New Medical Modalities in Management of Heart Failure with Reduced Ejection Fraction

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Objectives

- Review the history and prognosis of HFrEF
- Describe the optimal approach to the hospitalized patient
- Describe Guideline Directed Optimal Medical Therapy (GDMT)
- Identify the therapies of limited or no value
- Describe the rationale for development of the newest agents in management and their proper application

Define the Problem

- Heart Failure with Reduced Ejection Fraction (HFrEF)
  - Depending on the trial, LVEF either <40% 0r <35%
- After over 30 years of therapeutic development, HFrEF remains the most frequent cardiac cause of death

Historical Perspective

- Prior to 1975, treatment was diuretics and digoxin.
  - Mortality 20% at 1 year, 50% at 2 years, and 80% at three years
- Development of the concept of Bblocker use in 1985 with metoprolol
  - Reduced mortality/morbidity up to 35%
- Development of the concept of ACEI in 1995 with enalapril
  - Reduced mortality/morbidity by 16%
- Development of the concept of Angiotensin blockade with spironolactone in 1999
  - Reduced mortality by 30%

STAGES

- A: Risk factors without pathology or symptoms
- B: Presence of structural change without symptoms
- C: Structural change with symptoms
- D: Structural change with refractory symptoms

CLASSES

- I: No functional limitations
- II: Symptoms with physical activity, but no limitations
- III: Symptoms which limit activity
  - A: Limitations with >4 MET activities
  - B: Limitations with <4 MET activities
- IV: Symptoms at rest

Definition

- STAGES are fixed. NO reversal with therapy
- CLASSES apply to STAGE C and D
- CLASSES may vary in response to therapy

Epidemiology

- Incidence has not changed for many decades
  - 20/1000 age 60-69
  - 80/1000 age over 70
- Prevalence continues to rise annually as population ages

Racial Differences

- AA males: 4.5%
- White males: 2.7%
- AA females: 3.8%
- White females: 1.8%

Mortality

- Ross &Wang ,JAMA 2006
  - 30 day mortality: 1993- 12.8%; 2005- 10.8%
- Seattle Heart Failure Report, 2006
  - Mortality: 1 year- 12%; 2 years- 21%; 3 years- 30%
- Ammar, et al, Circ 2007
  - 5 year mortality: Stage C- 25%; Stage D- 80%

OPTIMAL APPROACH TO THE HOSPITALIZED PATIENT

EVALUATION

- Etiologic subgroups of Acute HFrEF
  - Acute Coronary Syndrome
  - Hypertensive urgency/emergency
  - Shock
  - Acute Renal Failure
  - Acute Right Heart Failure

Common Precipitating Factors

- Ischemia
- Medical Nonadherence
- Hypertension
- Paroxysmal Afib
- New anti-inotrope (Bblocker, CAB)
- Pulmonary Embolism
- New salt retaining medication (NSAID,Steroids, Thiazoladinediones)

Noninvasive Evaluation

- Chest Xray: Class I
- Echocardiogram: Class I
- Spect Imaging: Class IIb
  - Only in patients with known CAD or high risk, and who would be potential candidates for revascularization
- Viability Study: Class IIb
  - Only in patients with known CAD who are candidates for revascularization.
  - NOTE: STITCH trial did not support this guideline

BIOMARKERS

- BNP/ Pro-BNP Class I
  - Released from myocardium during strain
  - Excellent diagnostic and prognostic value
  - As guide to therapy, RCT's demonstrate mixed results.
    - Positive studies may be due to more close adherence to GDMT
    - Persistently high BNP is consistent marker of higher mortality and increased rehospitalization

BNP Caveat

- Obesity will falsely lower levels
- Many non-CHF causes of elevation
  - Age
  - Anemia
  - Acute Kidney Injury
  - Obstructive Sleep Apnea
  - Sepsis
  - Pulmonary Hypertension

Troponin Class I

- Elevated in HFrEF even without CAD
- Associated with impaired hemodynamics
- Marker of progressive LV dysfunction
- Correlates with increased mortality
- Decreasing troponin correlates with improving prognosis

Invasive Evaluation

- Pulmonary Artery Catheterization
  - Class I: Indicated when clinical assessment is unable to determine volume status in respiratory distress or impaired perfusion
  - Class IIA:
    - When systolic BP remains low in spite of appropriate therapy
    - Worsening renal function with therapy
    - When vasoactive agents are required
  - Caveat: All medical therapy study outcomes were clinical and NOT based on hemodynamic parameters

Coronary Angiography: Class IIB

- Presentation with known CAD and angina
- Presentation with known CAD and evidence of ischemia
- Presentation with high risk for CAD and unstable

Guideline Directed Medical Therapy

- Class I: Maintain outpatient GDMT unless hemodynamically unstable
- Class I: Start beta blocker AFTER optimization of volume status AND AFTER cessation of IV diuretics and IV drips
- Caution with initiation of beta blocker in patients who required IV inotropes during hospitalization

Diuretics

- Class I: Loop diuretic
- Class I: for those patients on outpatient loop diuretic, hospital dose should be the same or higher given IV
  - DOSE trial demonstrated that bolus or continuous infusion of loop diuretic are equally effective
- Class I: Maintain accurate I/O and daily weight

Diuretics

- Class IIA: If insufficient response to IV loop diuretic dose,
  - Increase in stepwise fashion
  - Add thiazide diuretic before IV loop diuretic dose
- Class IIB: Consider low dose dopamine infusion to increase perfusion and augment diuresis

Inotropes

Study	Medication	Hospital	Mortality
PROMISE	Mil	N/A	Increase
FIRST	Dob	N/A	Increase
OPTIME	Mil	NS	NS
ESCAPE	M/D	Increase	Increase
		Increase	Increase
ADHERE	M/D	NS	NS
DICE	Dob		

Parenteral Therapy

- IV Nitroglycerin Class IIB
  - Patients with HTN, CAD, Ischemia or MR
  - Problem is tachyphylaxis
- IV Nitroprusside Class IIB
  - Patients with HTN or severe MR
  - Requires Arterial Line monitor
  - Risk is hypotension and thiocyanate toxicity

IV Nisiritide Class IIB

- Relieves subjective dyspnea most effecively
- No RCT evidence of benefit regarding rehospitalization, hospital length of stay, renal function or mortality
- Risk is hypotension
- Longest half life of all agents

Vasopressin Antagonists Class IIB

- Indicated in patients with **neurologic** symptoms secondary to hyponatremia
- Indicated only in short term
- No data on benefit of long term administration

VTE Prophylaxis Class I

- Guidelines indicate only anticoagulation as Class I
- Trials are not specific for CHF patients
- Subgroup analysis recommends
  - Enoxaparin 40mg subq daily
  - Unfractionated Heparin 5,000 units TID subq
  - Fondiparinux not demonstrated to be effective
- Literature review shows NO support for use of compression stockings

Newest developments

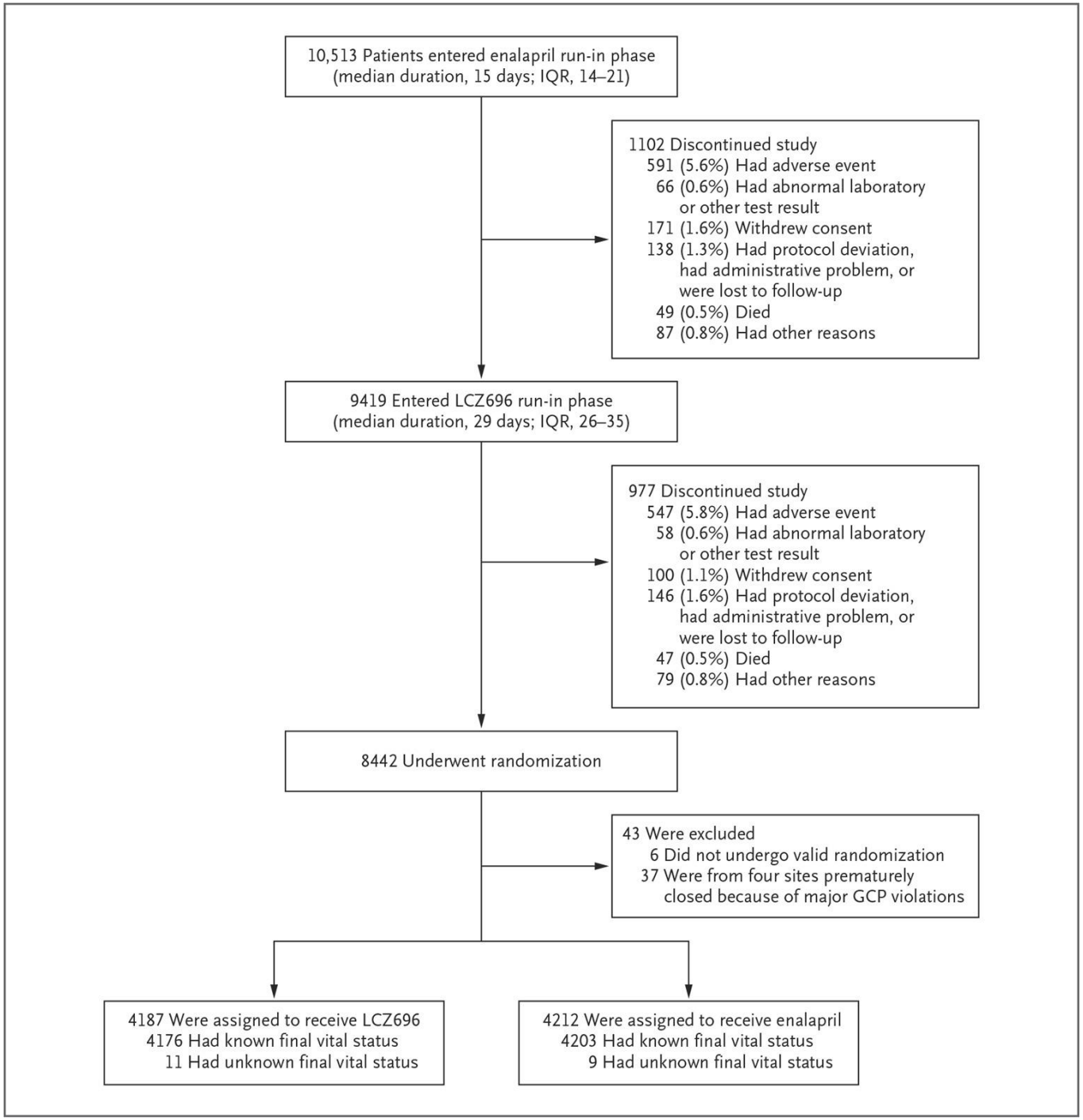
Neprilysin Inhibitor CLASS 1

- Rationale
  - Novel way to effect multiple pathways
    - Inhibits degradation of natriuretic peptides, bradykinin and adrenomodullin
    - Counteracts the neurohormonal hyperactivity in CHF
      - Vasoconstriction
      - Sodium retention
      - Maladaptive remodeling
  - Combination with RAS blocker more effective than either agent alone in small studies
  - ARB chosen for combination over ACEI due to excess incidence of angioedema

PARADIGM HF STUDY

- Angiotensin-Neprilysin Inhibition vs Enalapril in Heart Failure

McMurray et al. NEJM 2014: 371


10,513 Patients entered enalapril run-in phase
(median duration, 15 days; IQR, 14–21)
1102 Discontinued study
591 (5.6%) Had adverse event
66 (0.6%) Had abnormal laboratory or other test result
171 (1.6%) Withdrew consent
138 (1.3%) Had protocol deviation, had administrative problem, or were lost to follow-up
49 (0.5%) Died
87 (0.8%) Had other reasons
9419 Entered LCZ696 run-in phase
(median duration, 29 days; IQR, 26–35)
977 Discontinued study
547 (5.8%) Had adverse event
58 (0.6%) Had abnormal laboratory or other test result
100 (1.1%) Withdrew consent
146 (1.6%) Had protocol deviation, had administrative problem, or were lost to follow-up
47 (0.5%) Died
79 (0.8%) Had other reasons
8442 Underwent randomization
43 Were excluded
6 Did not undergo valid randomization
37 Were from four sites prematurely closed because of major GCP violations
4187 Were assigned to receive LCZ696
4176 Had known final vital status
11 Had unknown final vital status
4212 Were assigned to receive enalapril
4203 Had known final vital status
9 Had unknown final vital status

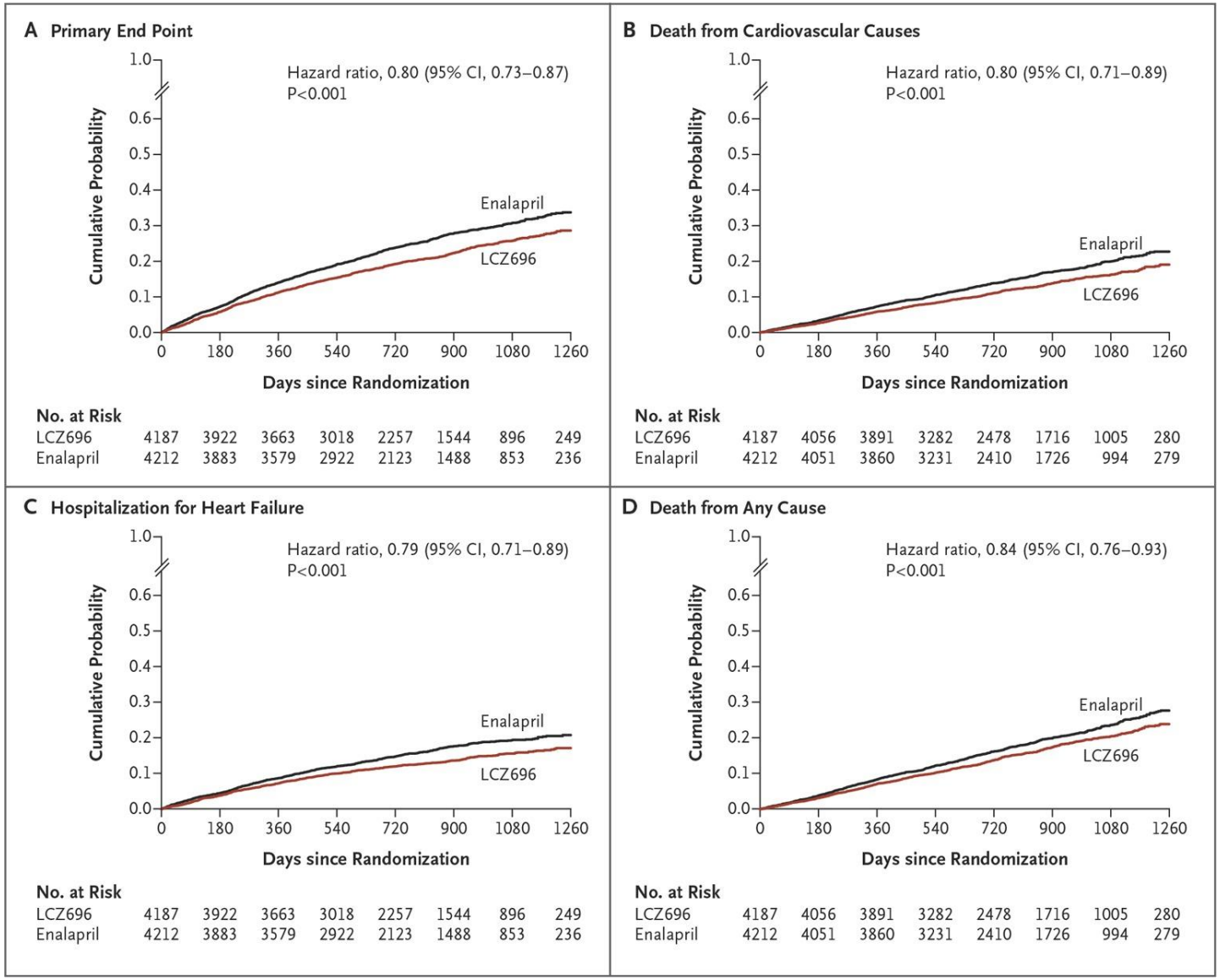

A Primary End Point
Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001
Cumulative Probability
1.0
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Enalapril
LCZ696
0 180 360 540 720 900 1080 1260
Days since Randomization
No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236
B Death from Cardiovascular Causes
Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279
C Hospitalization for Heart Failure
Hazard ratio, 0.79 (95% CI, 0.71–0.89)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236
D Death from Any Cause
Hazard ratio, 0.84 (95% CI, 0.76–0.93)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279

Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	–2.99±0.36	–4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

* Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.

† Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference.

‡ A total of 2670 patients in the LCZ696 group and 2638 patients in the enalapril group who did not have atrial fibrillation at the randomization visit were evaluated for new-onset atrial fibrillation during the study.

§ A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate (eGFR) from the value at randomization or a decrease in the eGFR of more than 30 ml per minute per 1.73 m^2, to less than 60 ml per minute per 1.73 m^2.

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P=0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P=0.56).

† Angioedema was adjudicated in a blinded fashion by an expert committee.

IVABRADINE CLASS IIA

- Reduces If current in sinus node which regulates heart rate.
- Minor affect on AV node
- Subgroup studies of other CHF trials demonstrated that CHF patients with slower heart rates had better overall outcomes

SHIFT TRIAL

- 6558 patients over age 18
- LVEF <35%
- NYHA Class II-IV
- Resting Heart rate >70
- Stable on GDMT for 4 weeks
- Dose titrated to Heart rate 50-60
- Placebo controlled
- Study duration two years

Outcomes

- Primary Endpoint (first hospitalization, CV death, or worsening heart failure)
  - Decreased 18%, p=0.001
- Secondary Endpoints
  - Death from Heart Failure reduced 26%, P=0.014
  - Hospitalization for Heart Failure reduced 26%, P=0.001
- Similar effect across all subgroups

Conclusions

- Initiate workup appropriate to the etiology
- GDMT
  - IV diuretic
  - Bblocker to continue, but do not start until volume optimal
  - ACEI/ARB
  - Spironolactone
  - Limited indications for IV vasoactives
  - Poor indication for IV inotropes
- Consider transitioning from ACEI/ARB to Neprilysin inhibitor, stopping ACE/ARB 36 hours prior
- Consider ivabridine in patients with HR > 70