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# Applying the New ACC/AHA Optimal Medical Guideline: Clinical Case Challenges

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# ACC/AHA Guideline Update



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## 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

COR	LOE	Recommendations
I	B-R	ACEi <u>OR</u> ARB <u>OR</u> ARNI in conjunction with beta-blockers + MRA (where appropriate) is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
I	B-R	In patients with chronic, symptomatic HFrEF NYHA class II or III who tolerate and ACE inhibitor or ARB, <u>replacement</u> by an ARNI is recommended to further reduce morbidity and mortality
III	B-R	ARNI should NOT be administered concomitantly with ACEi or within 36 hours of last ACEi dose
III	C=EO	ARNI should NOT be administered to patients with a history of angioedema

# ACC/AHA Guideline Update



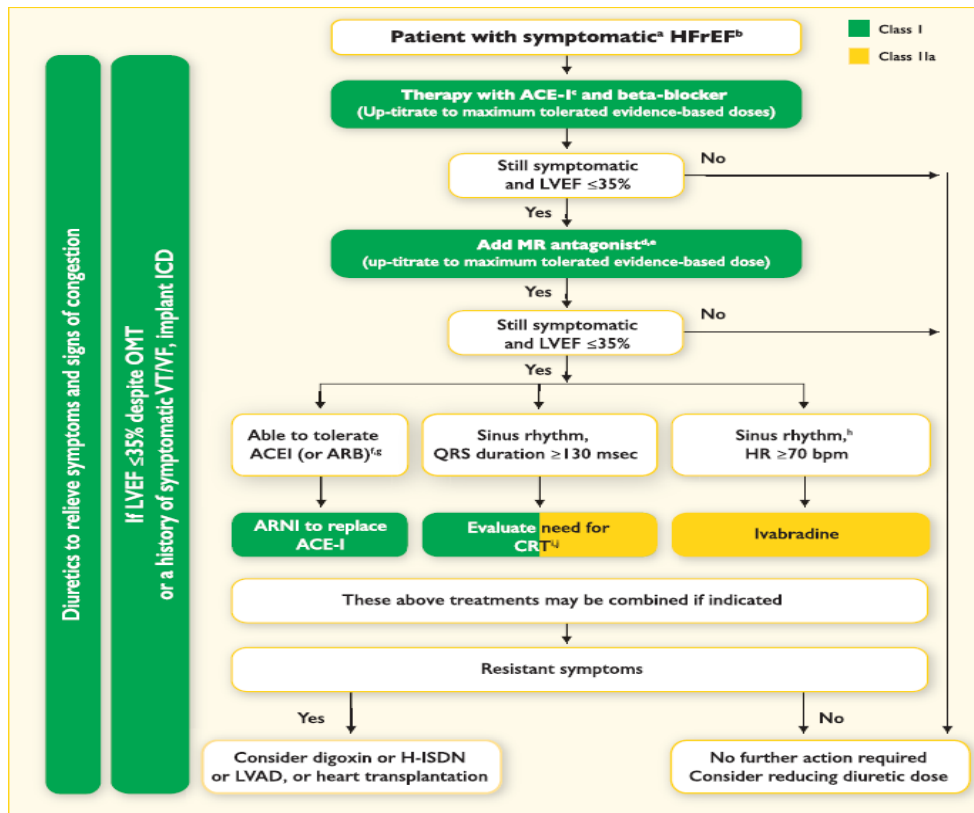
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COR	LOE	Recommendations
<b>Ila</b>	<b>B-R</b>	<b>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III), stable, chronic HFrEF (LVEF<math>\leq</math>35%) who are receiving GDMT , including a beta-blocker at maximally tolerated dose, and who are in sinus rhythm with a HR<math>\geq</math>70 bpm at rest</b>

# ESC HF Guideline Update



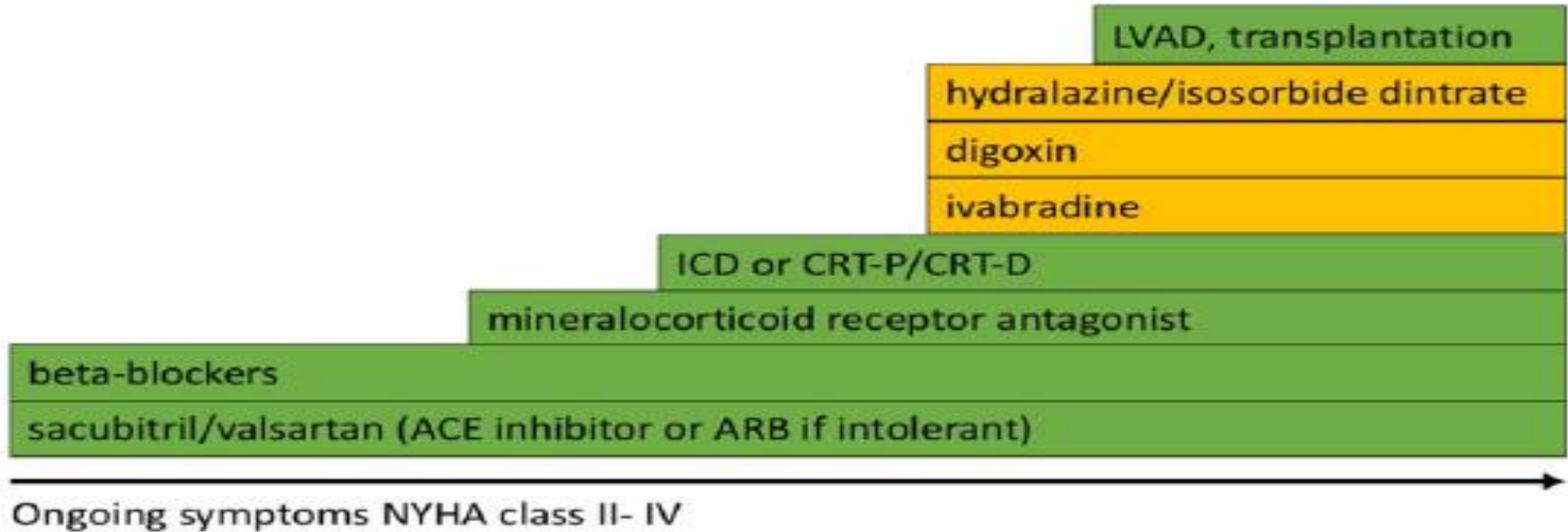
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# A New Paradigm?



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# Case #1

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**A 50 yo man with coronary heart disease, previous inferior MI, and ischemic cardiomyopathy (EF 30%) presents to your office for clinical follow up. He notes some dyspnea on climbing stairs, but is otherwise asymptomatic. He is currently treated with Lisinopril 40 mg daily, Carvedilol 6.25 mg bid, Spironolactone 25 mg daily, and furosemide 40 mg daily. His exam is notable for BP 100/70 mm Hg and HR 80 bpm. There is no jugular venous distension, lungs are clear, and there is no pedal edema. ECG confirms sinus rhythm with right bundle branch block, QRS duration 140 ms.**

# Question

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**Which of the following is the most appropriate next step?**

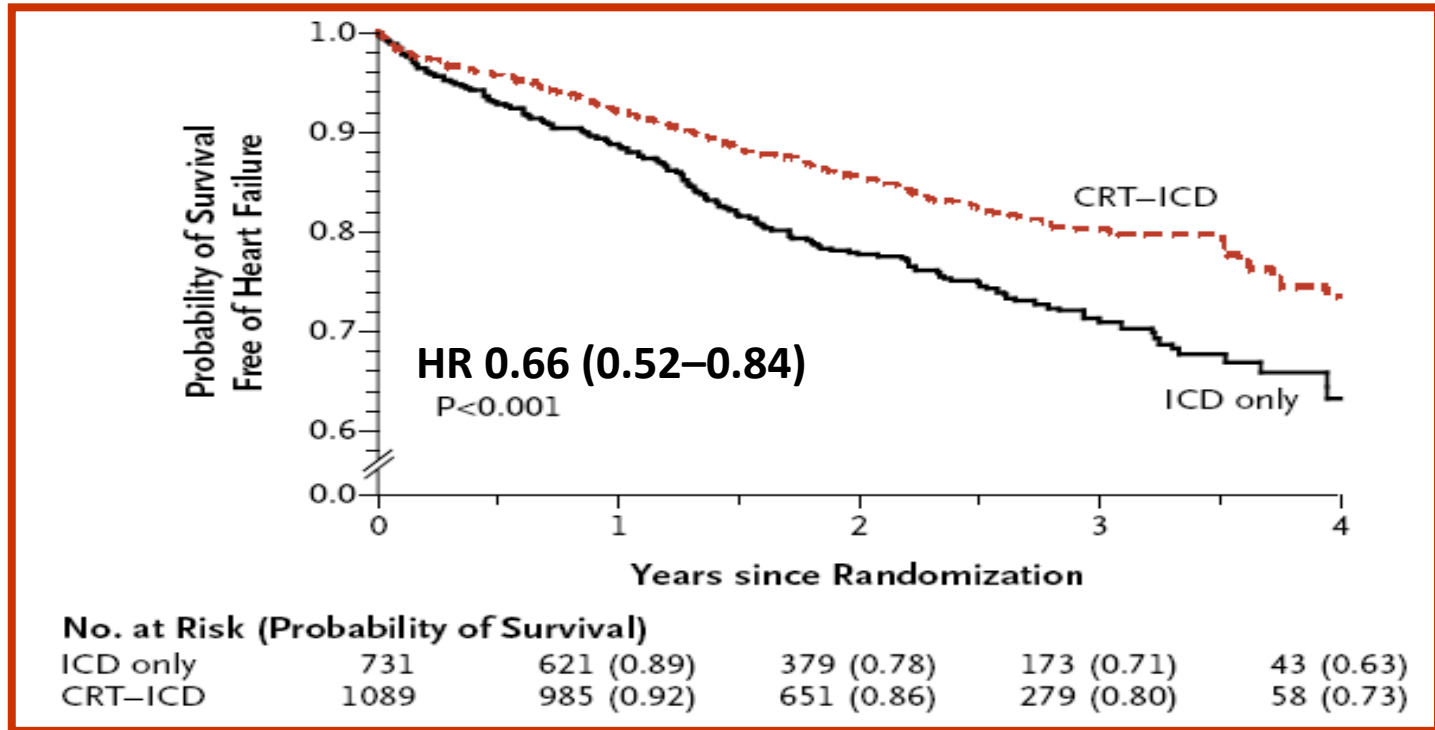
- A. Increase carvedilol to 12.5 mg bid**
- B. Refer for cardiac resynchronization therapy**
- C. Add Ivabradine 2.5 mg twice daily**
- D. Add digoxin 0.125 mg daily**
- E. Replace Lisinopril with Sacubitril/Valsartan 49/51 mg twice daily**

# Case #1

A 50 yo man with coronary heart disease, previous inferior MI, and ischemic cardiomyopathy (EF 30%) presents to your office for clinical follow up. He notes some **dyspnea on climbing stairs**, but is otherwise asymptomatic. He is currently treated with Lisinopril 40 mg daily, **Carvedilol 6.25 mg bid**, Spironolactone 25 mg daily, and furosemide 40 mg daily. His exam is notable for BP **100/70 mm Hg and HR 80 bpm**. There is no jugular venous distension, lungs are clear, and there is no pedal edema. ECG confirms **sinus rhythm with right bundle branch block, QRS duration 140 ms**.



# Cardiac Resynchronization Therapy in Patients with Mildly Symptomatic Heart Failure (MADIT-CRT)



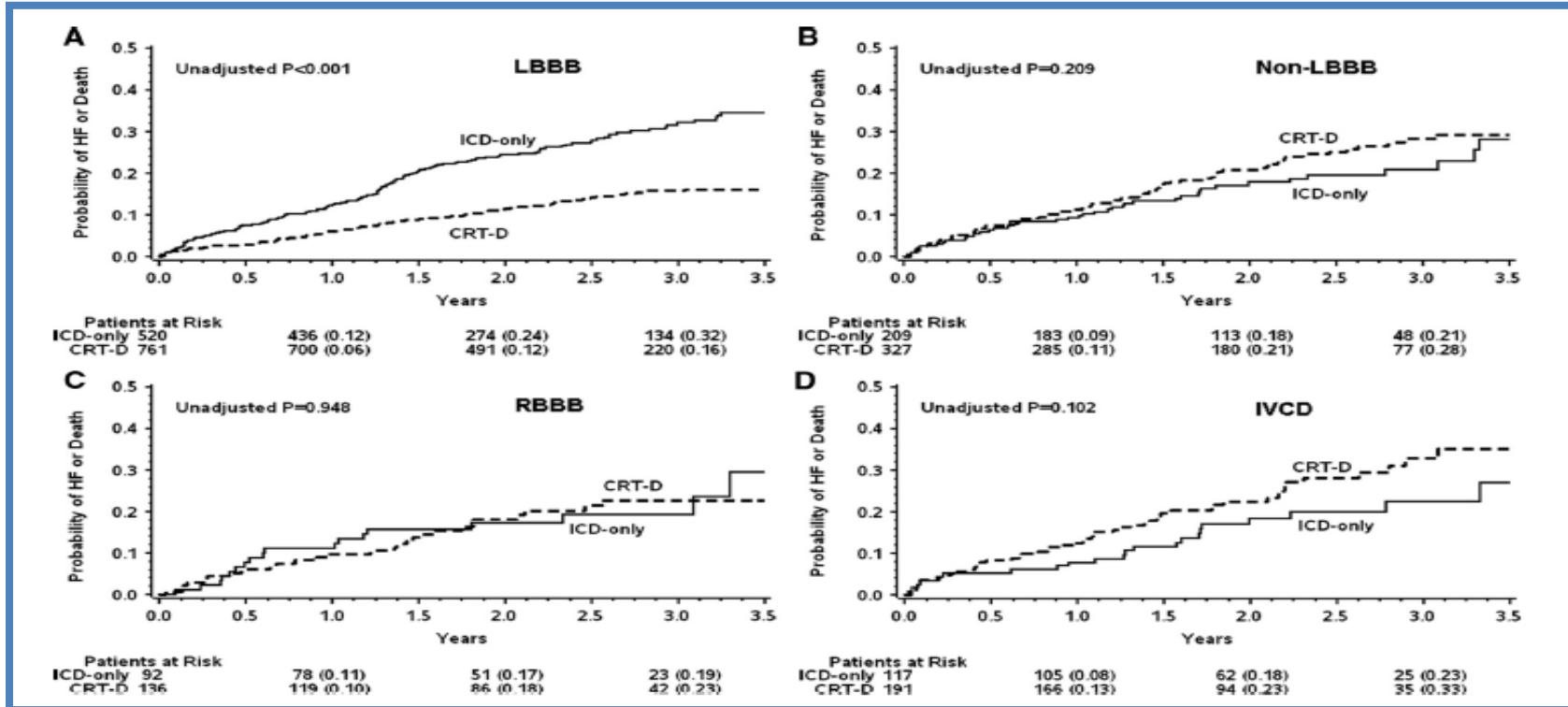
# QRS Morphology Matters

## *LBBB>>non-LBBB*



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# Effect of ivabradine on outcomes by $\beta$ -blocker doses

BB category (% of target dose)	Placebo event rate (%)	Hazard ratio	95 % CI	<i>P</i> heterogeneity	<i>P</i> Trend	<i>P</i> Trend adj**
PEP (CV death, HF hospitalisation)				0.35	0.056	0.135
No β-blocker	39.3	0.71	0.55-0.93			
BB, 25%	40	0.74	0.59-0.92			
BB, 25% to <50%	30.8	0.81	0.68-0.98			
BB, 50% to <100%	24.8	0.88	0.72-1.07			
BB, ≥100%	20.1	0.99	0.79-1.24			
HF hospitalisation				0.55	0.12	0.19
No β-blocker	29	0.62	0.45-0.85			
BB, 25%	29	0.68	0.52-0.89			
BB, 25% to <50%	22	0.74	0.59-0.93			
BB, 50% to <100%	18	0.83	0.65-1.05			
BB, ≥100%	14	0.84	0.63-1.11			

\*\*adjusted for interaction between baseline HR and randomised treatment

# Effects of Sacubitril/Valsartan by Beta-blocker dose

	LCZ696 n/N (%)	Enalapril n/N (%)	Hazard ratio (95% CI) LCZ696 vs enalapril	Subgroup by treatment int. p- value
Beta blocker target dose				
>=50%	416/1919 (21.68)	454/1848 (24.57)	0.85 (0.74, 0.97)	0.4377
<50%	424/1948 (21.77)	547/2027 (26.99)	0.79 (0.70, 0.90)	
No beta blocker	69/288 (24.0)	111/300 (37.0)	0.61 (0.45, 0.83)	

# CRT Guideline Update

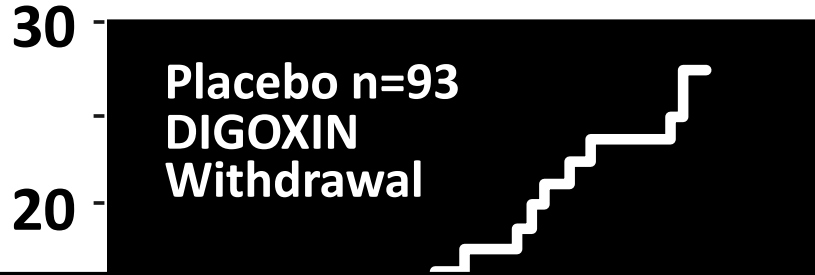
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- **Optimal Medical Therapy**
  - **Symptomatic HF**
    - **LBBB**
    - **QRS $\geq$ 150ms**

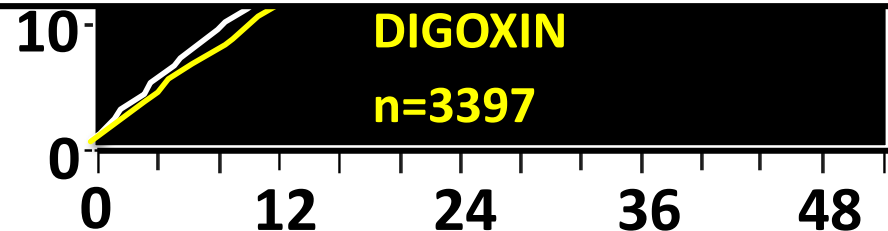
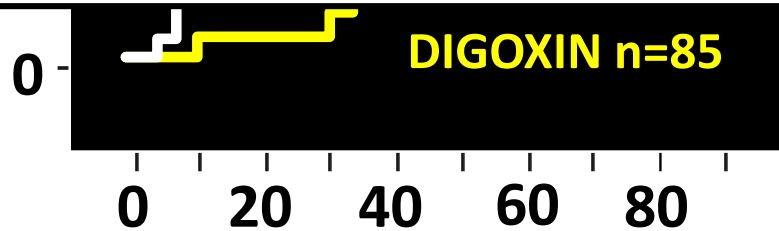
# Digoxin: Improvement in Symptoms But Not Survival



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**No incremental benefit (and potential harm) at  
Levels > 1.0 ng/mL**



**RADIANCE**

*N Engl J Med 1993;329:1*

**DIG Trial**

*N Engl J Med 1997;336:525*

# PARADIGM-HF: Safety

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
<b>Prospectively identified adverse events</b>			
Symptomatic hypotension	588 (14%)	388 (9.2%)	< 0.001
Serum potassium > 6.0 mmol/l	181 (4.3%)	236 (5.6%)	0.007
Serum creatinine ≥ 2.5 mg/dl	139 (3.3%)	188 (4.5%)	0.007
Cough	474 (11.3%)	601 (14.3%)	< 0.001

	LCZ696 (n=4187)	Enalapril (n=4212)
<b>Dose Reduction for adverse event</b>		
Dose reduction or interruption for hypotension	475 (11.3%)	327 (7.7%)
Dose reduction or interruption for hyperkalemia	151 (3.6%)	178 (4.2%)
Dose reduction or interruption for renal impairment	211 (5.0%)	236 (5.6%)

# Case #2

**A 54 year old man with an ischemic cardiomyopathy and a left ventricular ejection fraction of 25% has been managed with Lisinopril 5 mg daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg daily and furosemide 40 mg daily. His blood pressure today in the office is 120/70 and his resting heart rate is 78 beats/minute. He has NYHA Class II symptoms and on physical examination is not volume overloaded. His potassium today is 4.5 and his BUN/Creatinine are 18/1.2.**



# Question

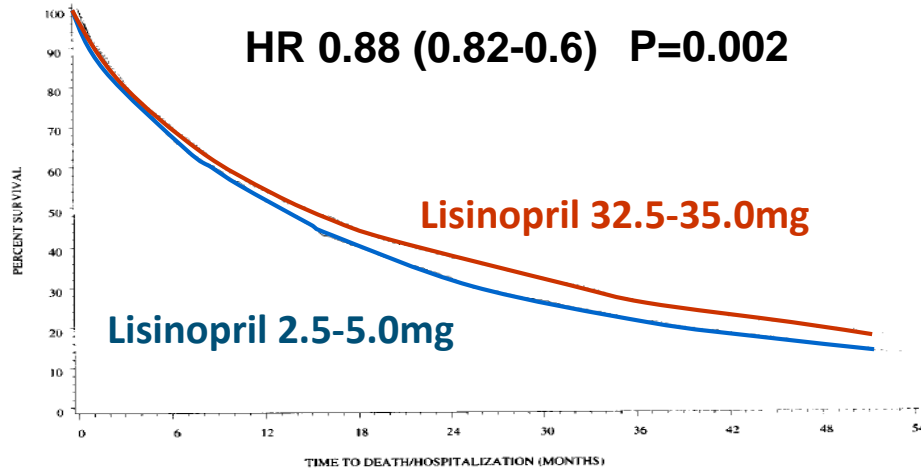
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**Which of the following should be done next in his management?**

- A. Increase spironolactone to 50 mg daily**
- B. Decrease furosemide to 20 mg daily**
- C. Increase carvedilol to 25 mg daily**
- D. Increase lisinopril to 10 mg daily**
- E. No changes to his medical therapy**

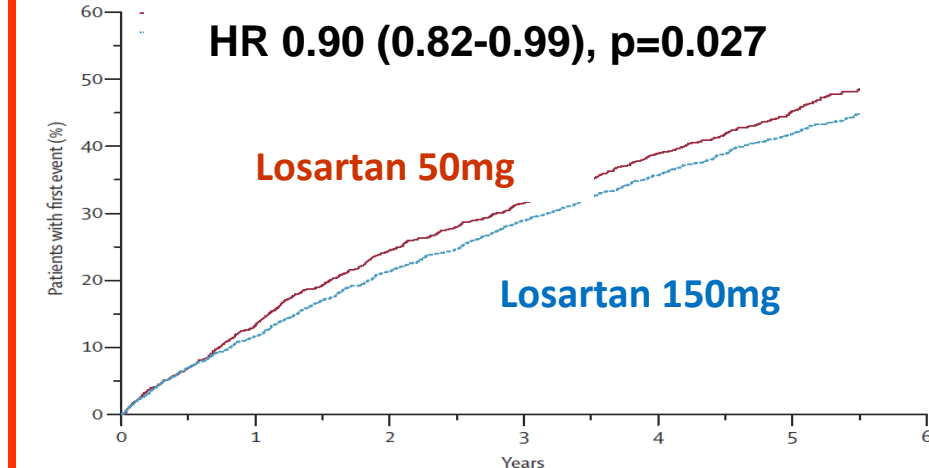


# Optimal Dosing of RAAS Antagonists



Time to Death or Hospitalization

**Favors High Dose**



Time to Death or HF Hospitalization

**Favors High Dose**

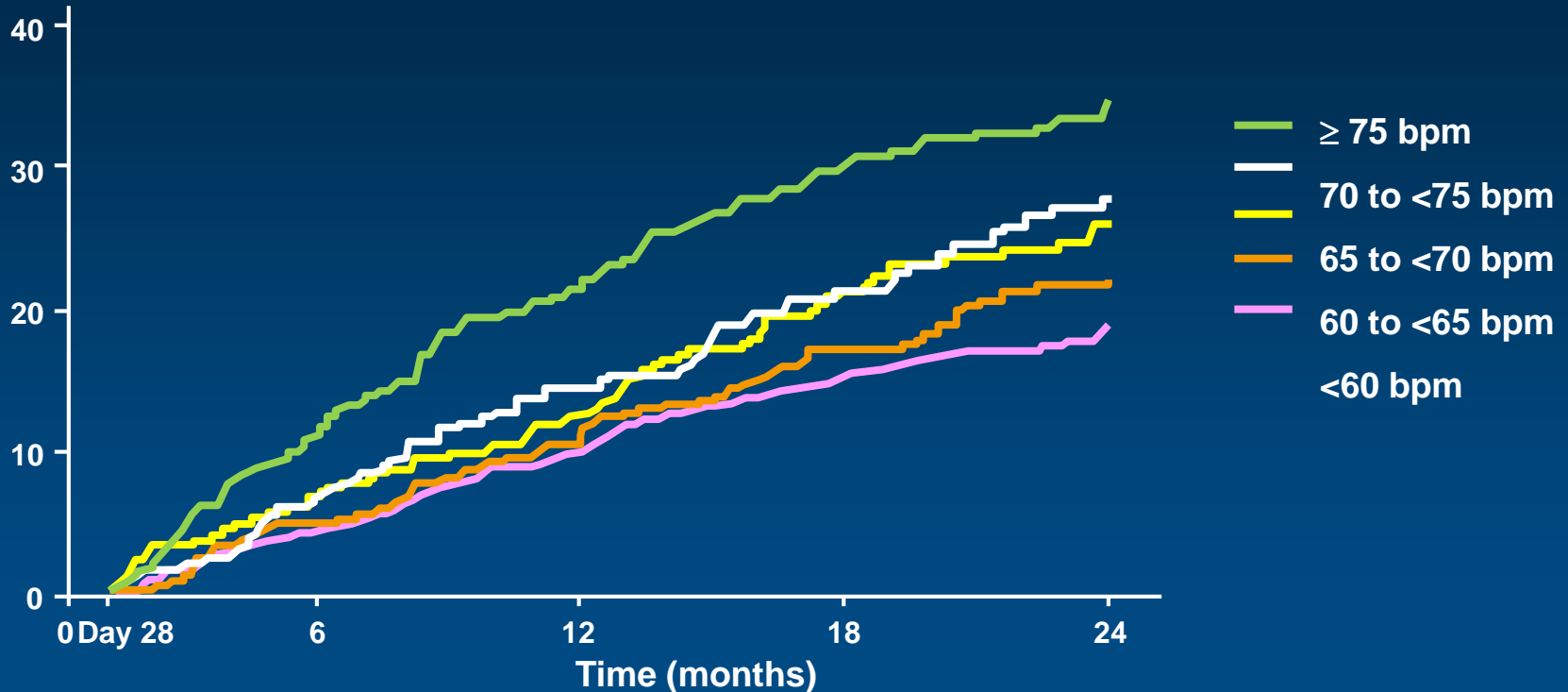
**Titrate as Tolerated to Doses Achieved in Clinical Trials**

Packer M, et al. Circulation 1999; 100: 2312-18

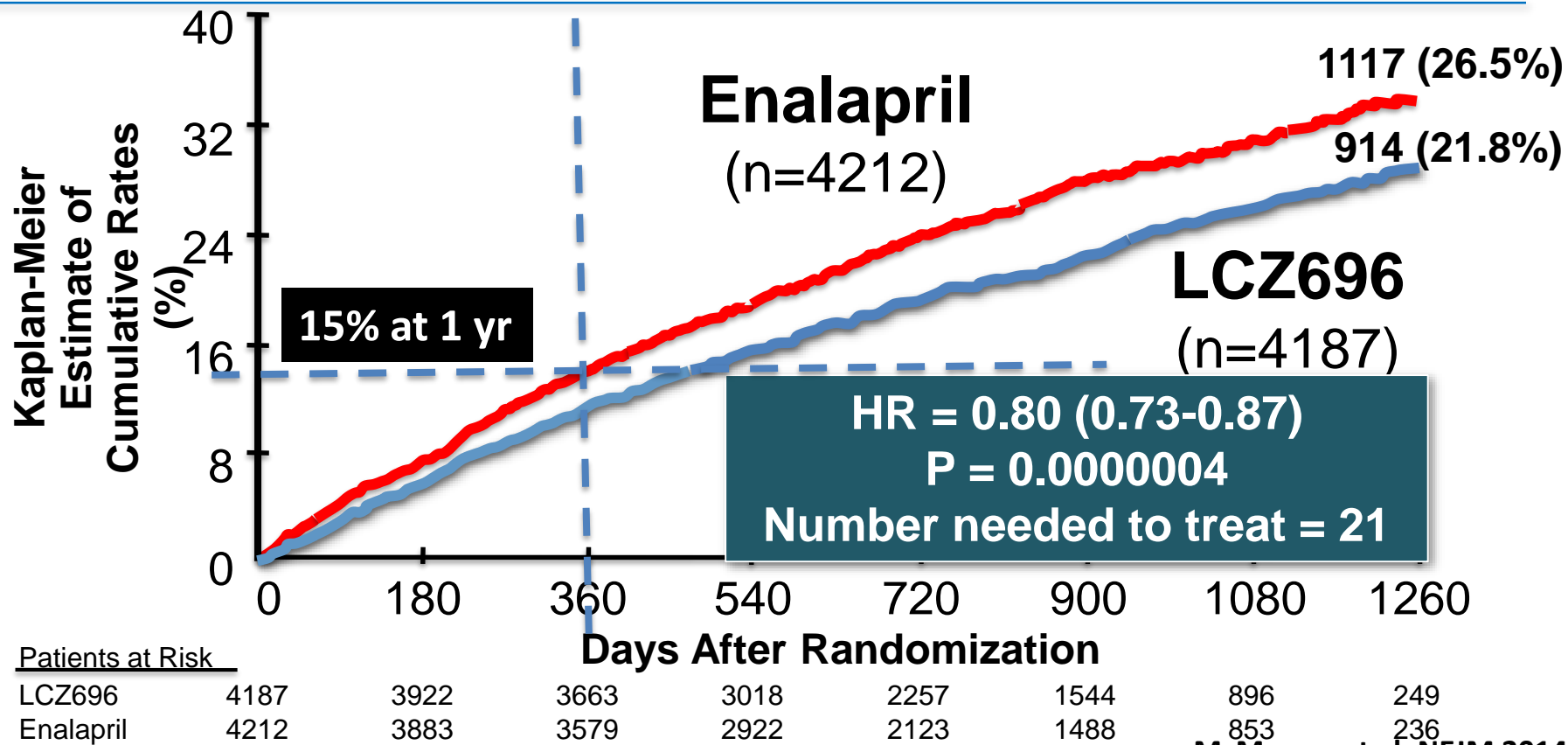
Konstam M, et al. Lancet 2009; 374: 1840-48

# Effect of ivabradine on outcomes according to HR achieved at 28 days

Patients with primary composite end point (%)



# PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)



# Case #3

A 64 year old African American man with HFrEF is referred to your outpatient clinic. Four months ago, he required hospitalization for new onset acute decompensated heart failure. At that time, he underwent coronary angiography which did not reveal any obstructive coronary lesions, and LVEF was 20%. He is ambulatory, but still dyspneic at rest, reports 3 pillow orthopnea and PND. He is treated with furosemide 60 mg twice daily, enalapril 5 mg once daily, metoprolol succinate 50 mg once daily and spironolactone 25 mg once daily. On exam, his BP is 90/60 mm Hg, HR is 60 bpm. He has marked JVD, bibasilar rales, S3, and 2+ pedal edema to knees. BNP is 1800 pg/mL, creatinine is 1.5 mg/dL, EGFR 57 mL/min/1.73 m<sup>2</sup>, potassium level is 4.5 mEq/L. ECG reveals sinus rhythm with LBBB, QRS duration 160 msec. Echocardiogram reveals LVEF 25 % with global hypokinesis, markedly dilated chambers, moderate mitral regurgitation.

# Question

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**Which of the following would you do next?**

- A. Substitute enalapril with valsartan/sacubitril (97mg/103mg) 200 mg twice daily within 24 hours**
- B. Discontinue enalapril and initiate sacubitril /valsartan (97mg/103mg) 200 mg twice daily after 3 days**
- C. Add sacubitril/valsartan 49/51 mg twice daily to current regimen**
- D. Increase enalapril to 10 mg twice daily and metoprolol succinate to 100 mg once daily**
- E. Increase furosemide and refer for cardiac resynchronization therapy**

# How to Initiate?

- **Initiation**

- 36 hour gap between discontinuation of ACE and initiation of sacubitril/valsartan

Population	Initial Dose
Routine	49/51 mg twice daily
Low dose ACE/ARB	24/26 mg twice daily
ACE/ARB naïve	
eGFR≤30 mL/min/m <sup>2</sup>	
Moderate Hepatic Impairment (Child-Pugh Class B)	
Elderly	

- **Titration**

- Double dose every 2-4 weeks until target dose of 97/103 mg twice daily is reached

# Patient Selection for Sacubitril/Valsartan

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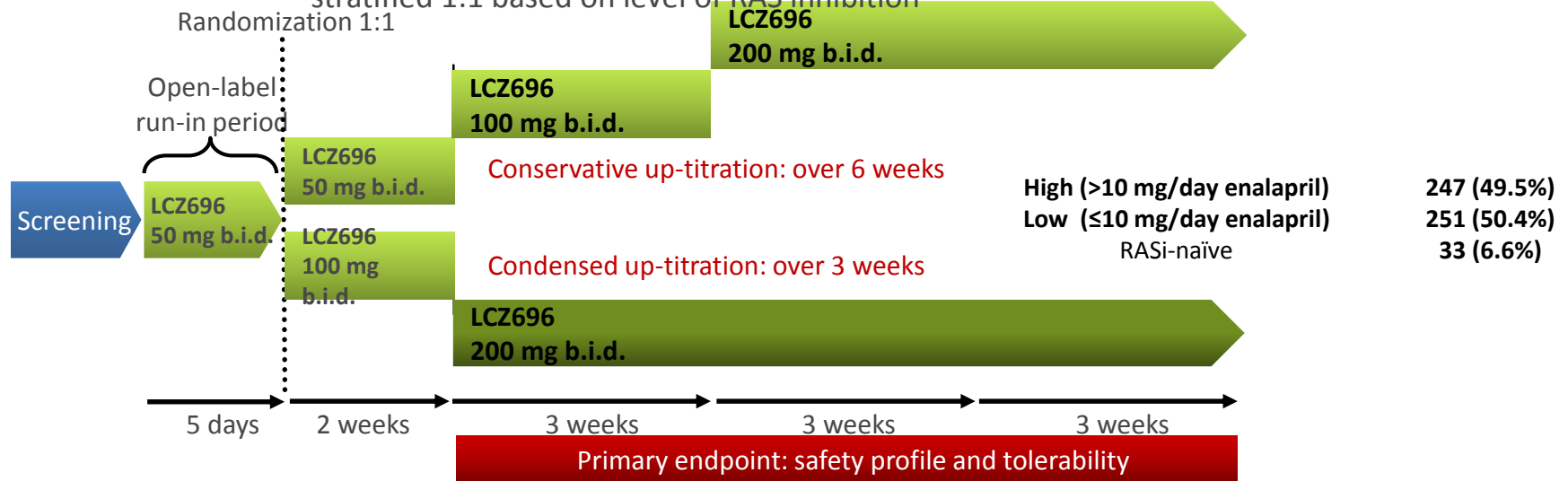
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- **Clear Indication**
  - NYHA II-III subjects tolerating ACE/ARB
- **Uncertain**
  - Subjects on low dose ACE/ARB
  - ACE/ARB naïve subjects
- **Need further data**
  - Stage D HF
  - Hospitalized HF patients
  - HF with Preserved EF

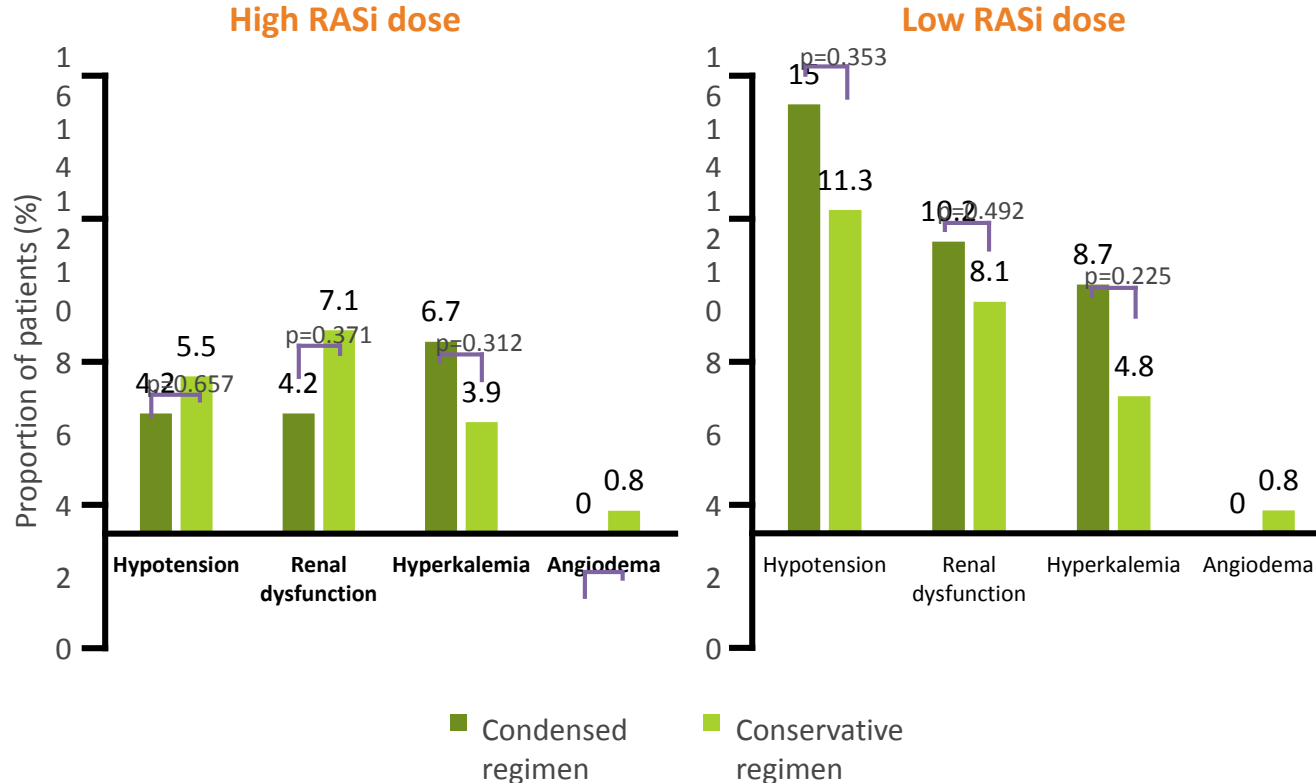


# TITRATION: Study Design

- Target patient population:
  - inpatients\* or outpatients with CHF (NYHA Class II–IV; LVEF  $\leq 35\%$ )
  - both naïve to or on any dose of ACEI/ARBs<sup>‡</sup>
  - stratified 1:1 based on level of RAS inhibition



# TITRATION: Adverse Events by Stratum



# PARADIGM-HF: Angioedema

	LCZ696 (n=4187)	Enalapril (n=4212)
<b>Angioedema (adjudicated)</b>	<b>19</b>	<b>10</b>
Medications, no hospitalization	16	9
Hospitalized; no airway compromise	3	1

## By Race

Black Subjects	2.4%	0.5%
Nonblack Subjects	0.4%	0.2%

# Case #4

A 36 year old woman with a familial cardiomyopathy is seen for evaluation. She was diagnosed 7 years ago while pregnant and was treated with neurohormonal blockade. An ICD was placed 6 years ago and she has had no ICD shocks. An echocardiogram performed 1 month ago revealed a left ventricular ejection fraction of 30%. She has been managed with enalapril 10 mg twice daily, carvedilol 25 mg twice daily, spironolactone 25 mg daily and furosemide 40 mg for the past 6 months but despite this she has NYHA Class 2 symptoms. An ECG today revealed normal sinus rhythm at 62 beats/minute and a left bundle branch block pattern with a PR interval of 180 ms and QRS duration of 160 ms. Blood pressure today is 95/60. Laboratories reveal a potassium of 4.0 and normal renal function.

# Question

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**Which of the following interventions has been shown to improve survival?**

- A. Add a left ventricular pacing lead**
- B. Add digoxin 0.125 mg daily**
- C. Add hydralazine 10 mg three times daily**
- D. Add amiodarone 200 mg daily**
- E. Add ivabradine 5 mg bid**

# Case #5

**A 69 year old woman of African descent with NYHA class III heart failure, reduced EF, due to a dilated cardiomyopathy & a known past medical history of stage II hypertension; she was last hospitalized 9 months prior. She is well treated with carvedilol 25 mg BID, spironolactone 25 mg QD, Lisinopril 5 mg BID, and ISDN/HYD (40/75 TID). An ICD is in place. She now has progressive symptoms, BP 118/78, P 82 bpm; clinical evidence of persistent mild volume overload (JVP ~ 12 cm H<sub>2</sub>O) and BNP 375 pg/ml. Serum creatinine 1.8 mg/dL; K<sup>+</sup> 4.1 mEq/dL.**

# Questions

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**What strategy for symptomatic heart failure is now reasonable?**

- A. advance carvedilol as tolerated to 50 mg BID; target HR reduction to 70 bpm or less**
- B. add ivabradine 5 mg bid**
- C. discontinue ACE-inhibitor and introduce valsartan/sacubitril**
- D. discontinue ISDN/HYD and add valsartan/sacubitril**
- E. Repeat hospitalization for diuresis; consider implantable pulmonary artery monitor**

# Alternative Vasodilator Strategies:

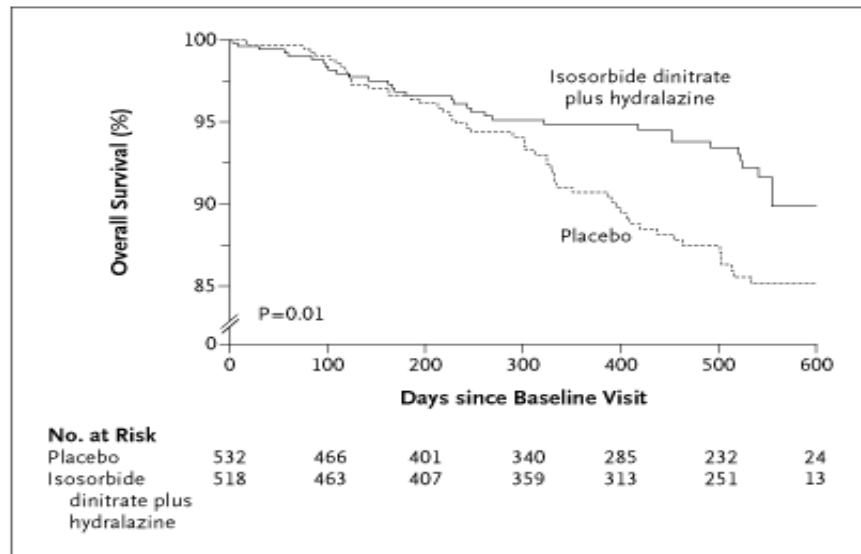


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## *The A-HeFT Trial (Hydralazine/Isordil)*

- 1050 NYHA III/IV AA pts
- Composite endpt (death, HF hosp, QOL), Terminated early
- Bidil (Hydralazine 37.5 mg + Isordil 20 mg) tablets tid
  - 68% at target
  - Mean dose 3.8 tablets
- Contemporary bkgd Rx
  - ACEI/ARB 87 %
  - Beta blkers 75 %
  - Spironolactone 40 %
- Adverse events common
  - HA 44% - Dizziness 29%



*Taylor A, et al. NEJM 2004; 351:2049-2057*



# Hydralazine/Nitrates: Guideline-Based Recommendations

## Pharmacological Treatment for Stage C HFrEF (cont.)



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.



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.



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Learn. Advance. Heal.*



## VIEWPOINT

# Valsartan/Sacubitril for Heart Failure Reconciling Disparities Between Preclinical and Clinical Investigations

**Arthur M. Feldman,  
MD, PhD**  
Departments of  
Medicine and  
Physiology, Lewis Katz  
School of Medicine at  
Temple U  
Philadelphia  
Pennsylvania



**Valsartan/sacubitril** (Entresto, Novartis) is a combination of the neprilysin inhibitor sacubitril and the angiotensin receptor antagonist valsartan. In July 2015, the US Food and Drug Administration (FDA) approved valsartan/sacubitril through the fast-track pathway

critical role in maintaining the homeostasis of A $\beta$  in the brain.<sup>2</sup> This is relevant because accumulation of A $\beta$  in the brain is associated with the pathogenesis of Alzheimer disease.<sup>3</sup> A $\beta$  homeostasis is regulated by a balance between A $\beta$  production through sequential cleavage of

European Heart Journal  
doi:10.1093/eurheartj/ehv015

## CURRENT OPINION

## Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split?

**Nicolas Vodovar<sup>1</sup>, Claire Paquet<sup>1,2</sup>, Alexandre Mebazaa<sup>1,3,4</sup>, Jean-Marie Launay<sup>1,5,6</sup>,  
Jacques Hugon<sup>1,2,4</sup>, and Alain Cohen-Solal<sup>1,4,7\*</sup>**

<sup>1</sup>UMRS 942 Inserm, 75010 Paris, France; <sup>2</sup>Clinical and Research Memory Center, Lariboisière Hospital, Paris, France; <sup>3</sup>Department of Anesthesiology and Intensive Care, Lariboisière Hospital, Paris, France; <sup>4</sup>Paris Diderot University, Sorbonne Paris Cité, Paris, France; <sup>5</sup>Department of Biochemistry, Lariboisière Hospital, Paris, France; <sup>6</sup>Centre for Biological Resources, Lariboisière Hospital, Paris, France; and <sup>7</sup>Department of Cardiology, Lariboisière Hospital, 2, Rue Ambroise Paré, 75475 Paris Cedex 10, France

Received 23 October 2014; revised 12 January 2015; accepted 13 January 2015

Feldman, JAMA 2016; 315: 25-26

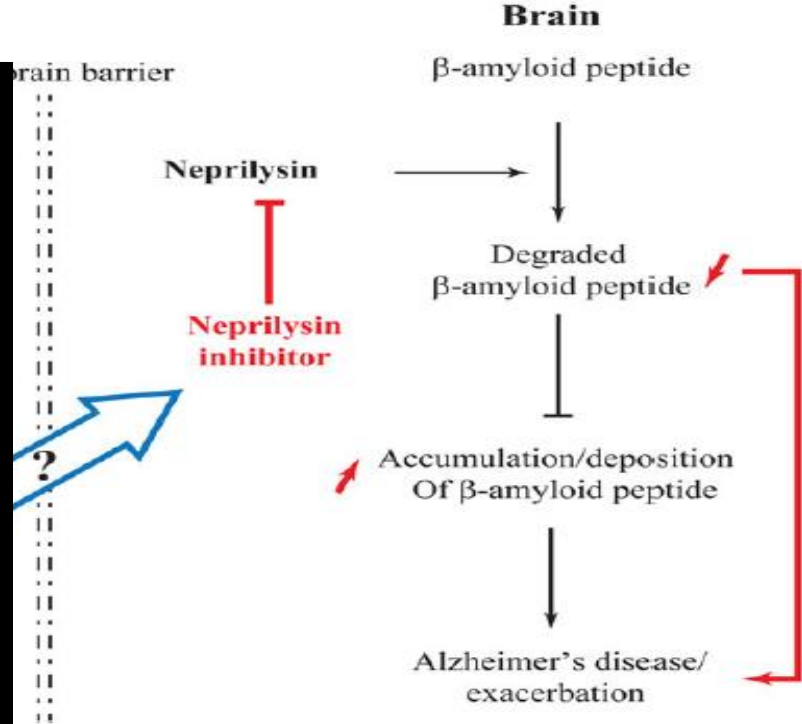
Vodovar, Eur Heart J 2015

# Neprilysin and $\beta$ -Amyloid

## Heart

Chronic heart failure

- Overexpression of neprilysin ameliorated the development of AD in a genetic model of Alzheimer disease.
- Disruption of the neprilysin gene elevated oligomeric A $\beta$  levels in the brain and accelerated the development of cognitive dysfunction in a genetic mouse model of Alzheimer disease
- HF patients have multiple risks for Alzheimer's Disease and blood-brain barrier disruption



# Neprilysin contributes to breakdown of Amyloid-beta in Brain

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- No increase in pathogenic Amyloid-beta subtypes in the brains of nonhuman primates or CSF of normal human volunteers receiving LCZ696<sup>1,2</sup>
- No increase in cognition, memory, or dementia-related events in PARADIGM-HF, but follow up was relatively short and executive function not systematically measured
- A large cognitive function substudy has been embedded in PARAGON-HF, and additional PET imaging studies are underway

# MME gene mutations

Rare Variants in *MME*, Encoding Metalloprotease  
Neprilysin, Are Linked to Late-Onset  
Autosomal-Dominant Axonal Polyneuropathies

AJHG

Annals of  
NEUROLOGY

Mutations in *MME* Cause  
an Autosomal-Recessive  
Charcot-Marie-Tooth Disease Type 2

- Whole exome sequencing of patients with late-onset Charcot-Marie-Tooth polyneuropathy
- Heterozygous rare loss of function and missense mutations in *MME*, the gene encoding for neprilysin
- Reduced tissue availability of neprilysin and impaired enzymatic activity
- No increase in B-amyloid deposition or cognitive dysfunction/dementia

Auer-Grumbach M, Am J Hum Gen 2016; 99: 607-623  
Higuchi Y, et al. Ann Neurol 2016; 79:659-72