Updates in Heart Failure Pharmacotherapy

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No disclosures
Objectives

- Describe the 2017 ACC/AHA/HFSA Heart Failure Guidelines
- Discuss newly available heart failure therapies
- Apply heart pharmacotherapy approaches to patient cases
- Understand the similarities and differences between treatments for heart failure
Definition of Heart Failure

“A complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.”

-ACCF/AHA, 2013
Heart Failure: A Growing Epidemic

- 5.7 million adults in the United States have heart failure
- 650,000 patients diagnosed annually
- One in 9 deaths in 2009 included heart failure as contributing cause
- Half of people who develop heart failure die within 5 years of diagnosis

Heart Failure: Projected Prevalence and Cost

<table>
<thead>
<tr>
<th>Year</th>
<th>All Cardiovascular Disease</th>
<th></th>
<th>Heart Failure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence (%)</td>
<td>Cost (Billions)</td>
<td>Prevalence (%)</td>
<td>Cost (Billions)</td>
</tr>
<tr>
<td>2010</td>
<td>36.9</td>
<td>$272.5</td>
<td>2.8</td>
<td>$24.7</td>
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<tr>
<td>2015</td>
<td>37.8</td>
<td>$358</td>
<td>3</td>
<td>$32.4</td>
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<tr>
<td>2020</td>
<td>38.7</td>
<td>$470.3</td>
<td>3.1</td>
<td>$42.9</td>
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<tr>
<td>2025</td>
<td>39.7</td>
<td>$621.6</td>
<td>3.3</td>
<td>$57.5</td>
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<td>2030</td>
<td>40.5</td>
<td>$818.1</td>
<td>3.5</td>
<td>$77.7</td>
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<tr>
<td>% Change</td>
<td>9.9</td>
<td>200</td>
<td>25</td>
<td>215</td>
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</table>

$30.7 billion in annual costs in the United States

Classification of Heart Failure

- Heart failure with preserved ejection fraction (HFpEF)
  - Variably classified
  - Stiff ventricle -> decreased compliance/relaxation
  - Therapy aimed at co-morbidities and risk factor reduction

- Heart Failure with Reduced Ejection Fraction (HFrEF)
  - Inability to contract or empty
  - EF ≤ 40%
  - Widely studied

Therapy Aimed to Reduce Mortality

Effect of Adding Medications/Devices

- ICD
- Aldosterone Antagonists
- Beta-blocker
- ACEi
- No Medical Therapy

Levy et al. Circulation. 2006;113:1424-1433
HFrEF: Conventional Therapy

- **Reduction in Preload/Afterload**
  - ACEi
  - ARBs
  - Isosorbide/hydralazine
  - ARNI

- **Reduction in Sympathetic Nervous System**
  - Beta-blockers
  - Ivabradine

- **Reduction in Volume**
  - Loop diuretics
  - Aldosterone antagonists

- **Increased Contractility**
  - Digoxin

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor
Goals of Heart Failure Pharmacotherapy

- Prevention
  - Halt myocardial damage
  - Prevent recurrence of symptoms
  - Delay progression of heart failure

- Improve Quality of Life
  - Clinical improvement
  - Increase exercise capacity
  - Avoidance of adverse effects from treatment
Compensatory Mechanisms

Increased SVR → Increased Afterload → Neurohormonal Response → Perfusion → CO → Volume → Increased Preload → Na/H2O Retention
Targets for Heart Failure Medical Therapy
Vasodilator Landmark Trial Timeline

VHeFT I
1986
hydralazine/ISDN

1987
Consensus
enalapril

VHeFT II
1991
hydralazine/ISDN

1994
SOLVD

2001
Val-HeFT
valsartan

2003
CHARM-Alternative
candesartan

2004
AHeFT
Hydralazine/ISDN
VHeFT I
- Randomized controlled trial
- Population: 642 men
  - Mild-moderate systolic dysfunction
- Intervention
  - Prazosin 20mg/day
  - Hydralazine 300mg/day+ISDN 160mg/day
  - Placebo
- Results
  - Reduction in mortality with hydralazine/ISDN
  - Improvement in LVEF with hydralazine/ISDN

VHeFT II
- Randomized controlled trial
- Population: 804 men
  - Mild to moderate heart failure
- Intervention
  - Enalapril 20mg/day
  - Hydralazine 300mg/day+ISDN 160mg/day
- Results
  - Reduction in mortality with enalapril (p=0.016)
  - Fewer patients discontinued enalapril

African-American Heart Failure Trial (A-HeFT)

- Randomized controlled trial
- Population: 1050 participants
  - NYHA III-IV
  - Background therapy with ACEi/ARB, beta blocker, aldosterone antagonists
- Intervention:
  - Placebo vs. Isosorbide dinitrate/Hydralazine (BiDil®)
    - target dose 120mg/day Isosorbide dinitrate/225mg/day Hydralazine
- Results:
  - 43% Reduction in all cause death
  - 33% relative reduction in rate of first hospitalization

Patient Selection for Hydralazine/Isosorbide dinitrate (ISDN)

Stage C HFrEF

ACEi + Beta-blocker

Persistently symptomatic African Americans NYHA III-IV

Hydralazine/ISDN

Given instead of ACEi/ARB for intolerant patients

Hydralazine/ISDN

Initial Doses:
- Hydralazine 25mg tid
- ISDN 20mg tid
- Titrated every 2 weeks

Yancy CW et. al. J Am Coll Cardiol. Epub ahead of print 22 Dec 2017
CONSENSUS
- Randomized controlled trial
- Population: n=253
  - NYHA IV
  - LVEF < 35%
- Intervention:
  - Placebo vs. enalapril
    - Target dose 40mg/day
- Results:
  - 40% reduction in mortality over 6 months

SOLVD
- Randomized controlled trial
- Population: n=2569
  - NYHA I-IV
  - LVEF < 35%
- Intervention:
  - Placebo vs. enalapril
    - Target dose 20mg/day
- Results:
  - 16% Risk reduction in mortality
  - 33% relative reduction in rate of 1st hospitalization
  - Improved quality of life

CHARM-Alternative

- Randomized controlled trial
- Population: 2028 participants
  - LVEF < 40%
  - NYHA II-IV
- Intervention:
  - Tested ARB in ACEi intolerant patients
  - Placebo vs. Candesartan
    - target dose 32mg/day
- Results:
  - 12% reduction in cardiovascular deaths
  - Reduction in hospitalization


Cardiovascular Death or Hospital Admission for Heart Failure
PARADIGM-HF

- Randomized controlled trial
- Population: 2569 participants
  - NYHA II-IV
  - LVEF < 35%
- Intervention:
  - Enalapril vs. LCZ 696
    - Enalapril target dose 20mg/day
    - LCZ 696 target dose 200mg BID
- Results:
  - Reduction in cardiovascular death
  - Reduction in hospitalizations

Death from cardiovascular disease or hospitalization for heart failure

Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001

Sacubitril-valsartan Mechanism of Action

**Renin Angiotensin System**
- Angiotensinogen (liver secretion)
  - Angiotensin I
  - Angiotensin II
  - AT₁ receptor

**Heart Failure**

**Natriuretic Peptide System**
- ANP
- BNP
- CNP
- Adrenomedullin
- Substance P
- Bradykinin
- Angiotensin II
- Others

**Angiotensin II Blockade**
- Valsartan
- Sacubitril

**Vasodilation**
- Lower blood pressure
- Reduced sympathetic tone
- Reduced aldosterone levels
- Natriuresis/Diuresis

**Vasocorrection**
- Elevated blood pressure
- Increased sympathetic tone
- Aldosterone elevation
- Increased fibrosis
- Ventricular hypertrophy

**Inactive fragments**
- NT-pro BNP (not a substrate for nephrilysin)
### 2017 ACC/AHA/HFSA Guideline: Vasodilator Recommendations

<table>
<thead>
<tr>
<th>Vasodilator</th>
<th>Class of Recommendation (COR)</th>
<th>Level of Evidence (LOE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi</td>
<td>Class I Strong</td>
<td>Level A High Quality</td>
</tr>
<tr>
<td>ARB</td>
<td>Class IIa Moderate</td>
<td>Level B-R Randomized</td>
</tr>
<tr>
<td>ARNI</td>
<td>Class IIb Weak</td>
<td>Level B-NR Non-randomized</td>
</tr>
<tr>
<td>H/ISDN</td>
<td>Class III No benefit</td>
<td>Level C-LD Limited Data</td>
</tr>
<tr>
<td></td>
<td>Class III Harm</td>
<td>Level C-EO Expert Opinion</td>
</tr>
</tbody>
</table>

- **ACEi**: Class I, Level A
- **ARB**: Class I, Level A
- **ARNI**: Class I, Level B-R
- **H/ISDN**: Class I, Level A

- **Class III** Harm: Level C-EO Expert Opinion

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Persistently symptomatic African Americans

*Instead of ACEi/ARB for intolerant patients*

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**Beta-blocker Titration:**
- Start at a low dose when hemodynamically stable
- Minimum of 2 weeks between dose increases
- Avoid abrupt discontinuation

**ACEi Titration:**
- Start a low dose
- Increase doses no sooner than every 2 weeks
- Aim to complete titration in 3-6 months

Yancy CW et. al. J Am Coll Cardiol. Epub ahead of print 22 Dec 2017
Beta-blocker Landmark Trial Timeline

CIBIS I
1994
bisoprolol

carvedilol
U.S Carvedilol
1996

CIBIS II
MERIT HF
1999
metoprolol succinate

carvedilol vs. metoprolol tartrate
COMET
2003
## HFrEF: Beta-blocker trials

### U.S. Carvedilol
- **Population:** n=1094
  - NYHA II-IV
  - LVEF ≤ 35%
- **Intervention:**
  - Placebo vs. carvedilol
    - ≤85kg: 25mg BID
    - >85kg: 50mg BID
- **Results:**
  - 65% reduction in death
  - 38% reduction in risk of death or hospitalization

### CIBIS II
- **Population:** n=2647
  - NYHA II-IV
  - LVEF ≤ 35%
- **Intervention:**
  - Placebo vs. bisoprolol
    - 10mg daily
- **Results:**
  - 65% reduction in death
  - 38% reduction in risk of death or hospitalization

### MERIT HF
- **Population:** n=3991
- **Intervention:**
  - Placebo vs. metoprolol succinate
    - 200mg daily
- **Results:**
  - 34% reduction in all-cause mortality
  - 41% reduction in sudden cardiac death

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SHIFT: Ivabradine in Heart Failure

- Randomized controlled trial
- Population: 6505 participants
  - NYHA II-IV
  - LVEF ≤ 35%
  - Resting HR>70 bpm, NSR
- Intervention:
  - Ivabradine or placebo
    - Target HR: 50-60bpm
- Results:
  - Significant reduction in composite primary outcome
  - Driven by a reduction in re-hospitalizations

Death from cardiovascular disease or hospitalization for heart failure

Swedberg K et al. Lancet 2010; 376:875-85lp
**Ivabradine Mechanism of Action**

- ↓ Spontaneous pacemaker activity at the sinus node
- Blocks hyperpolarization-activated cyclic nucleotide-gated (HCN) channel to selectively inhibit $I(f)$-current
- ↓ HR

Corlanor (Ivabradine) [Package Insert]. Thousand Oaks, CA: Amgen; April 2015
### SHIFT: Incidence of Ivabradine Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Ivabradine vs. Placebo(%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>25% vs. 29%</td>
<td>p=0.0005</td>
</tr>
<tr>
<td>Symptomatic Bradycardia</td>
<td>5% vs. 1%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic Bradycardia</td>
<td>6% vs. 1%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>9% vs. 8%</td>
<td>p=0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>3% vs. 1%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>1% vs. &lt;1%</td>
<td>p=0.042</td>
</tr>
</tbody>
</table>

Swedberg K et al. Lancet 2010; 376:875-85lp
2017 ACC/AHA/HFSA Guidelines: Heart Rate Lowering Agents

Beta-Blockers

- **Ivabradine**

**COR** | **LOE**
---|---
I | A

Use of 1 of the 3 beta blockers proven to reduce mortality:
- Metoprolol succinate
- Bisoprolol
- Carvedilol

May be beneficial to reduce heart failure hospitalizations who are receiving guideline directed medical therapy (GDMT).

Guideline Directed Medical Therapy in Heart Failure by Classification

Central Illustration: Characterization of HFrEF, HFrEF, and HFrEF

Case 1: HFrEF Medical Management

- DT 38yo AAM with non-ischemic cardiomyopathy (EF 25%)
- Diagnosed 6 months ago
- Past Medical History
  - CKD Stage II (baseline Scr 1.2mg/dL)
  - LV thrombus
  - Hypertension
- Referred to the pharmacy HF clinic for medication titration

- Labs:
  - 139 104 12
  - 4.3 122 1.3
  - 88

- Home Medication List
  - Losartan 50mg daily
  - Metoprolol succinate 100mg daily
  - Isosorbide dinitrate 10mg TID
  - Hydralazine 50mg TID
  - Warfarin 7.5mg alternating with 5mg
  - Aspirin 81mg daily
  - Spironolactone 12.5mg daily
Case 1: HFrEF Medical Management

- Patient presents to pharmacy clinic and reports NYHA class III symptoms
- Vital signs: pulse 88bpm, BP 135/82mmHg, SpO₂ 98%
- Height: 167cm
- Weight: 153lbs
  - Weight trend: +5 pounds since last visit
- Physical exam: LEE 1+ and elevated JVP of 8cm
Question 1: What is the best approach to optimizing DT’s medical therapy?

- A. Increase spironolactone to 25mg daily
- B. Increase losartan to 100mg daily
- C. Increase both isosorbide dinitrate 20mg TID and hydralazine to 75mg TID
- D. Switch losartan 50mg daily to sacubitril/valsartan 24-26mg by mouth twice daily
Transiting from ACEi/ARB to ARNI

Starting Dose

<table>
<thead>
<tr>
<th>Dose ACEi</th>
<th>Dose ARB</th>
<th>Dose sacubitril-valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10mg enalapril BID or equivalent</td>
<td>≤ 160mg daily valsartan or equivalent</td>
<td>24-26mg twice daily</td>
</tr>
<tr>
<td>&gt; 10mg enalapril BID or equivalent</td>
<td>&gt; 160mg daily valsartan or equivalent</td>
<td>49-51mg twice daily</td>
</tr>
</tbody>
</table>

Target Dose: 97-103mg twice daily

Yancy CW et. al. J Am Coll Cardiol. Epub ahead of print 22 Dec 2017
**ARNI Considerations**

- **36 Hour Wash-out**
  - Only required for transition from an ACEi
  - Reduces the risk of angioedema
  - Both ACE-Inhibitor and sacubitril ↑ bradykinin
    - Increased risk for angioedema

Entresto (sacubitril and valsartan) [Package Insert]. East Hanover, NJ: Novartis; July 2015
**ARNI Monitoring and Adverse Effects**

- **Monitoring:**
  - Basic metabolic panel
  - Baseline and post-initiation
  - Blood pressure
  - NT-proBNP (Not BNP)

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### PARADIGM-HF: Incidence of Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Sacubitril-Valsartan (n=4203)</th>
<th>Enalapril (n=4229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Entresto (sacubitril and valsartan) [Package Insert]. East Hanover, NJ: Novartis; July 2015
Case 1 Continued

- DT has been visiting your clinic for the past two months and has returned for a follow up visit
- CC: excessive fatigue attributed to his recent increase in metoprolol succinate
Case 1 Continued

- Vital Signs:
  - Pulse 80bpm
  - BP 109/75mmHg
  - SpO₂ 99%
- Height: 167cm
- Weight: 149lbs
- Physical exam: trace LEE and JVP 5cm

- Home Medication List:
  - Sacubitril/valsartan 49/51mg BID
  - Metoprolol succinate 150mg daily
  - Warfarin 7.5mg alternating with 5mg
  - Aspirin 81mg daily
  - Spironolactone 25mg daily
Question 2: What is the next best approach to optimize DT’s regimen?

- A. Switch metoprolol succinate to qHS
- B. Convert to carvedilol 25mg PO BID
- C. Start ivabradine 2.5mg PO BID
- D. Start ivabradine 5mg PO BID
- E. A and D only
Initiation of Ivabradine

Indications:
- EF≤35%; NYHA II-III
- Maximally tolerated dose of beta blocker
- Normal sinus rhythm + resting HR ≥70bpm

Flowchart:
1. Confirm Max/Tolerated Dose Beta blocker
2. Resting HR ≥ 70bpm
3. Ivabradine
   - 2.5mg BID
   - 5mg BID
4. Re-assess HR in 2-4 weeks
5. Titrate to HR 50-60

Key Points:
- Age < 75 years
- Age ≥ 75 years
- History of conduction abnormalities
Classification of Heart Failure

- Heart failure with preserved ejection fraction (HFpEF)
  - Variably classified
  - Stiff ventricle -> decreased compliance/relaxation
  - Therapy aimed at co-morbidities and risk factor reduction

- Heart Failure with Reduced Ejection Fraction (HFrEF)
  - Inability to contract or empty
  - EF ≤ 40%
  - Widely studied

Goals of Treatment

- Control blood pressure
- Control heart rate
  - Typically <70bpm
- Maintain euvolemia
- Reduce preload (caution)

Morbidity Reduction

- ARBs (IIB)
- Aldosterone antagonists (IIB-R)

Volume and BP Control

- Diuretics (IC)
- ACE inhibitors (IIC)
- Beta blockers (IIC)
HFpEF: Landmark Trials

CHARM-Preserved: 2003
- candesartan
- nebivolol

PEP-CHF: 2006
- perindopril
- irbesartan

Aldo-DHF: 2013
- spironolactone

SENIORS: 2005

I-PRESERVE: 2008

TOPCAT: 2014

TOPCAT: Regional Analysis

**TOPCAT**
- Spironolactone 12.5mg-45mg daily vs. placebo
- No significant reduction in morbidity and mortality

**TOPCAT Regional Analysis**
- North American post-hoc analysis
- Demonstrated significant improvement in morbidity and mortality with spironolactone

TOPCAT: Regional Analysis

B

CV Death

C

Heart Failure Hospitalization

### 7.3.3. Pharmacological Treatment for Stage C HFpEF: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Stage C HFpEF</th>
<th>Comment/Rationale</th>
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<tbody>
<tr>
<td><strong>COR</strong></td>
<td><strong>LOE</strong></td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
</tr>
</tbody>
</table>
Recommendation (III-BR): Routine use of nitrates or PDE-5 inhibitors to increase activity or QOL in patients with HFpEF is ineffective

- Nitrates
  - This is based on the NEAT-HFpEF trial, patients were randomized to either isosorbide mononitrate or placebo and found no benefit
  - This does not apply to HFpEF and symptomatic CAD

- PDE-5 inhibitors:
  - The RELAX trial randomized patients with reduced exercise tolerance to PDE-5 inhibition with sildenafil or placebo. No improvement in O2 consumption or exercise tolerance.
AHA/ACCF/HFSA 2017 Update
Comorbidity Management

- Hypertension
- Anemia
- Sleep Apnea
Case 3: HFpEF Medical Management

- CB is a 58yo WF with HFpEF (EF>60%) who was recently discharged from the hospital after 2 weeks of intravenous diuresis

- Past Medical History
  - TVR (bioprosthetic)
  - Cryo maze ablation
  - LAA clip
  - 2-3+ MR
  - Atrial fibrillation
  - Hypertension
  - Morbid obesity (BMI 50)
  - NASH Cirrhosis
  - OSA on CPAP
  - Prior stroke
  - Asthma
Case 3: HFpEF Medical Management

- Vital signs:
  - Pulse 71bpm
  - BP 145/91mmHg
  - SpO₂ 98%
- Height: 165cm
- Weight trend: 285lbs, +5 pounds since hospital discharge
- Labs
<table>
<thead>
<tr>
<th>138</th>
<th>97</th>
<th>20</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7</td>
<td>25</td>
<td>0.82</td>
<td>0.95</td>
</tr>
</tbody>
</table>

- Home Medication list
  - Lisinopril 2.5mg daily
  - Metoprolol succinate 50mg PO BID
  - Atorvastatin 40mg daily
  - KCl 40meq daily
  - Paroxetine 10mg daily
  - Aspirin 81mg daily
  - Gabapentin 300mg PO QHS
  - Albuterol inhaler PRN
  - Torsemide 20mg PO BID
  - Warfarin 7.5mg daily
Question 3: What is CB’s BP goal?

- A. <140/90mmHg
- B. <120/80mmHg
- C. <130/80mmHg
- D. All of the above
Treat HTN to Reduce Incidence of HF

• **Recommendation (I-BR): Stage A HF, increased risk, optimal BP in those with HTN**
  - Blood pressure goal should be <130/80mmHg
  - SPRINT trial:
    - Large RCT, patients with increased CV risk*
    - Control of BP to a SBP<120mmHg was associated with a significant ↓ incidence of HF and overall ↓ in CV death
  - BP measurements taken in office are typically 5-10mmHg higher than research measurements, thus goal is <130/80mmHg
  - Targeting a significant reduction in systolic BP in those at risk of CV disease is a novel strategy to prevent HF

*Age>75, vascular disease, CKD, Framingham Score> 15%)

Treating HTN in Stage C HFrEF

- **Recommendation (I-CEO):** Patients with HFrEF and HTN should be prescribed GDMT titrated to attain systolic BP < 130 mmHg
  - Not specifically evaluated in randomized trial of HF patients
  - GDMT for HFrEF should consider a BP reduction consistent with a threshold now associated with improved clinical outcomes but not yet proven in HF

Treating HTN in Stage C HFpEF

- Recommendation (I-CLD): Patients with HFpEF and persistent HTN, GDMT titrated to attain a systolic BP<130mmHg
  - Avoid nitrates for HTN treatment
  - Beta blockers, ACE inhibitors, and ARBs
  - RAAS inhibition with ACE inhibitor, ARB, and possibly an ARNI are the preferred choices
  - Limited guidance regarding alpha blockers, beta blockers, and CCBs

# A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, controlled, open-label, multi-centre trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion Criteria</td>
<td>≥50 YO, SBP 130-180mmHg, and increased risk of cardiovascular events± (≠diabetics)</td>
</tr>
<tr>
<td>Methods</td>
<td>Randomized to SBP target of &lt;120mmHg (Intensive group) or &lt;140mmHg (standard group)</td>
</tr>
<tr>
<td>Patient Population</td>
<td>9361 patients, 28.2% ≥75 YO, 20% had CVD, 30% AA, Baseline BP 139.7/78mmHg, average Framingham Risk score 20.1%</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Composite endpoint of MI, ACS, stroke, HF, or death from CV causes</td>
</tr>
<tr>
<td></td>
<td>• Intensive group: mean SBP was 121.4mmHg</td>
</tr>
<tr>
<td></td>
<td>• Standard group: mean SBP was 136.2mmHg</td>
</tr>
<tr>
<td></td>
<td>• Primary endpoint: intensive group 1.65% per year vs. standard group 2.19% per year (HR 0.75, p=0.003)</td>
</tr>
<tr>
<td>Safety</td>
<td>Rates of adverse events such as hypotension*, syncope, acute kidney injury or failure* were higher in the intensive group vs. the standard group</td>
</tr>
</tbody>
</table>

±clinical or subclinical CVD other than stroke, CKD, eGFR 20-60ml/min/1.73m², 10 year risk of CVD ≥15%, or age ≥75 YO
* p<0.05
### Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Treatment</th>
<th>Standard Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>% per year</td>
<td>no. of patients (%)</td>
<td>% per year</td>
</tr>
<tr>
<td>All participants</td>
<td>(N = 4678)</td>
<td></td>
<td>(N = 4683)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome†</strong></td>
<td>243 (5.2)</td>
<td>1.65</td>
<td>319 (6.8)</td>
<td>2.19</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>97 (2.1)</td>
<td>0.65</td>
<td>116 (2.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>40 (0.9)</td>
<td>0.27</td>
<td>40 (0.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Stroke</td>
<td>62 (1.3)</td>
<td>0.41</td>
<td>70 (1.5)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>62 (1.3)</td>
<td>0.41</td>
<td>100 (2.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>37 (0.8)</td>
<td>0.25</td>
<td>65 (1.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>155 (3.3)</td>
<td>1.03</td>
<td>210 (4.5)</td>
<td>1.40</td>
</tr>
<tr>
<td>Primary outcome or death</td>
<td>332 (7.1)</td>
<td>2.25</td>
<td>423 (9.0)</td>
<td>2.90</td>
</tr>
<tr>
<td><strong>Participants with CKD at baseline</strong></td>
<td>(N = 1330)</td>
<td></td>
<td>(N = 1316)</td>
<td></td>
</tr>
<tr>
<td>Composite renal outcome‡</td>
<td>14 (1.1)</td>
<td>0.33</td>
<td>15 (1.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>≥50% reduction in estimated GFR§</td>
<td>10 (0.8)</td>
<td>0.23</td>
<td>11 (0.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Long-term dialysis</td>
<td>6 (0.5)</td>
<td>0.14</td>
<td>10 (0.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Incident albuminuria¶</td>
<td>49/526 (9.3)</td>
<td>3.02</td>
<td>59/500 (11.8)</td>
<td>3.90</td>
</tr>
<tr>
<td><strong>Participants without CKD at baseline</strong></td>
<td>(N = 3332)</td>
<td></td>
<td>(N = 3345)</td>
<td></td>
</tr>
<tr>
<td>≥30% reduction in estimated GFR to &lt;60 ml/min/1.73 m²∥</td>
<td>127 (3.8)</td>
<td>1.21</td>
<td>37 (1.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Incident albuminuria¶</td>
<td>110/1769 (6.2)</td>
<td>2.00</td>
<td>135/1831 (7.4)</td>
<td>2.41</td>
</tr>
</tbody>
</table>
### Study Design

Subanalysis of the SPRINT trial – to determine whether there was a difference in ADHF events in the prespecified subgroups and three levels of baseline SBP

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Subanalysis of the SPRINT trial – to determine whether there was a difference in ADHF events in the prespecified subgroups and three levels of baseline SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>9361 patients, 28.2% ≥75 YO, 20% had CVD, 30% AA, Baseline BP 139.7/78mmHg, average Framingham Risk score 20.1%</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>ADHF Events</td>
</tr>
<tr>
<td></td>
<td>• Standard group 103 events (2.2%) vs. Intensive group 65 events (1.4%), HR 0.63, p= 0.003</td>
</tr>
<tr>
<td></td>
<td>• Benefit seen in all prespecified subgroups</td>
</tr>
<tr>
<td></td>
<td>• Incidence ADHF led to 27-fold increase of CV death (p&lt;0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Intensive Treatment % (# Events)</th>
<th>Standard Treatment % (# Events)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.39% (65)</td>
<td>2.20% (103)</td>
<td>0.63 (0.46, 0.85)</td>
<td>0.21</td>
</tr>
<tr>
<td>Previous CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.72% (24)</td>
<td>1.51% (51)</td>
<td>0.48 (0.29, 0.78)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.08% (41)</td>
<td>3.95% (52)</td>
<td>0.73 (0.48, 1.10)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75yr</td>
<td>0.89% (30)</td>
<td>1.34% (45)</td>
<td>0.67 (0.42, 1.06)</td>
<td>0.69</td>
</tr>
<tr>
<td>&gt;=75yr</td>
<td>2.66% (35)</td>
<td>4.40% (58)</td>
<td>0.59 (0.38, 0.89)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.40% (42)</td>
<td>2.41% (73)</td>
<td>0.57 (0.39, 0.83)</td>
<td>0.39</td>
</tr>
<tr>
<td>Female</td>
<td>1.37% (23)</td>
<td>1.82% (30)</td>
<td>0.76 (0.44, 1.31)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>1.33% (43)</td>
<td>2.35% (75)</td>
<td>0.56 (0.38, 0.81)</td>
<td>0.26</td>
</tr>
<tr>
<td>Black</td>
<td>1.51% (22)</td>
<td>1.88% (28)</td>
<td>0.82 (0.47, 1.44)</td>
<td></td>
</tr>
<tr>
<td>Previous CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.04% (39)</td>
<td>1.68% (63)</td>
<td>0.62 (0.41, 0.92)</td>
<td>0.99</td>
</tr>
<tr>
<td>Yes</td>
<td>2.77% (26)</td>
<td>4.27% (40)</td>
<td>0.62 (0.37, 1.02)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 132 mmHg</td>
<td>1.01% (16)</td>
<td>1.93% (30)</td>
<td>0.51 (0.27, 0.93)</td>
<td>0.75</td>
</tr>
<tr>
<td>&gt;132 to &lt;145 mmHg</td>
<td>1.41% (21)</td>
<td>2.07% (32)</td>
<td>0.68 (0.38, 1.17)</td>
<td></td>
</tr>
<tr>
<td>&gt;= 145 mmHg</td>
<td>1.74% (28)</td>
<td>2.59% (41)</td>
<td>0.67 (0.41, 1.09)</td>
<td></td>
</tr>
</tbody>
</table>
**Recommendations for Treatment of Hypertension in Patients With HFrEF**

References that support recommendations are summarized in Online Data Supplement 34.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>1. Adults with <strong>HFrEF and hypertension</strong> should be prescribed GDMT (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>titrated to attain a BP of less than 130/80 mm Hg.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>2. Nondihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF (1).</td>
</tr>
</tbody>
</table>

**Recommendations for Treatment of Hypertension in Patients With HfPEF**

References that support recommendations are summarized in Online Data Supplements 35 and 36.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>1. In adults with HfPEF who present with symptoms of volume overload,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diuretics should be prescribed to control hypertension.</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>2. Adults with <strong>HfPEF and persistent hypertension</strong> after management of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>volume overload should be prescribed ACE inhibitors or ARBs and beta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blockers titrated to attain SBP of less than 130 mm Hg (1-6).</td>
</tr>
</tbody>
</table>
**Comparing the Guidelines**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AHA/ACCF/HFSA 2017 Heart Failure Update</th>
<th>ACC/AHA 2017 High Blood Pressure in Adults Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk for HF</td>
<td>&lt;130/80mmHg</td>
<td>&lt;130/80mmHg</td>
</tr>
<tr>
<td>Heart failure</td>
<td>HFrEF</td>
<td>HFrEF</td>
</tr>
<tr>
<td>BP Goal</td>
<td>SBP &lt;130mmHg</td>
<td>SBP &lt;130mmHg</td>
</tr>
<tr>
<td>Pharmacologic Therapy</td>
<td>GDMT</td>
<td>RAAS Inhibitors (ACE-Inhibitors, ARBs) preferred</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Beta blockers</td>
</tr>
<tr>
<td>BP Goal for Heart Failure</td>
<td>&lt;130/80mmHg</td>
<td></td>
</tr>
</tbody>
</table>

- GDMT = Goal-Directed Medical Therapy
- SBP = Systolic Blood Pressure
- BP = Blood Pressure
- RAAS = Renin-Angiotensin-Aldosterone System
- ACE = Angiotensin-Converting Enzyme
- ARBs = Angiotensin Receptor Blockers

**BP Goal for Heart Failure is**

- **<130/80mmHg**
Question 3: What is CB’s BP goal?

- A. <140/90mmHg
- B. <120/80mmHg
- C. <130/80mmHg
- D. All of the above
Question 4: What is the next best approach to optimize CB’s regimen?

- A. lisinopril
- B. metoprolol tartrate
- C. spironolactone
- D. torsemide
AHA/ACCF/HFSA 2017 Update
Comorbidity Management

- Hypertension
- Anemia
- Sleep Apnea
Anemia

- **Recommendation (IIB-BR):** NYHA II and III HF and iron deficiency, IV iron replacement might be reasonable to improve functional status and QOL
  - FAIR-HF: improvement in NYHA class and functional capacity
  - CONFIRM-HF: larger cohort, improvement in 6 minute walk
  - Meta-analysis of 5 prospective trials, IV iron statistically significant improvements in functional capacity and LVEF. No mortality reduction.
  - There is uncertain evidence base for oral iron repletion in the setting of anemia associated with HF

- **Recommendation (III-BR):** ESAs should not be used to improve morbidity and mortality
  - STAMINA-HeFT, large RCT darbepoetin alfa was not associated with significant clinical benefits
  - Increased risk of thromboembolic events and fatal/nonfatal strokes

Sleep Disordered Breathing

- Common comorbidity in heart failure
- Approximately 50% of heart failure patients have sleep apnea
- Contributes to HFpEF
- Heart failure patients with sleep apnea may have less daytime sleepiness
### Recommendations for Treatment of Sleep Disorders

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>In patients with NYHA class II–IV HF and suspicion of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable (200, 201).</td>
<td><strong>NEW:</strong> Recommendation reflects clinical necessity to distinguish obstructive versus central sleep apnea.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Online Data Supplement G.</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>B-R</td>
<td>In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness (204).</td>
<td><strong>NEW:</strong> New data demonstrate the limited scope of benefit expected from CPAP for obstructive sleep apnea.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Online Data Supplement G.</td>
<td></td>
</tr>
</tbody>
</table>

Sleep disorders are common in patients with HF. A study of adults with chronic HF treated with evidence-based therapies found that 61% had either central or obstructive sleep apnea (202). It is clinically important to distinguish obstructive sleep apnea from central sleep apnea, given the different responses to treatment. Adaptive servo-ventilation for central sleep apnea is associated with harm (203). Continuous positive airway pressure (CPAP) for obstructive sleep apnea improves sleep quality, reduces the apnea-hypopnea index, and improves nocturnal oxygenation (200, 201).

In patients with sleep apnea, a trial evaluated the impact of CPAP with usual therapy versus usual therapy alone on subsequent cardiovascular events, including HF (204). In this RCT of >2,700 patients, there was no evidence of benefit on cardiovascular events at a mean follow-up of 3.7 years for CPAP plus usual care compared with usual care alone. Improvements in sleep quality were noteworthy and represented the primary indication for initiating CPAP treatment (204). However, in patients with atrial fibrillation (AF) (a frequent comorbidity noted with HF), the use of CPAP for obstructive sleep apnea was helpful. In a trial of 10,132 patients with AF and obstructive sleep apnea, patients on CPAP treatment were less likely to progress to more permanent forms of AF than were patients without CPAP (205).
Summary and Conclusions

**HFreF**
- Switch to **ARNI** if appropriate to ↓ morbidity and mortality
- Use **ivabradine** in HR >70bpm on optimal beta blocker dose

**HFpEF**
- Consider **aldosterone antagonist** in appropriate patients to ↓ morbidity
- Avoid nitrates and PDE-5 inhibitors

**Both**
- BP goal <130/80mmHg
- Anemia
  - IV iron
  - Avoid ESAs
- Test for **sleep apnea** and treat if present

• Anemia
  - IV iron
  - Avoid ESAs
  - Test for sleep apnea and treat if present
Updates in Heart Failure Pharmacotherapy

MEGAN VALENTE, PHARMD, BCACP
KATHLEEN FAULKENBERG, PHARMD, BCPS