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Clinical Meeting & Exhibition

Heart Failure Advanced Therapeutic Approaches: Know When to Hold 'em and When to Fold 'em

Tuesday, December 6, 2016

4:00 PM to 5:15 PM

ACPE # 0204-0000-16-266-L01-P

Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

Learning Objectives

- Interpret clinical trial data with angiotensin receptor/neprilysin inhibitors (ARNI) and ivabradine in heart failure with reduced ejection fraction
- Interpret clinical trial data with spironolactone in heart failure with preserved ejection fraction
- Compare and contrast the new recommendations in the heart failure guidelines with previous guidelines
- Recommend appropriate heart failure treatment regimens for patients with reduced and preserved ejection fractions

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Heart Failure with Reduced Ejection Fraction (HFrEF): Guideline Based Approaches and Role of Angiotensin Receptor/Neprilysin inhibitor (ARNI) and Ivabradine in Heart Failure Management

Joel C. Marrs, Pharm.D., FASHP, FCCP, FNLA, BCPS, BCACP, CLS, ASH-CHC
Associate Professor, Department of Clinical Pharmacy
University of Colorado Anschutz Medical Campus

Learning Objectives

- ***Interpret clinical trial data with angiotensin receptor/neprilysin inhibitors (ARNI) and ivabradine in heart failure with reduced ejection fraction***
- Interpret clinical trial data with spironolactone in heart failure with preserved ejection fraction
- ***Compare and contrast the new recommendations in the heart failure guidelines with previous guidelines***
- ***Recommend appropriate heart failure treatment regimens for patients with reduced and preserved ejection fractions***

Polling Question-Which of the following best describes you?

- A Never managed a HFrEF patient on sabubitril/valsartan
- B Have initiated sacubitril/valsartan in a HFrEF patient
- C Have transitioned HFrEF patient from ACE-I or ARB to sacubitril/valsartan
- D Both B and C

Polling Question-Which of the following best describes you?

A Never managed a HFrEF patient on ivabradine

B Have initiated ivabradine in a HFrEF patient

C Have managed a HFrEF patient on ivabradine

D Both B and C

Polling Question: Which treatments have been shown to decrease morbidity and mortality in patients with HFrEF?

A ACE-Is or ARBs

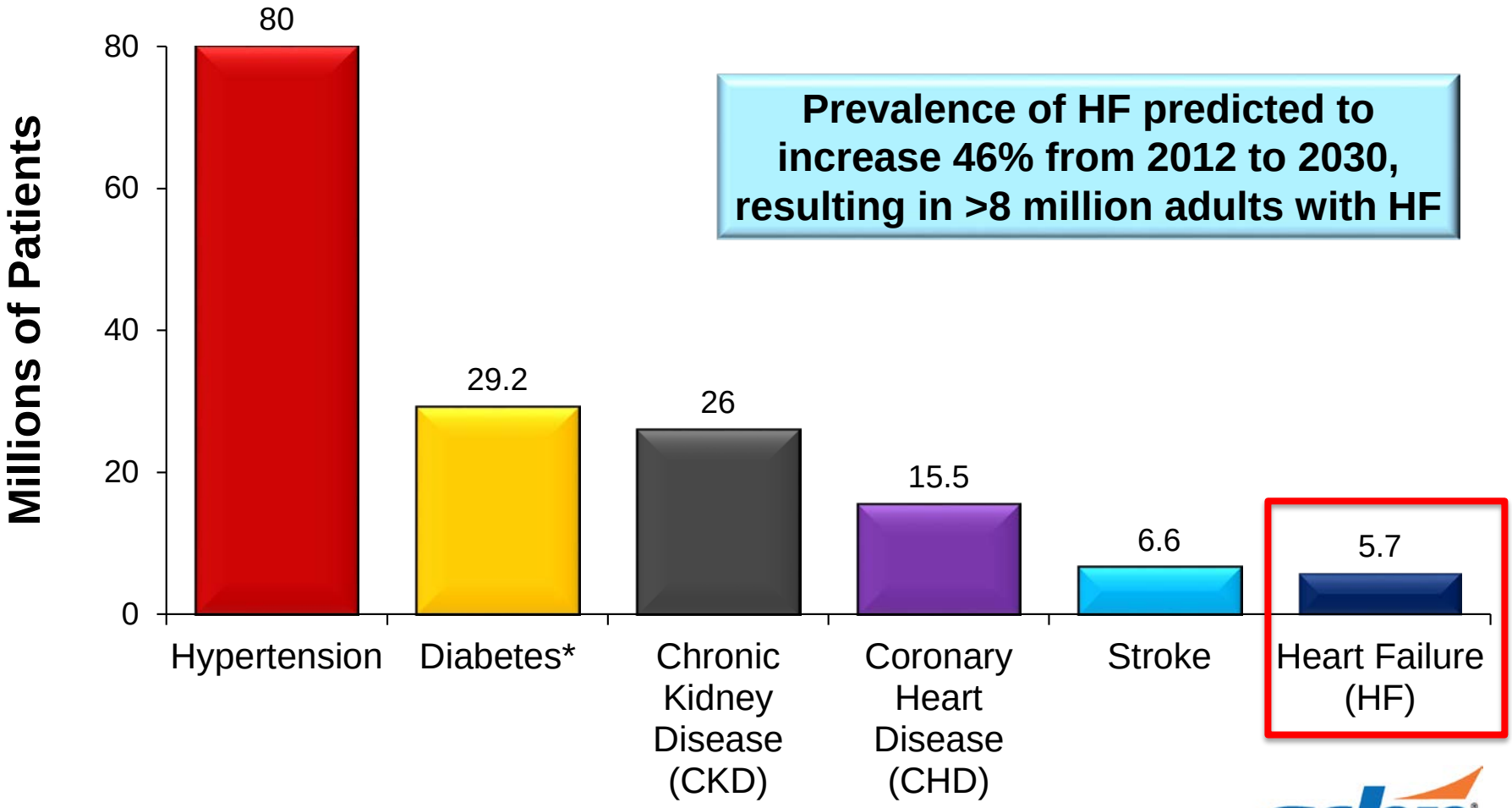
B Beta-blockers

C Sacubitril/valsartan

D All of the Above

American Heart Association (AHA)

Heart Disease and Stroke Statistics—2016 Update



*Includes diagnosed and undiagnosed patients

Mozaffarian D, et al. Circulation 2016;133(4):447-54. doi: 10.1161/CIR.0000000000000366.

Definition of HFrEF and HFpEF

Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HF*r*EF)	≤40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HF*r*EF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HF*p*EF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, borderline	41 to 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF*p*EF.
b. HF*p*EF, improved	>40	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

EF indicates ejection fraction; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and HF*r*EF, heart failure with reduced ejection fraction.

Circulation 2013;128:e240-e327.

Heart Failure Severity and Classification

NYHA Functional Classification

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause HF symptoms
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

ACCF/AHA HF Staging

Stage	Description
A	At high risk for HF but without structural heart disease or symptoms of HF
B	Structural heart disease but without signs or symptoms of HF
C	Structural heart disease with prior or current symptoms of HF
D	Refractory HF requiring specialized interventions

Circulation 2013;128:e240-e327.

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Treatment Approaches in HFrEF

HFrEF: GDEM Therapeutic Approach: 2013 ACCF/AHA Guideline

- Shown to reduce morbidity and mortality
  - Angiotensin converting enzyme inhibitors (ACE-I) (Class I, LOE A)
  - Beta-blockers (Class I, LOE A)
  - Angiotensin II receptor blockers (ARB) (Class IIa, LOE A)
  - Aldosterone receptor antagonists (Class I, LOE A)
  - Hydralazine/isosorbide dinitrate in African-Americans (Class I, LOE A)
- Shown to reduce morbidity
  - Digoxin (Class IIa, LOE B)
- Shown to improve symptoms in patients with edema
  - Loop diuretics (Class I, LOE C)

GDEM = guideline-directed evaluation and management

Circulation 2013;128:e240-e327.

Clinical Trial Benefits in Stage C HFrEF

Pharmacotherapy	Mortality (RRR) %	Mortality NNT (3 yrs)	HF Hosp. (RRR) %
ACE-I or ARB	17	26	31
Beta Blocker	34	9	41
Aldosterone Antagonists	30	6	35
Hydralazine/Nitrate	43	7	33

Circulation 2013;128:e240-e327.

PARADIGM-HF

- RCT of 8442 patients with NHYA class II-IV HF and a LVEF < 40% with a mean follow-up of 27 months
- Treatment: angiotensin receptor-neprilysin inhibitor LCZ696 200 mg twice daily or enalapril 10 mg twice daily
- Primary Outcome:
  - Composite of CV death or hospitalization for HF
- Primary Outcome Results:
  - LCZ696 21.8% (914/4187) vs enalapril 26.5% (1117/4212)
  - HR 0.80 (95% CI 0.73 to 0.87; P < 0.001)

N Engl J Med 2014;371:993-1004.

PARADIGM-HF – Baseline Demographics

Characteristics	LCZ696	Enalapril
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Female (%)	21.0	22.6
White (%)	66.0	66.0
Systolic BP (mm Hg)	122 ± 15	121 ± 15
Heart Rate (beats/min)	72 ± 12	73 ± 12
Serum Creatinine (mg/dL)	1.13 ± 0.3	1.12 ± 0.3
Ejection Fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA Class I (%)	4.3	5.0
NYHA Class II (%)	71.6	69.3
NYHA Class III (%)	23.1	24.9

N Engl J Med 2014;371:993-1004.

PARADIGM-HF – Baseline Treatment

Characteristics	LCZ696	Enalapril
Diuretic (%)	80.3	80.1
Digoxin (%)	29.2	31.2
Beta blocker (%)	93.1	92.9
Aldosterone antagonist (%)	54.2	57.0
Implantable cardioverter-defibrillator (%)	14.9	14.7
Cardiac resynchronization therapy (%)	7.0	6.7

N Engl J Med 2014;371:993-1004.

PARADIGM-HF: Secondary Efficacy Outcomes

- **CV Death**:
  - LCZ696 13.3% (558/4187) vs enalapril 16.5% (693/4212)
  - **HR 0.80 (95% CI 0.71 to 0.89; P < 0.001)**
- **Hospitalization for HF**:
  - LCZ696 12.8% (537/4187) vs enalapril 15.6% (658/4212)
  - **HR 0.79 (95% CI 0.71 to 0.89; P < 0.001)**

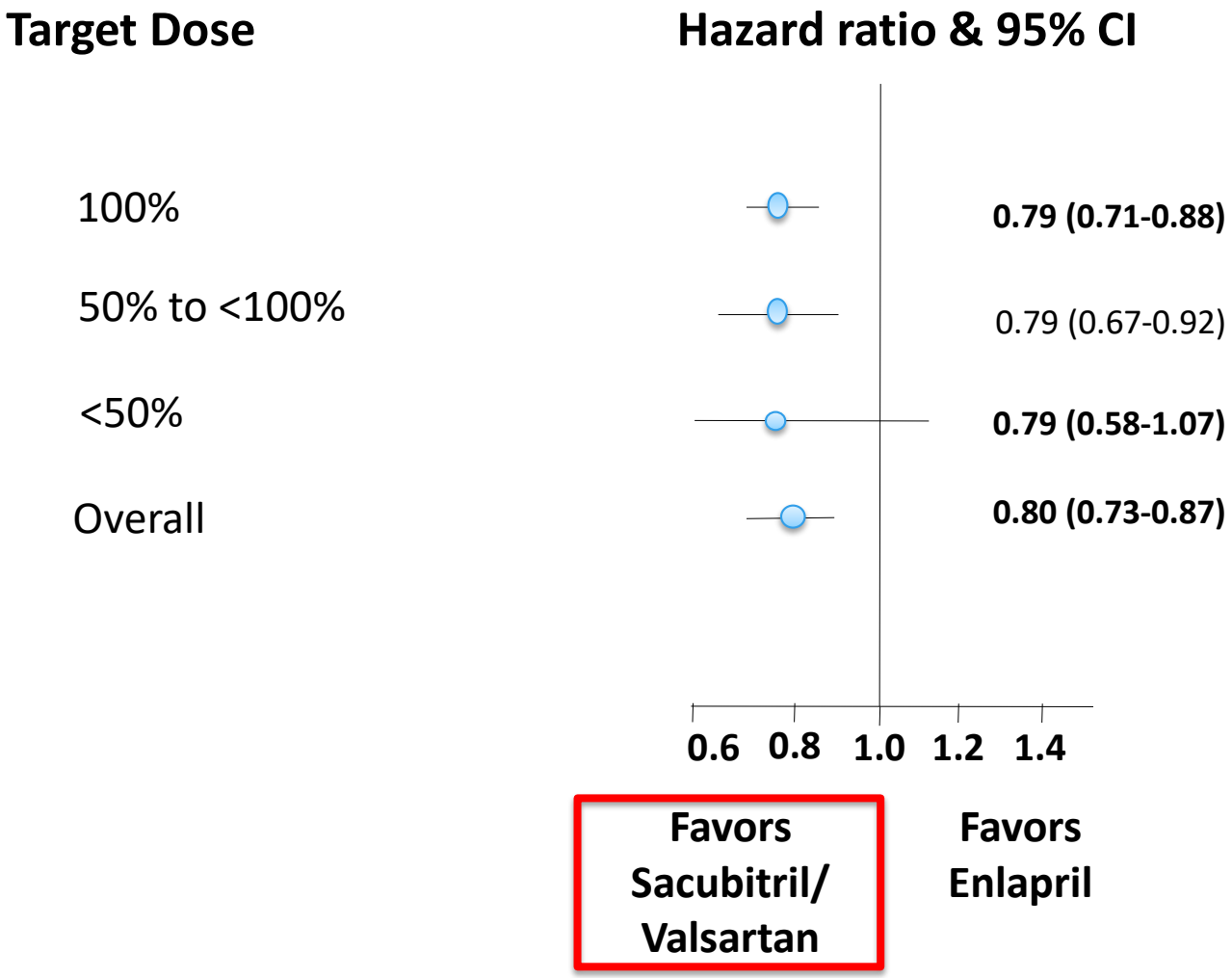
N Engl J Med 2014;371:993-1004.

PARADIGM-HF: Safety Outcomes

- **Symptomatic Hypotension**:
  - LCZ696 14.0% (588/4187) vs enalapril 9.2% (388/4212) **P < 0.001**
- **Elevated Serum Creatinine (> 2.5 mg/dL):**
  - LCZ696 3.3% (139/4187) vs enalapril 4.5% (188/4212) **P = 0.007**
- **Elevated Serum Potassium (> 6.0 mmol/L):**
  - LCZ696 4.3% (181/4187) vs enalapril 5.6% (236/4212) **P = 0.007**
- **Angioedema:**
  - LCZ696 0.45% (19/4187) vs enalapril 0.2% (10/4212) P = 0.13

N Engl J Med 2014;371:993-1004.

PARADIGM-HF: Post-hoc Analysis (Low dose vs Target Dose) CV Death or HF Hospitalization



Eur J Heart Fail. 2016 Jun 10. doi: 10.1002/ejhf.580. [Epub ahead of print]

Cost-Effectiveness Analysis: Sacubitril/Valsartan

- Is Sacubitril/valsartan cost-effective in patients with HFrEF?
- Findings
  - Sacubitril/valsartan decrease morbidity and mortality when compared to enalapril in HFrEF
  - Sacubitril/valsartan has an incremental cost-effectiveness ratio (ICER) of **US $45,017 per quality-adjusted life year (QALY) gained**
- Take-home message
  - **Sacubitril/valsartan is cost-effective when compared to enalapril in NYHA II-IV HFrEF when using the commonly accepted willingness to pay threshold of $50,000 per QALY gained.**

JAMA Cardiol. 2016;1(6):666-672

Sacubitril/Valsartan (Entresto®)

- Neprilysin inhibitor and angiotensin II receptor blocker
- Indicated to reduce the risk of CV death and hospitalization in HFrEF (NYHA Class II-IV)
- Dosage: 49/51 mg BID with titration to 97/103 mg BID after 2-4 weeks as tolerated
- **If switching from an ACE inhibitor to sacubitril/valsartan allow a washout period of 36 hours between administration of the two drugs**
- Contraindications:
  - Hypersensitivity, history of angioedema (ACE inhibitor or ARB), concomitant ACE inhibitor, concomitant renin inhibitor
- Adverse effects: hypotension, hyperkalemia, cough, dizziness, renal failure

Entresto® Prescribing Information. August 2015

ACC/AHA/HFSA 2016 Focused Update: ARNI Therapy

Class I Recommendations	Level of Evidence
Inhibition of RAS with ACE-Is (Class I; LOE A) or ARBs (Class I; LOE A), or ARNI (Class I; LOE B-R) in conjunction with B-blocker and aldosterone antagonist in selected patients in HFrEF to decrease morbidity and mortality	B-R
HFrEF NYHA Class II-III patients who tolerate ACE-I or ARB, replacement with ARNI is recommended to further reduce morbidity and mortality	B-R

Class III Recommendations	Level of Evidence
ARNI should not be administered concomitantly with ACE-I or within 36 hours of the last dose of ACE-I	B-R
ARNI should not be administered to patients with a history of angioedema	EO

Circulation. 2016 Sep 27;134(13):e282-93.
J Am Coll Cardiol. 2016 Sep 27;68(13):1476-88.
J Card Fail. 2016 Sep;22(9):659-69.

GDEM = guideline-directed evaluation and management

Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT)

- RCT of 6558 patients with NHYA class II-IV HF and a LVEF < 35% in sinus rhythm with a HR ≥ 70 bpm
- Median follow-up of 23 months
- Treatment: Ivabradine titrated to max of 7.5 mg twice daily or placebo
- Primary Outcome:
  - **Composite of CV death or hospitalization for HF**
- Primary Outcome Results:
  - Ivabradine 24% (793/3241) vs placebo 29% (937/3264)
  - **HR 0.82 (95% CI 0.75 to 0.90; P < 0.0001)**

Lancet 2010;376:875-85.

SHIFT – Baseline Demographics

Characteristics	Ivabradine	Placebo
Age (years)	60.7 ± 11.2	60.1 ± 11.5
Female (%)	24.0	23.0
White (%)	**89.0**	**89.0**
Systolic BP (mm Hg)	122.0 ± 16.1	121.4 ± 15.9
Heart Rate (beats/min)	79.7 ± 9.5	80.1 ± 9.8
eGFR (mL/min/1.73m^2)	74.6 ± 22.9	74.8 ± 23.1
Ejection Fraction (%)	29.0 ± 5.1	29.0 ± 5.2
NYHA Class I (%)	**49**	**49**
NYHA Class II (%)	**50**	**50**
NYHA Class III (%)	2	2

Lancet 2010;376:875-85.

SHIFT – Baseline Treatment

Characteristics	Ivabradine	Placebo
Diuretic (%)	84	83
ACE-I (%)	**79**	**78**
ARB (%)	**14**	**14**
Beta blocker (%)	**89**	**90**
Aldosterone antagonist (%)	**61**	**59**
Digoxin (%)	22	22
Implantable cardioverter-defibrillator (%)	3	4
Cardiac resynchronization therapy (%)	1	1

Lancet 2010;376:875-85.

SHIFT: Secondary Efficacy Outcomes

- **All Cause Death**:
  - Ivabradine 16% (503/3241) vs placebo 17% (552/3264)
  - HR 0.90 (95% CI 0.80 to 1.02; P = 0.092)
- **CV Death**:
  - Ivabradine 14% (449/3241) vs placebo 15% (491/3264)
  - HR 0.91 (95% CI 0.80 to 1.03; P = 0.128)
- **Hospitalization for HF**:
  - Ivabradine 16% (514/3241) vs placebo 21% (672/3264)
  - **HR 0.74 (95% CI 0.66 to 0.83; P < 0.0001)**

Lancet 2010;376:875-85.

SHIFT: Safety Outcomes

- **Any Adverse Event**:
  - Ivabradine 75% (2439/3232) vs placebo 74% (2423/3260) P =0.303
- **Heart Failure**:
  - Ivabradine 25% (804/3232) vs placebo 29% (937/3260) **P = 0.0005**
- **Symptomatic Bradycardia**:
  - Ivabradine 5% (150/3232) vs placebo 1% (32/3260) **P < 0.0001**
- **Asymptomatic Bradycardia**:
  - Ivabradine 6% (184/3232) vs placebo 1% (48/3260) **P < 0.0001**
- **Atrial Fibrillation**:
  - Ivabradine 9% (306/3232) vs placebo 8% (251/3260) **P = 0.012**

Lancet 2010;376:875-85.

Ivabradine (Corlanor®)

- Hyperpolarization-activated cyclic nucleotide-gated channel blocker
- Indicated to reduce the risk of hospitalization in HFrEF (EF < 35%) if
  - Sinus rhythm with resting heart rate ≥ 70 beats per minute

    and
  - On maximally tolerated doses of beta blockers or have a contraindication to beta-blocker
- Dosage: 5 mg BID with titration to 7.5 mg BID after 2 weeks based on HR
- Contraindications:
  - ADHF, BP < 90/50 mm Hg, sick sinus syndrome, 3rd degree AV block, HR < 60; sever hepatic impairment; pacemaker
- Adverse effects: bradycardia, HTN, atrial fibrillation

Corlanor® Prescribing Information. April 2015

ACC/AHA/HFSA 2016 Focused Update: Ivabradine

Class IIa Recommendations	Level of Evidence
Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic NYHA Class II-III stable chronic HFrEF with EF < 35% who are receiving GDEM, including a B-blocker at maximum tolerated dose, and who are in sinus rhythm with a HR > 70 bpm at rest	B-R

GDEM = guideline-directed evaluation and management

Circulation. 2016 Sep 27;134(13):e282-93.
J Am Coll Cardiol. 2016 Sep 27;68(13):1476-88.
J Card Fail. 2016 Sep;22(9):659-69.

Case-Based Question

A 55 year-old Caucasian male with chronic HFrEF (EF = 32%, 3 mo ago) presents to the clinic for routine follow-up. The patient's PMH is significant for diabetes mellitus, stage 3 CKD, HTN, and a MI 3 years ago. His current BP is 124/80 mm Hg with a HR of 62 bpm. His HF regimen includes furosemide 40 mg QAM, Lisinopril 40 mg daily, carvedilol 25 mg BID, and spironolactone 25 mg daily

Which of the following is the best plan to optimize his HF regimen to decrease his risk of morbidity and mortality?

- A Add hydralazine and isosorbide dinitrate
- B Discontinue lisinopril and start sacubitril/valsartan
- C Start ivabradine
- D Increase carvedilol dose

Key Takeaways

- Key Takeaway #1
  - Sacubitril/valsartan significantly improves outcomes specifically CV mortality and HF hospitalization when its compared to and ACE-I in HFrEF

- Key Takeaway #2
  - When switching patients from an ACE-I to an ARNI caution should be taken into account regarding risk of hypotension

- Key Takeaway #3
  - Ivabradine significantly reduces risk of HF hospitalization in patients with HFrEF receiving guideline directed standard therapy when HR is greater than 70 on maximum tolerated beta-blocker doses

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Heart Failure with Preserved Ejection Fraction (HFpEF): Guideline Based Approaches and Role of Spironolactone in Heart Failure Management

Robert L. Page, Pharm.D. MSPH, FCCP, FASHP, FHFSA, FASCP, FAHA, BCPS, CGP
Professor, Department of Clinical Pharmacy
Clinical Specialist, Division of Cardiology
University of Colorado Anschutz Medical Campus

Learning Objectives

- Interpret clinical trial data with angiotensin receptor/neprilysin inhibitors (ARNI) and ivabradine in heart failure with reduced ejection fraction
- ***Interpret clinical trial data with spironolactone in heart failure with preserved ejection fraction***
- ***Compare and contrast the new recommendations in the heart failure guidelines with previous guidelines***
- ***Recommend appropriate heart failure treatment regimens for patients with reduced and preserved ejection fractions***

Which of the following reduces mortality in patients with HFpEF?

A Lisinopril

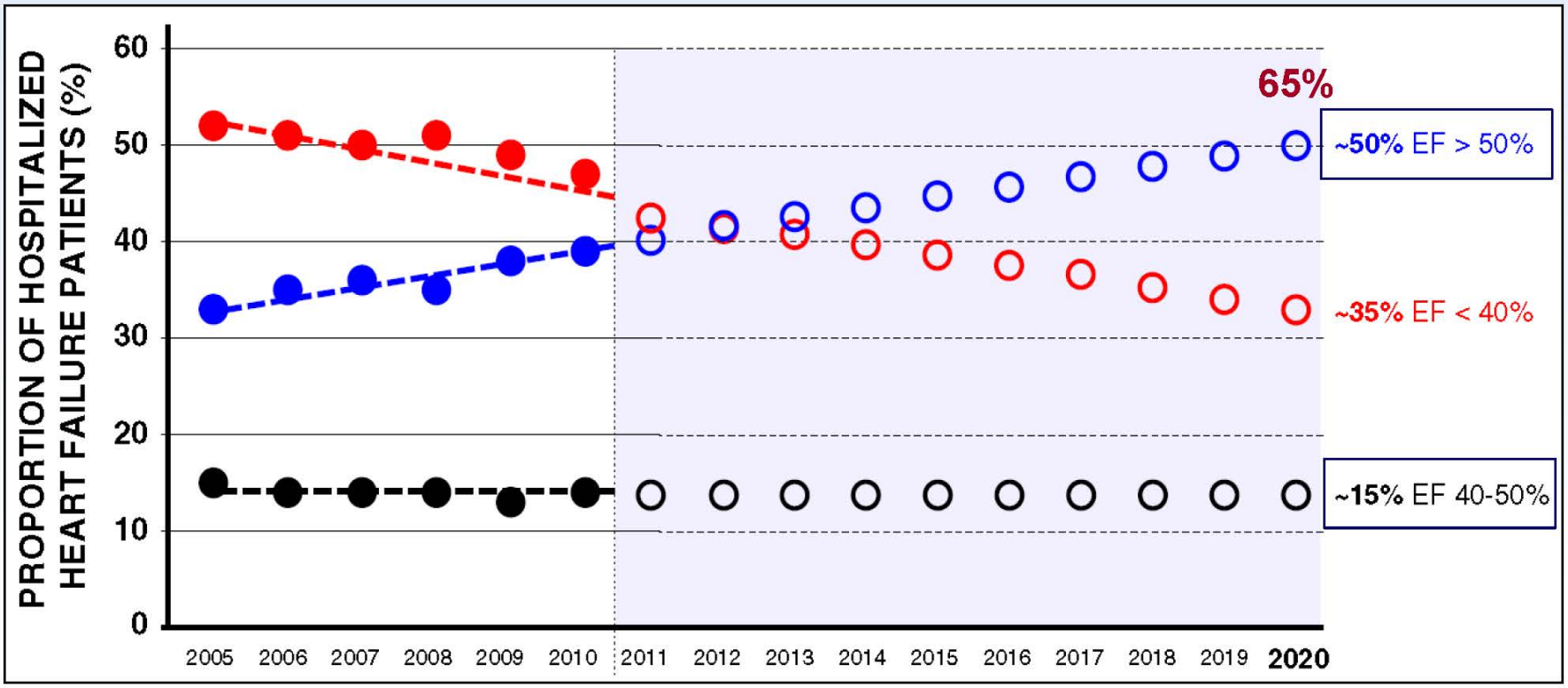
B Digoxin

C Metoprolol succinate

D None of the above

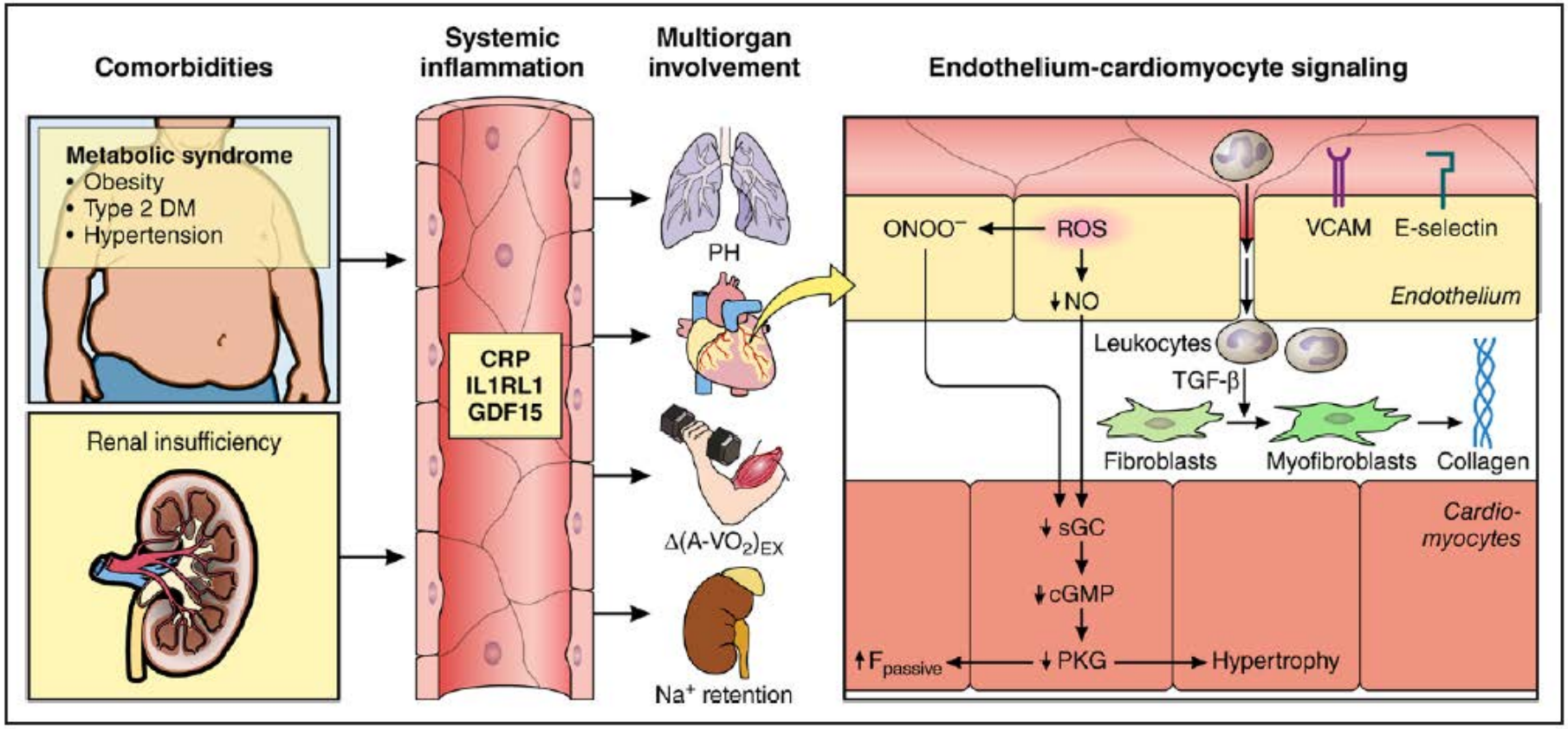
Epidemiology of HFpEF

Get With the Guidelines-Heart Failure (GWTG-HF) Study , N=110,621, USA
using actual data on the proportion of hospitalization patients



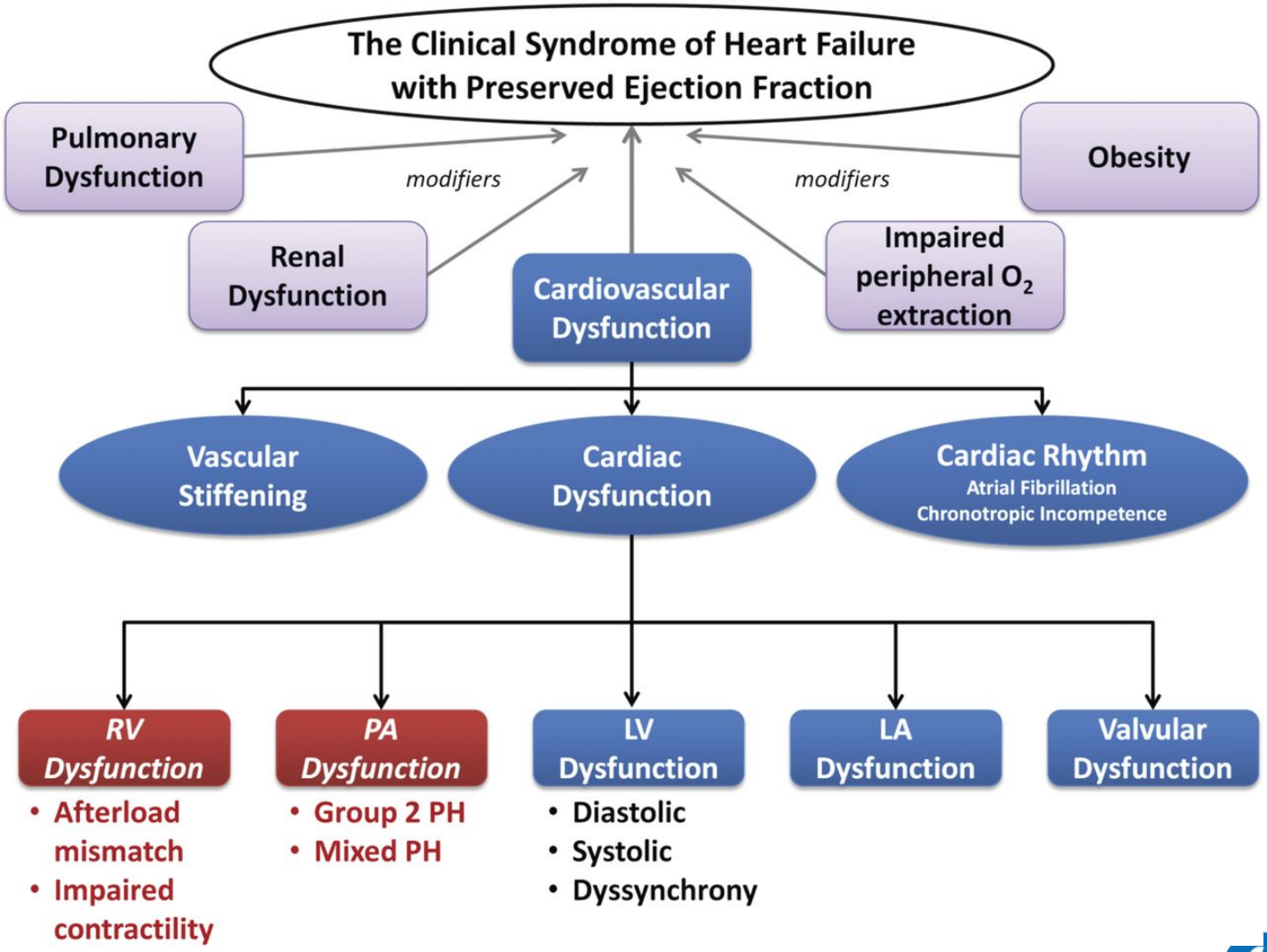
Curr Heart Fail Rep 2013; 10: 401-410.

Overview of HFpEF Phenotype



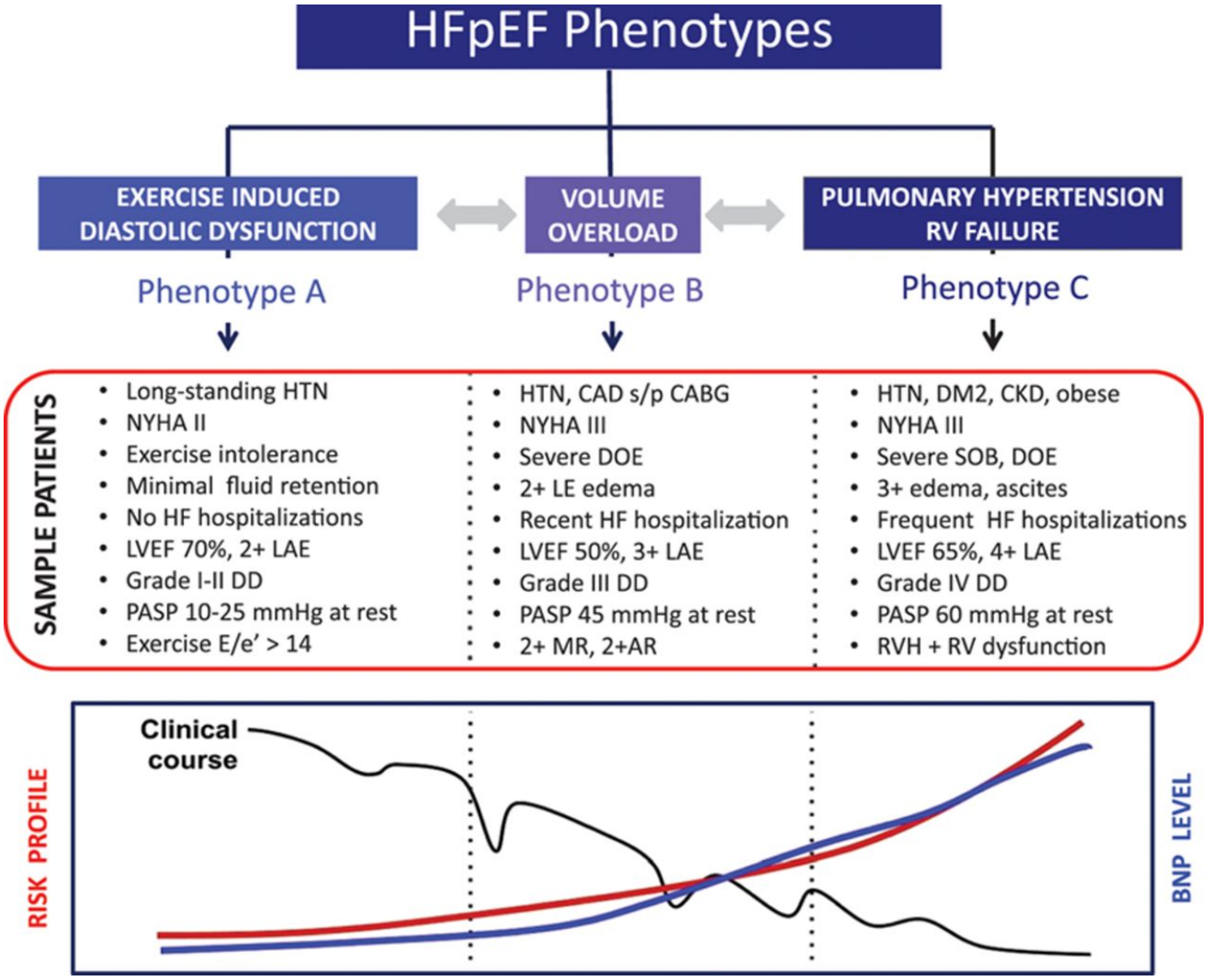
Circ Res. 2014;115:79-96.

Overview of HFpEF Phenotype



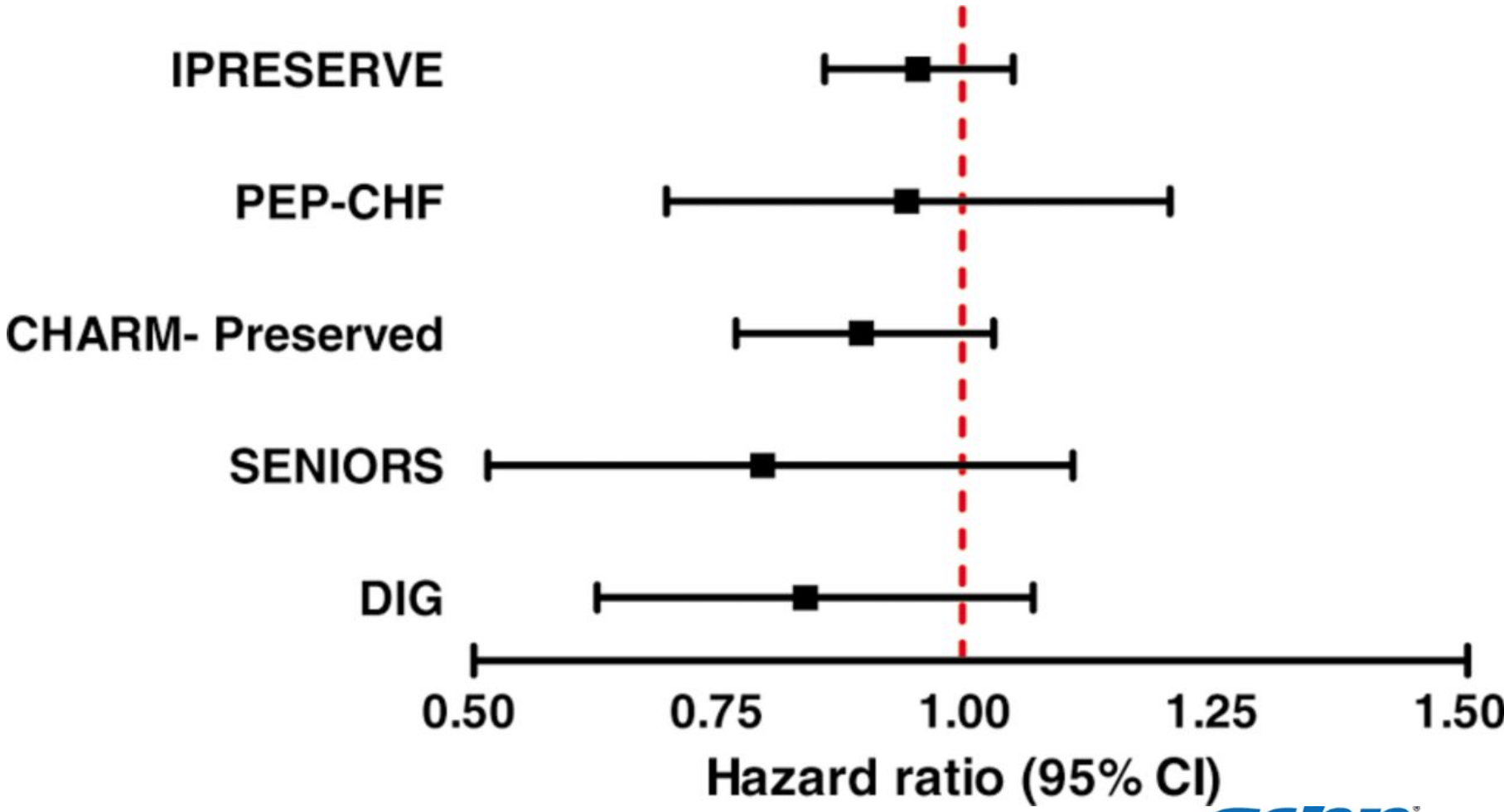
Circ Res. 2014;115:79-96.

Overview of HFpEF Phenotype



JACC 2014; 64: 1765-1774.

Summary of Large HFpEF Trials



Heart Fail Clin. 2014;10:511-23.

ACCF/AHA 2013 Guideline Summary

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B
Diuretics should be used for relief of symptoms due to volume overload	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF	IIa	C
ARBs might be considered to decrease hospitalizations in HFpEF	IIb	B
Nutritional supplementation is not recommended in HFpEF	III: No Benefit	C

JACC. 2013;62:e147-e239.

Which of the following reduces mortality in patients with HFpEF?

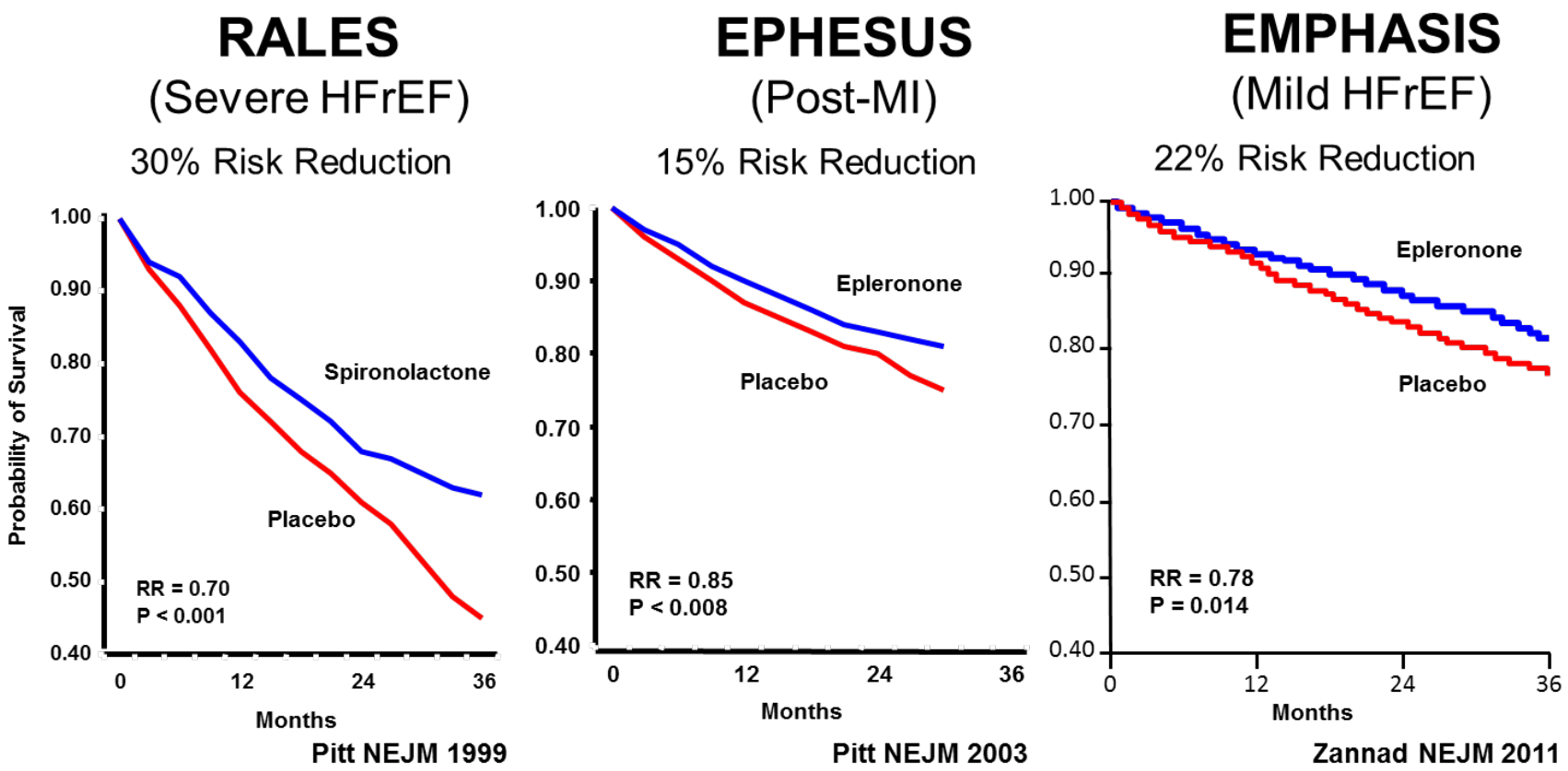
A Lisinopril

B Digoxin

C Metoprolol succinate

D None of the above

MRAs in HFrEF



Heart Fail Clin. 2014;10:511-23.

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

Marc A. Pfeffer MD, PhD, on behalf of the TOPCAT Investigators

TOPCAT Trial Executive Committee

Inder Anand, Susan Assmann, Robin Boineau, Akshay Desai, Jerome Fleg, David Lathrop, Eldrin Lewis, Sonja McKinlay, Maureen Montrond, Marc Pfeffer, Bertram Pitt (Chair), Scott Solomon, George Sopko, Nancy Sweitzer, Song Yang.

ClinTrials.gov NCT00094302

HHS Contract # HHSN268200425207C

NIH National Heart, Lung, and Blood Institute

neri New England Research Institutes

BWH BRIGHAM AND WOMEN'S HOSPITAL

N Engl J Med. 2014; 370:1383-1392.

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Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

- **Objective**
  - To determine if treatment with spironolactone can produce a clinically meaningful reduction in the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, compared with placebo, in adults with HF-Preserved EF.
- **Inclusions:**

  Symptomatic Heart Failure, Age ≥ 50, LVEF ≥ 45%, stratified according to:
  - Hospitalization within the past year for management of heart failure, or
  - Elevated natriuretic peptides (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)
- **Major Exclusions:**

  eGFR<30 mL/min/1.7m^2, serum potassium ≥5 mmol/L, uncontrolled hypertension, AF with rate > 90/min, recent ACS, restrictive, infiltrative, or hypertrophic cardiomyopathy

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

- **International (6) multi-center (270), double-blind, placebo-controlled randomized trial**
- **Randomization, 1:1 within each stratum, to either**
  - Spironolactone, 15, 30, 45 mg daily, or matching placebo
- **80% power to detect a 20% relative reduction in primary events (CVD, HF hosp, or aborted cardiac arrest): 551 adjudicated primary events (approximately 3,515 subjects)**
  - Assuming 3-year placebo primary outcome rate of 17.4%
  - Log-rank test, two-sided $p<0.05$, ITT

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

Outcome	# and % of Subjects with Event, and Event Rate		Hazard Ratio (95% CI) p-value
	Spironolactone (N = 1722)	Placebo (N = 1723)	
Primary Outcome	**320 (18.6%)** 5.9/100pt-yr	**351 (20.4%)** 6.6/100pt-yr	**0.89** (0.77-1.04) P=0.138
Primary Components			
CV Mortality	**160 (9.3%)** 2.8/100pt-yr	**176 (10.2%)** 3.1/100pt-yr	**0.90** (0.73-1.12) P=0.354
Aborted Cardiac Arrest	**3 (<1%)** 0.05/100pt-yr	**5 (<1%)** 0.09/100pt-yr	**0.60** (0.14-2.50) P=0.482
Hospitalization for Heart Failure	**206 (12.0%)** 3.8/100pt-yr	**245 (14.2%)** 4.6/100pt-yr	**0.83** (0.69-0.99) P=0.042

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

No significant differences were found in either:

- **The number of patients**
  - spironolactone 835 (48.5%) vs. placebo 855 (49.6%)

  or
- **The total reports of SAEs**
  - spironolactone 2395 vs. placebo 2387

However, . . .

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

Of 22 pre-specified, only 1 - Stratum - showed a significant interaction with treatment

Enrolled by:	Spiro	Placebo	Hazard Ratio (95% CI) P-value
Natriuretic peptide	**78/490** (15.9%)	**116/491** (23.6%)	**0.65** (0.49-0.87) **0.003**
Heart Failure Hosp	**242/1232** (19.6%)	**235/1232** (19.1%)	**1.01** (0.84-1.21) **0.923**

***P=0.013 for interaction**

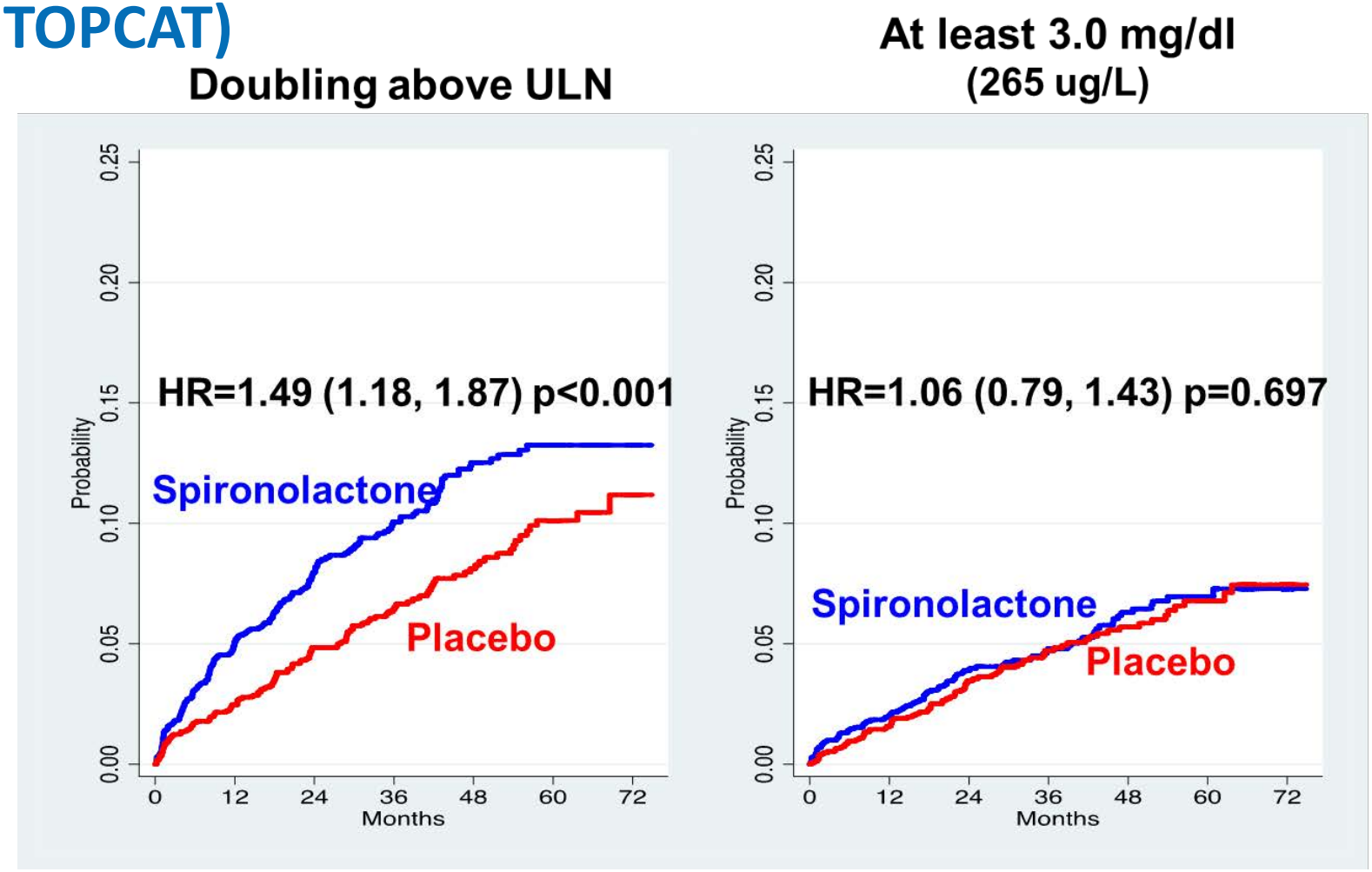
Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

Potassium*	Spiro	Placebo	P (chi-sq)
Hyperkalemia (≥ 5.5 mmol/L)	**322** (18.7%)	**157** (9.1%)	**<0.001**
Hypokalemia (<3.5 mmol/L)	**279** (16.2%)	**394** (22.9%)	**<0.001**

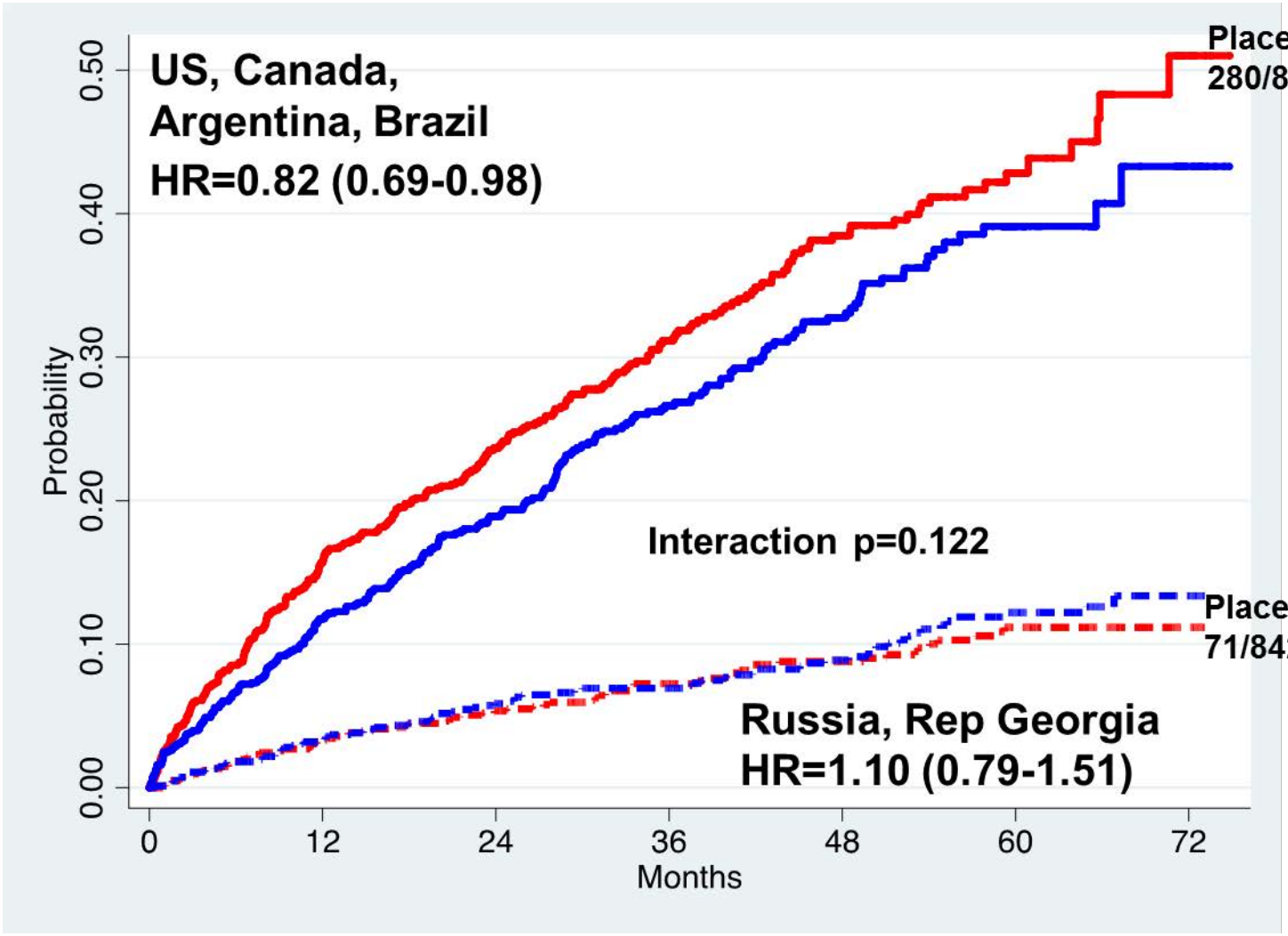
No deaths related to hyperkalemia were reported.

***Monitoring at each dose change and visit**

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

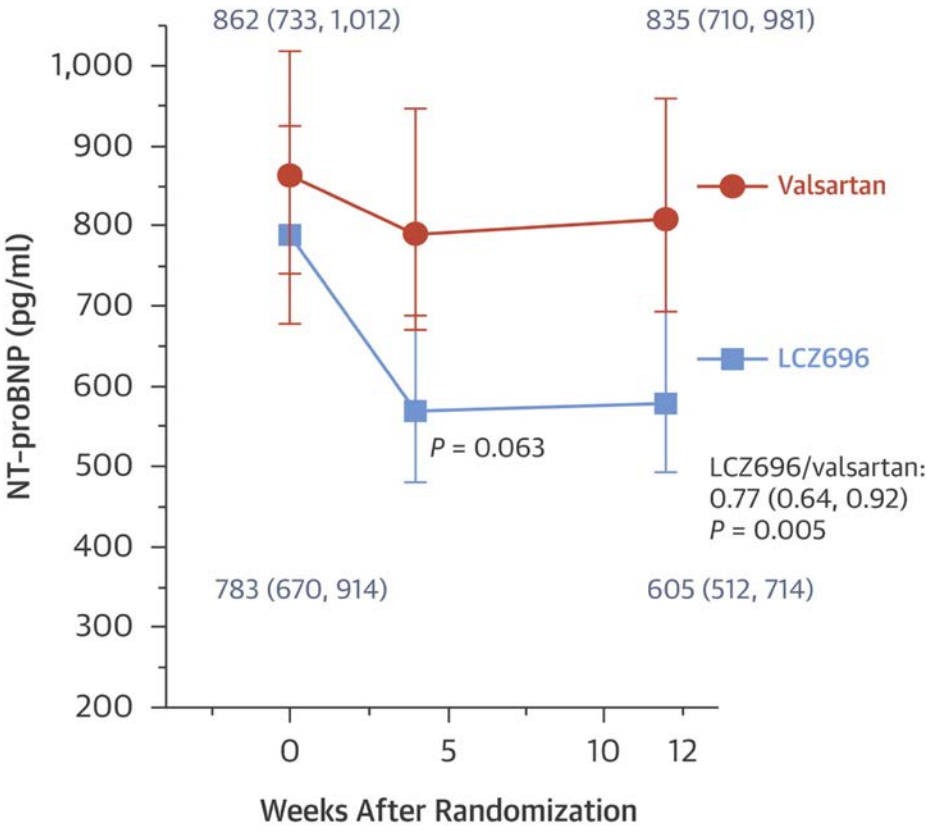


Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT): Regional Differences



Circulation. *2015*;131:34-42

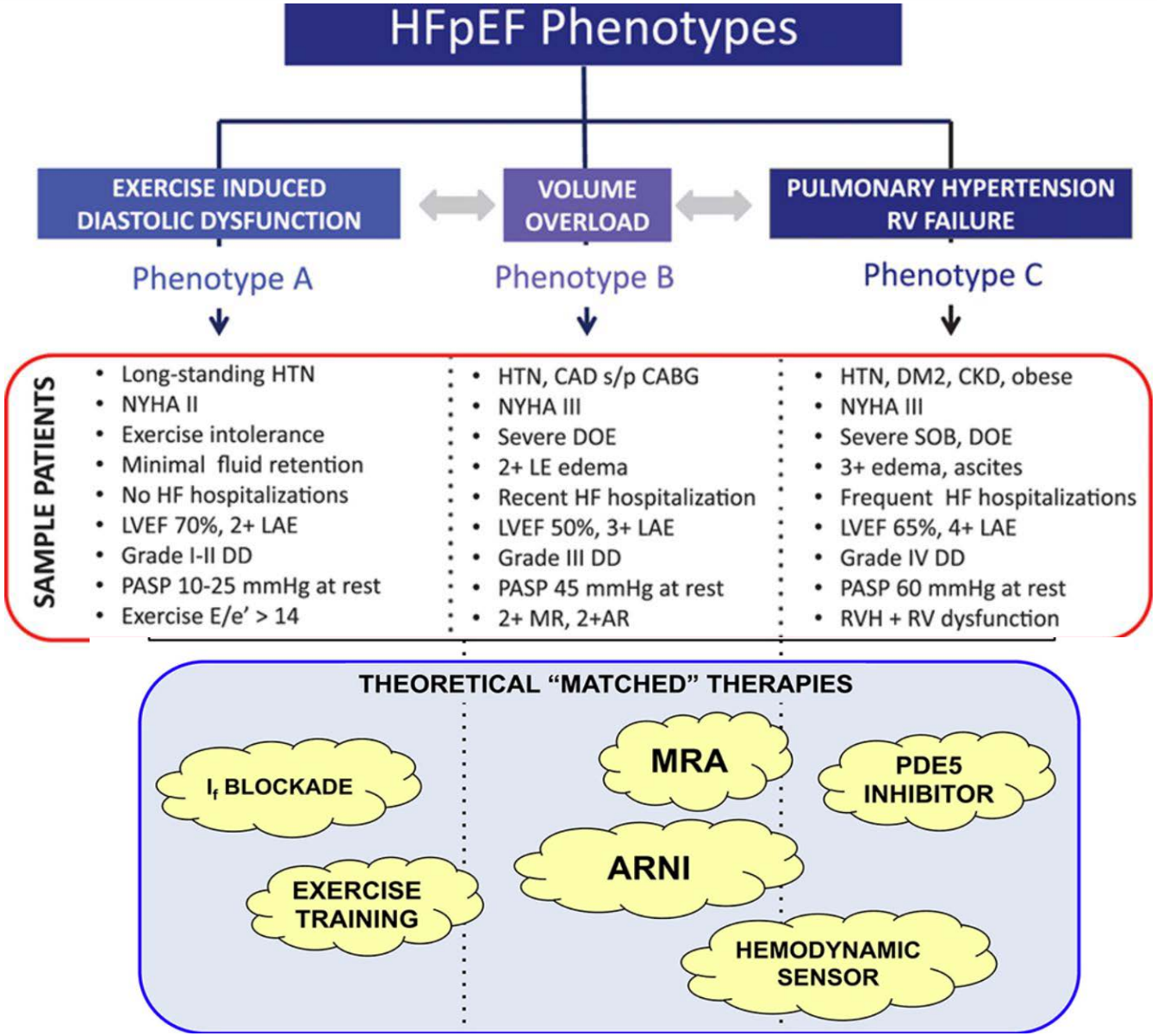
The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) Trial



- Reduced NT-proBNP
- Reduced LA size
- Improved NYHA Class
- PARAGON OUTCOME Trial

Lancet. 2012;380:1387-1395.

Treatment Based on Phenotype



JACC 2014; 64: 1765-1774.

Monitoring Guidelines

Guidelines: check potassium and renal function baseline, three and seven days after initiation, monthly for three months, then quarterly. Restart monitoring cycle if ACE inhibitor or ARB added or their dose increased.

Eplerenone labeling: check potassium and renal function three to seven days after starting a moderate CYP3A4 inhibitor (e.g., verapamil, fluconazole). Contraindicated with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole.

Case

A 70-year-old woman was referred to her family physician by the emergency department for follow-up of shortness of breath, orthopnea and swelling of her legs that she had experienced for two months. She had no other symptoms and was taking amlodipine 10 mg daily, glipizide 10 mg daily, and lisinopril 10 mg daily for hypertension and diabetes. On physical examination, her blood pressure was 160/92 mm Hg and pulse rate was 70 beats/min. Estimated central venous pressure was 12 (normal ≤ 8) cm H_2O. Cardiac examination was unremarkable, and there were bibasilar crackles on lung auscultation. She had bilateral pedal pitting edema. This is her second admit for these symptoms.

In the emergency department, test results for electrolyte levels and renal function were within normal limits. An electrocardiogram showed sinus rhythm and left ventricular hypertrophy. An echocardiogram showed an ejection fraction of 56%, concentric left ventricular hypertrophy with no substantial valvular abnormalities.

JACC. 2013;62:e147-e239.

Which of the following would be the best treatment option for this patient?

A. Add digoxin

B. Change lisinopril to irbesartan

C. Add spironolactone

D. Add sacubitril/valsartan

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Key Takeaways

- Key Takeaway #1
  - Treatment of HFpEF may be dependent upon the phenotype of patient.

- Key Takeaway #2
  - Spironolactone may be considered based on the US phenytope from the TOPCAT trial. The ARNIs may play a role in HFpEF based on surrogate markers.

- Key Takeaway #3
  - Do not underestimate the effects of spironolactone on serum creatinine and potassium. Hyperkalemia is a real adverse effect with the MRAs.