HEART FAILURE: IN THE TRENCHES AND BEYOND THE GUIDELINES

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DISCLOSURES

• NONE

PARADIGM-HF TRIAL

• HF results in activation of neurohormones
• Hemodynamically detrimental neurohormones increase salt/water retention, vasoconstrict, and adversely remodel LV
• Hemodynamically beneficial neurohormones counteract adverse neurohormones
• In HF, the balance is shifted towards unfavorable neurohormones and degradation of beneficial neurohormones

Unfavorable Neurohormones: NE, AVP, RAAS, endothelin, cytokines
Beneficial Neurohormones: ANP, BNP, CNP, Adrenomedullin, substance P
Neprilysin degrades beneficial Neurohormones
Antagonizing neprilysin results in potentiation of beneficial neurohormones

Sacubitril inhibits neprilysin
Valsartan is an AT1 receptor antagonist
Combination of ACEI-sacubitril results in unacceptable rate of angioedema
Combine sacubitril and valsartan and compare it to ACEI-PARADIGM-HF TRIAL

LCZ696 (sacubitril-valsartan, now called Entresto) vs. enalapril
N=8442
Inclusion: LVEF 35%, NYHA II-IV, on GDMT
Primary Endpoint: Composite of CV death or HF hospitalization.
Study was designed to detect a difference in CV death
PARADIGM-HF TRIAL

- Median follow-up 27 months
- Patient characteristics:
  - Male: 78-79%
  - Caucasian: 66%
  - Ischemic CM: 59-60%
  - NYHA Functional Class I: 4-5%; II: 70%; III 21%; IV <1%

PARADIGM-HF TRIAL RESULTS

- Trial terminated early after 27 months due to overwhelming benefit with LCZ696 over enalapril
- LCZ696 was superior to enalapril by:
  - 20% RRR CV death (p<0.001)
  - 21% RRR HF hospitalization (p<0.001)
  - 16% RRR all cause death (p<0.001)

PARADIGM-HF RESULTS

PARADIGM IN THE TRENCHES

- Sacubitril-Valsartan is superior to either ACEI or ARB in improving survival and decreasing HF hospitalization
- HFrEF therapy with ACEI is officially second-best therapy
- HFrEF therapy with ARB without sacubitril is officially second-best therapy

PARADIGM IN THE TRENCHES

- Convert all NYHA II-III HFrEF patients now on ACEI or ARB to sacubitril-valsartan IF POSSIBLE
- Allow 36-48 hours between the last dose of ACEI and first dose of sacubitril-ARB
- If ARB is contraindicated, so is sacubitril-valsartan
- NEVER COMBINE ACEI and sacubitril-valsartan

CHAMPION TRIAL

- Increases in intracardiac and pulmonary artery pressures are the cause of clinical congestion and are apparent several days-weeks before the onset of worsening signs, symptoms, and hospital admission for ADHF
- Pressure elevation is independent of and occurs earlier than changes in weight
- Early intervention targeting these pressures may reduce the risk of ADHF hospitalization
The aim of this randomized, multicenter, single blind, controlled study was to evaluate the safety of the system and the efficacy of PA pressure-guided therapy on HF hospitalization.

**Champion Trial**

- Wireless PA hemodynamic monitoring vs. NO monitoring + standard care
- N= 550
- Primary endpoint: rate of HF hospitalizations at 6 months
- Inclusion: NYHA III HF patients on GDMT with ≥ 1 HF hospitalization in the past 12 months

NYHA III HF patients irrespective of LVEF and who had been hospitalized for HF within the past 12 months were implanted with the CardioMEMS PA sensor (n=550); patients were randomized to either the treatment group (HF management guided by PA pressure measurements, n=270), or the control group (standard of care management, n=280).

Mean follow-up time was 15 months.

Both primary safety and efficacy endpoints were met.

Patients had a 98.6% freedom from device or system-related complications (95% CI 97.3-99.4) with no pressure sensor failures (95% CI 99.3-100.0).

The rate of HF hospitalizations at 6 months was reduced by 28% in the treatment group (p=0.0002).

During the first 6 months of follow-up, compared to the control group, the treatment group had:
- A greater reduction in PA pressure (−156. v. 33 mean area under the curve, p<0.008)
- Fewer patients admitted to the hospital for HF (20% treatment group vs. 29% control group, p< 0.03)
- More days alive outside of the hospital (174.4 + 31.1 vs. 172.1 + 37.8 days, p= 0.02)

During the entire follow-up (mean 15 months), PA pressure guided therapy (treatment group) significantly reduced HF hospitalization by 37% compared to the control group (p<0.0001).

The treatment group had a lower risk of death or freedom from first HF hospitalization during the entire follow-up period compared to the control group (p=0.0086).
CHAMPION TRIAL RESULTS

- PA pressure-guided therapy reduces HF hospitalizations and improves quality of life in patients with reduced or preserved ejection fraction.

CHAMPION RESULTS

- Indicated in NYHA III patients, irrespective of LVEF, on optimal doses of GDMT, one HF hospitalization in the past 12 months.
- FDA approved to decrease HF hospitalization.

CHAMPION TRIAL: IN THE TRENCHES

- Useful in patients frequently hospitalized for ADHF.
- PA pressure increases up to 3 weeks before hospitalization independent of weight change and symptoms allowing diuresis and prevention of hospitalization.

CHAMPION TRIAL: IN THE TRENCHES

- Evaluate PA pressures as often as desired: daily to once weekly.
- When PA pressures are increasing, increase the diuretic or nitrate.
- When PA pressures are decreasing excessively, decrease the diuretic or nitrate.
**SHIFT TRIAL**

- In HFrEF patients with sinus rhythm, a resting HR > 70 is a risk factor for mortality and HF hospitalizations in patients with CAD and LV dysfunction.
- HR reduction reduces the risk of death and HF hospitalizations.
- Ivabradine is an inhibitor of the “funny” channel in the SA node allowing the slowing of the sinus rate without decreasing BP or acting as a negative inotrope.

**SHIFT TRIAL**

- **Lancet** 2010; 376: 875-885
- Ivabradine v. placebo
- Inclusion: LVEF ≤ 35%, NYHA II-IV, HF admission in the past 12 months, HR > 70, sinus rhythm, on GDMT
- N = 6558
- Primary endpoint: composite of CV death or HF hospitalization

**SHIFT TRIAL**

- Purpose: To determine the effect of ivabradine on CV outcomes, symptoms, and quality of life in patients with chronic heart failure and systolic dysfunction.
- Design: randomized, double blind, parallel-group, controlled trial.
- Baseline therapy: 89% were on beta blockers.

**SHIFT TRIAL: PRIMARY ENDPOINT RESULTS**

- 24% in Ivabradine group vs. 29% in placebo group (HR 0.82, CI 0.75-0.90, p<0.0001)
- RRR 18%
- ARR 5%
- NNT: 30 over 23 months of treatment
Only 56% were receiving >50% of target dose of beta blocker
Would outcome of the trial have been different if all patients were on optimum dose of beta blocker?

FDA approved to decrease HF hospitalization in HF patients with LVEF <35%, NYHA II-IV, sinus rhythm, on GDMT
Useful if HFrEF HR>70 in sinus rhythm on maximum tolerated beta blocker dose to decrease HF hospitalization

Continuous positive airway pressure can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea

Sleep disordered breathing is common in HF patients
61% of HF patients have either central or obstructive sleep disordered breathing
Obstructive sleep apnea is common in HFpEF
Central sleep apnea is common in HFrEF

The primary treatment for obstructive sleep apnea is nocturnal continuous positive airway pressure
Benefits of CPAP in HF patients: improved cardiac function, sympathetic activity, and HRQOL
**SLEEP DISORDERED BREATHING (SDB): IN THE TRENCHES**

- SLB is common - screen all HF patients for SDB with an overnight oximetry
- Obstructive sleep apnea is suspected by common symptoms. Central sleep apnea may be asymptomatic.
- If overnight oximetry demonstrates ≥ 5 minutes of O2 saturation ≤ 88%, obtain sleep study

**EXERCISE AND CARDIAC REHAB: GUIDELINES**

- **CLASS I**
  - Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status
- **CLASS IIa**
  - Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality

**EXERCISE AND CARDIAC REHAB: IN THE TRENCHES**

- After hospital discharge for ADHF, refer to cardiac rehab if LVEF ≤ 35%
- If outpatient, NYHA II-III HFrEF, and LVEF ≤ 35%, refer to cardiac rehab
- HFrEF patients benefit from exercise, but cardiac rehab is not reimbursed.
  - Recommend 30 minutes of moderate intensity exercise 3 times weekly and increase duration and frequency with time

**DIURETICS: THE GUIDELINES**

- **CLASS I**
  - Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms

**DIURETICS: SELECTION OF PATIENTS**

- Prescribe to all patients who have evidence of and to most patients with a prior history of fluid retention.
- Diuretics should generally be combined with an ACE inhibitor, beta blocker, and aldosterone antagonist

**DIURETICS: INITIATION AND MAINTENANCE**

- Most commonly used loop diuretic for HF treatment is furosemide, but some patients respond more favorably to bumetanide or torsemide (both have increased bioavailability relative to furosemide)
- The ultimate goal of diuretic treatment is to eliminate clinical evidence of fluid retention
- Diuretics are generally combined with moderate dietary Na restriction
DIURETICS: INITIATION AND MAINTENANCE

- Decongest until all evidence of fluid retention has resolved, then switch to a maintenance dose
- Adjust the maintenance dose based on daily weight and, in NYHA III patients, PA pressure monitoring

DIURETICS: INITIATION AND MAINTENANCE

- If diuretic unresponsiveness occurs, consider the following differential diagnosis:
  - High dietary Na intake
  - NSAID use
  - Renal function has deteriorated

DIURETICS: RISKS OF TREATMENT

- Electrolyte depletion
  - Hypokalemia
  - Hypomagnesemia
  - Hypocalcemia
- Fluid depletion
  - Hypovolemia
  - Renal insufficiency

DIURETICS: IN THE TRENCHES

- Used to treat signs and symptoms of congestion, not reduced LVEF
- Decongest until all signs and symptoms of congestion resolve
- Best combination: loop diuretic + Na restriction + GDMT for HFrEF

DIURETICS: IN THE TRENCHES

- Monitor for electrolytes and intravascular volume depletion
- Diuretics (and nitrates) are best administered in NYHA III patients based on outpatient PA pressure monitoring

ACE INHIBITORS: GUIDELINES

- CLASS I
  - In all patients with a recent or remote history of MI or ACS and reduced EF, ACE inhibitors should be used to prevent symptomatic HF and reduce mortality
  - ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality
ACE INHIBITORS IN STAGE B HF:
GUIDELINES

- CLASS I
  - ACE inhibitors should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history or MI

ACE INHIBITORS: SELECTION OF PATIENTS

- Use ACEI in all patients with asymptomatic LV dysfunction (LVEF < 40%) unless contraindicated (ACCF stage B HF)
- Use in all patients with HFrEF (LVEF < 40%) with current or prior symptoms (ACCF stage C HF)
- Use with caution in patients with CREA >3, bilateral renal artery stenosis, or SBP < 80 mm Hg

ACE INHIBITORS: SELECTION OF PATIENTS

- ACEI is contraindicated in patients with a history of angioedema with previous ACEI exposure
- ACEI is contraindicated in pregnancy or if a patient plans to become pregnant

ACEI: INITIATION AND MAINTENANCE

- There appear to be no difference among ACEI in their effects on symptoms or survival.
- Initiate at low doses and monitor K and renal function within 1-2 weeks of initiation
- Uptitrate to doses that have been shown to reduce the risk of CV events in clinical trials

ACEI: RISKS OF TREATMENT

- 2 principal actions of ACEI: angiotensin suppression and kinin potentiation
- Adverse effects are also due to angiotensin suppression and kinin potentiation

ACEI: RISKS OF TREATMENT

- Angiotensin suppression: hypotension, hyperkalemia, and renal insufficiency
- Kinin Potentiation: cough and angioedema
ACEI: RISKS OF TREATMENT
- Other adverse effects include rash and taste disturbance
- 10-20% of patients will experience a cough
- Before discontinuing ACEI due to cough, be sure cough is truly due to ACEI

ACEI: IN THE TRENCHES
- Use in all patients with LVEF ≤ 40% unless contraindicated
- Start with low dose, monitor vitals and labs, and increase every 2 weeks to goal doses used in clinical trial
- Do not discontinue ACEI due to cough until pulmonary congestion is excluded

ANGIOTENSIN RECEPTOR BLOCKER (ARB): GUIDELINE
- CLASS I
  - ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality.
- CLASS IIa
  - ARBs are reasonable to reduce morbidity and mortality as alternatives to ACEI as first line therapy for patients with HFrEF, especially for patients already taking ARBs for other indications, unless contraindicated

ANGIOTENSIN RECEPTOR BLOCKER: GUIDELINES
- CLASS III
  - Routine combined use of an ACEI, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF.

ARB: SELECTION OF PATIENTS
- ARBs are used in patients with HFrEF who are ACEI intolerant due to cough or possibly angioedema.
- May be used as an alternative to ACEI in patients already taking an ARB for another reason.
- ARB has identical indications to ACEI and is used in HFrEF patients who are unable to tolerate ACEI due to cough or angioedema

ARB: INITIATION AND MAINTENANCE
- Start at low dose and uptitrate every 2 weeks if possible
  - Losartan 25 mg daily
  - Candesartan 4 mg daily
  - Valsartan 40 mg BID
### ARB: INITIATION AND MAINTENANCE

- Monitor K, renal function, and BP 1-2 weeks after initiation.
- Titration is achieved by doubling the dose.

### ARBS: IN THE TRENCHES

- 3 ARBs have been studied in HFrEF: valsartan, losartan, and candesartan.
- Uptitrate to doses used in survival trials.
- Use ARB rather than ACEI in HFrEF when ACEI cannot be used due to cough and possibly angioedema.

### ARBS: IN THE TRENCHES

- If ACEI is contraindicated due to renal insufficiency, hypotension, or hyperkalemia, so is ARB.
- Use the combination of nitrate-hydralazine in HFrEF patients who cannot tolerate ACEI or ARB due to hyperkalemia, renal insufficiency, or hypotension.
- Never combine ACEI, ARB, and aldosterone antagonist.

### BETA BLOCKERS: GUIDELINES

- Use of 1 of the 3 beta blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality.

### BETA BLOCKERS IN STAGE B HF: GUIDELINES

- CLASS I
  - In all patients with a recent or remote history of MI or ACS and reduced EF, evidence-based beta blockers should be used to reduce mortality.
  - Beta blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI.

### BETA BLOCKERS: SELECTION OF PATIENTS

- Use evidence based beta blocker in all patients with asymptomatic LV dysfunction (LVEF < 40%) unless contraindicated (ACCF stage B HF).
- Use in all patients with HFrEF (LVEF ≤40%) with current or prior symptoms (ACCF stage C HF).
**BETA BLOCKERS: SELECTION OF PATIENTS**

- Prescribe to all patients with stable HFrEF unless contraindicated
- Prescribe as soon as HFrEF is diagnosed when stable and congestion-free irrespective of NYHA functional class
- Do not wait for up titration of ACEI dose before initiating beta blocker

**BETA BLOCKERS: SELECTION OF PATIENTS**

- In patients with a current or recent history of fluid retention, beta blockers should not be prescribed without diuretics
- Beta blockers may be considered in patients with reactive airway disease or asymptomatic bradycardia but should be used cautiously with persistent symptoms of either condition

**BETA BLOCKERS: INITIATION AND MAINTENANCE**

- Initiate at very low dose and gradually increase every 2-4 weeks if low doses tolerated
- Up titrate to the maximally tolerated dose and attempt to reach the target doses used in clinical trials even if asymptomatic and stable at lower doses.

**BETA BLOCKER: INITIATION AND MAINTENANCE**

- CARVEDILOL
  - Starting dose: 3.125 mg BID
  - Target dose: 25 mg BID (50 mg BID if wt> 85 kg)
- METOPROLOL SUCCINATE
  - Starting dose: 12.5-25 mg daily
  - Target dose: 200 mg daily

**BETA BLOCKER: INITIATION AND MAINTENANCE**

- BISOPROLOL
  - Starting dose: 1.25 mg daily
  - Target dose: 10 mg daily

**BETA BLOCKER: RISKS OF TREATMENT**

- 4 types of adverse reactions to monitor when initiating or up titrating beta blockers
  - Bradycardia or AV block
  - Fatigue
  - Increased congestion and worsening HF
  - Hypotension
**Beta Blocker: Risk of Treatment**

- Bradycardia or Heart Block
  - Do not limit the dose of beta blocker because of bradycardia or AV block alone if not hypotensive. Consider permanent pacemaker implantation rather than limiting beta blocker dose.
  - Inability to increase the beta blocker dose due to bradycardia or AV block in the presence of stable BP is an indication for permanent pacemaker implantation.

**Beta Blocker: In the Trenches**

- Use only evidence-based beta blockers in HFpEF: carvedilol, bisoprolol, or metoprolol succinate.
- Give the once daily ACEI or ARB at night, allowing daytime uptitration of the evidence-based beta blocker during the day.
- If congestion increases with beta blocker, increase diuretic.

**Beta Blocker: In The Trenches**

- If hypotensive with beta blocker use without congestion, decrease diuretic or ACEI dose.
- In HFpEF patients, do not limit beta blocker or ACEI dose for asymptomatic hypotension unless SBP <80 mm Hg.
- Remember that bradycardia or AV block can always be paced. Both CRT and beta blockers improve survival.

**Beta Blocker: Risk of Treatment**

- Fluid Retention and Worsening HF
  - Do not consider this an indication to permanently withdraw treatment.
  - Treatment of congestion and worsening HF requires intensification of conventional therapy.
  - Increased congestion requires intensification of diuretic therapy.

**Beta Blockers: Risks of Treatment**

- Fatigue
  - Multifactorial symptom that may or may not be related to beta blocker.
  - Before discontinuing the beta blocker because of fatigue, consider other fatigue etiologies including sleep disordered breathing, overdiuresis, or depression.
**HFpEF: THE GUIDELINES**

- **CLASS I**
  - Systolic and diastolic BP should be controlled in patients with HFpEF in accordance with published clinical practice guidelines to prevent morbidity
  - Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF

- **CLASS IIa**
  - Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HFpEF despite GDMT
  - Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptomatic HF
  - The use of beta blocking agents, ACEI, and ARBs in patients with hypertension is reasonable to control BP in patients with HFpEF

**HFpEF: THE EVIDENCE**

- **CHARM PRESERVE:** Lancet 2003; 362: 777-81
  - Candesartan significantly reduced HF hospitalization only and there was NO improvement in CV death

  - Irbesartan treatment resulted in no difference in death or CV hospitalization. No difference in any subgroup was noted.

- **PEP-CHF:** Eur Heart J 2006; 27: 2338-45
  - Study was underpowered for the primary endpoint (all cause mortality or unplanned HF hospitalization)

**HFpEF THERAPY POST GUIDELINES**

- **TOPCAT:** N Eng J Med 2014; 370: 1383-92
  - N= 3445
  - Symptomatic HF LVEF ≥ 45%
  - Spironolactone (15-45 mg/day v. placebo)
  - Primary Endpoint: Composite of CV death, aborted cardiac arrest, or HF hospitalization
  - Results: only HF hospitalization was significantly reduced

- **TOPCAT: ARE WE SURE OF THE RESULTS??**
  - 6 trial centers: West v. East
  - US, Canada, Argentina, and Brazil -> the west
  - Republic of Georgia, Russia -> the east
  - Western trial centers: ALL ENDPOINTS DEMONSTRATED STATISTICALLY SIGNIFICANT REDUCTION WITH SPIRONOLACTONE
  - Eastern trial centers: Only HF hospitalization demonstrated a statistically significant reduction
**HFpEF Therapy Post Guidelines**

*TOPCAT: Why the Difference??*
- Inclusion criteria into the trial: Either elevated BNP or un-adjudicated HF hospitalization within the past year
  - 80% of eastern patients were included with an un-adjudicated HF hospitalization, 20% had elevated BNP
  - 50% of western patients were included with an un-adjudicated HF hospitalization, 50% had elevated BNP
- Everyone (both east and west) included in the trial with an elevated BNP benefitted!!
- How many un-adjudicated HF hospitalizations in the east were truly HF?

**HFpEF Therapy Post Guidelines**

*TOPCAT: Did the Eastern Patients Truly Have HF? Did They Truly Receive the Study Drug?*
- West: administration of spironolactone resulted in significantly more elevation of K, increase of Cr, and decrease of BP
- East: administration of spironolactone resulted in minimal elevation of K, increase of Cr, and decrease of BP

**Tophome Message**
- Spironolactone is appropriate for all HFpEF patients barring contraindications to reduce HF hospitalization (irrespective of geography)
- In the west, spironolactone reduces CV mortality
- If your patient has hyperkalemia, AKI, or hypotension due to spironolactone, consider this: don't discontinue spironolactone—just send them to Russia.

**Statins: Guidelines**

*Class III (No Benefit)*
- Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use

**Statins: The Evidence**

- There was no statistical difference between rosvastatin 10 mg daily versus placebo in composite of time to first event of death from CV causes and nonfatal MI/CVA
- No effect of rosvastatin in time to death or CV hospitalization versus placebo

**Statins**

- Statins prevent new onset HF
- Statins have favorable effects on inflammation, oxidative stress, and vascular performance
**STATINS**

- CORONA and GISSI-HF demonstrate rosuvastatin has neutral effects on long term outcomes in chronic HF when added to GDMT
- Statin therapy should NOT be prescribed primarily for the treatment of HF to improve clinical outcomes.

**STATINS: IN THE TRENCHES**

- Use statin according to guidelines for hyperlipidemia (LDL>190), documented atherosclerosis, diabetics age 40-75 with LDL 70-189, and as primary prevention in those with Pooled Cohort Analysis 10 year risk of ASCVD > 7.5%
- Do not start statin solely for HFpEF - no benefit
- PERHAPS consider statin for HFpEF with CRP>2

**HYDRAZINE-NITRATE COMBINATION: GUIDELINES**

- **CLASS I**
  - The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III-IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated

- **CLASS IIa**
  - A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated

**HYDRAZINE-NITRATE COMBINATION: EVIDENCE**


**HYDRAZINE-NITRATE COMBINATION: HISTORY**

- V-HeFT: use of hydralazine and ISDN reduced mortality but not hospitalizations in patients with HF treated with digoxin and diuretics but not an ACEI or beta blocker.
### Hydralazine-Nitrate Combination: History

**V-HeFT II:** (hydralazine + ISDN versus enalapril) - enalapril produced more favorable effects of survival over hydrazine-nitrate combination

**A-HeFT:** fixed dose combination nitrate and hydralazine improved survival in African Americans with LVEF < 35% or (<45% with LVEDD >6.5 cm) with NYHA III-IV functional capacity

- Patients were on standard therapy with ACE (70%) or ARB (17%), beta blocker (74%), diuretics (90%), digoxin (60%), and spironolactone (39%)

### Hydralazine-Nitrate Combination: African Americans

**A-HeFT:** Combination significantly improved primary endpoint ($p=0.01$)

- Self-identified as African American
- LVEF $\leq 35\%$ or < 45% with LVEDD > 6.5 cm, NYHA III-IV
- Fixed dose of ISDN/hydralazine + ACEI or ARB + beta blocker + aldosterone antagonist v. placebo + ACEI or ARB + beta blocker + aldosterone antagonist
- Primary Endpoint: Composite score of weighted values for All cause death, first HF hospitalization, and change in QoL score

### Hydralazine-Nitrate Combination: Dosing

**Initiation**
- Fixed Dose: one tablet contains 20 mg ISDN and 37.5 mg hydralazine
- One tab TID
- Individual tabs: start with hydralazine 10 mg TID + ISDN 10 mg TID

**Maintenance**
- Fixed Dose: Up titrate to 2 tabs TID
- Individual tabs: Goal is 120 mg/day ISDN and 300 mg/day of hydralazine

### Hydralazine-Nitrate Combination: Patient Selection

- Use in African American HfPEF patients who remain symptomatic despite concomitant use of ACEI or ARB, beta blockers, and aldosterone antagonists.
- Use in all patients with HFPEF in whom ACEI and ARB are contraindicated due to hyperkalemia, renal insufficiency, or hypotension

### Hydralazine-Nitrate Combination: Risks of Treatment

- Adherence is poor because of the large number of tablets required, frequency of administration, and high incidence of adverse reactions.
- Frequent adverse effects:
  - Headache
  - Dizziness
  - GI complaints
**HYDRAZINE-NITRATE COMBINATION: IN THE TRENCHES**

- Use in African Americans with LVEF < 35%, already on GDMT, and still have NYHA III-IV symptoms
- Use in all HFrEF patients who cannot tolerate ACEI or ARB because of renal insufficiency, hyperkalemia, or hypotension
- Titrate does to doses used in survival trials

**DIGOXIN: GUIDELINES**

- **CLASS IIa**
  - Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalization for Heart Failure.

**DIGOXIN: THE BASICS**

- Treatment with digoxin for 1-3 months can improve: HRQOL, and exercise tolerance
- These benefits are seen regardless of:
  - Underlying rhythm (NSR v AF), cause of HF (ischemic v nonischemic), or concomitant therapy (with or without ACEI)

**DIGOXIN: THE BASICS**

- Treatment with digoxin for 2-5 years will have no effect on mortality but modestly reduces the combined risk of death and hospitalization

**DIGOXIN: THE EVIDENCE**

- **DIG**: N Engl J Med 1997; 336: S25-33
  - Digoxin does not improve mortality but decreases HF hospitalization
  - Patients withdrawn from digoxin therapy developed worsening heart failure and decreased functional capacity
- **PROVED**: J Am Coll Cardiol 1993; 22: 955-62
  - Patients withdrawn from digoxin therapy showed worsened maximal exercise capacity, increased incidence of treatment failures, and decreased time to treatment failure.

**DIGOXIN: SELECTION OF PATIENTS**

- Consider adding digoxin in patients with persistent symptoms of HFrEF notwithstanding optimal uses of ACEI or ARB, beta blocker, aldosterone antagonist, and diuretics.
Digoxin may be added to the initial regimen in patients with severe symptoms who have not yet responded symptomatically during GDMT per ACCF/AHA guidelines (full text version).

If an African American patient with HFrEF has persistent symptoms (NYHA III-IV) with optimal doses of ACEI or ARB, beta blocker, diuretic, and aldosterone antagonist, use hydralazine-nitrate combination + digoxin.

In the presence of HFrEF + a fib, a beta blocker is the drug of choice for rate control. If the rate is not controlled, digoxin may be added.

Initiated and maintained dose is usually 0.125-0.25 mg/daily. Use 0.125 mg every other day if any risks are present: age >70, low lean body mass, or impaired renal function.

There is NO reason to use loading doses of digoxin to initiate therapy for HF patients. If they are stable on digoxin with therapeutic levels and no symptoms of toxicity, do not withdraw digoxin (RADIANCE, PROVED trial results).

Digoxin is usually well tolerated. Principle adverse reactions occur primarily when digoxin is administered in large doses, especially in the elderly.
**Digoxin: Risks of Treatment**

- Major adverse effects:
  - Arrhythmias: ectopic and re-entrant rhythms, heart block
  - GI: anorexia, nausea, vomiting
  - Neurologic: visual disturbances, disorientation, confusion

- Overt digoxin toxicity is commonly associated with serum digoxin levels > 2 ng/mL
- Toxicity may occur with lower digoxin levels in the presence of hypokalemia, hypomagnesemia, or hypothyroidism

- Digoxin level increases with concomitant:
  - Erythromycin, clarithromycin, verapamil, quinidine, propranolol, itraconazole, dronedarone, cyclosporine, amiodarone
  - Decrease the digoxin dose when above meds are combined with digoxin

- Low lean body mass and impaired renal function can elevate serum digoxin levels
- Remember: Keep the digoxin level between 0.5-0.9 ng/mL

**Digoxin: In the Trenches**

- Digoxin decreases HFpEF hospitalizations. Use in those frequently hospitalized with HFpEF
- Keep the digoxin level between 0.5-0.9
- Use in HFpEF patients still symptomatic after diuretics, ACEI or ARB, beta blocker, and aldosterone antagonist

- Prescribe 0.125 mg daily
- Prescribe 0.125 mg every other day if age >70, lean body mass, renal dysfunction, or concomitant meds which increase digoxin level
**OMEGA-3 FATTY ACIDS: GUIDELINES**

- Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA II-IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.

**OMEGA-3 FATTY ACIDS: THE EVIDENCE**

  - N=6975 patients
  - NYHA II-IV chronic HF
  - 1 gram omega-3 PUFA (830 mg – 882 mg EPA/DHA) daily v placebo
  - All cause mortality reduced from 29% (with placebo) to 27% (with omega-3 PUFA)
  - CV death or CV hospital admission was also significantly reduced

**OMEGA-3 POLYUNSATURATED FATTY ACID: IN THE TRENCHES**

- The use of omega-3 PUFA supplementation is reasonable as adjunctive therapy in patients with chronic HF (both HFrEF and HFpEF)
- Use the same concentration of EPA and DHA as used in GISSI-HF trial (EPA/DHA 830 mg/882 mg per day)