44 yr old female presents with 4 months exertional SOB, and edema

Hx: DOE now with ADL's. No PND or orthopnea. No chest pain, (+) palpitations
Exam: 108/84, 90 regular, 18, 95% RA
JVP 6 cm at 45 degrees, Basilar rales, (+) Gallop with displaced PMI to anterior axillary line.
Liver 16 cm span, 3+ edema

ECG: Sinus, NS ST, T wave changes, QRS 140 msec RBBB
Echo: 4 chamber dilated CM with EF 20%
Tp I < 0.01, BNP 850
Stages, Phenotypes and Treatment of HF

**At Risk for Heart Failure**

**STAGE A**
- At high risk for HF but without structural heart disease or symptoms of HF
- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
  - Patients:
    - Using cardiotoxins
    - With family history of cardiomyopathy

**THERAPY**
- Goals:
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- Drugs:
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

**STAGE B**
- Structural heart disease but without signs or symptoms of HF
- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**THERAPY**
- Goals:
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- Drugs:
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
- In selected patients:
  - ICD
  - Revascularization or valvular surgery as appropriate

**STAGE C**
- Structural heart disease with prior or current symptoms of HF
- e.g., Patients with:
  - Known structural heart disease and HF signs and symptoms

**THERAPY**
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use:
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Strategies:
  - Identification of comorbidities
- Treatment:
  - Diuresis to relieve symptoms of congestion
  - Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
  - Revascularization or valvular surgery as appropriate
- In selected patients:
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

**Heart Failure**

**STAGE D**
- Refractory HF
- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**THERAPY**
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient's end-of-life goals
- Options:
  - Advanced care measures
  - Heart transplant
  - Chronic dialysis
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation
Classification of Recommendations and Levels of Evidence

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>Multiple populations evaluated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td></td>
</tr>
<tr>
<td>- Recommendation that the procedure or treatment is useful/effective</td>
<td></td>
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<tr>
<td>- Sufficient evidence from multiple randomized trials or meta-analyses</td>
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<table>
<thead>
<tr>
<th>LEVEL B</th>
<th>Limited populations evaluated*</th>
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<table>
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<tr>
<th>LEVEL C</th>
<th>Very limited populations evaluated*</th>
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<td>Only consensus opinion of experts, case studies, or standard of care</td>
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<tr>
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<td></td>
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<td>- Only expert opinion, case studies, or standard of care</td>
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A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
Pharmacologic Treatment for Stage C HFrEF

HFrEF Stage C
NYHA Class I – IV
Treatment:

Class I, LOE A
ACEI or ARB AND
Beta Blocker

For all volume overload,
NYHA class II-IV patients
Add
Class I, LOE C
Loop Diuretics

For persistently symptomatic
African Americans,
NYHA class III-IV
Add
Class I, LOE A
Hydral-Nitrates

For NYHA class II-IV patients,
Provided estimated creatinine
>30 mL/min and K+ < 5.0 mEq/dL
Add
Class I, LOE A
Aldosterone Antagonist
Indications for CRT Therapy

Patient with cardiomyopathy on GDMT for ≥3 mo or on GDMT and ≥40 d after MI, or with implantation of pacing or defibrillation device for special indications

- LVEF <35%
  - Evaluate general health status
  - Comorbidities and/or frailty limit survival with good functional capacity to < 1 y
  - Continue GDMT without implanted device

Acceptable noncardiac health

Evaluate NYHA clinical status

NYHA class I
- LVEF ≤30%
- QRS ≥150 ms
- LBBB pattern
- Ischemic cardiomyopathy
- QRS ≥160 ms
- Non-LBBB pattern

NYHA class II
- LVEF ≤35%
- QRS ≥150 ms
- LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS 120-149 ms
- LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS ≥150 ms
- Non-LBBB pattern
- Sinus rhythm
- QRS ≤150 ms
- Non-LBBB pattern

NYHA class III & Ambulatory class IV
- LVEF ≤35%
- QRS ≥150 ms
- LBBB pattern
- Sinus rhythm
- LVEF ≥35%
- QRS ≤150 ms
- LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS ≥150 ms
- Non-LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS 120-149 ms
- Non-LBBB pattern
- Sinus rhythm

Special CRT Indications
- Anticipated to require frequent ventricular pacing (≥40%)
- Atrial fibrillation, If ventricular pacing is required and rate control will result in near 100% ventricular pacing with CRT

Colors correspond to the class of recommendations in the ACCF/AHA Table 1.

Benefit for NYHA class I and II patients has only been shown in CRT-D trials, and while patients may not experience immediate symptomatic benefit, late remodeling may be avoided along with long-term HF consequences. There are no trials that support CRT-pacing (without ICD) in NYHA class I and II patients. Thus, it is anticipated these patients would receive CRT-D unless clinical reasons or personal wishes make CRT-pacing more appropriate. In patients who are NYHA class III and ambulatory class IV, CRT-D may be chosen but clinical reasons and personal wishes may make CRT-pacing appropriate to improve symptoms and quality of life when an ICD is not expected to produce meaningful benefit in survival.
Figure 2. Treatment of HFrEF Stage C and D

Colors correspond to COR in Table 1. For all medical therapies, dosing should be optimized and serial assessment exercised.

* See text for important treatment directions.
† Hydral-Nitrates green box: The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored.
‡ See 2013 HF guideline (9).
§ Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; COR, Class of Recommendation; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy-device; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; K+, potassium; LBBB, left bundle-branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR, normal sinus rhythm; and NYHA, New York Heart Association.
alternatives for patients with ACE inhibitor–induced angioedema, caution is advised because some patients have also developed angioedema with ARBs. Head-to-head comparisons of an ARB versus ARNI for HF do not exist. *For those patients for whom an ACE inhibitor or ARNI is inappropriate, use of an ARB remains advised.*

| I | ARNI: B-R | In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (138). | NEW: New clinical trial data necessitated this recommendation. |

**See Online Data Supplements 1 and 18.**

Benefits of ACE inhibitors with regard to decreasing HF progression, hospitalizations, and mortality rate have been shown consistently for patients across the clinical spectrum, from asymptomatic to severely symptomatic HF. Similar benefits have been shown for ARBs in populations with mild-to-moderate HF who are unable to tolerate ACE inhibitors. In patients with mild-to-moderate HF (characterized by either 1) mildly elevated natriuretic peptide levels, BNP [B-type natriuretic peptide] > 150 pg/mL or NT-proBNP [N-terminal pro-B-type natriuretic peptide] ≥ 600 pg/mL; or 2) BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL with a prior hospitalization in the preceding 12 months) who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNI (valsartan/sacubitril; 200 mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan/sacubitril compound compared with enalapril. The target dose of the ACE inhibitor was consistent with that known to improve outcomes in previous landmark clinical trials (129). This ARNI has been approved for patients with symptomatic HFrEF and is intended to be substituted for ACE inhibitors or ARBs. HF effects and potential off-target effects may be complex with inhibition of the nephrilysin enzyme, which has multiple biological targets. Use of an ARNI is associated with hypotension and a low-frequency incidence of angioedema. To facilitate initiation and titration, the approved ARNI is available in 3 doses that include a dose that was not tested in the HF trial; the target dose used in the trial was 97/103 mg twice daily (147). Clinical experience will provide further information about the optimal titration and tolerability of ARNI, particularly with regard to blood pressure, adjustment of concomitant HF medications, and the rare complication of angioedema (14).

| III: Highest | B-R | ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (148, 149). | NEW: Available evidence demonstrates a potential signal of harm for a concomitant use of ACE inhibitors and ARNI. |
**Functional Class II-III**

**EF < 36%**

- 35% 2 year Mortality
- 40% RR reduction
- 21% Mortality
- 50-60% RR reduction
- 8-10% Mortality
- 20-25% RR reduction
- 6-8% Mortality

ACEi or ARB ←

Betablocker

K sparing diuretic

PARADIGM-HF Nejm 371: 993-1004, 2014

Angiotensin-Neprilysin Inhibition (Entresto $$$) 16% RR 2.8% AR versus Enalapril

**Symptoms Despite GDMT**

Device Treatment

ICD +/- CRT

20-25% Relative Risk Reduction

Data stronger for Ischemic Cardiomyopathy
MADIT II
NEJM 2002; 346: 877-883

- N=1232 prior MI, LVEF <=30% (No NYHA class IV, MI < 1 month, CABG < 3 month)
- 70% receiving ACEI, beta-blockers, and diuretics
- Halted Nov 20, 2001 by safety committee
- Survival is better with an AICD for those patients with remote MI (> 1 months ago) and an EF < or = 30%
  - 21 month 14.2% versus 19.8% (p=0.016)

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All-cause Mortality Non-CRT Group

<table>
<thead>
<tr>
<th>Study Name</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIOVIRT</td>
<td>0.87 (0.31, 2.43)</td>
<td>3.16</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>0.65 (0.40, 1.06)</td>
<td>14.06</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>0.74 (0.57, 0.96)</td>
<td>47.97</td>
</tr>
<tr>
<td>CAT</td>
<td>0.83 (0.45, 1.52)</td>
<td>8.94</td>
</tr>
<tr>
<td>DANISH Non-CRT Group</td>
<td>0.83 (0.58, 1.19)</td>
<td>25.86</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p=NS)</td>
<td>0.76 (0.63, 0.91)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis

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Mahesh Anantha Narayanan et al. JACEP 2017, Jacep.
2017.02.008

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