delivered during the absolute refractory period. CCM signals impact the biology of the failing muscle local and, over time, distal to the site of signal delivery. These myocardial effects ultimately contribute to favorable clinical effects. CCM = cardiac contractility modulation; MLWHFQ = Minnesota Living With Heart Failure questionnaire; NYHA = New York Heart Association.
• FIX-HF-5C trial
• NYHA III-IV
• QRS <130 m, NSR, on GDMT, not indicated for CRT
• EF>=25% -<=45%
• RCT, N 160, F/U 24 wks
• Improvement in VO2, QOL, NYHA functional class and 6MHWT

FDA approval in 2019-

NYHA class III + LVEF 25-45%

-Improves 6MHW, QOL and functional status of NYHA

Abraham WT, et al. JACC Heart Failure 2018;6:874-883
RCT, multicenter,
Mod-severe or severe secondary MR
Symptomatic HF despite GDMT
EF 20%-50%, LVESD <=7 cm, exclude
RVSP >70 mm Hg
Endpoint – HF hospitalization
N 614, f/u 24 m
36% vs 68% in medical therapy

Divergent result in MITRA-FR; need for
GDMT prior to referral
Device Therapy to improve Heart Failure Symptoms

Device Option for HFrEF

- Narrow QRS (<120 ms)
  - NYHA II
    - LVEF ≤35%
      - BAT
  - NYHA III
    - LVEF ≤25%
      - BAT
    - LVEF 25-35%
      - BAT
    - LVEF 35-45%
      - CCM
    - LVEF ≤35%
      - CRT

- Wide QRS (>120 ms)
  - LVEF 20-50%, >3+ MR
    - Mitraclip
Summary: what is new (since 2016)?

• SGLT2i, Vericiguat and Tafadimis
• Adoption of SGLT2i and Vericiguat in ESC guidelines
• Devices for narrow QRS (BAT and CCM)
• Mitraclip for severe secondary MR