

Management of Heart Failure in 2020

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Disclosures

Consultant:

- Novartis Pharmaceuticals, Abbott, Amgen, AstraZeneca, Alnylam, Biofourmis, Boston Scientific, Boehringer-Ingelheim, DalCor Pharma, Relypsa, Regeneron, Merck

Research Grants

- Novartis, Alnylam, AstraZeneca



Congestive Heart Failure:

Learning Objectives

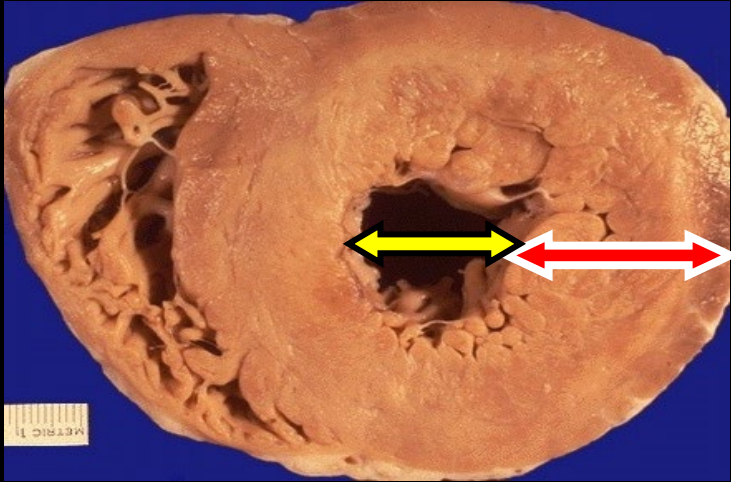
- **Discuss pathophysiology and classification of HF**
- **Outline approach to diagnosis and evaluation of heart failure patients with reduced EF**
- **Apply evidenced-based therapy to the population with heart failure and reduced EF, incorporating recent guideline updates**

The Heart Failure Epidemic

	Prevalence	Incidence	Mortality	Hospital Discharges	Cost
Total population	5,700,000	670,000	277,193	990,000	\$39.2 billion

Leading Cause of hospitalization in adults > 65 years

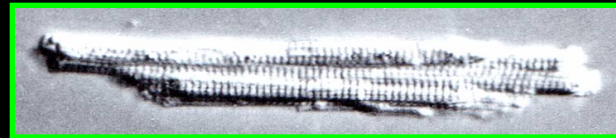
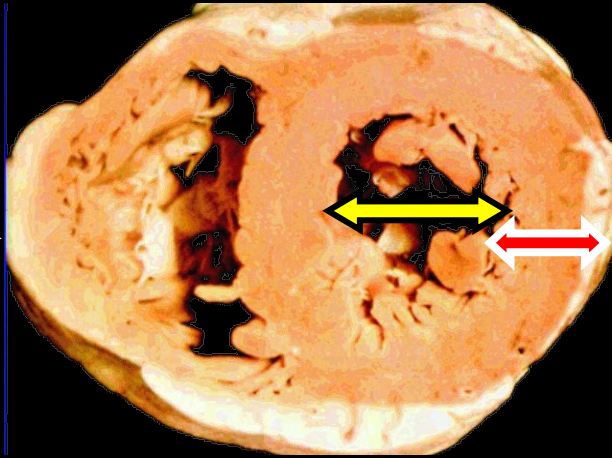
Pathology of Heart Failure



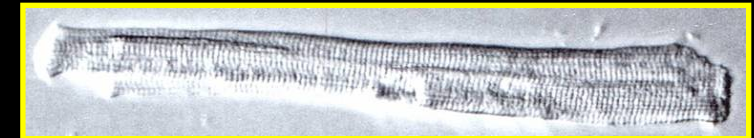
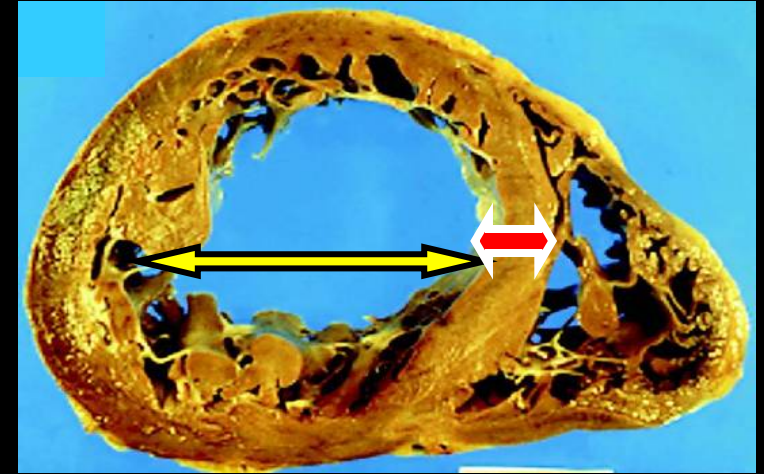
HF-PEF

Concentric Remodeling

↑ Thickness
↔ Volume
↓ Volume / Mass



normal



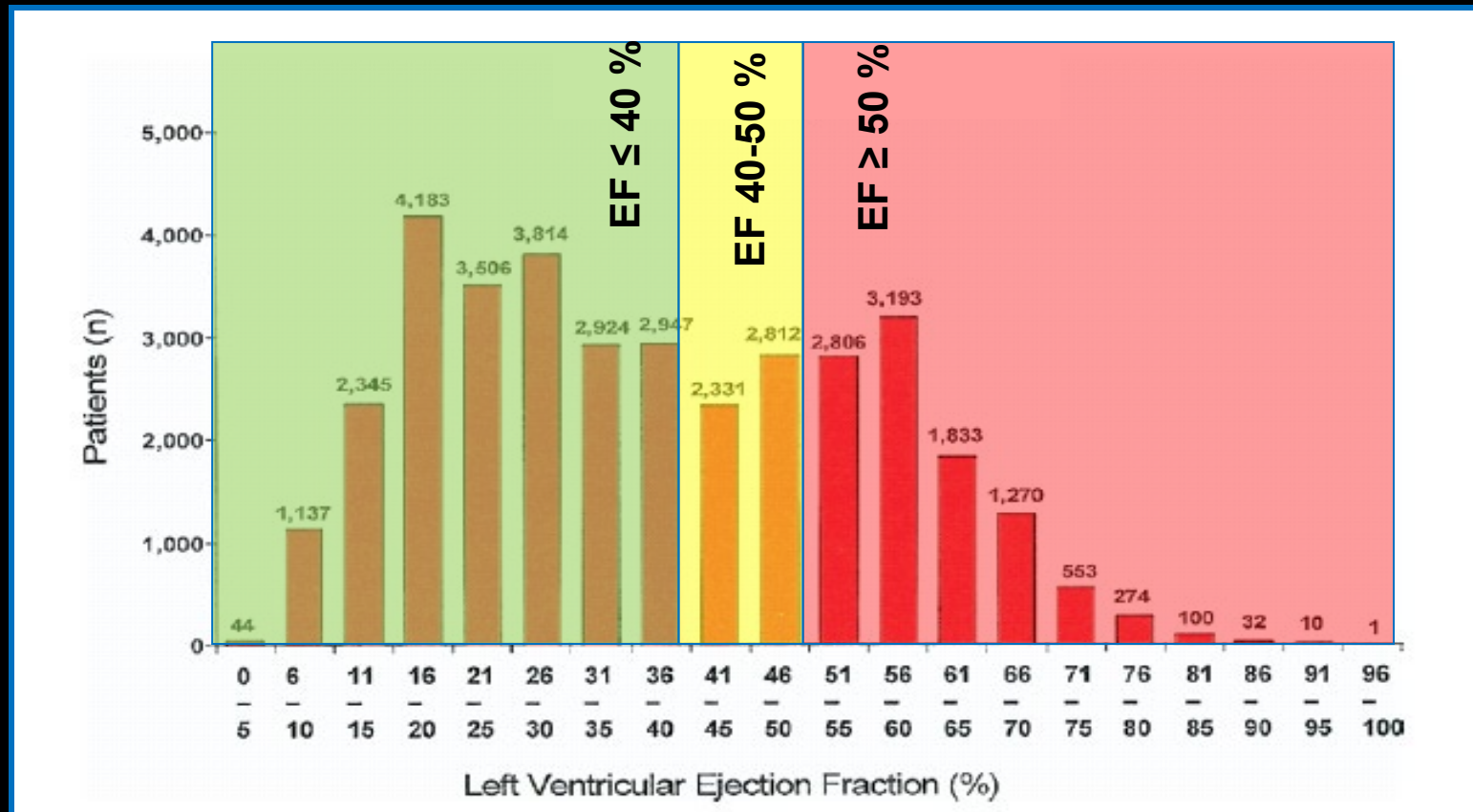
HF-Reduced EF

Eccentric Remodeling

↔ Thickness
Volume ↑ Volume / Mass

↑

Distribution of EF in Patients Hospitalized with HF



HF-PEF vs. HFrEF

- Older
- Female
- HTN
- CKD
- ↓ CAD

Heart Failure is a Clinical Diagnosis

Major criteria

- Orthopnea / PND
- Venous distension
- Rales
- Cardiomegaly
- Acute pulm edema
- JVD > 16 cm
- HJR
- S3

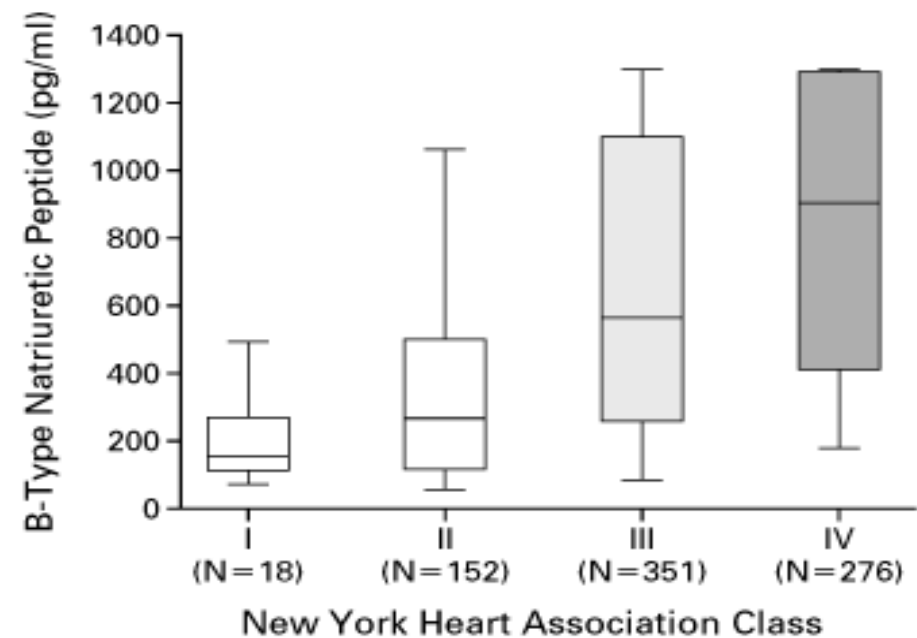
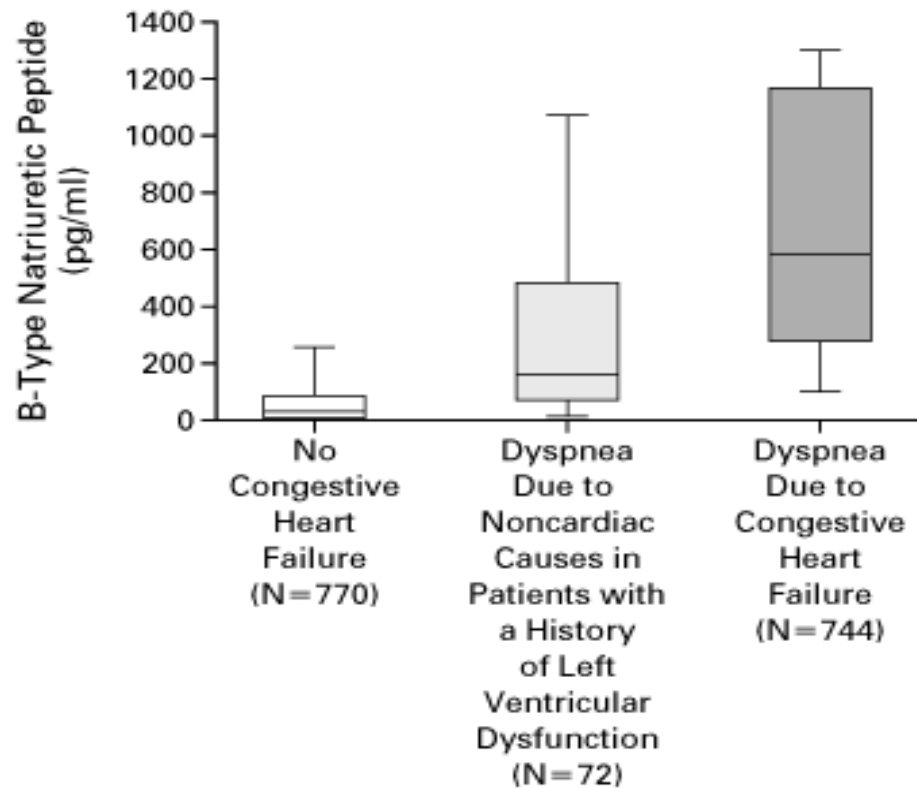
Minor criteria

- Ankle edema
- Night cough
- Exertional dyspnea
- Hepatomegaly
- Pleural effusion
- Tachycardia (>120)
- Decreased VC
- Weight loss w/ CHF tx

CHF = 2 major or 1 major + 1 minor

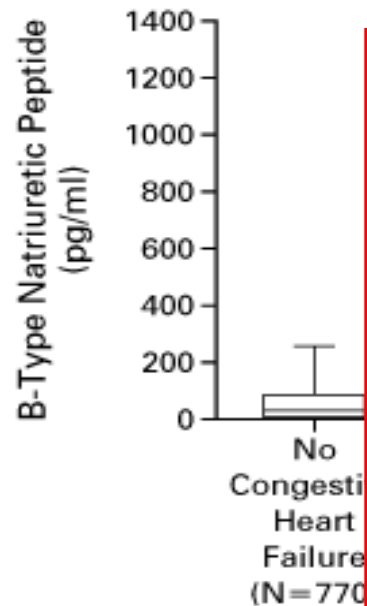
BNP for Diagnosis

1586 pts presenting to EW with dyspnea



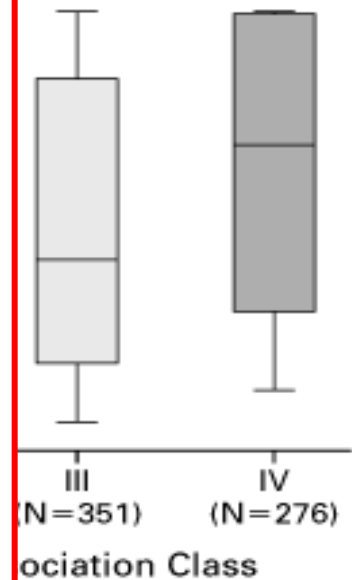
BNP for Diagnosis

1586 pts presenting to EW with dyspnea



BNP ≥ 100 pg/mL:
Positive Predictive Value 79%
Negative Predictive Value 89%

NT-pro BNP ≥ 900 pg/mL:
Positive Predictive Value 77%
Negative Predictive Value 92%



Limitations of BNP

- **Biologic Variability**
 - Levels may increase with age, female gender, pressure overload, renal failure
 - Levels decrease with obesity, treatment (e.g., carvedilol, spironolactone)
- **Levels are lower in HF with preserved EF**
- **Insufficient specificity for use as a screening tool**

Limitations of BNP

- **Biologic Variability**
 - Levels may increase with age, female gender, pressure overload, renal failure

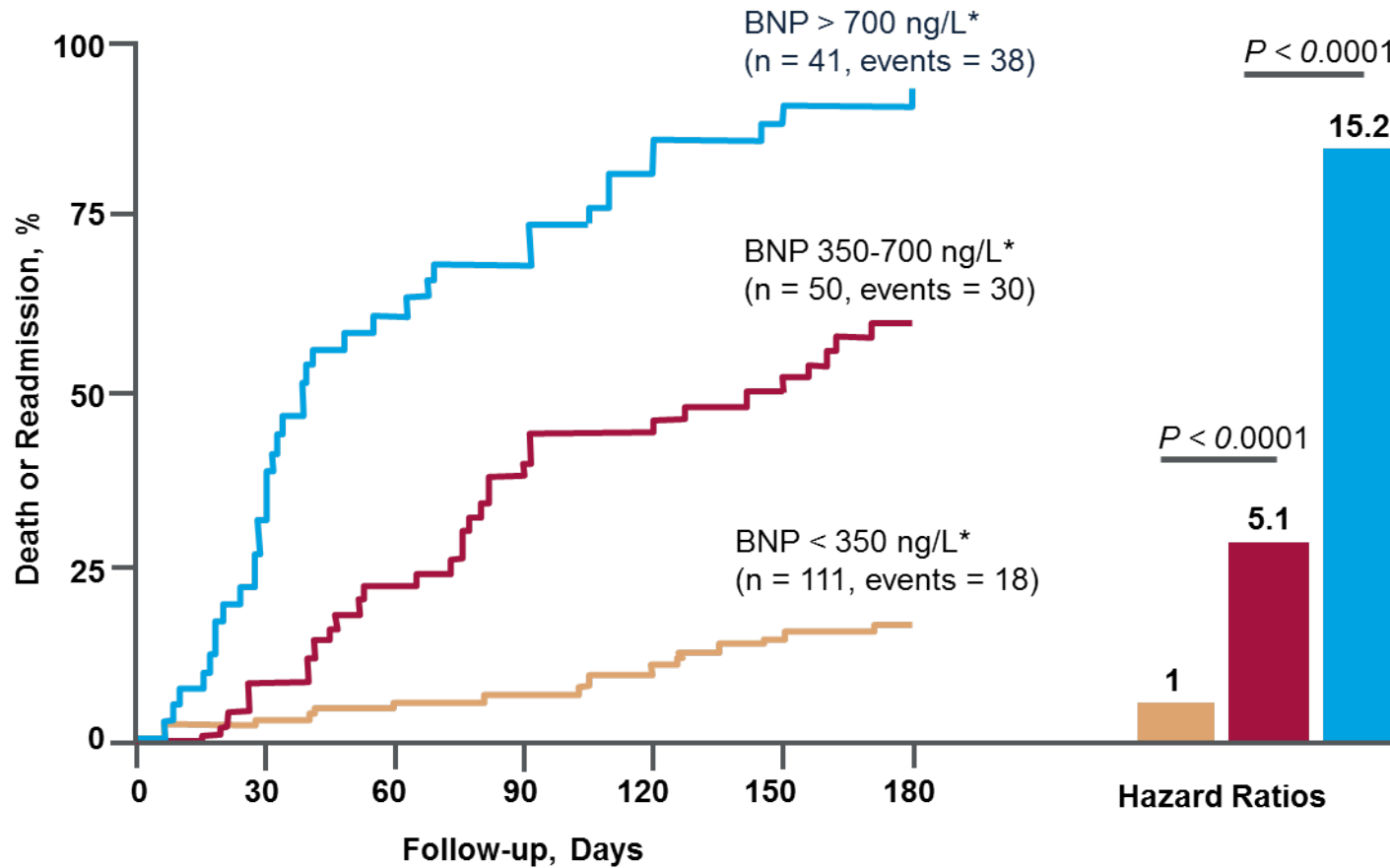
The measurement of BNP is primarily useful when there is diagnostic uncertainty

- **Levels are lower in HF with preserved EF**
- **Insufficient specificity for use as a screening tool**

Pre-Discharge BNP Is A Strong Predictor of Post-Discharge Events

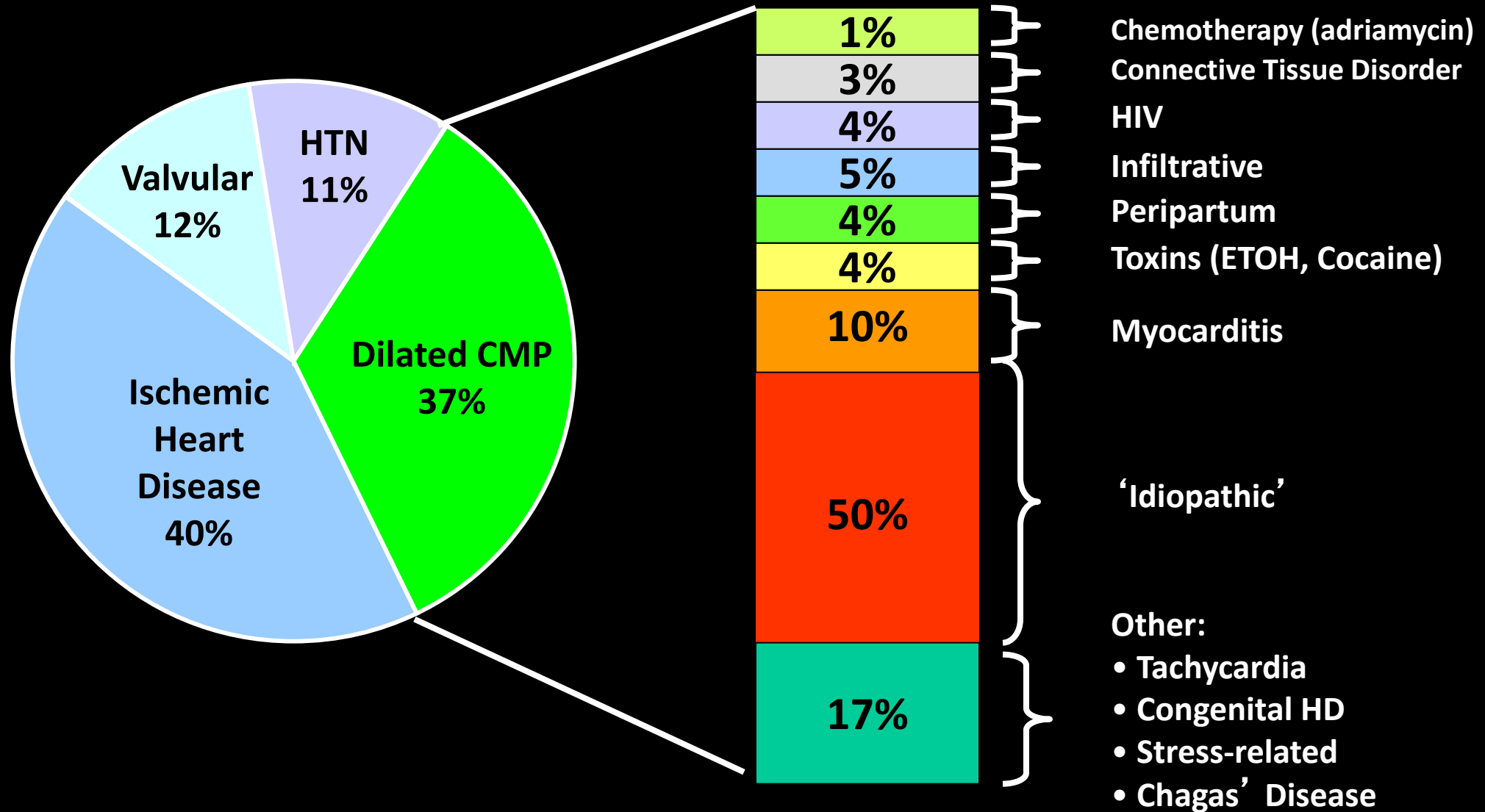


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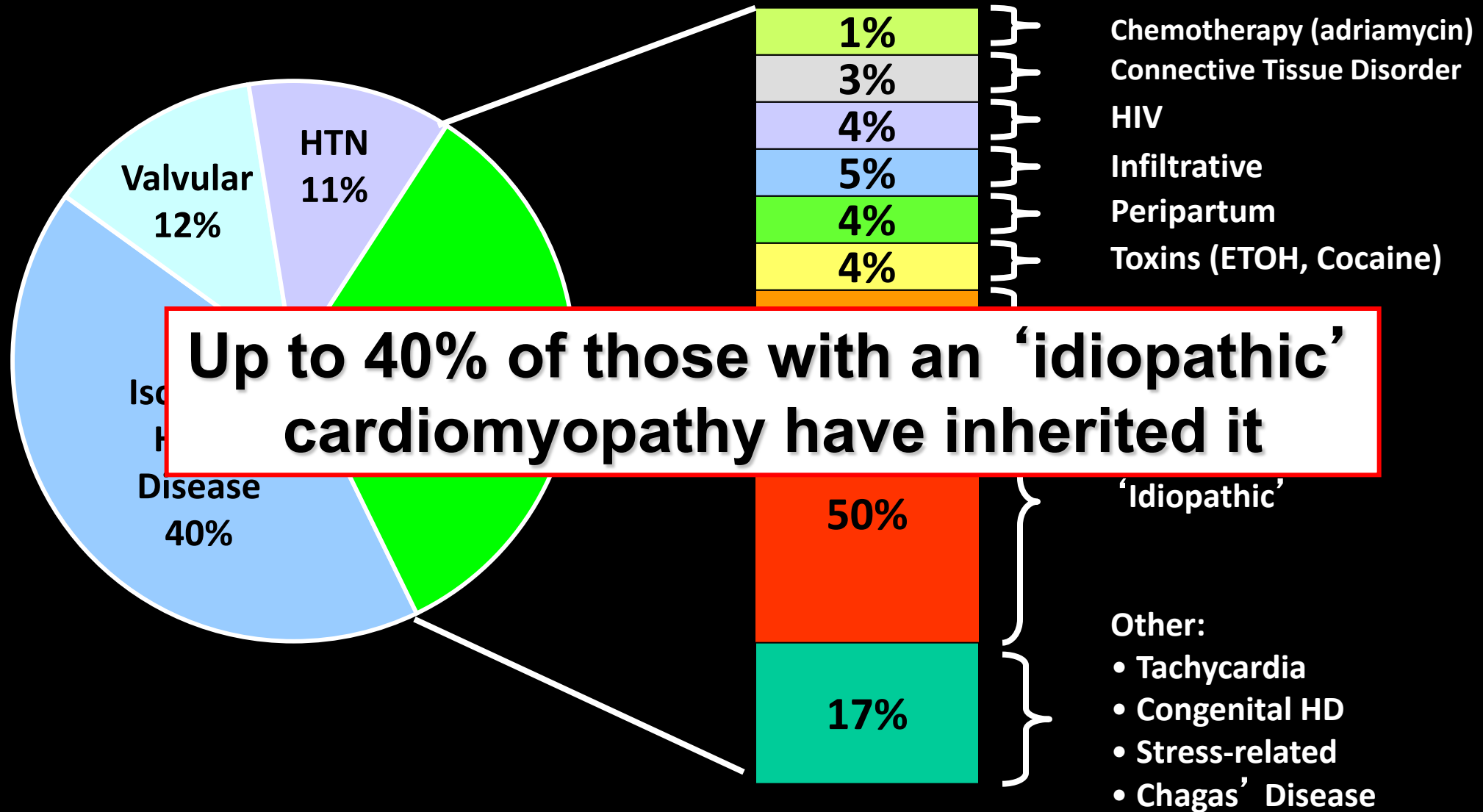


Causes of Heart Failure





Causes of Heart Failure



Initial workup of newly diagnosed HF

In all cases:

- History, exam, EKG
- Echo
 - ?MR, LVEDD, RV fxn
- Labs
 - TSH, ferritin, Na, Cr
- Exercise testing
 - Prognosis, ?Tx
- Assessment for CAD
 - one of the few reversible causes

In selected cases:

- Labs
 - Metanephrines
 - BNP?
- Catheterization
 - CAD
 - Hemodynamics
- Endomyocardial biopsy
 - If infiltrative diseases being considered

Staging Heart Failure: A New Paradigm

ACC/AHA Classification

A. At risk patients without structural heart disease

B. Structural heart disease without symptoms

C. Structural heart disease with prior or current symptoms

D. Refractory heart failure

Progressive Disease

NYHA Classification

I. Cardiac disease without functional limitation

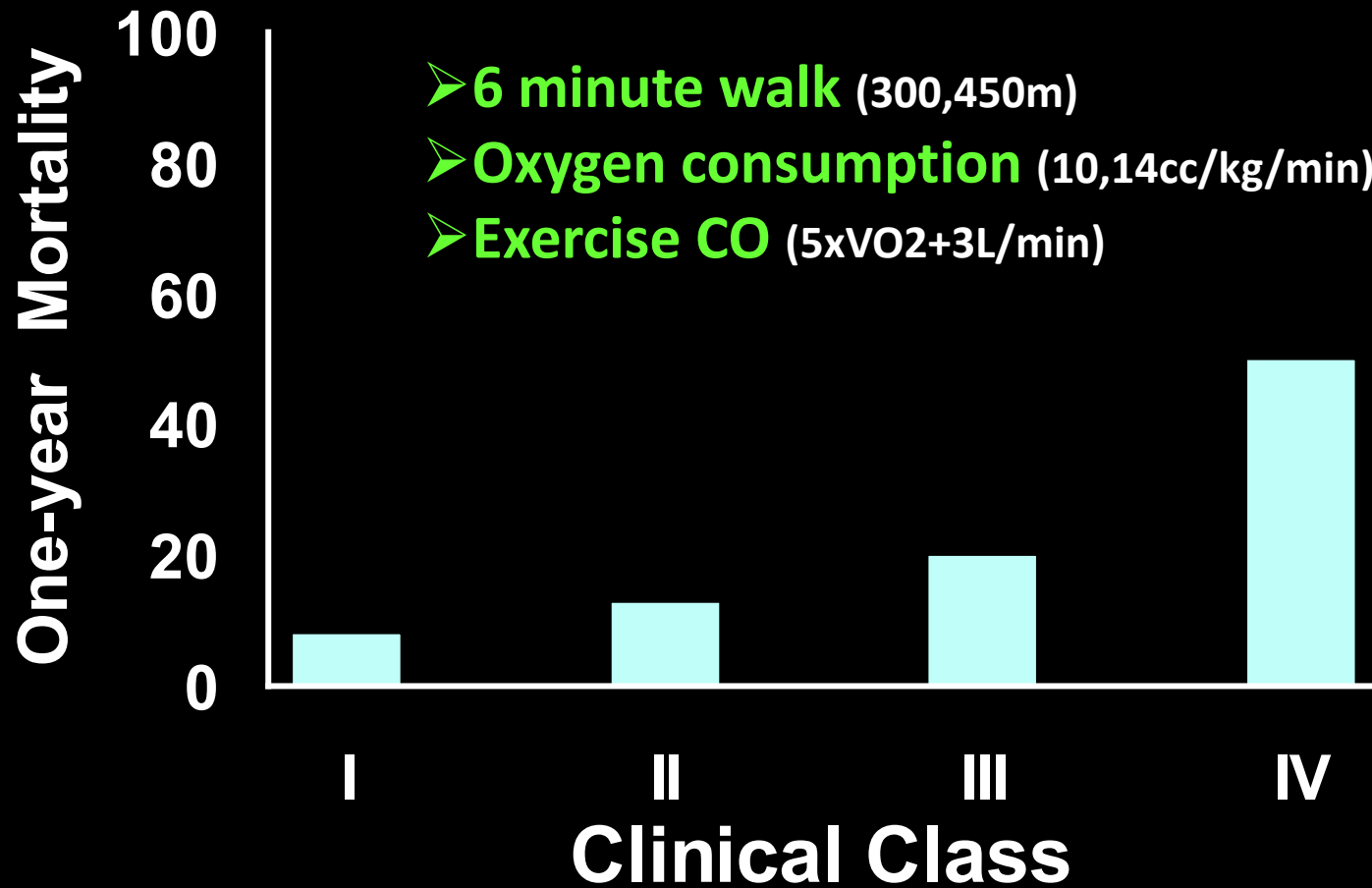
II. Slight limitation of physical activity

III. Marked limitation of physical activity

IV. Inability to carry on physical activity without discomfort

Worsening QOL

Clinical Class Remains the #1 Predictor Of Mortality in Heart Failure



SAVE
SOLVD
VHeFT
CONSENSUS
Hy-C
GESICA
Pre-TRD 1000



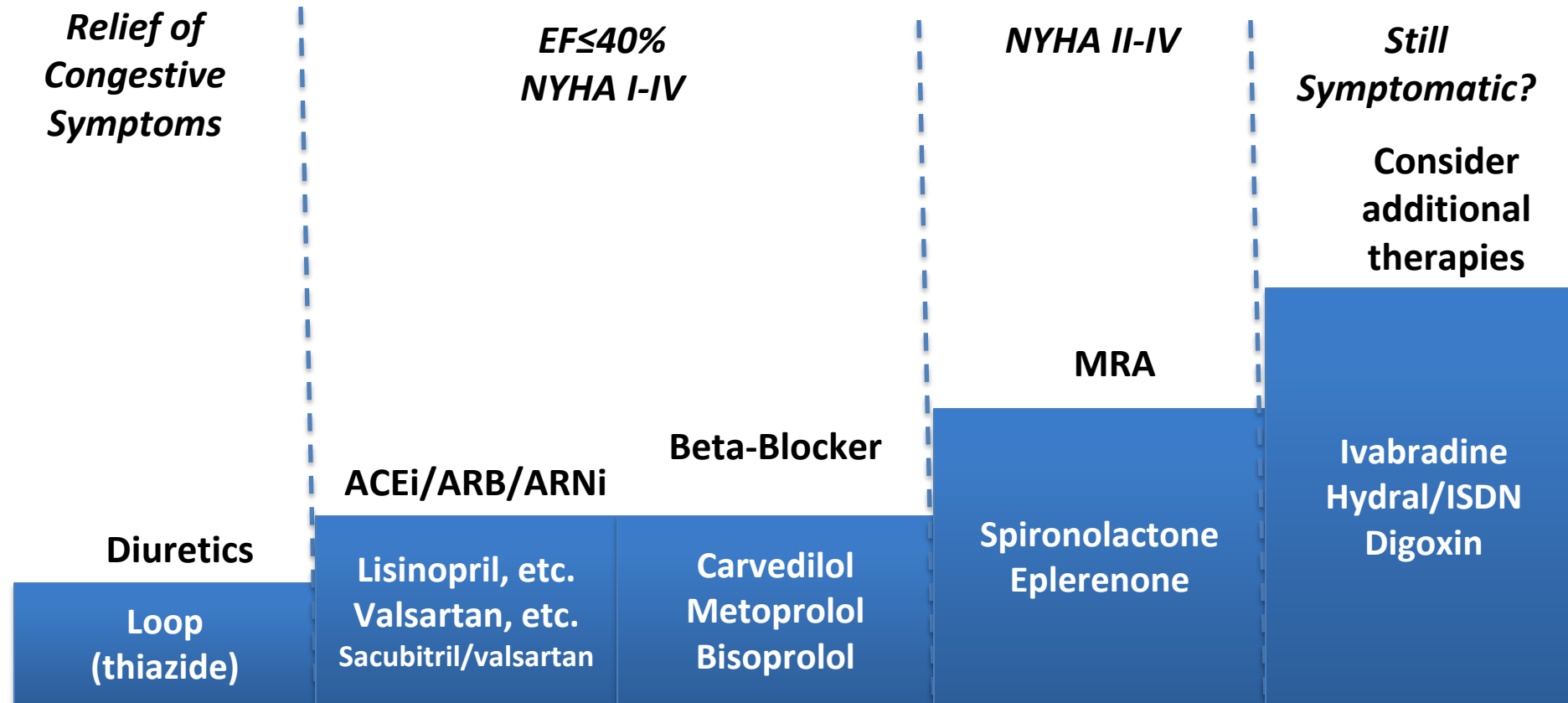
Goals of Therapy for Symptomatic HF: Stage C HF

- Address precipitating factors
- Initiate Rx to prevent dz progression and mortality
- Improve sx's and end-organ perfusion
- Reduce LOS and re-hospitalization
- *Identify and treat the causative/inciting factor*
- *Neurohormonal blockade*
- *Manage related risks (sudden cardiac death)*
- *Lower PCWP*
- *Increase CO*
- *Pt education*
- *Longitudinal dz management programs*

Guideline-Directed Medical Management of HF with Reduced EF



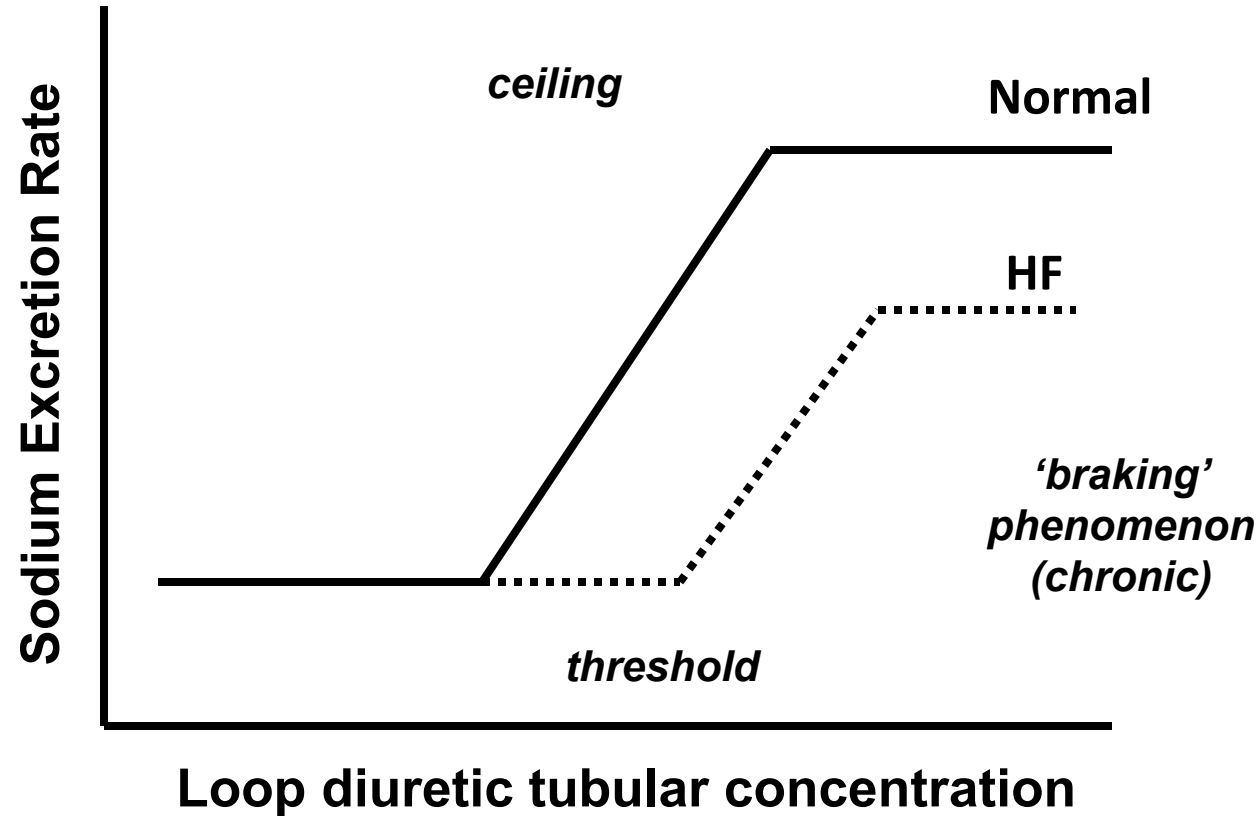
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Diuretics for Heart Failure

	Examples	Maximum Effect (% of filtered Na load)	Site of action in nephron
Carbonic Anhydrase Inhibitors	Acetazolamide	3-5%	Proximal Tubule
Loop Diuretics	Furosemide, Bumetanide, Torsemide	20-25%	Thick ascending limb of Loop of Henle
Thiazide Diuretics	HCTZ, metolazone	5-8%	Early distal tubule
Potassium-Sparing Diuretics	Spirolactone, amiloride	2-3%	Late Distal tubule and collecting duct

Loop Diuretic Pharmacodynamics

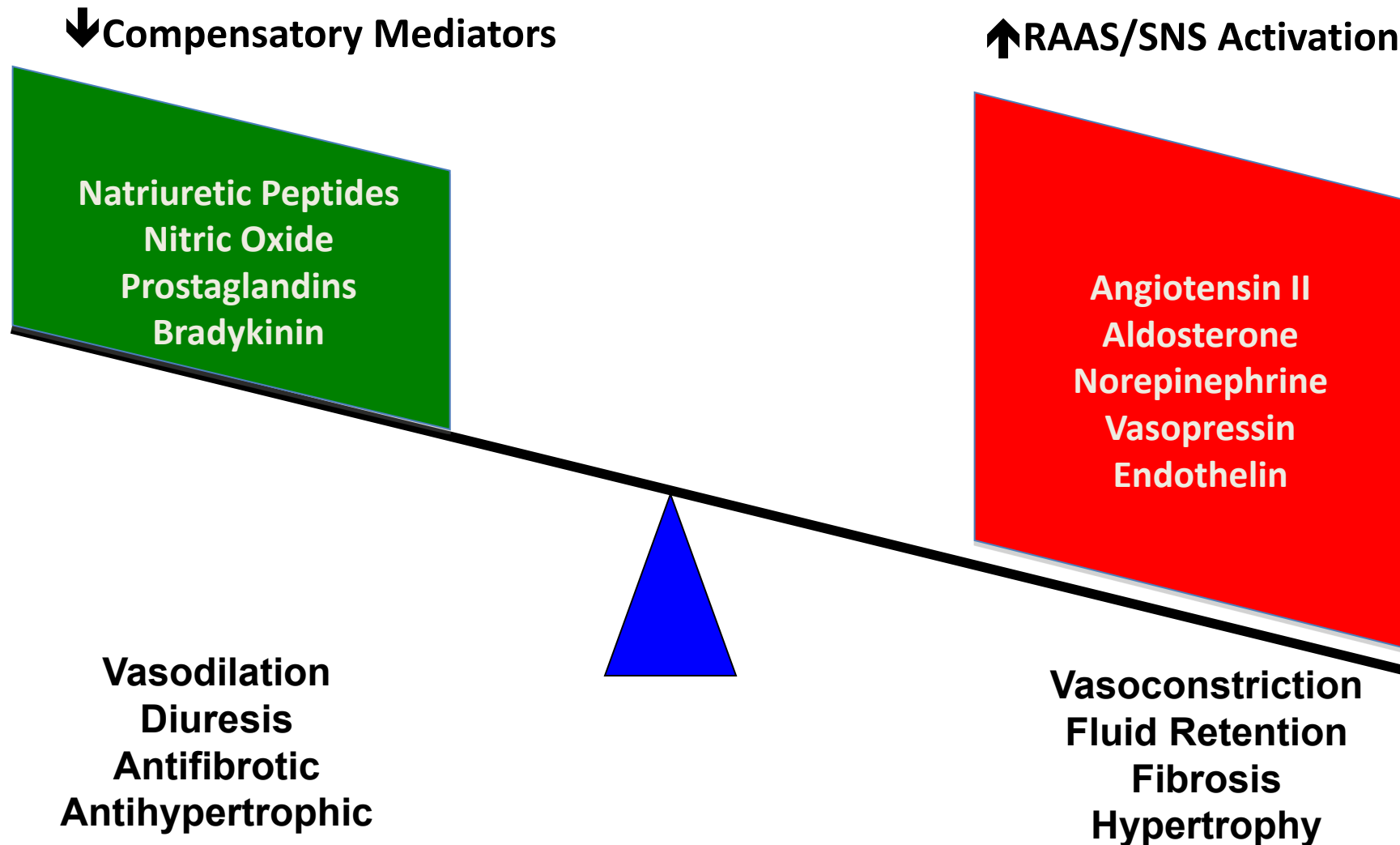


- Use an adequate initial dose
- Avoid overdosing
- More frequent administration of effective doses
- Combination diuretic therapy for diuretic resistance

Neurohormonal Balance in Heart Failure

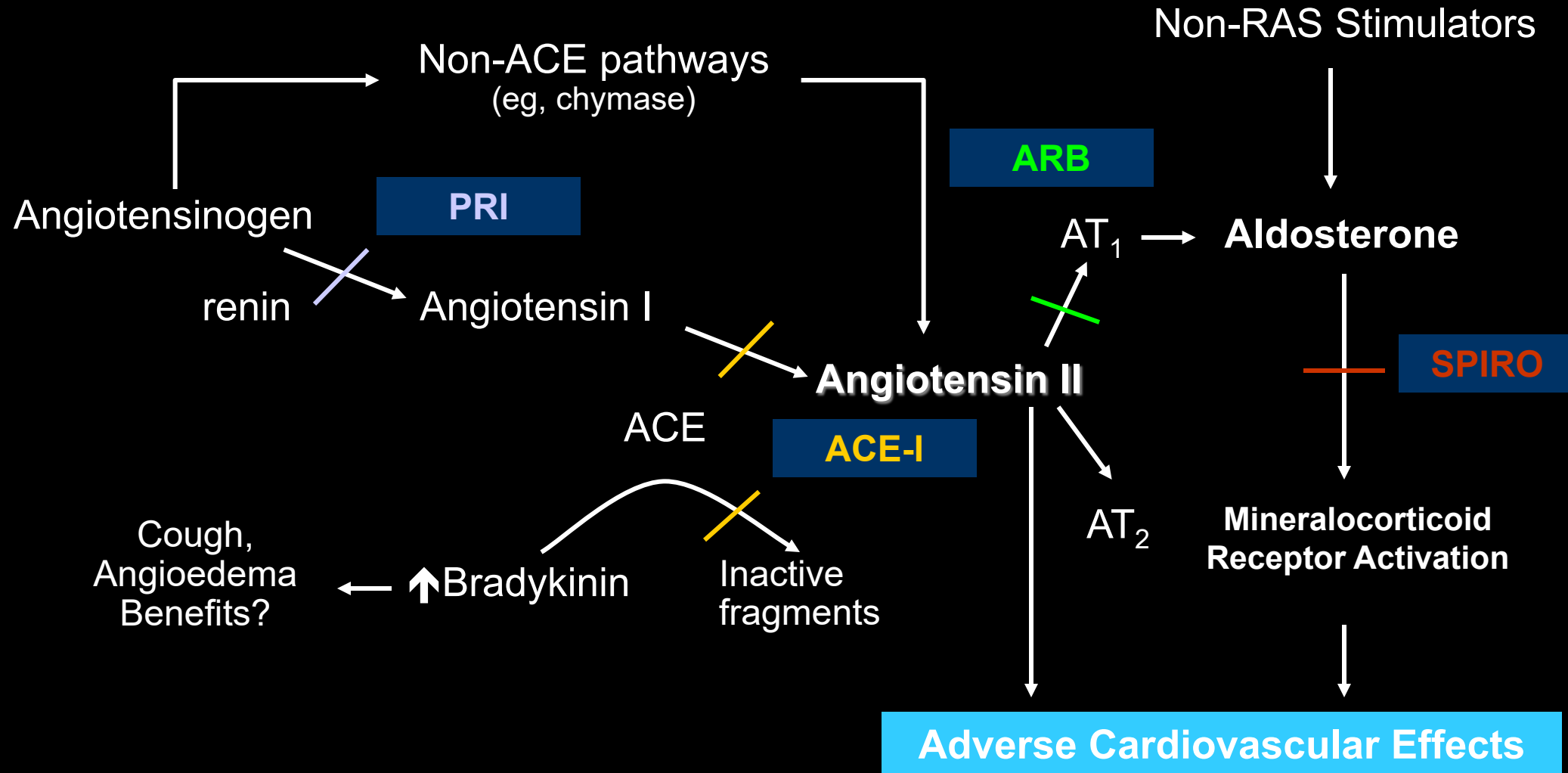


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Renin-Angiotensin-Aldosterone System



ACE-Inhibitors in Heart Failure

- Improve symptoms, clinical status, and exercise capacity
- Improve cardiac function
- Reduce hospitalizations
- Attenuate remodeling
- Prolong survival
- Reduce vascular events (ie. HOPE)



Outcome Trials of ACE Inhibitors in Heart Failure

	<u>Patients</u>	<u>NYHA Class</u>	<u>Placebo Mortality</u>	<u>Hazard ratio</u>
V-HeFT II	804	I-III	25% (Hyd/Iso)	0.72
CONSENSUS I	253	IV	44%	0.66
SOLVD Tx	2569	II-III	40%	0.84
SOLVD Px	4228	I	16%	0.91
SAVE	2231	Post MI EF<40%	25%	0.81
ISIS-4	58,050	24h post MI	7.7%	0.93

ARBs in Heart Failure

- ACEI does not produce long-term suppression of Angiotensin II (“escape phenomenon”)
- Angiotensin II can be generated by other pathways
- Circulating Ang II inhibition may not be equivalent to tissue Ang II inhibition
- 8-12 % of pts cannot tolerate ACEI

ARB Trials in Heart Failure

	<u>ELITE I/II</u>	<u>ValHEFT</u>	<u>CHARM</u>	<u>OPTIMAAL</u>	<u>VALIANT</u>
<i>Patients (n)</i>	NYHA II-IV 722/3152	NYHA II-IV 5010	NYHA II-IV 2548	Acute MI/CHF 5477	Acute MI/CHF 14,808
<i>Study Design</i>	Losartan or Captopril	Valsartan and ACEI	Candesartan and ACEI	Losartan or Captopril	Valsartan, Captopril, or both
<i>β-blocker</i>	16% / 23%	35 %	55 %	79 %	70 %
<i>Mortality</i>	No difference	No difference	No difference	Captopril better	No differences
<i>HF Hosp</i>	No difference	Both better	Both better	Capt better	Both better
<i>Other</i>	Losartan better tolerated	↑ Mort. w/ β-blker	↓ Mort. w/ β-blker	Losartan better tolerated	↓ BP w/ both

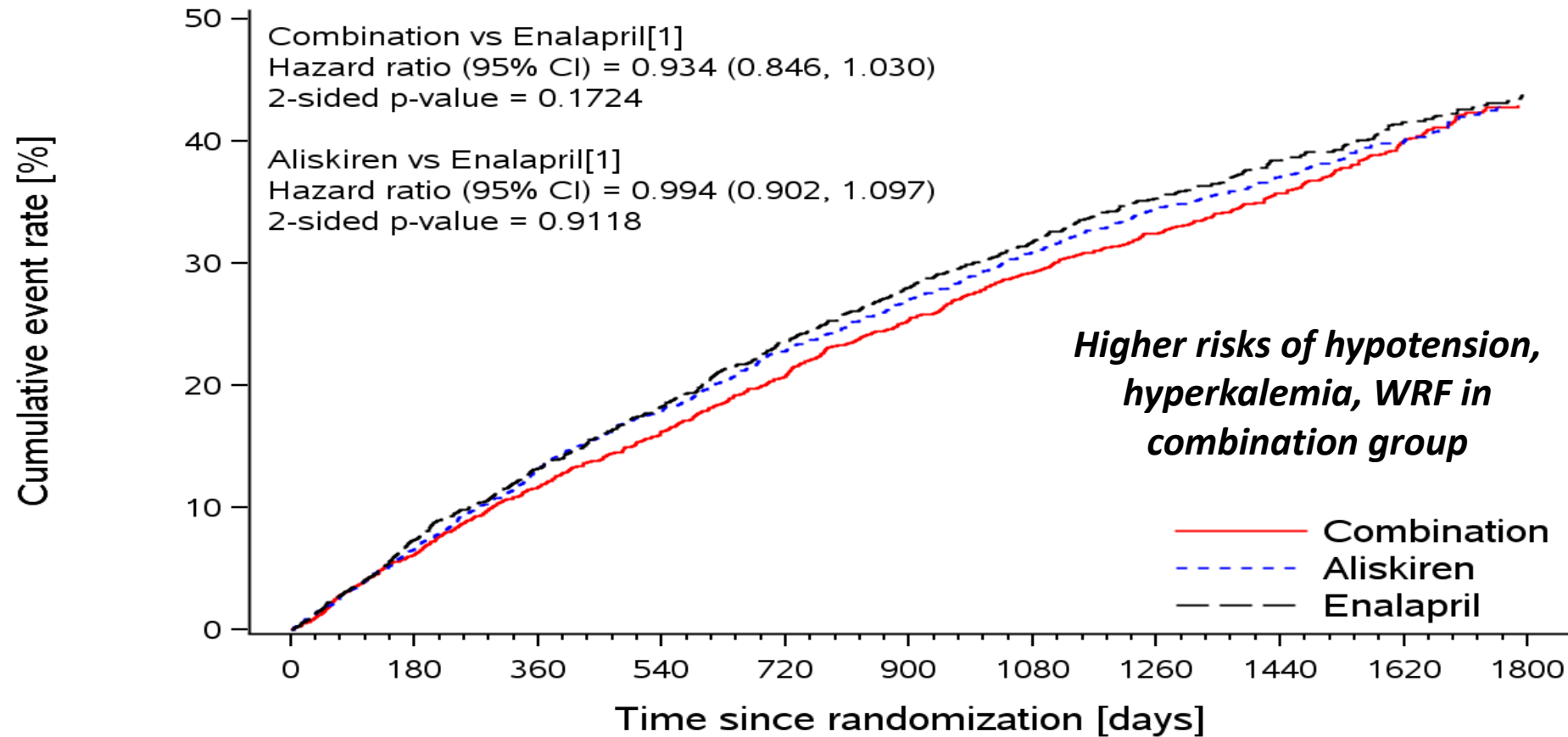
ARB Trials in Heart Failure

	<u>ELITE I/II</u>	<u>ValHEFT</u>	<u>CHARM</u>	<u>OPTIMAAL</u>	<u>VALIANT</u>
Patients <i>(n)</i>	NYHA II-IV	NYHA II-IV	NYHA II-IV	Acute MI/CHF	Acute MI/CHF

ARBs are excellent and proven alternatives to ACE inhibitors

<i>β-blocker</i>	16% / 23%	35 %	55 %	79 %	70 %
<i>Mortality</i>	No difference	No difference	No difference	Captopril better	No differences
<i>HF Hosp</i>	No difference	Both better	Both better	Capt better	Both better
<i>Other</i>	Losartan better tolerated	↑ Mort. w/ β-blker	↓ Mort. w/ β-blker	Losartan better tolerated	↓ BP w/ both

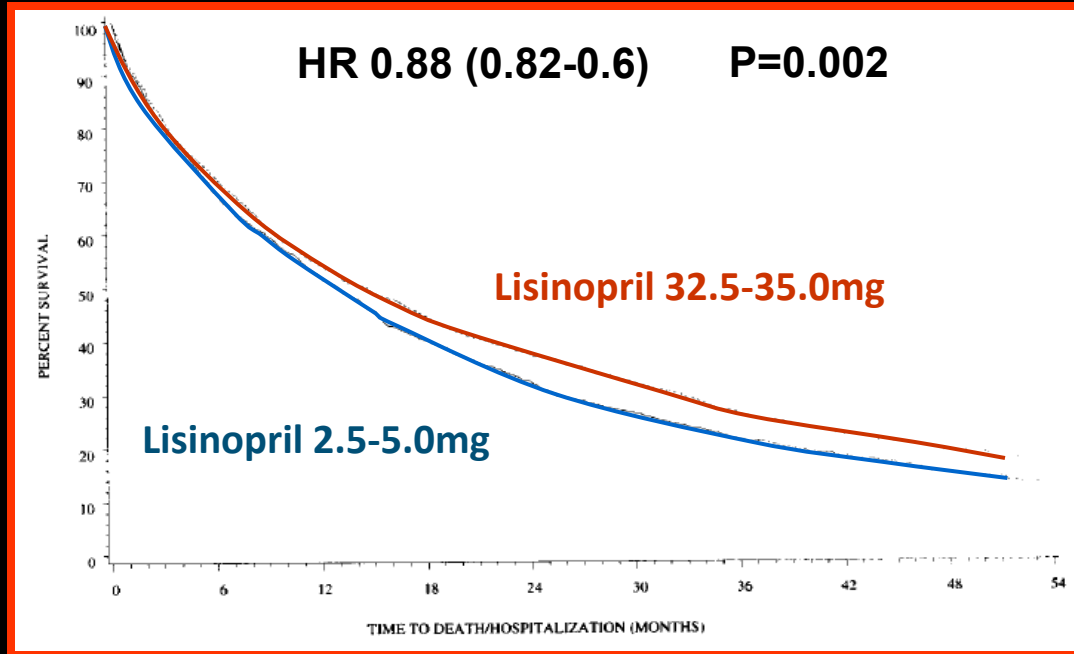
No role for Renin Inhibition with Aliskiren in HF with reduced EF



	Patients at risk										
Combination	2340	2137	1959	1809	1562	1307	1085	895	689	456	273
Aliskiren	2340	2127	1934	1761	1510	1288	1064	888	681	474	282
Enalapril	2336	2128	1947	1766	1513	1268	1044	866	679	452	281

Optimal Dosing of RAAS Antagonists

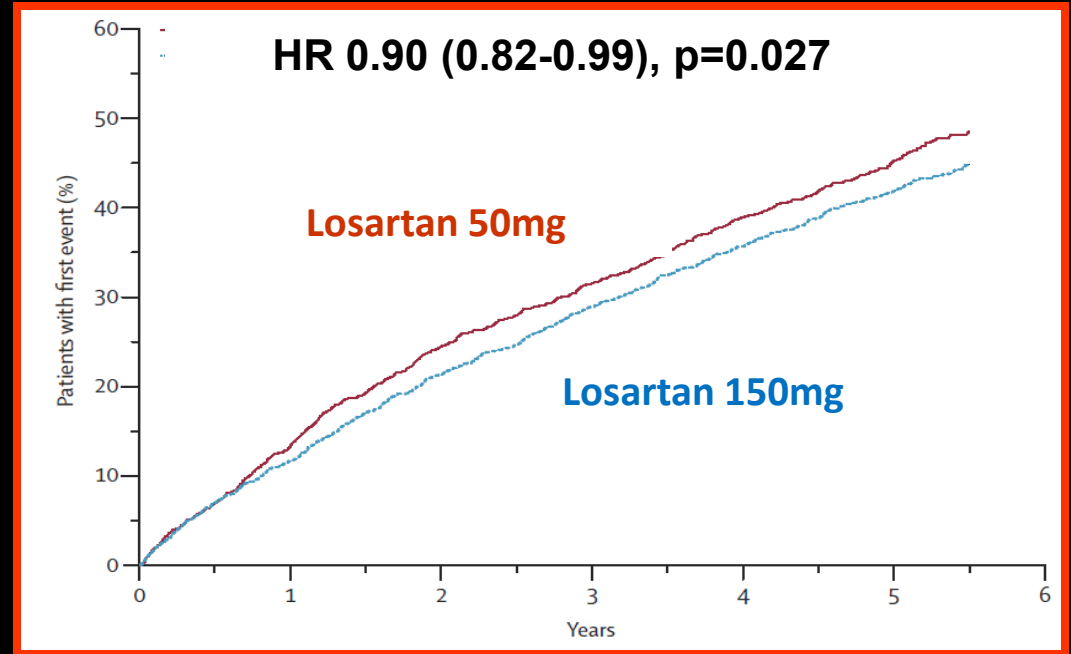
ATLAS



Time to Death or Hospitalization

Favors High Dose

HEAAL



Time to Death or HF Hospitalization

Favors High Dose

Titrate as Tolerated to Doses Achieved in Clinical Trials

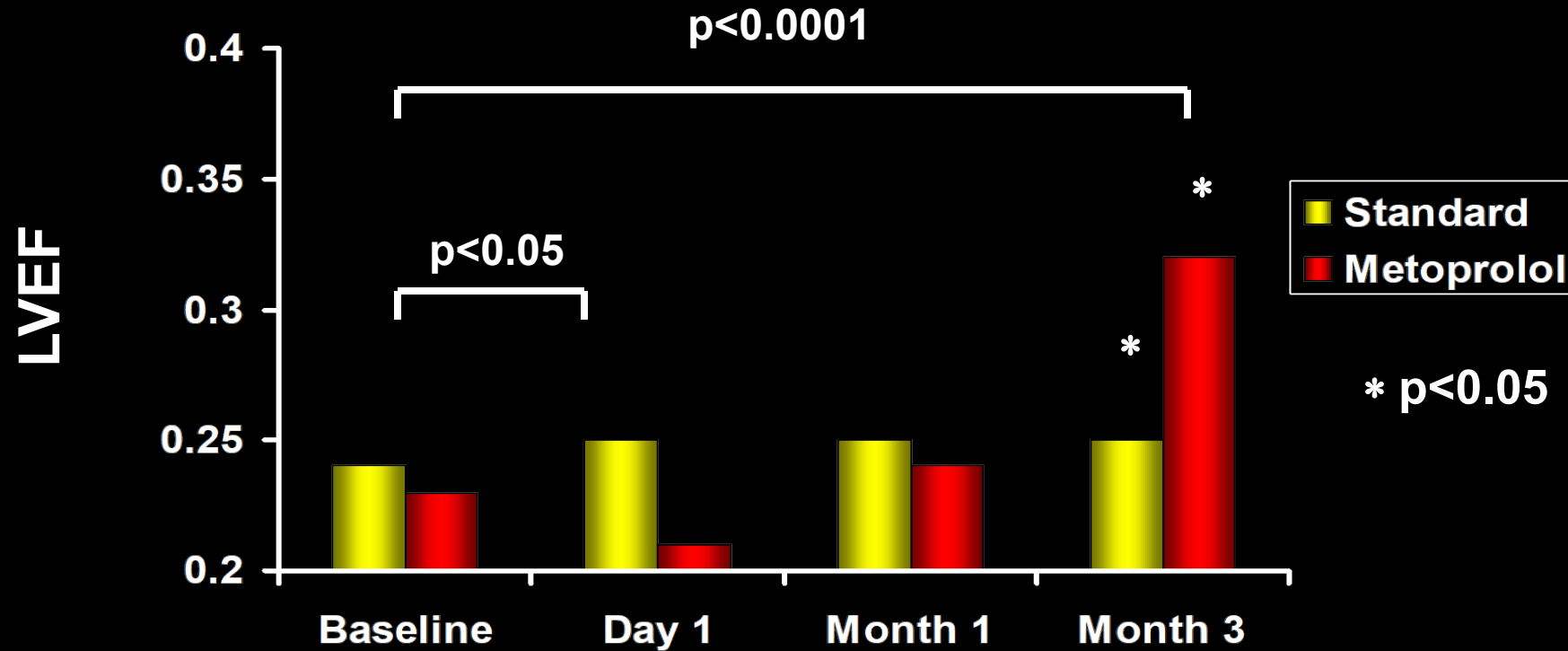
Packer M, et al. Circulation 1999; 100: 2312-18

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

How Do Beta Blockers Improve Heart Failure?

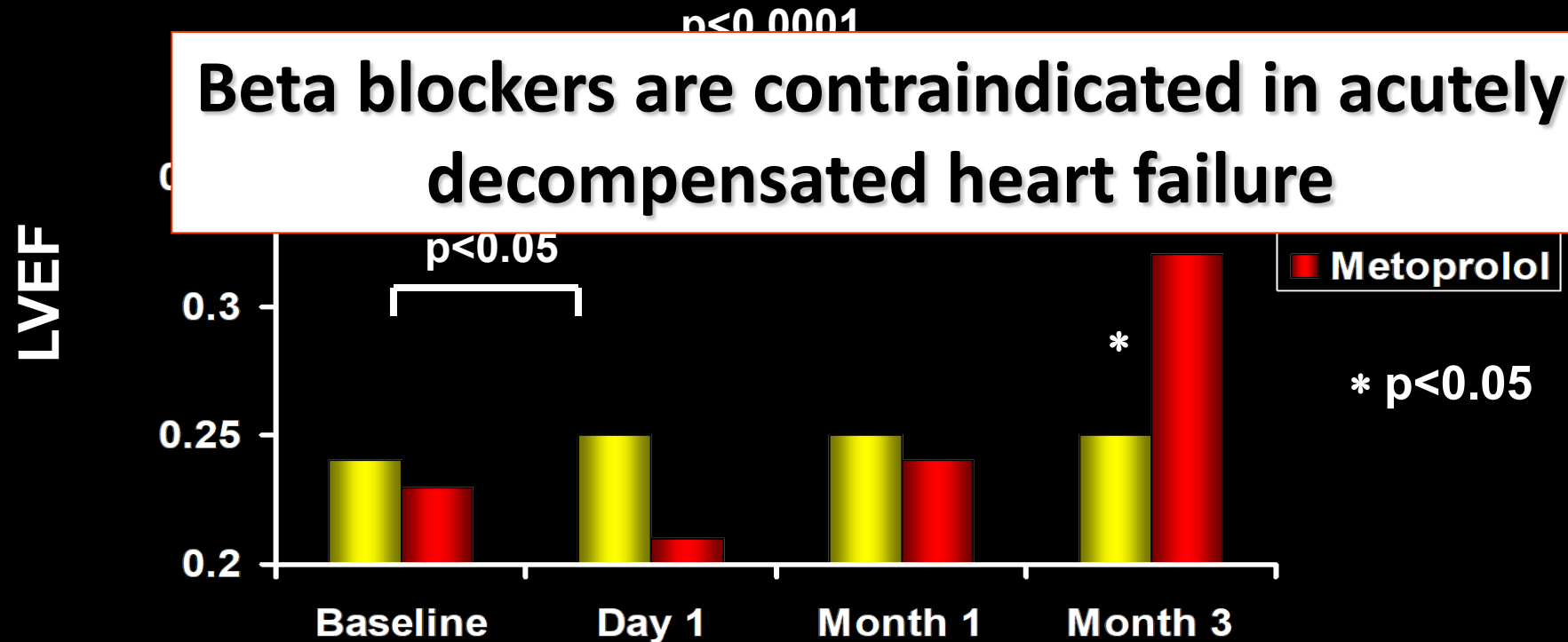
- Upregulation of beta receptors
- Improved coupling of beta receptors to secondary intracellular signals
- Alterations in myocardial metabolism
- Improved calcium transport
- Increased protein synthesis and message expression
- Inhibition of renin-angiotensin system
- Inhibition of endothelin and cytokine release

Effect of Beta Blockade on Ejection Fraction over Time



Hall, JACC 1995

Effect of Beta Blockade on Ejection Fraction over Time



β-Blocker Trials in Symptomatic HF

Trial	Target Dose (mg/d)	Mean Dose (mg/d))	Annual Mortality		
			Control	β-blocker	RRR (%)
Bisoprolol					
CIBIS I	5	3.8	11.0	8.7	NS
CIBIS II	10	7.5	13.2	8.8	34
Bucindolol					
BEST	100-200	76	17	15	NS
Metoprolol					
MDC	100-150	108	11.1	11.9	NS
MERIT-HF	200	159	11.0	7.2	34
Carvedilol					
US Carvedilol	12.5-100	45	14.4	5.9	65
COPERNICUS	50	37	18.5	11.4	38

Clinical Pharmacology of Beta-Adrenergic Antagonists

	<u>β_1/β_2 Receptor Selectivity</u>	<u>Vasodilator Mechanism</u>	<u>Lipid Solubility</u>
Bisoprolol	120	0	0
Metoprolol	75	0	0
Carvedilol	10-40	α_1 antagonist	++
Bucindolol	1	Direct	++
Labetalol	1	α_1 antagonist	++

COMET

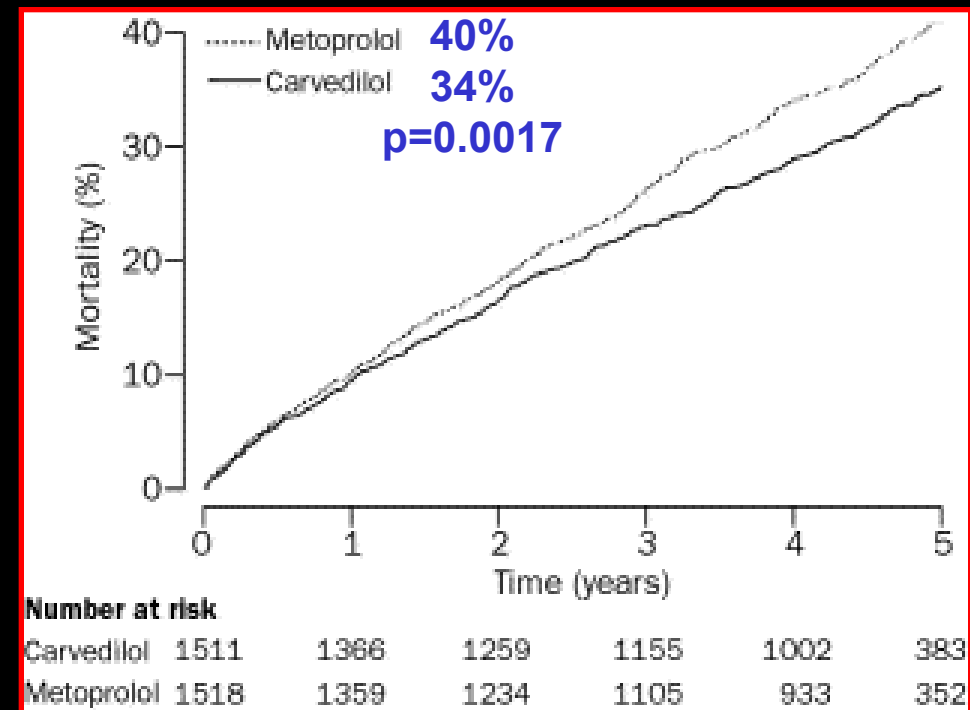
Is Carvedilol Better than Metoprolol?

- 3029 pts NYHA II-III
- Carvedilol 25mg bid (41.8 mg)
- Metoprolol tartrate 50 mg bid (85 mg)
(Same resting HR in both groups)

○ MERIT-HF

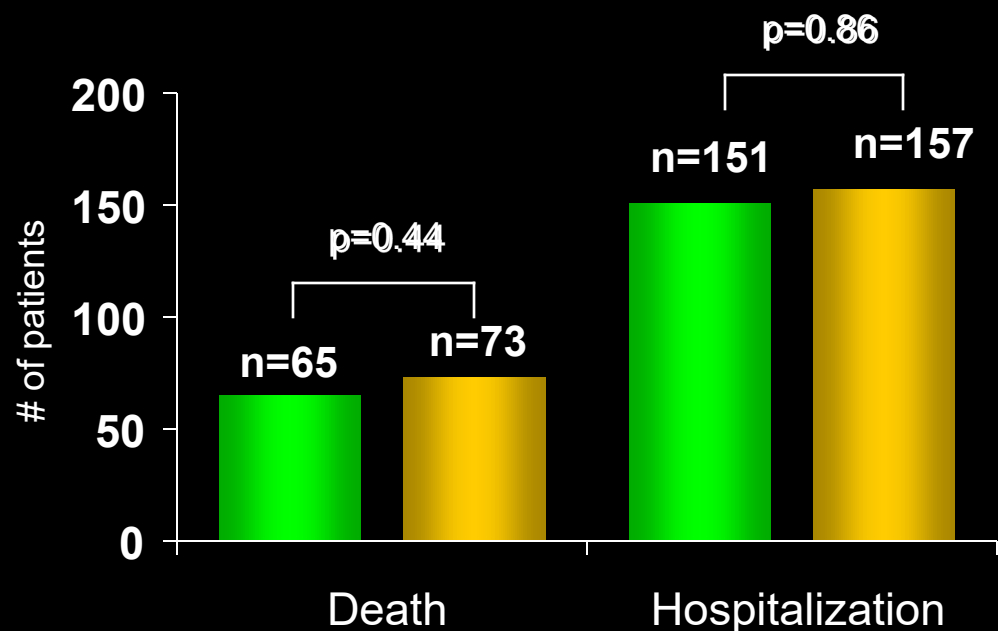
- Metoprolol succinate 200 mg (159 mg)
= Metoprolol tartrate 106 mg

- Composite endpt (mortality
And all cause admission)
 - 74% Carvedilol
 - 76% Metoprolol
 - $p = 0.122$



Which drug first?

ACE-I vs. Beta Blocker



■ Beta-blocker bisoprolol ■ ACE-inhibitor enalapril

CIBIS III

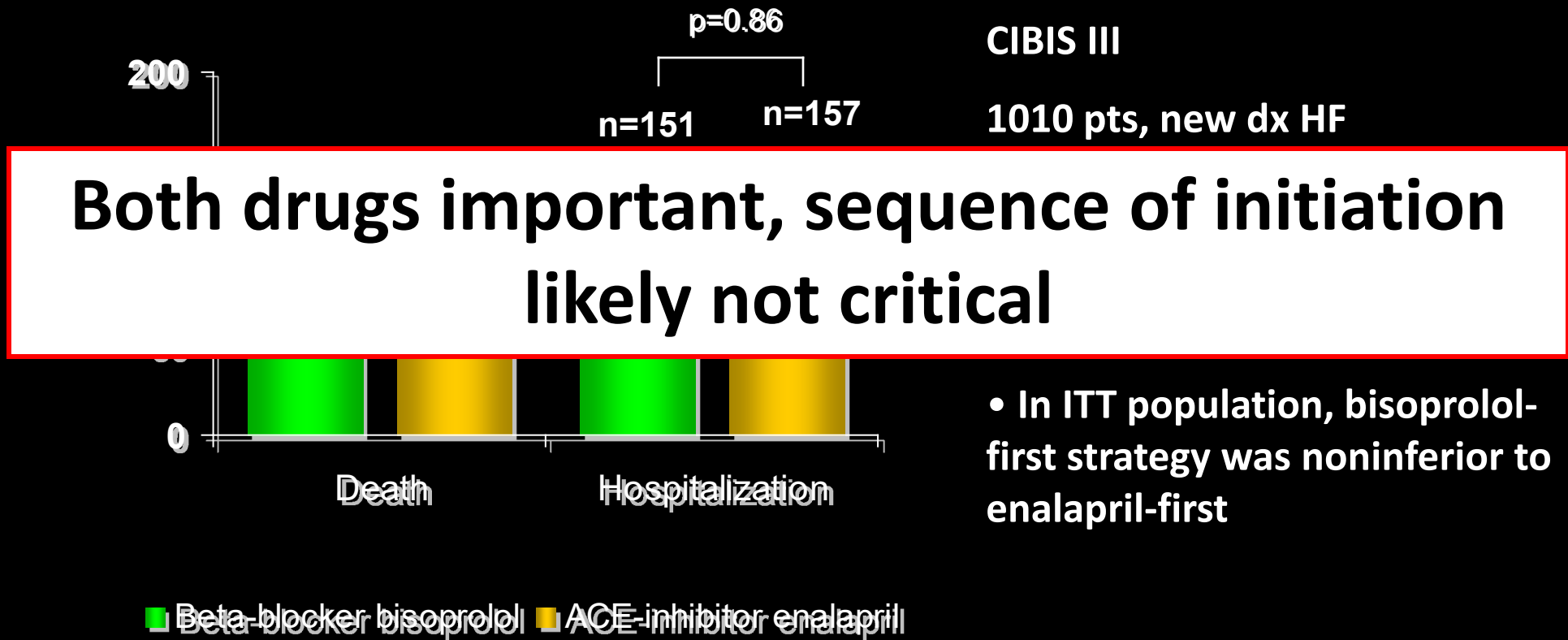
1010 pts, new dx HF

NYHA II-III, EF≤35%

Monotherapy for 6 mos,
followed by combination rx

- In ITT population, bisoprolol-first strategy was noninferior to enalapril-first

Which drug first? ACE-I vs. Beta Blocker



Aldosterone Antagonists in HF

Trial	N	LVEF	NYHA	End-pt	HR
RALES ¹	1663	≤ 35%	III-IV	All cause mortality	0.7, p<0.001
EPHESUS ²	6632	Post-MI EF < 40%	II <i>or</i> I w/ DM	All cause mortality	0.85, P=0.008
EMPHASIS-HF ³	2737	EF < 30% <i>or</i> EF 30-35% w/ QRS > 130	II	CV death or HF hosp.	0.63, p<0.0001

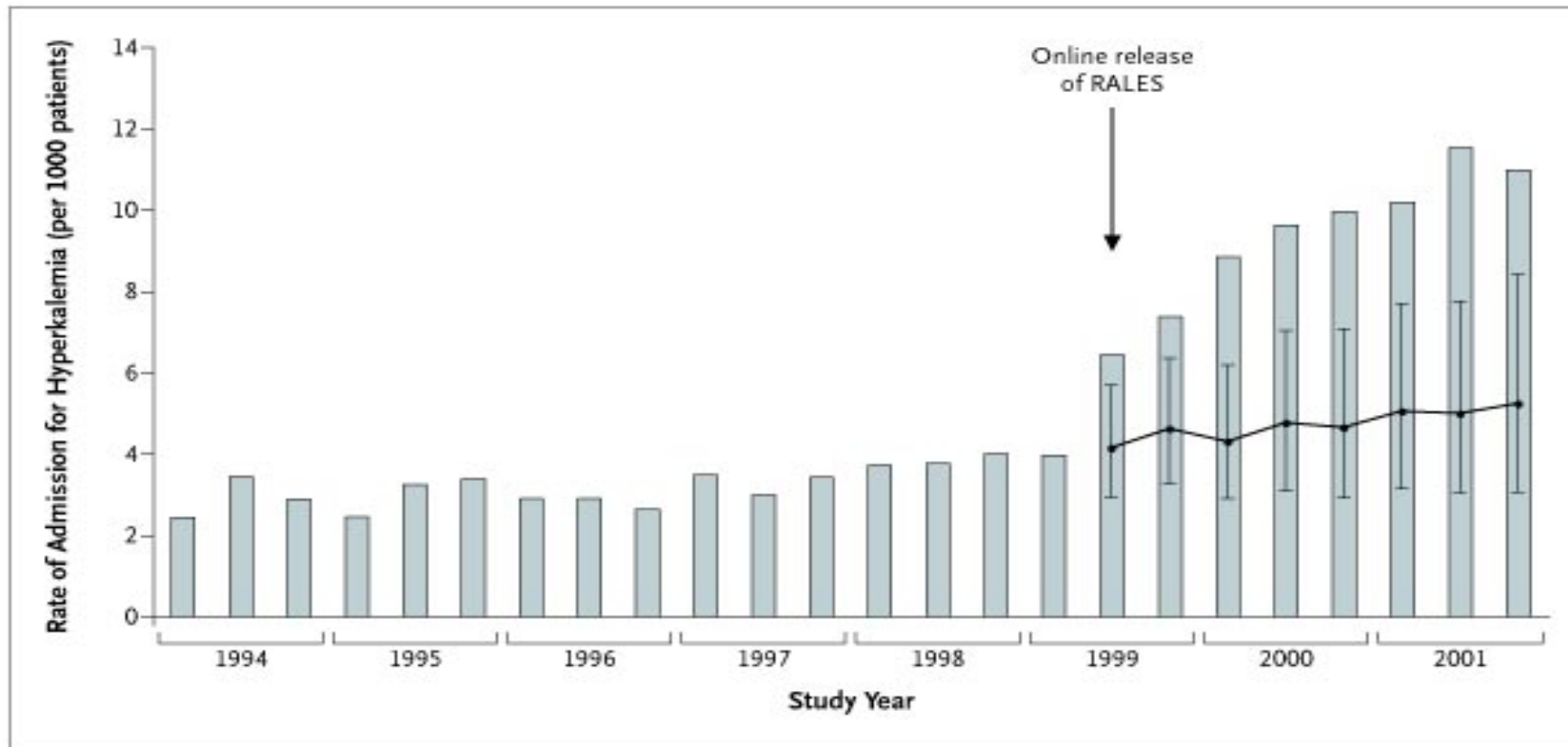
¹Pitt, B et al. NEJM 1999;341:709-17;

²Pitt B et al. NEJM 2003;348:1309-21;

³Zennad F et al. NEJM 2011;364:11-21

Aldosterone Antagonists: Safety

Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors (before/after RALES)

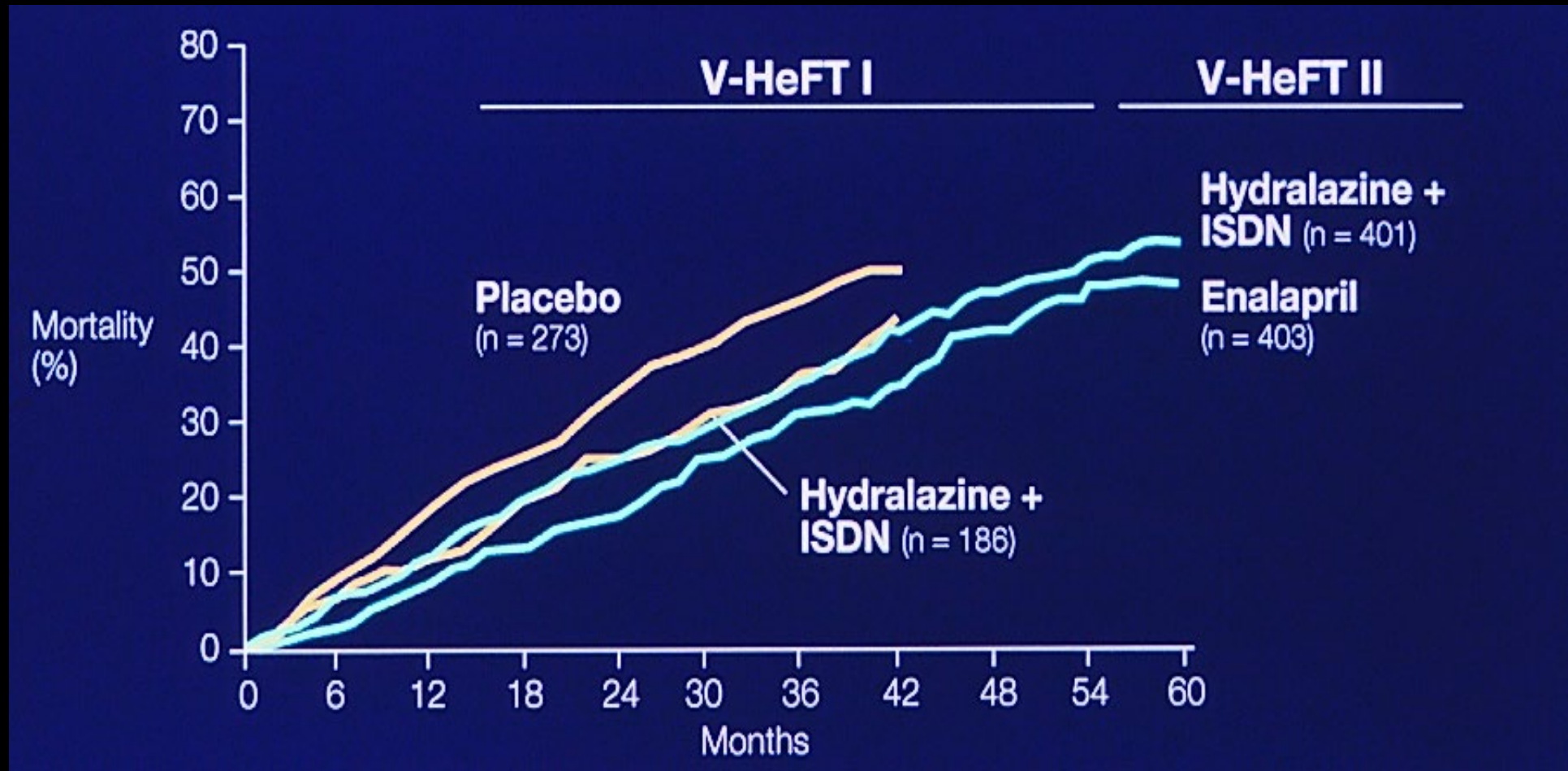


Aldosterone Receptor Antagonists

- Consider in most patients with symptomatic heart failure and $EF \leq 40\%$, after optimization of ACEi/ARB and Beta-Blocker
- Monitor potassium and renal function frequently
- **Avoid** in patients with prior hyperkalemia or advanced CKD
- **Caution** in subgroups at high risk, such as diabetes, elderly
- **Avoid** combination of ACEi + ARB + spironolactone
- Spironolactone likely equivalent to eplerenone as long as dosing is adequate



Effect of Hydralazine/Isordil in Symptomatic HF



RR at 2 years:

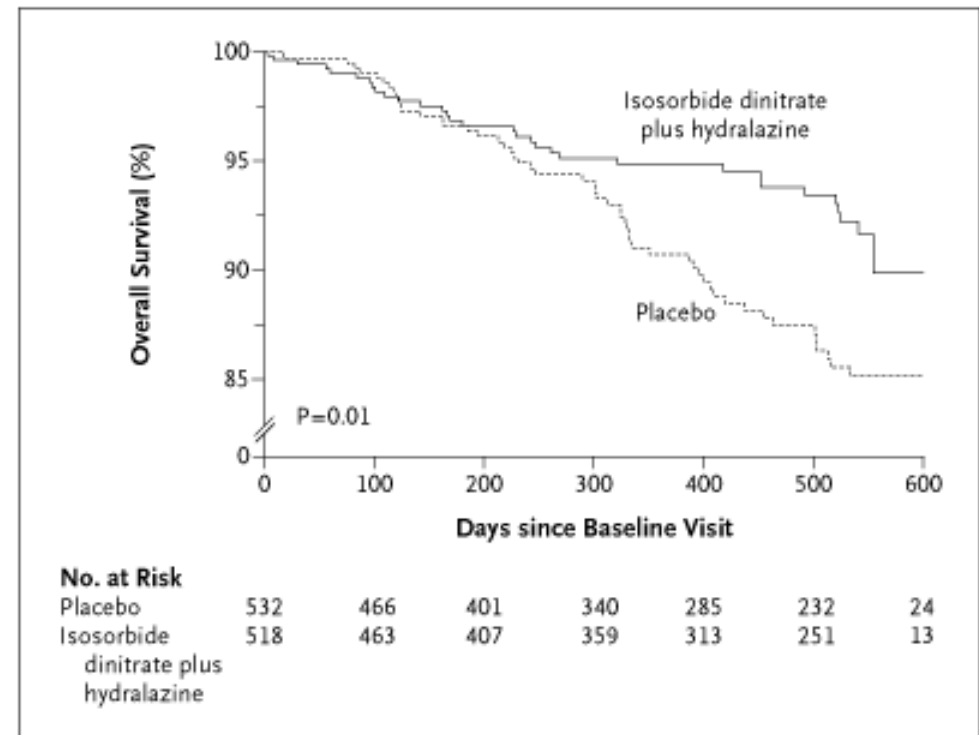
— V-HeFT I 34% (p=0.028)

— V-HeFT II 28% (p=0.016)

Alternative Vasodilator Strategies:

The A-HeFT Trial (Hydralazine/Isordil)

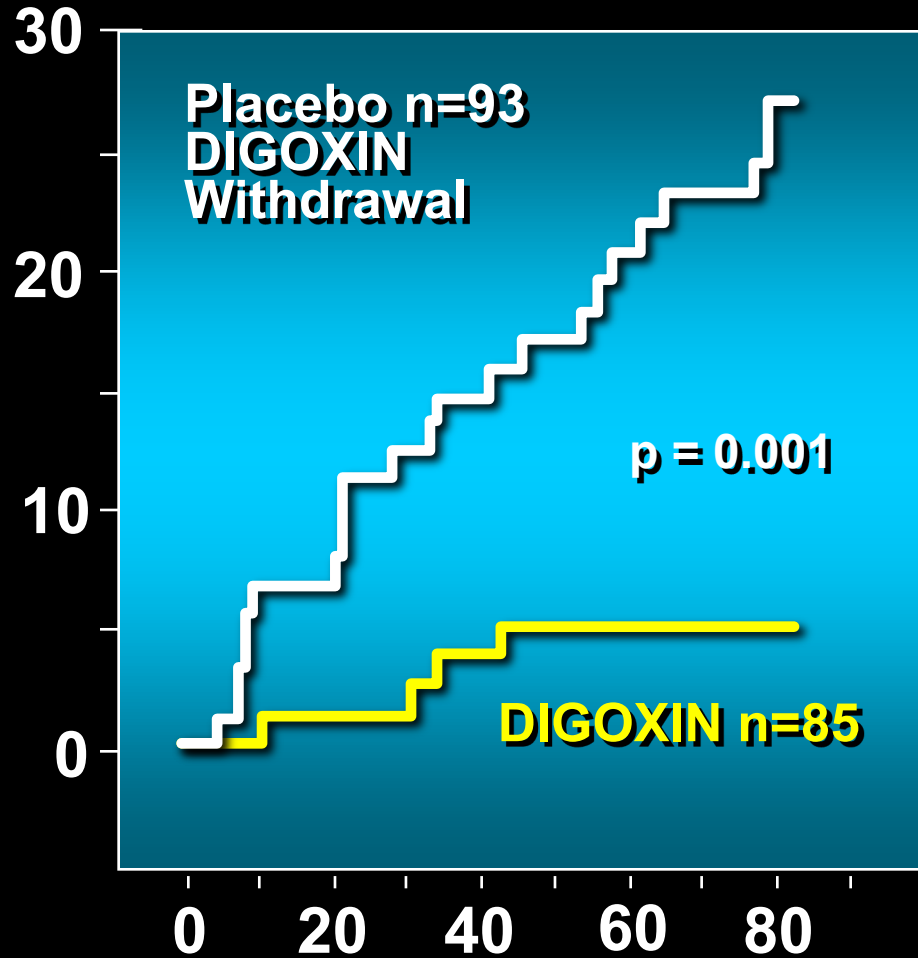
- 1050 NYHA III/IV AA pts
- Composite endpt (death, HF hosp, QOL), Terminated early
- Bidil (Hydralazine 37.5 mg + Isordil 20 mg) 2 tablets tid
 - 68% at target
 - Mean dose 3.8 tablets
- Contemporary bkgd Rx
 - ACEI/ARB 87 %
 - Beta blkers 75 %
 - Spironolactone 40 %
- Adverse events common
 - HA 44% - Dizziness 29%



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

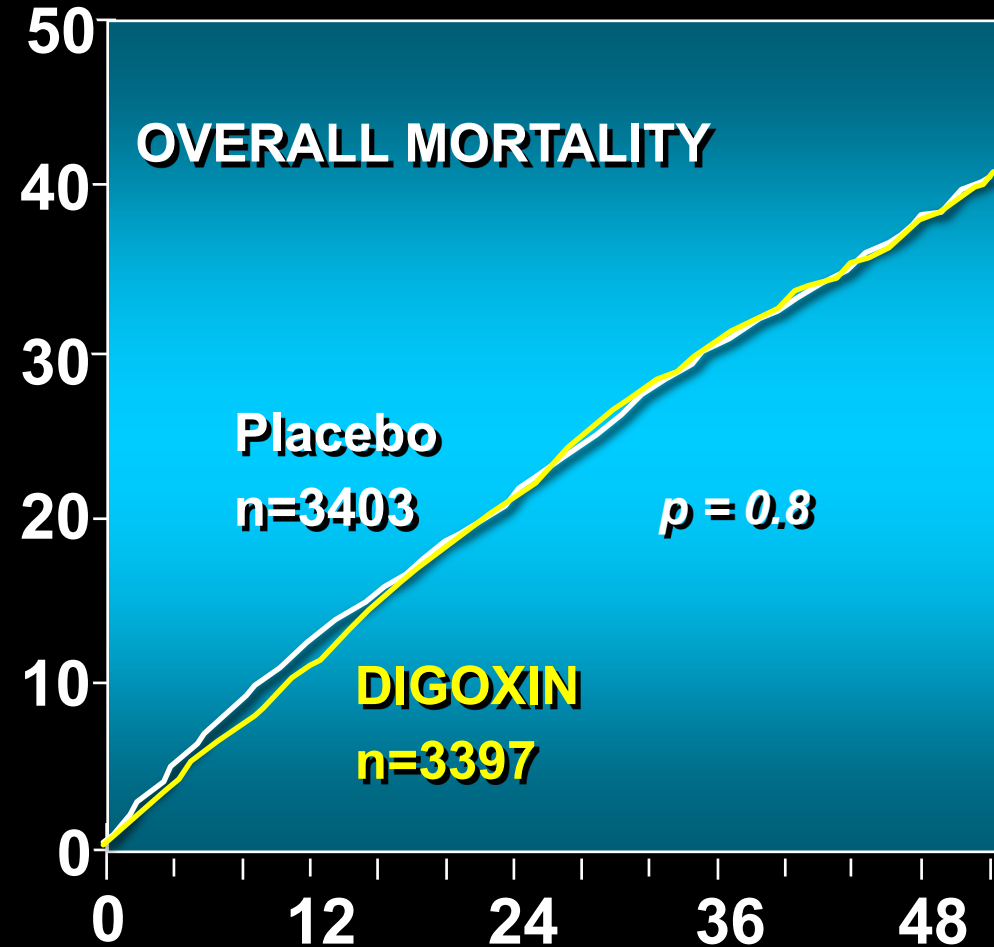


Digoxin: Improvement in Symptoms But Not Survival



RADIANCE

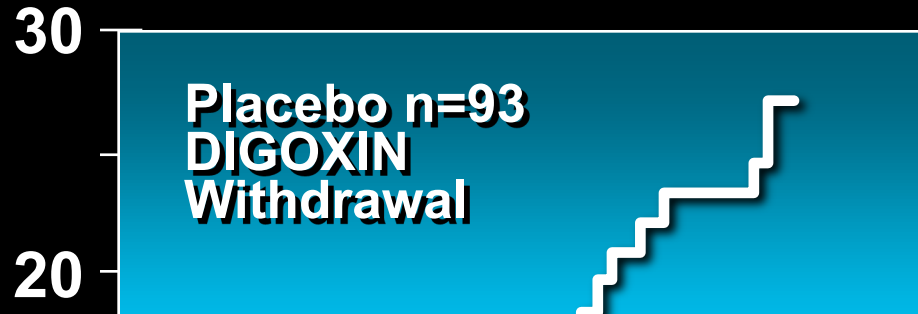
N Engl J Med 1993;329:1



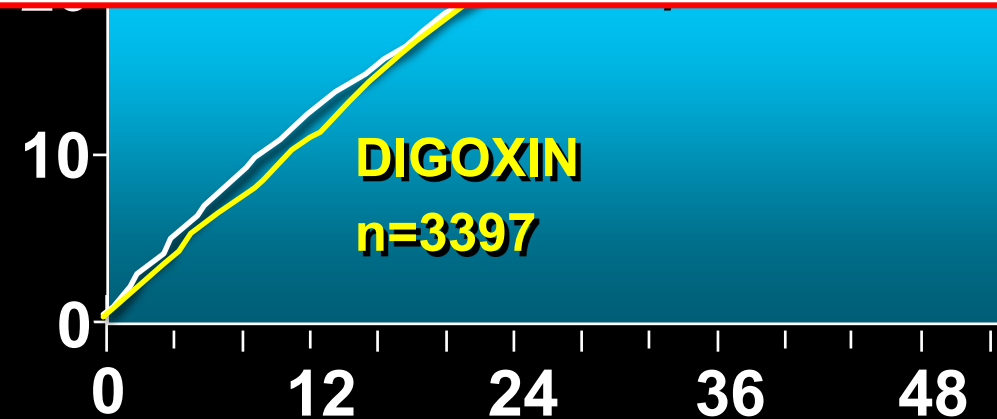
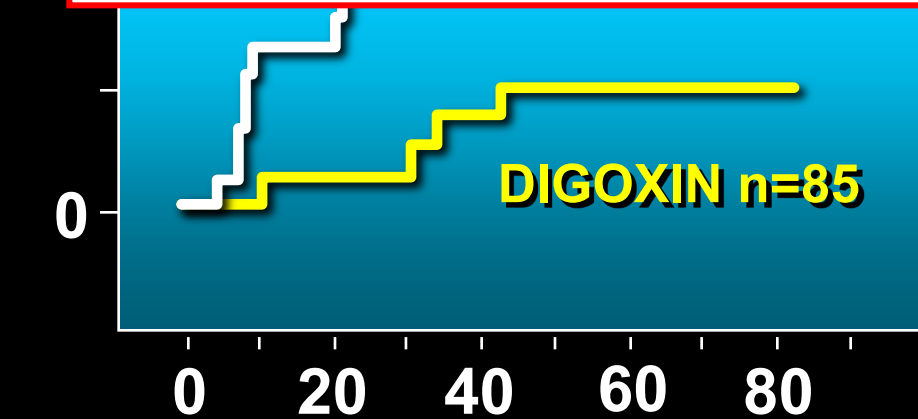
DIG Trial

N Engl J Med 1997;336:525

Digoxin: Improvement in Symptoms But Not Survival



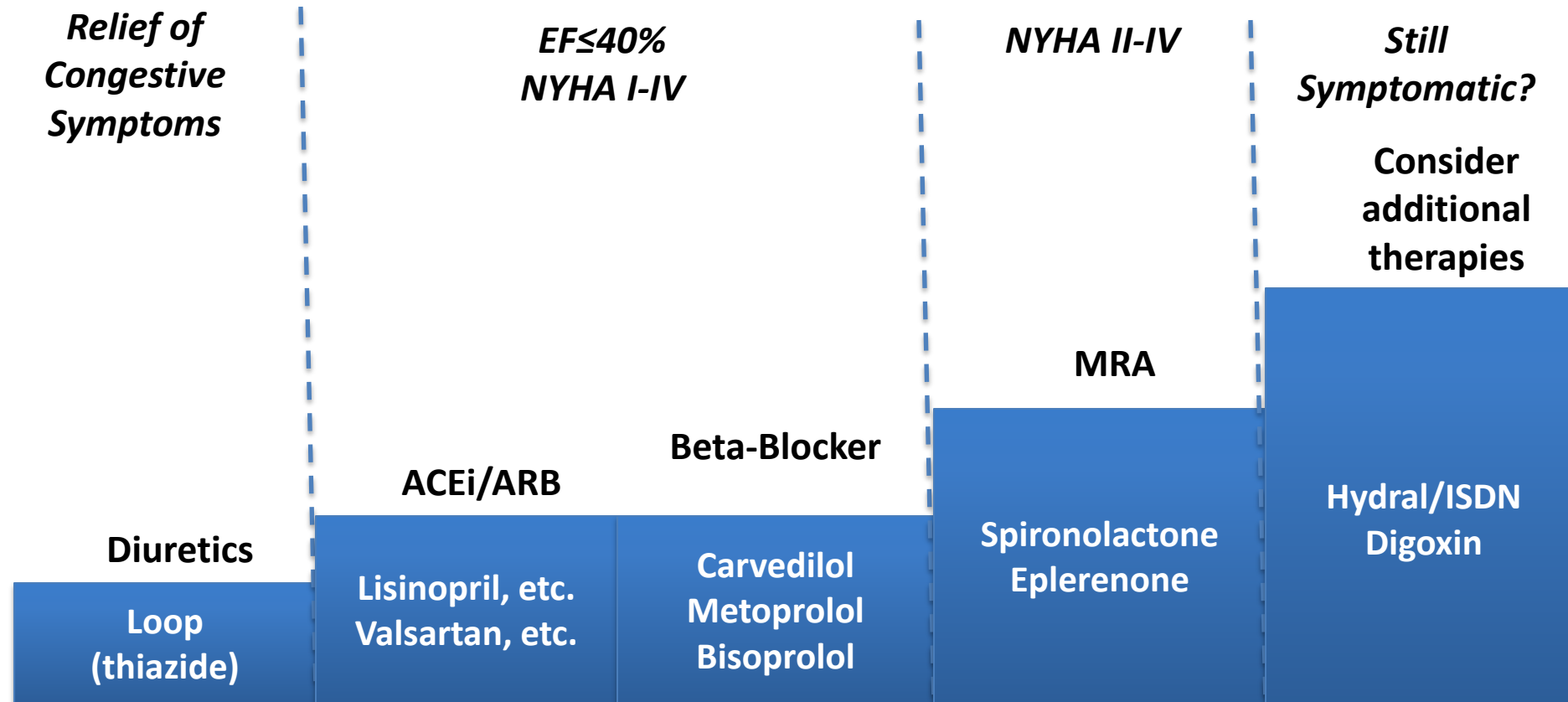
No incremental benefit (and potential harm) at Levels > 1.0 ng/mL



Guideline-Directed Medical Management of HF: 2013

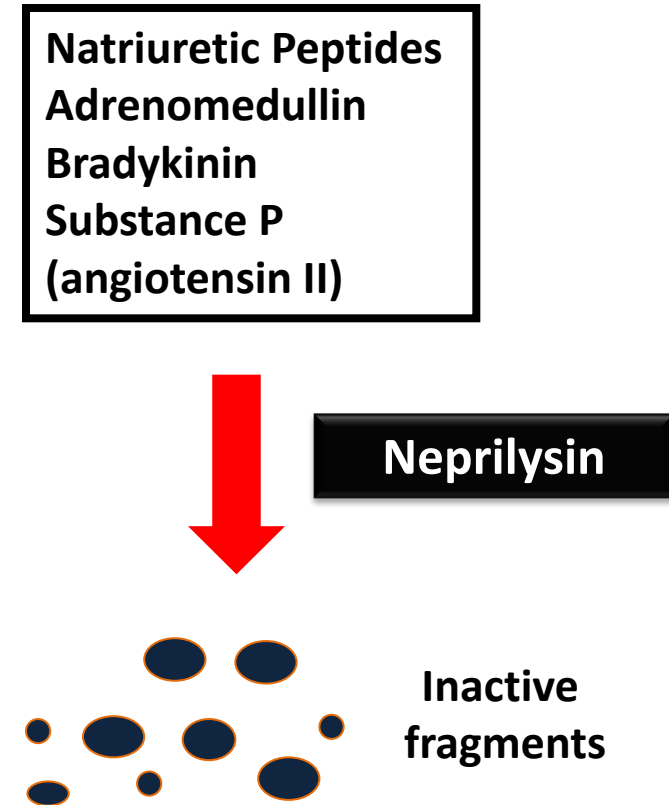


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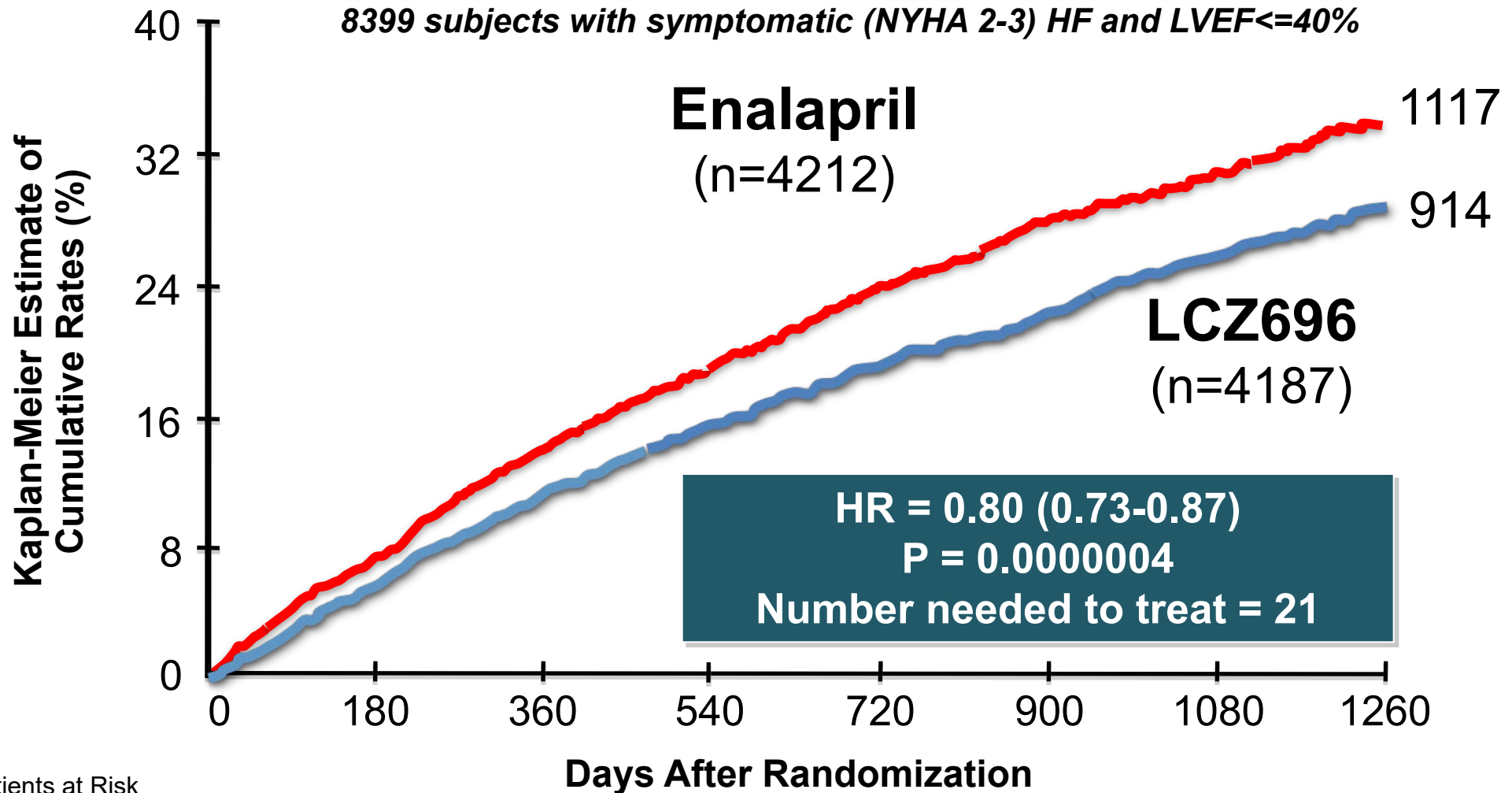


Neprilysin as a Therapeutic Target

- Neprilysin is responsible for the breakdown of a number of endogenous vasoactive peptides, including the natriuretic peptides
- Inhibition of neprilysin potentiates the action of those peptides
- Because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors must be co-administered with a RAAS blocker
- The combination of a neprilysin inhibitor and an ACE-inhibitor is associated with unacceptably high rates of angioedema



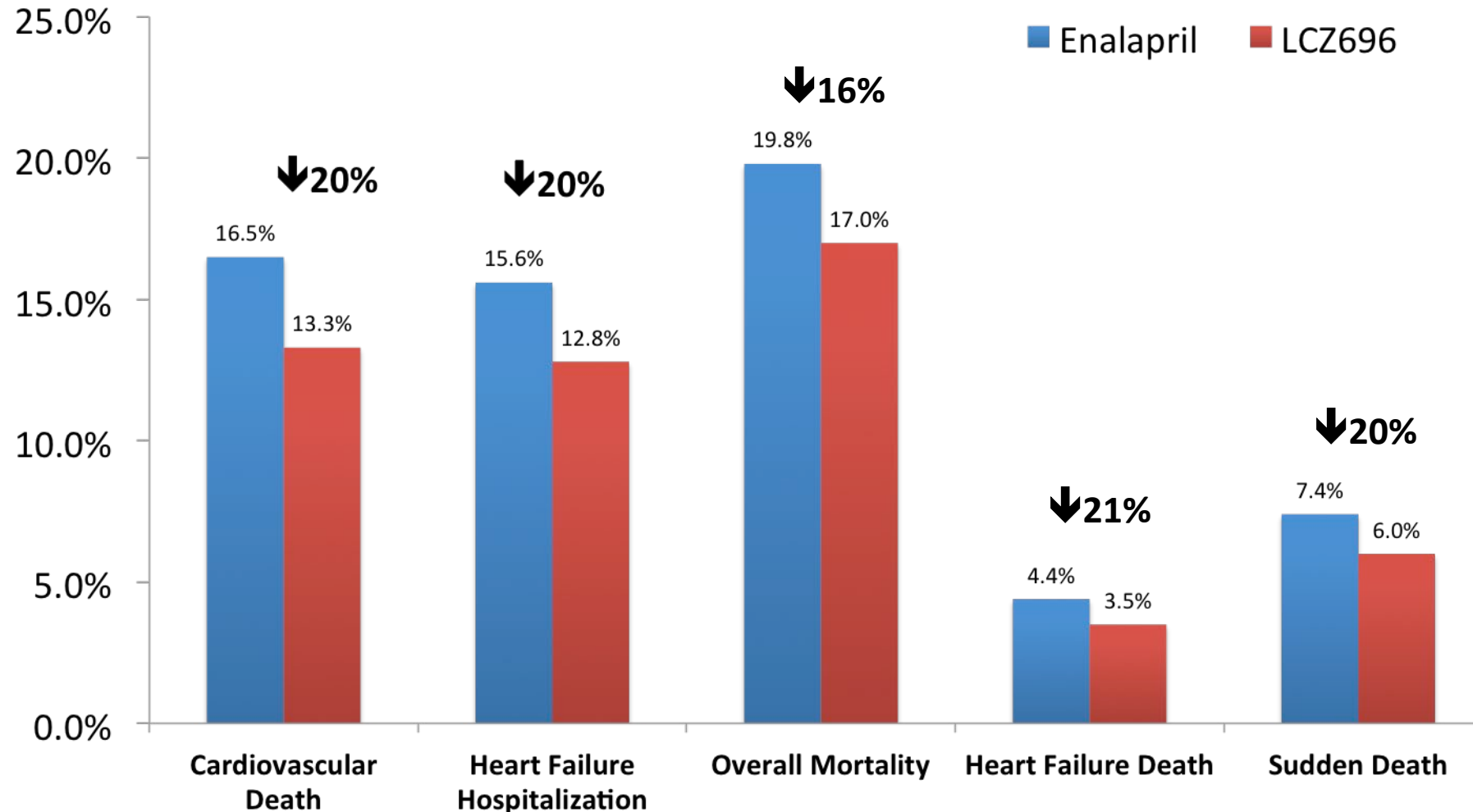
PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)



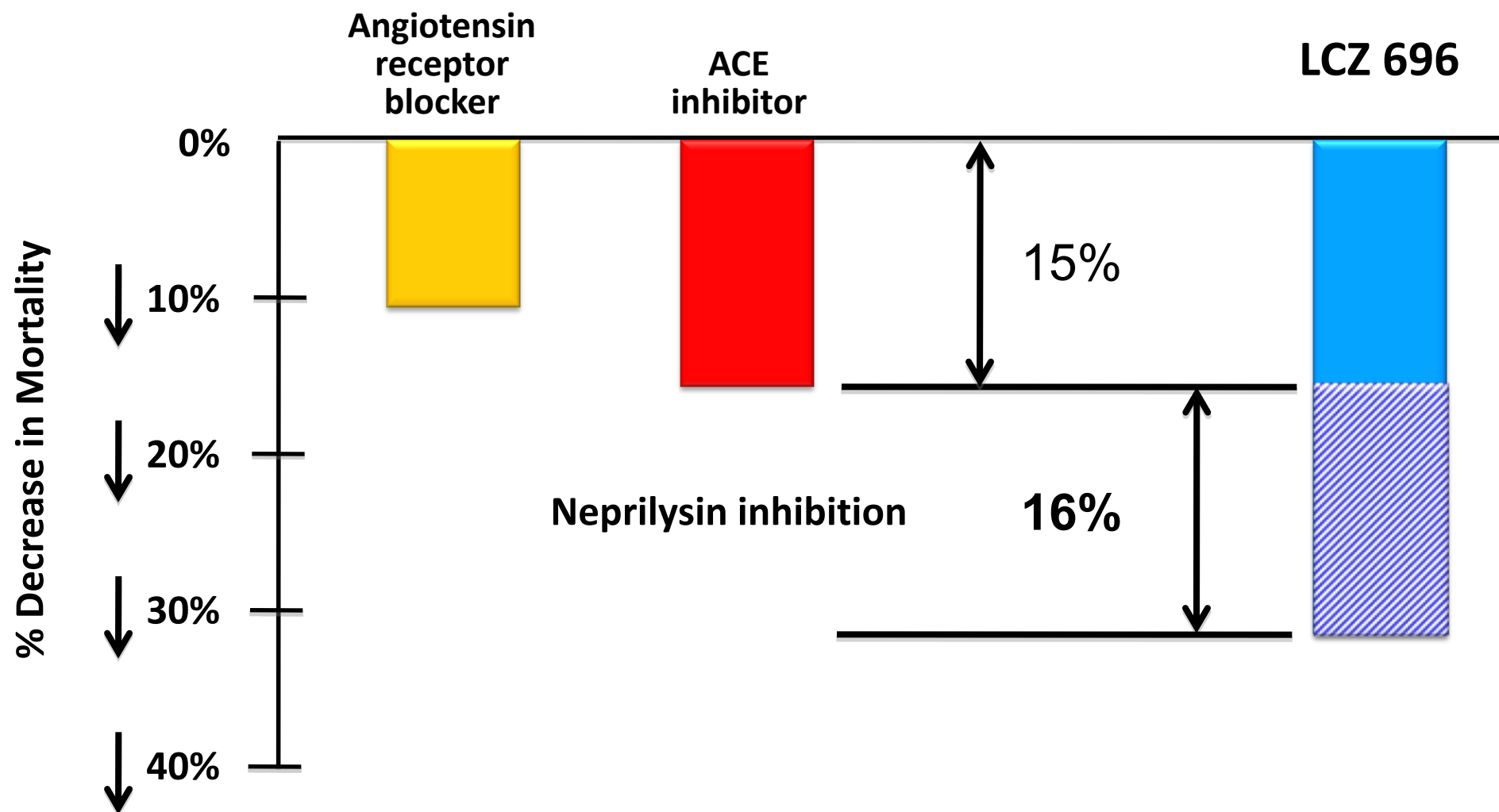
Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Other Key Endpoints



Doubling of Survival over ACE/ARB



PARADIGM-HF: Safety

	LCZ696 (n=4187)	Enalapril (n=4212)	p value
Hypotension (%)			
symptoms	14.0	9.2	< 0.001
symptoms and SBP < 90 mmHg	2.7	1.4	<0.001
No increase in discontinuations for BP-related events			
Renal impairment (%)			
Cr ≥ 2.5 mg/dl	3.3	4.5	0.007
Cr ≥ 3.0 mg/dl	1.5	2.0	0.10
LCZ696 group had numerically more nonserious angioedema, but no excess in the number of serious angioedema			
K ⁺ > 6.0 mmol/l	4.3	5.6	0.007
Cough (%)	11.3	14.3	< 0.001

Guideline Update

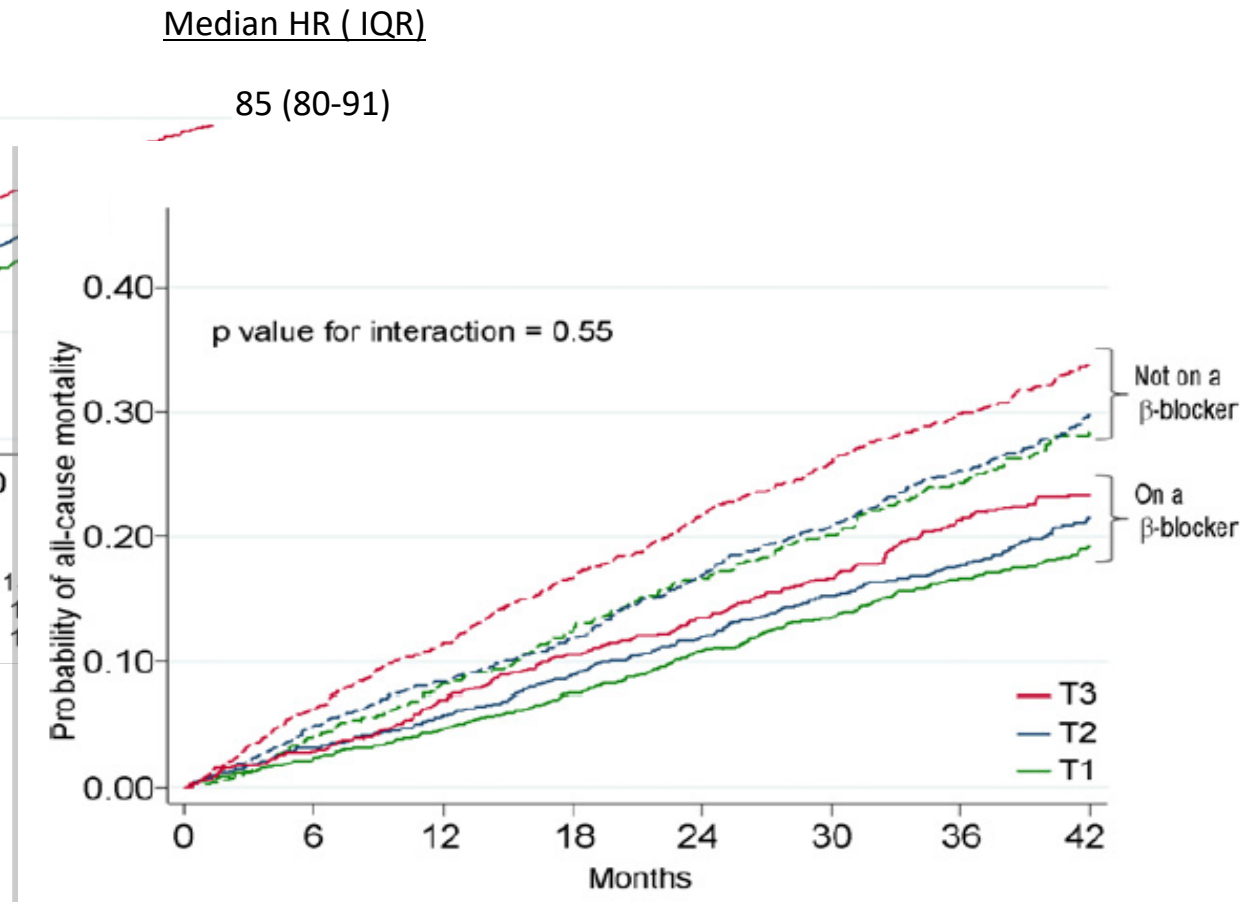
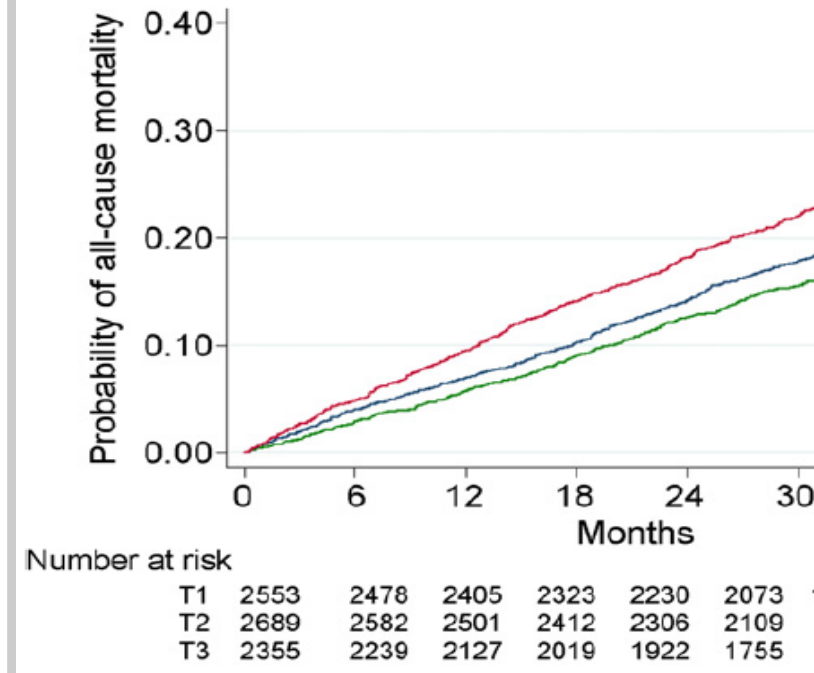
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

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

Impact of Heart Rate on Outcomes



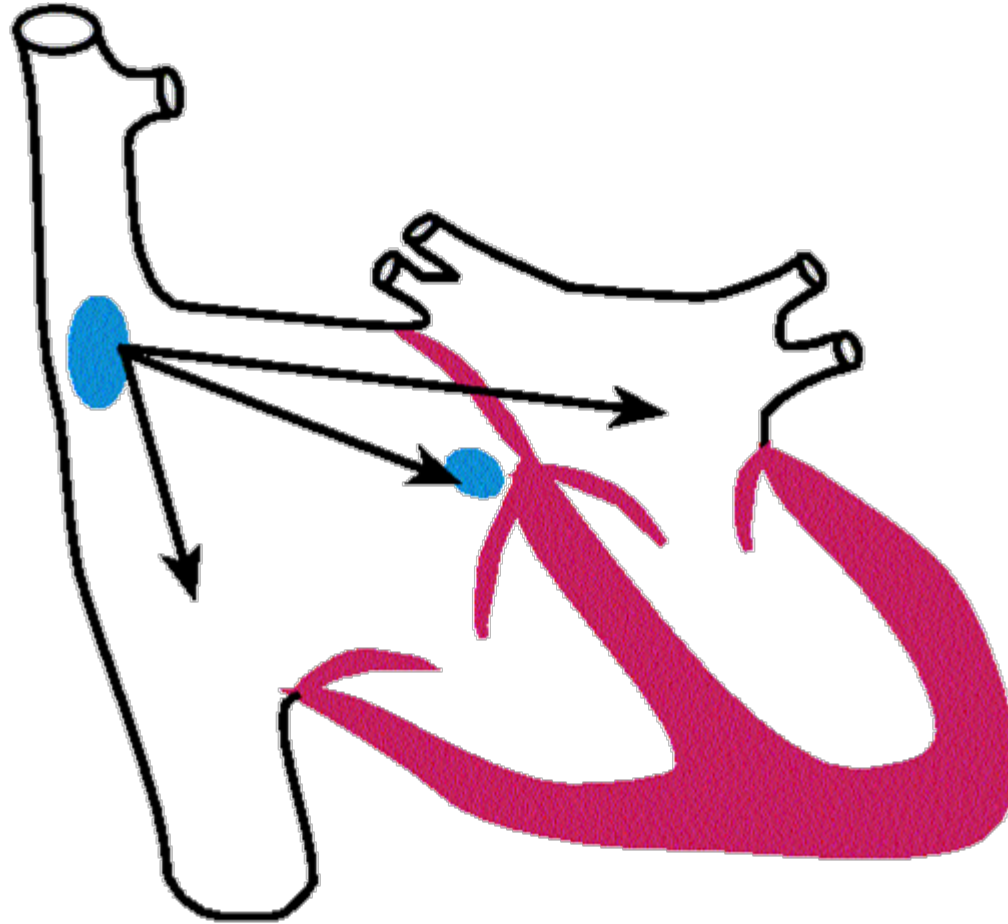
CHARM-Overall



Sinus node inhibition



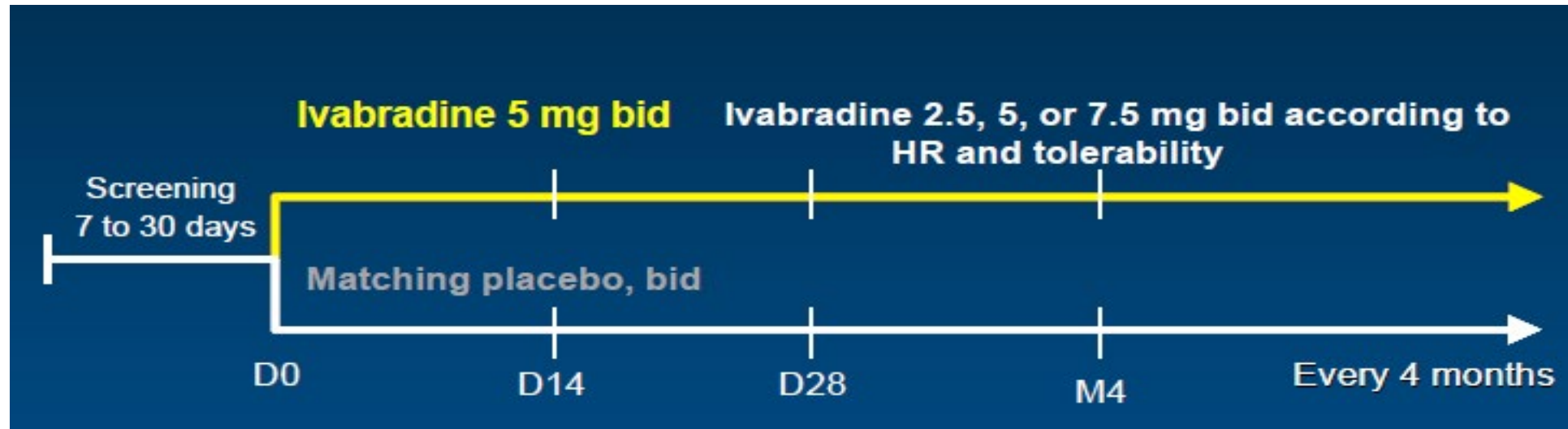
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I_f current inhibition with ivabradine

Sinus Node Inhibition in Chronic Heart Failure

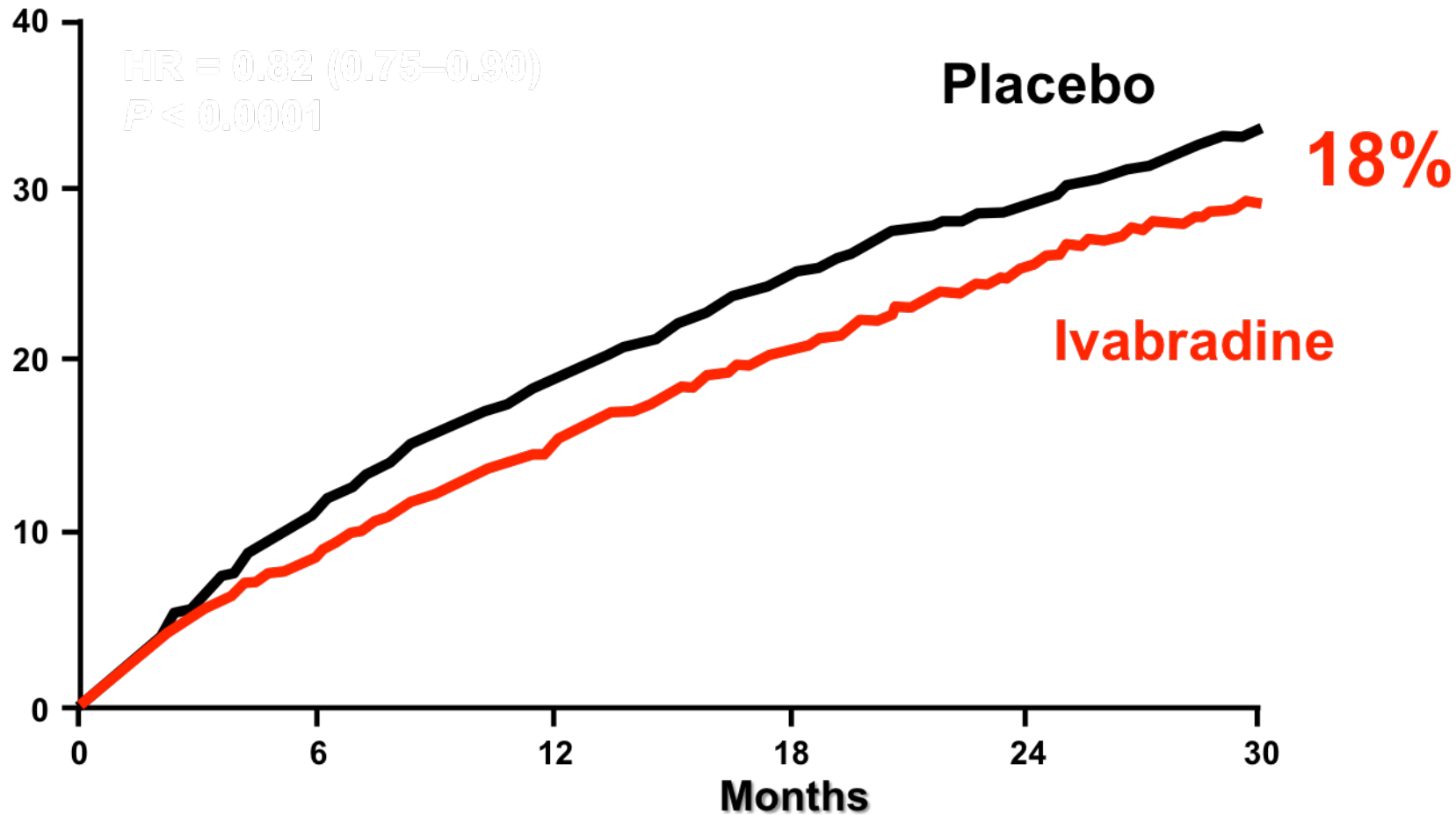
- **Hypothesis:** Heart rate reduction through sinus node inhibition will improve outcomes in chronic heart failure
- **Population:** 6558 patients with HF, NYHA II-IV symptoms, LVEF $\leq 35\%$, HF hospitalization in prior 12 months, and HR ≥ 70 beats/min. GDMT including a beta-blocker at target or maximally tolerated dose.
- **Primary endpoint:** CV death or HF hospitalization





Primary composite endpoint (CV death or hospital admission for worsening HF)

Cumulative frequency (%)

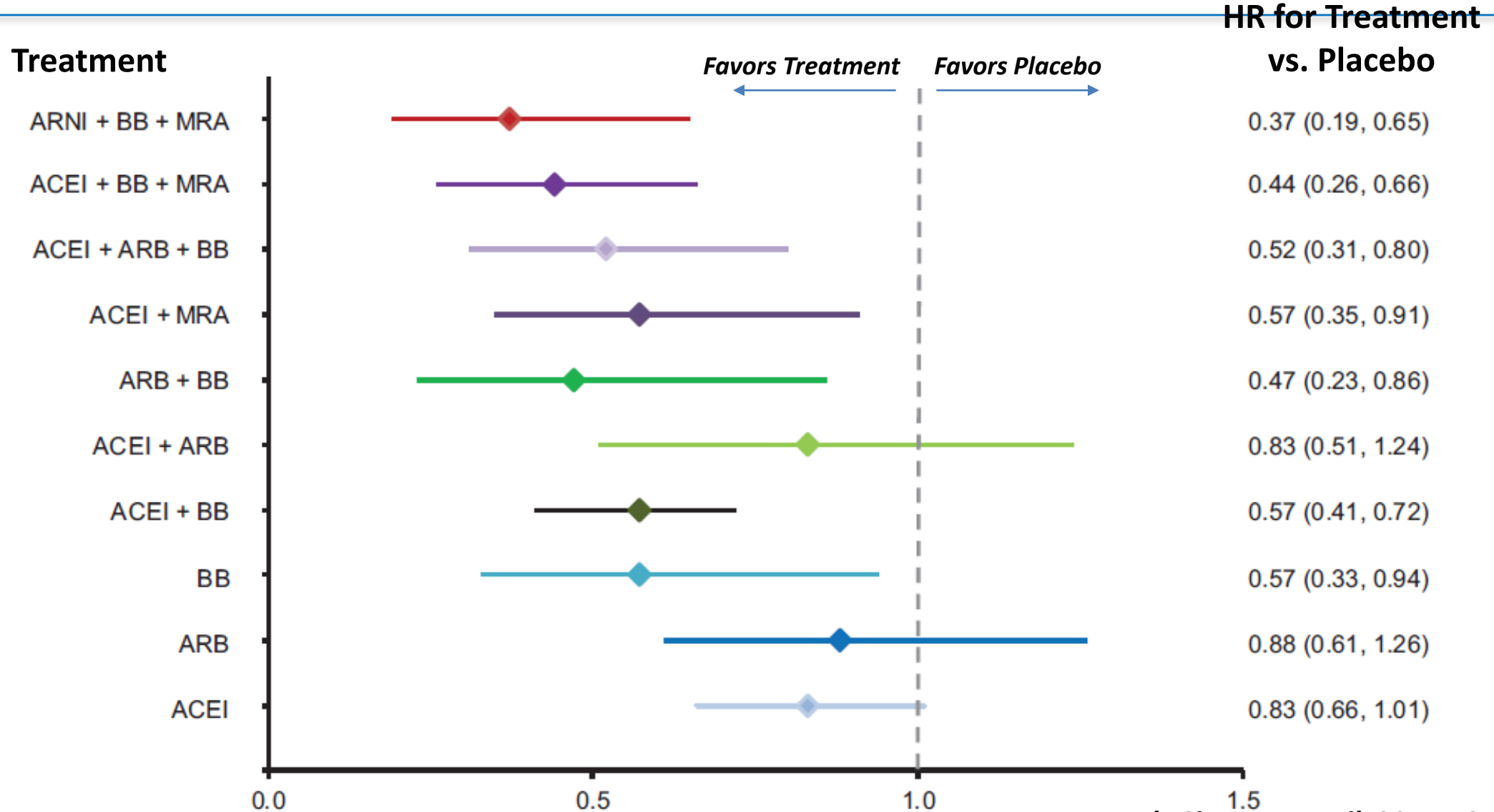


Guideline Update

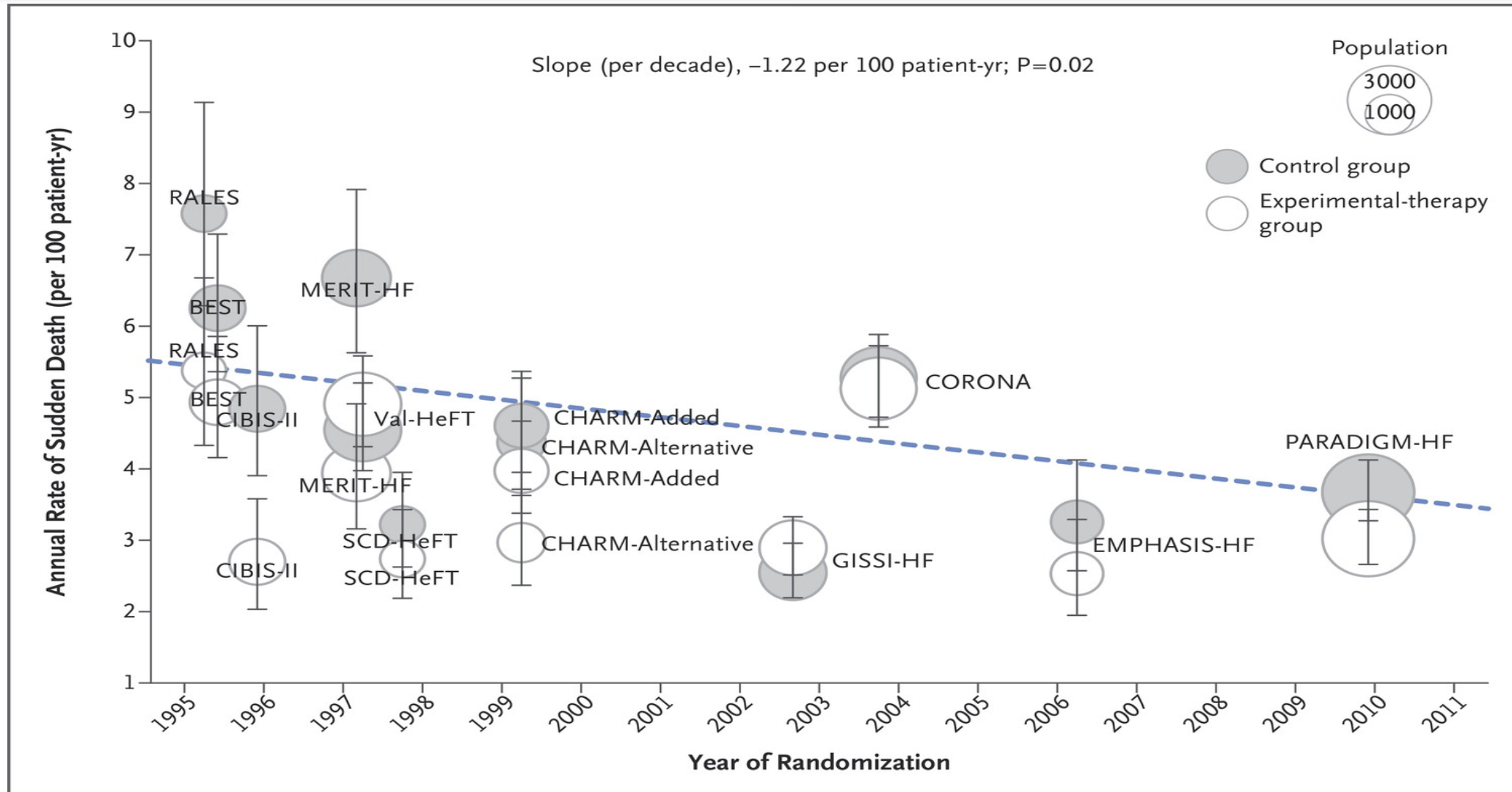
COR	LOE	Recommendations
Ia	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III), stable, chronic HFrEF (LVEF≤35%) who are receiving GDMT , including a beta-blocker at maximally tolerated dose, and who are in sinus rhythm with a HR≥70 bpm at rest

- The incremental benefits of ivabradine are more pronounced in patients with higher resting heart rates
- The magnitude of HR reduction achieved with ivabradine+ β -blockade is the principal determinant of subsequent outcome

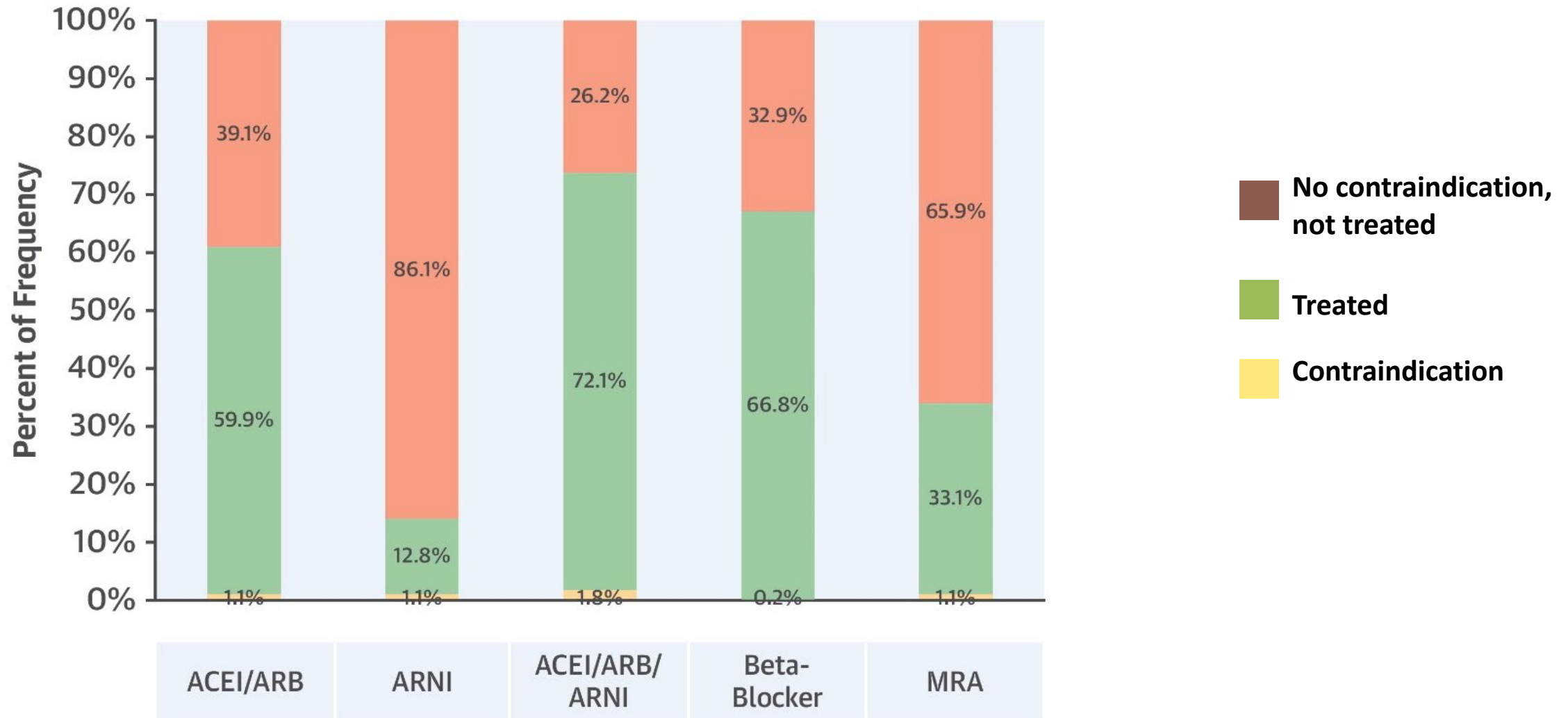
Incremental Mortality Reductions With Application of GDMT



Declining Rates of Sudden Death with effective pharmacologic therapy of HFrEF

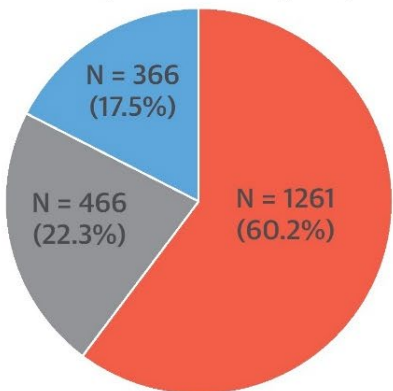


Utilization of Guideline-Directed Therapies for HFrEF: CHAMP Registry

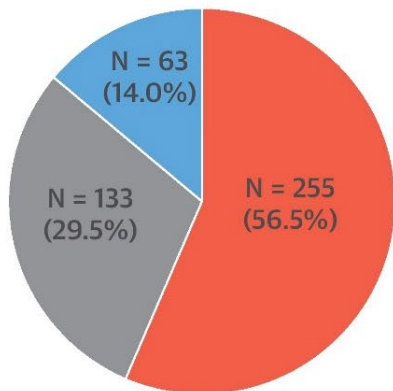


Dosing of Guideline-Directed Therapies for HFrEF: CHAMP Registry

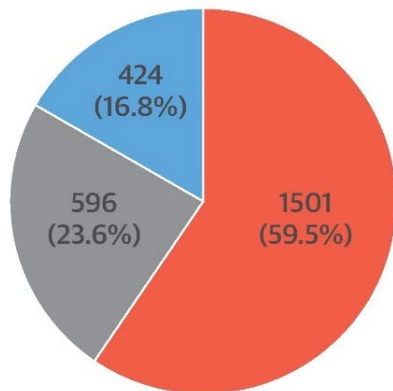
Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin II Receptor Blocker (ARB)



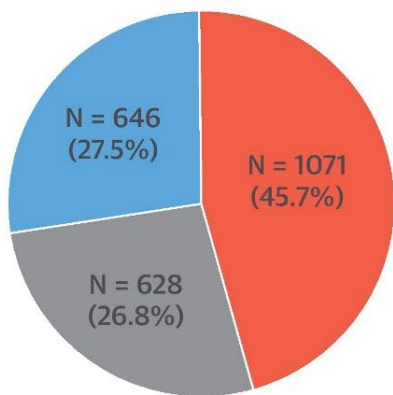
Angiotensin Receptor-Neprilysin Inhibitor (ARNI)



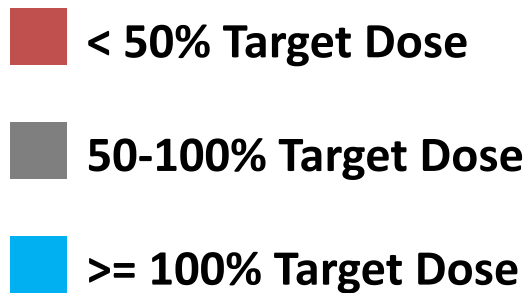
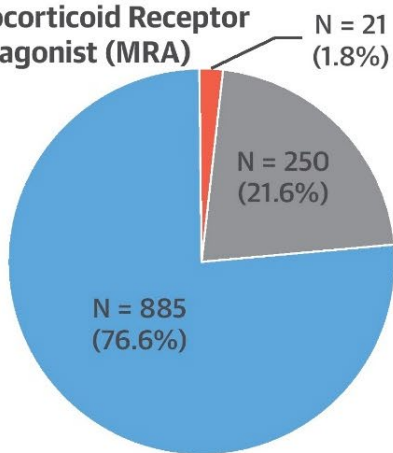
ACEI/ARB/ARNI



Beta-Blocker

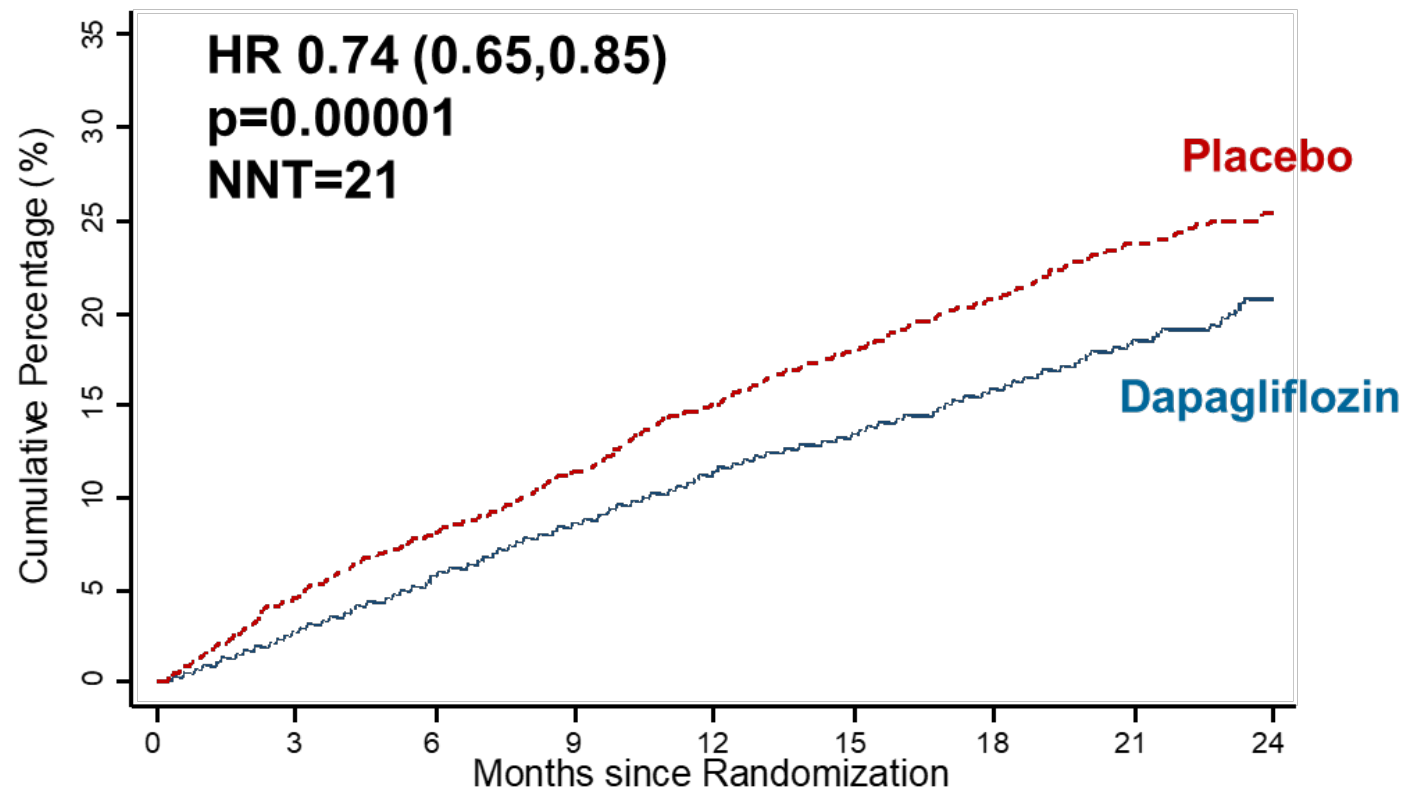


Mineralocorticoid Receptor Antagonist (MRA)



Primary composite outcome

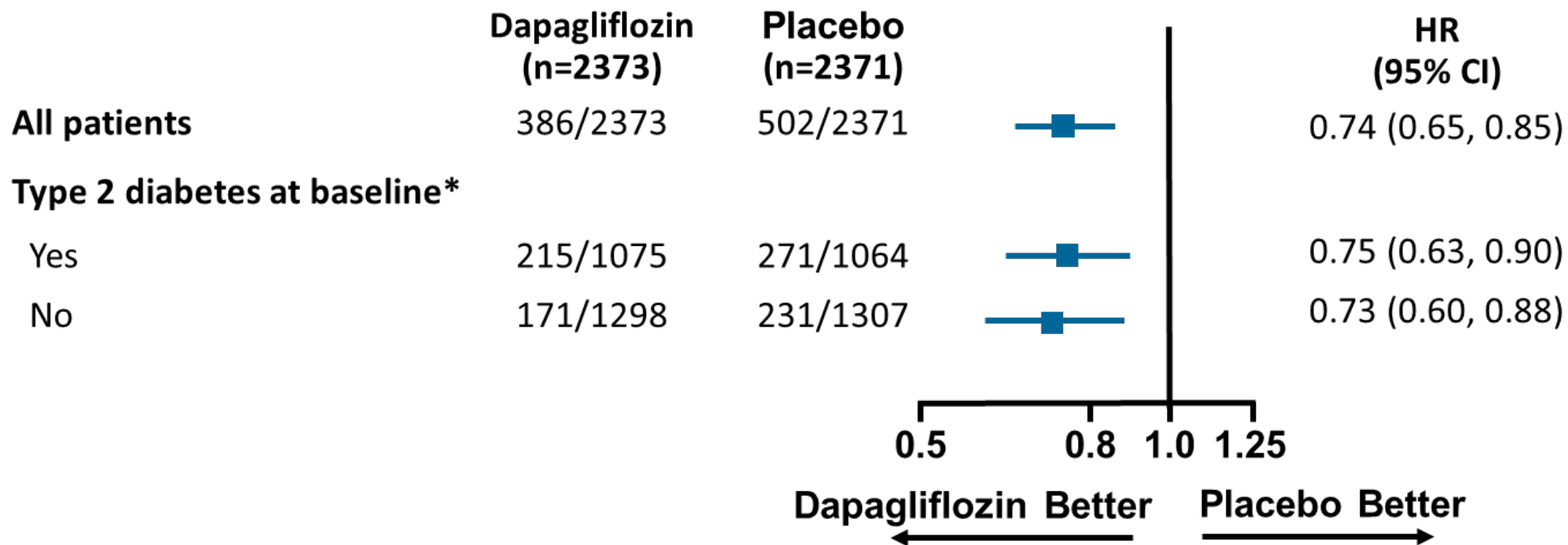
CV Death/HF hospitalization/Urgent HF visit



Number at Risk

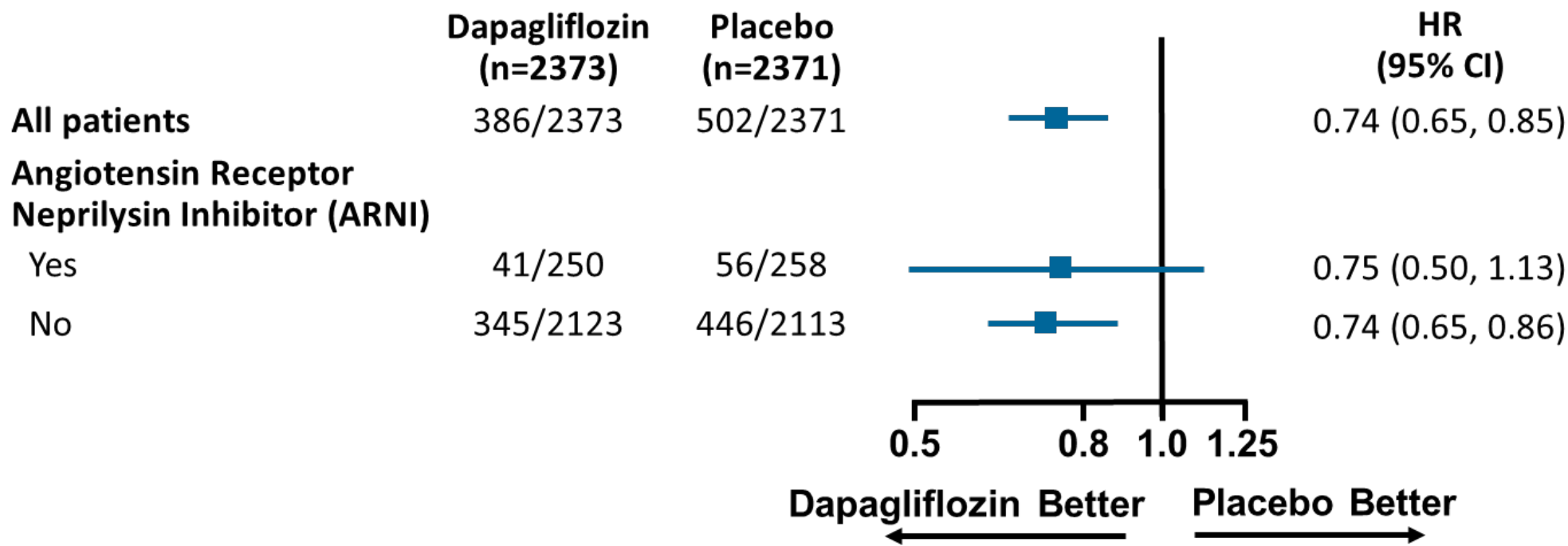
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

No diabetes/diabetes subgroup: Primary endpoint



*Defined as history of type 2 diabetes or HbA1c $\geq 6.5\%$ at both enrollment and randomization visits.

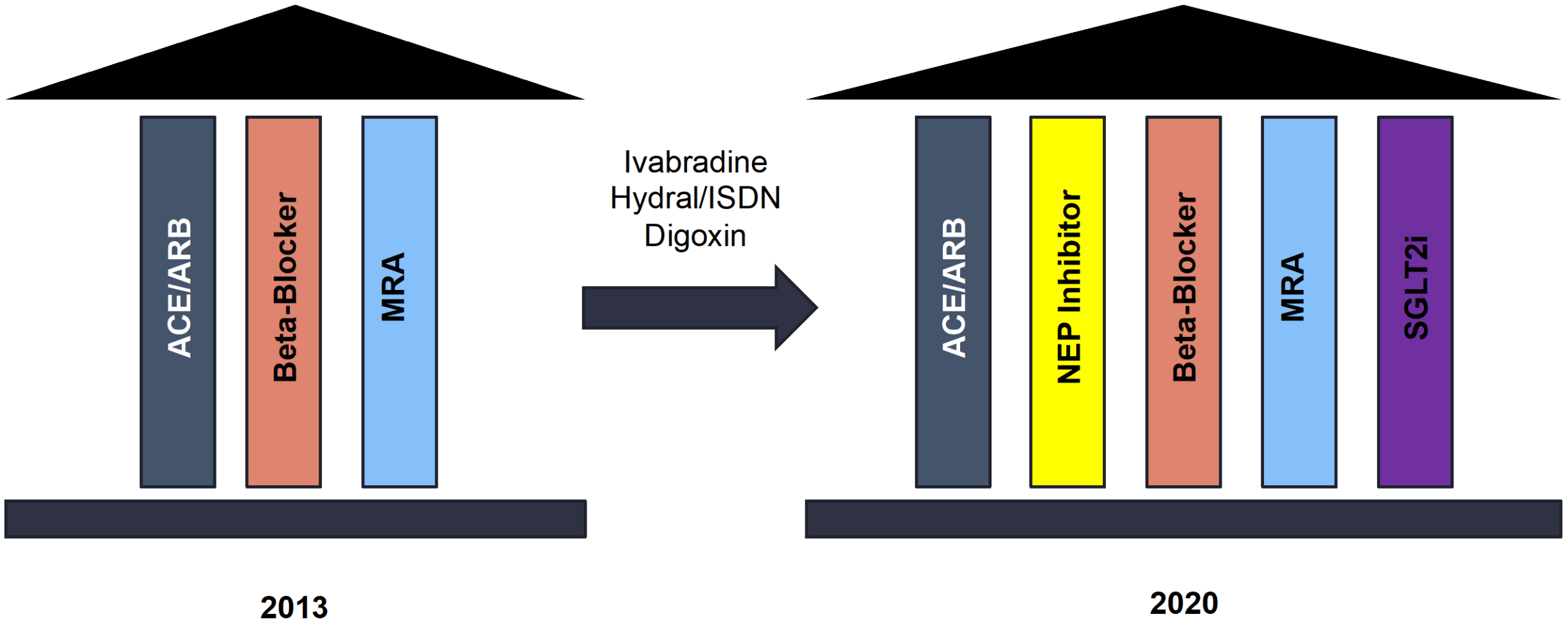
ARNI/no ARNI *post hoc* subgroup: Primary endpoint



Evolving Foundational Therapy for HFrEF



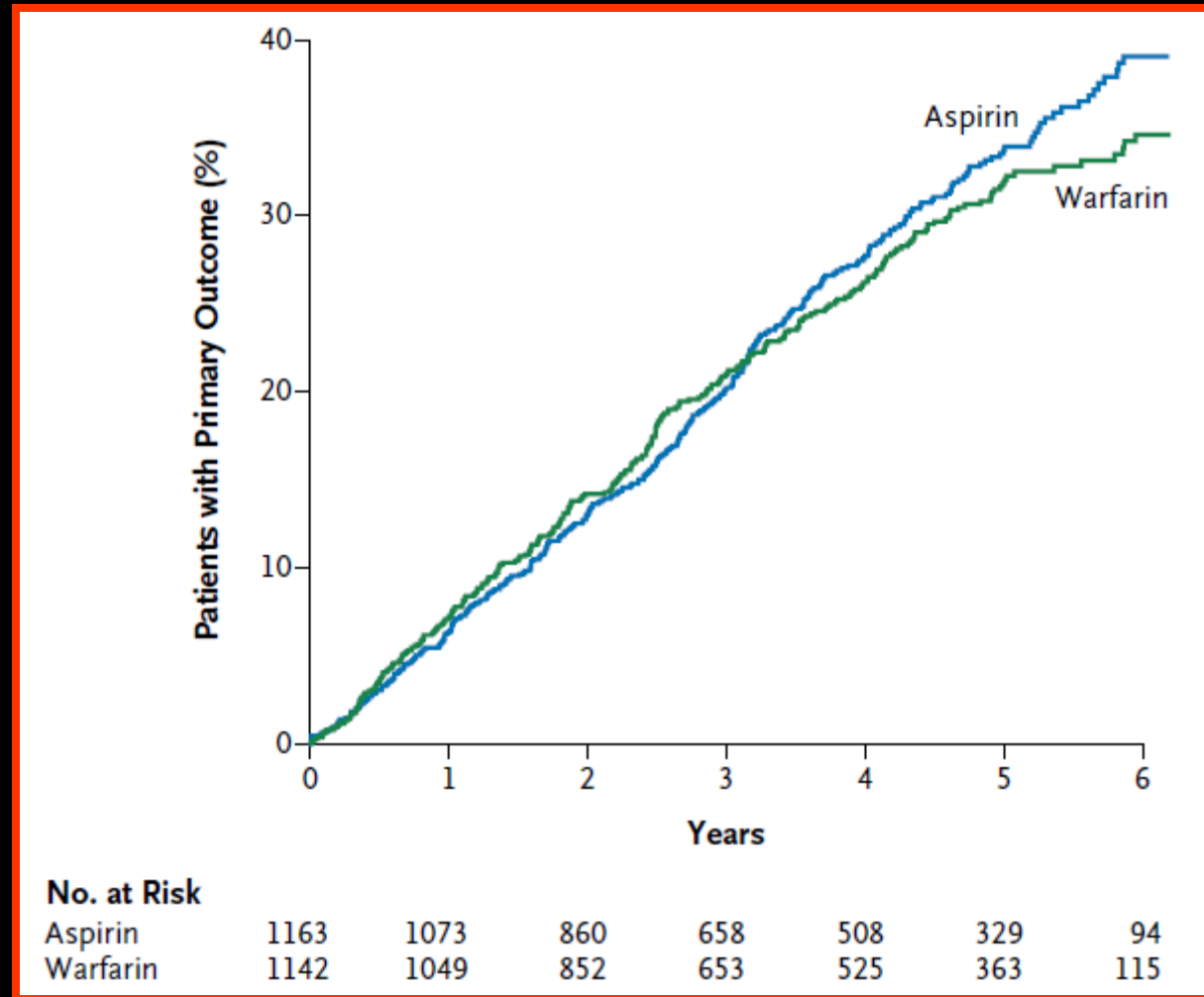
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Heart Failure Management: More Than Just Drugs

- Dietary counseling
- Patient education
- Physical activity
- Medication compliance
- Aggressive follow-up
- Nonpharmacologic Therapies
 - CRT
 - Sleep Disordered Breathing
- Management of Related Risks
 - Sudden Death (ICD implantation)
 - Thromboembolism/Stroke

Anticoagulation in Patients with Heart Failure and Sinus Rhythm (WARCEF)

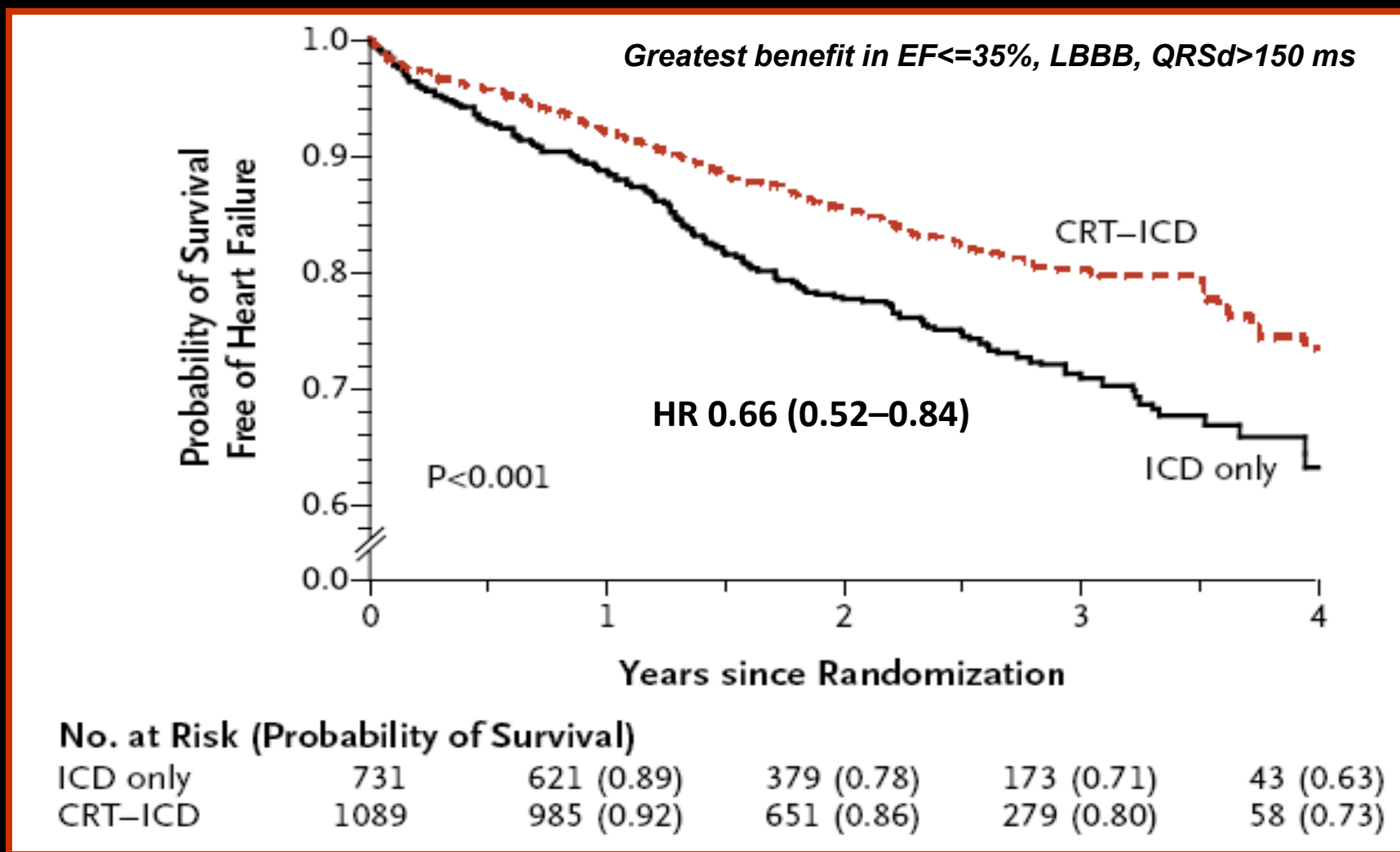


Reduced risk of ischemic stroke with warfarin offset by increase in major hemorrhage

Indications for ICD Therapy in HF

- Cardiac Arrest
- Sustained VT
- EF<40%, CAD, NSVT, inducible VT
- EF<30%, > 40d post-MI or 3mths post-revascularization, NYHA I-III
- EF<35%, Non-ischemic CMP, NYHA II-III
- *Contraindicated in NYHA IV, unless bridge to advanced therapies*

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



HF and Preserved EF: What Little We Know

Class I

- **Control hypertension**
- Chronotropic control
- Judicious use of diuretics

Class II

- Revascularization
- Restoring sinus rhythm
- Beta blkers, CaCh blkers

Table 8. Recommendations for Treatment of Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

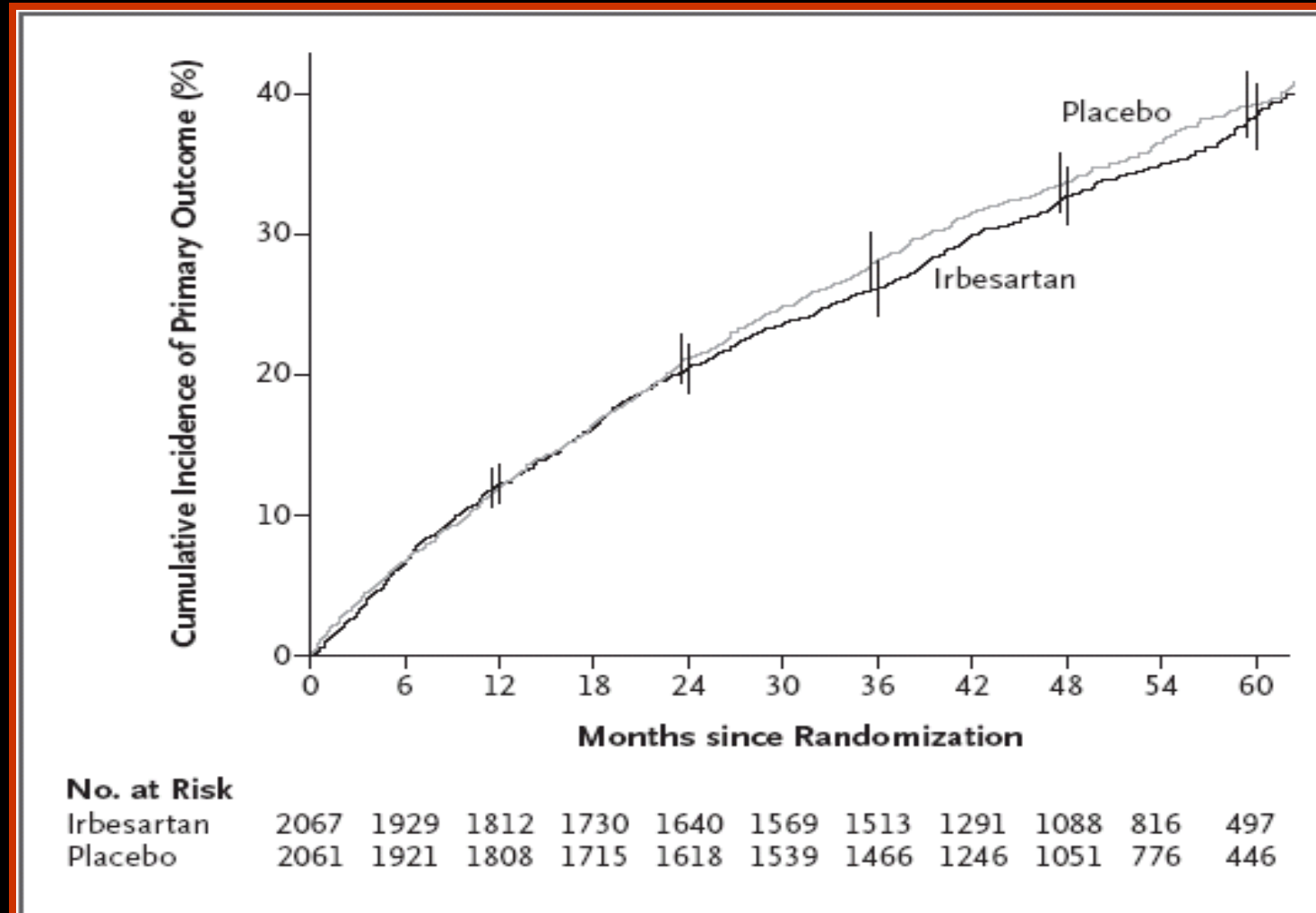
Recommendation	Class	Level of Evidence
Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.	I	A
Physicians should control ventricular rate in patients with atrial fibrillation.	I	C
Physicians should use diuretics to control pulmonary congestion and peripheral edema.	I	C
Physicians might recommend coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.	IIa	C
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.	IIb	C
The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.	IIb	C
The use of digitals to minimize symptoms of heart failure might be considered.	IIb	C

Clinical Outcome Trials in HF-PEF

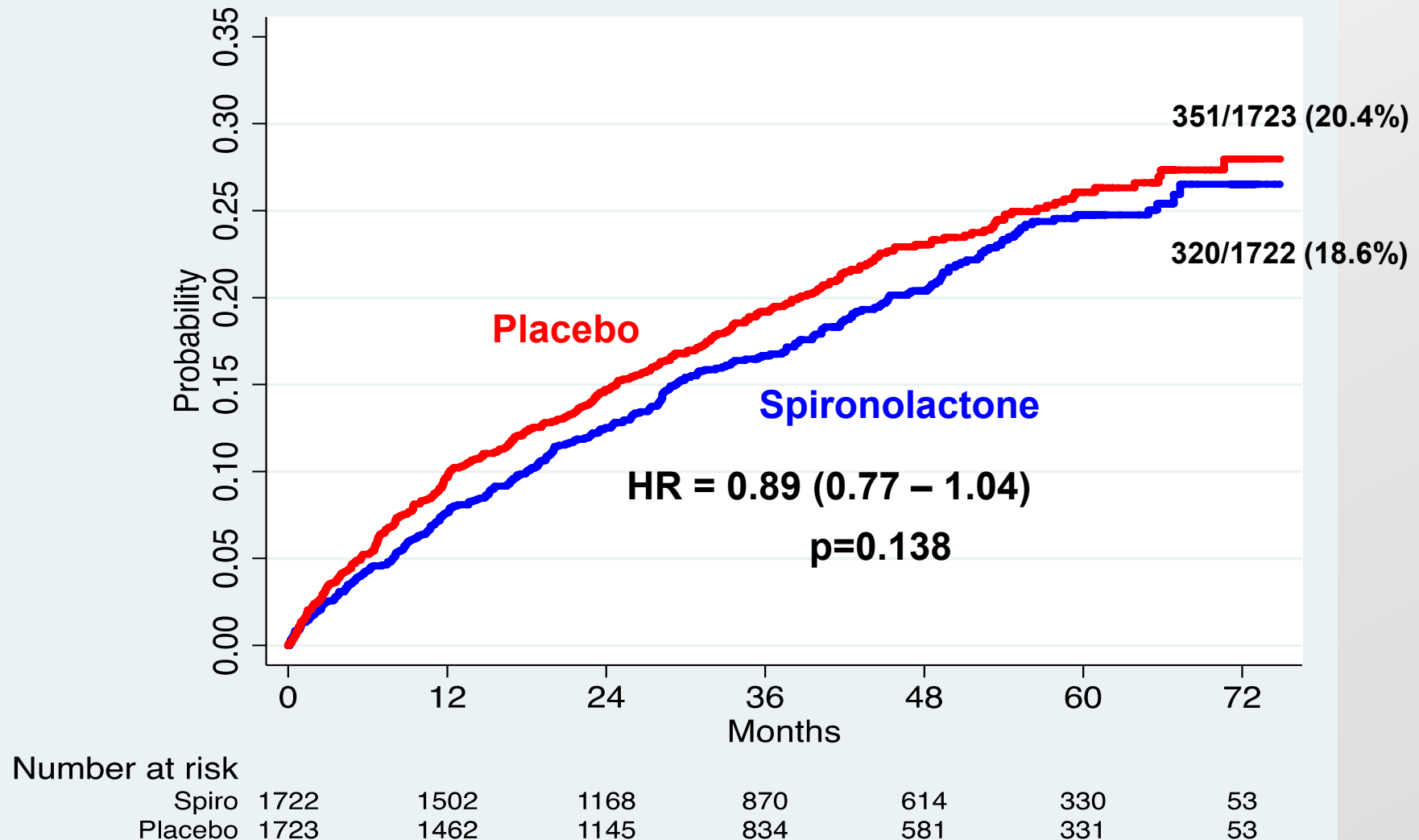
	CHARM	I-PRESERVE	DIG-PEF	PEP-CHF
N	3,023	4,133	988	850
Therapy	Candesartan	Irbesartan	Digoxin	Perindopril
Age (y)	67	72	67	75
Female	40%	60%	41%	55%
NYHA class	0/61/37/2	0/21/76/3	20/58/21/1	--/75/25/--
LVEF (%)	54	59	>45	64
1' Outcome	CV death/HF Hosp	Death/CV hosp	HF Death/HF Hosp	Death/HF hosp
Hazard Ratio	0.89 (0.77-1.03)	0.95 (0.86-1.05)	0.82 (0.63-1.07)	0.92 (0.70-1.21)

I-PRESERVE:

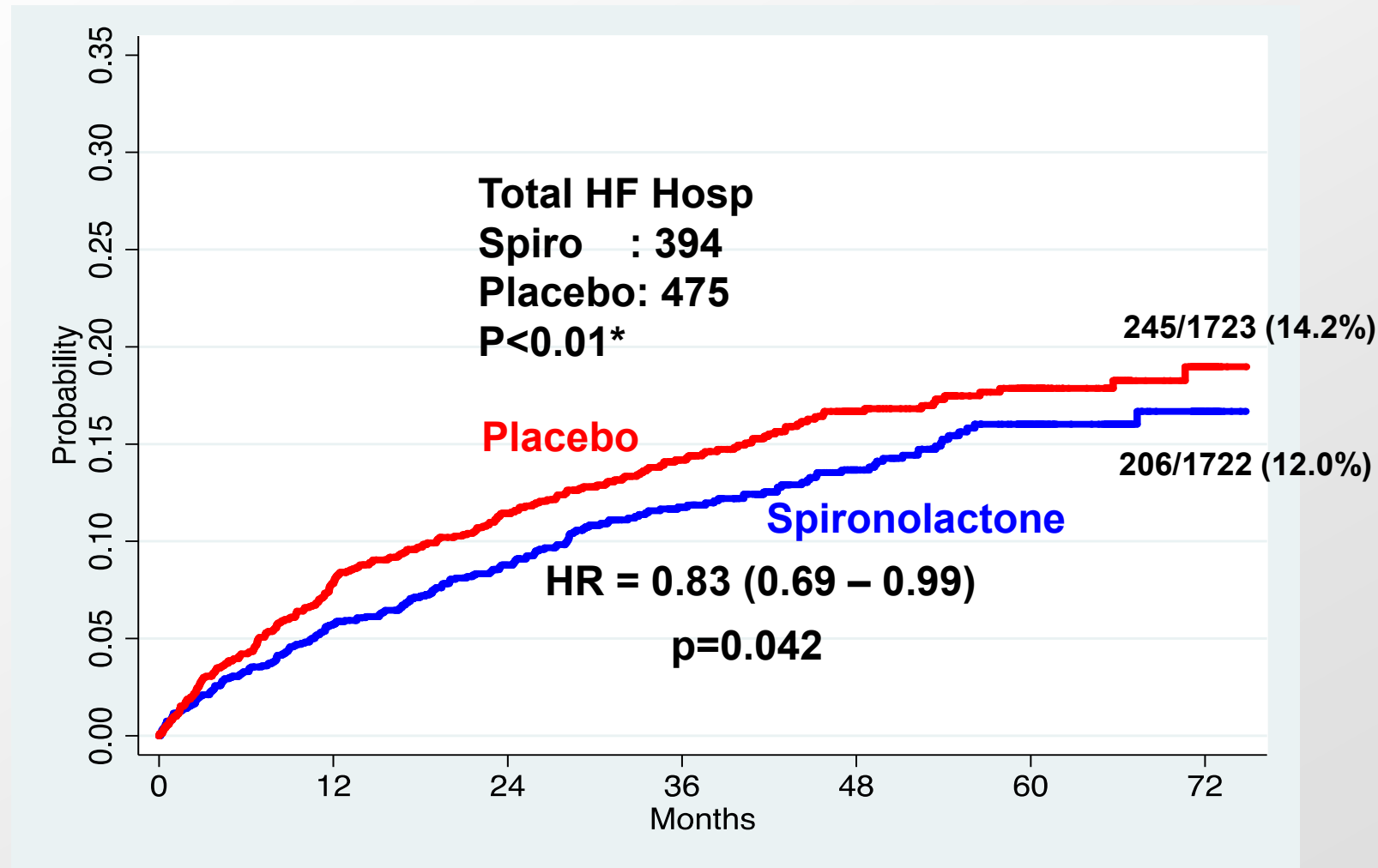
All Cause Death or CV Hospitalization



TOPCAT : 1^o Outcome (CV Death, HF Hosp, or Resuscitated Cardiac Arrest)



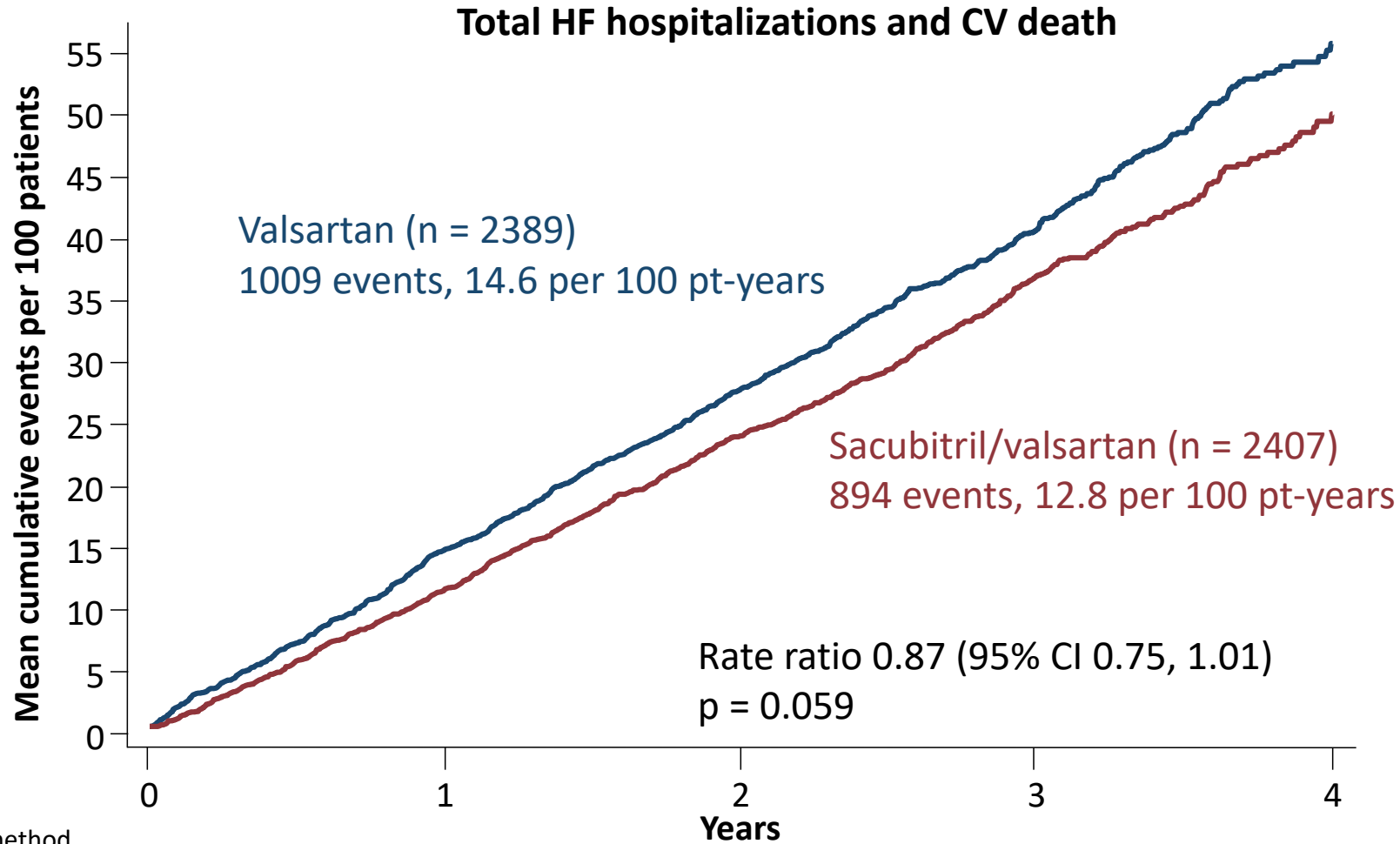
Heart Failure Hospitalizations



*poisson regression

PARAGON-HF primary results

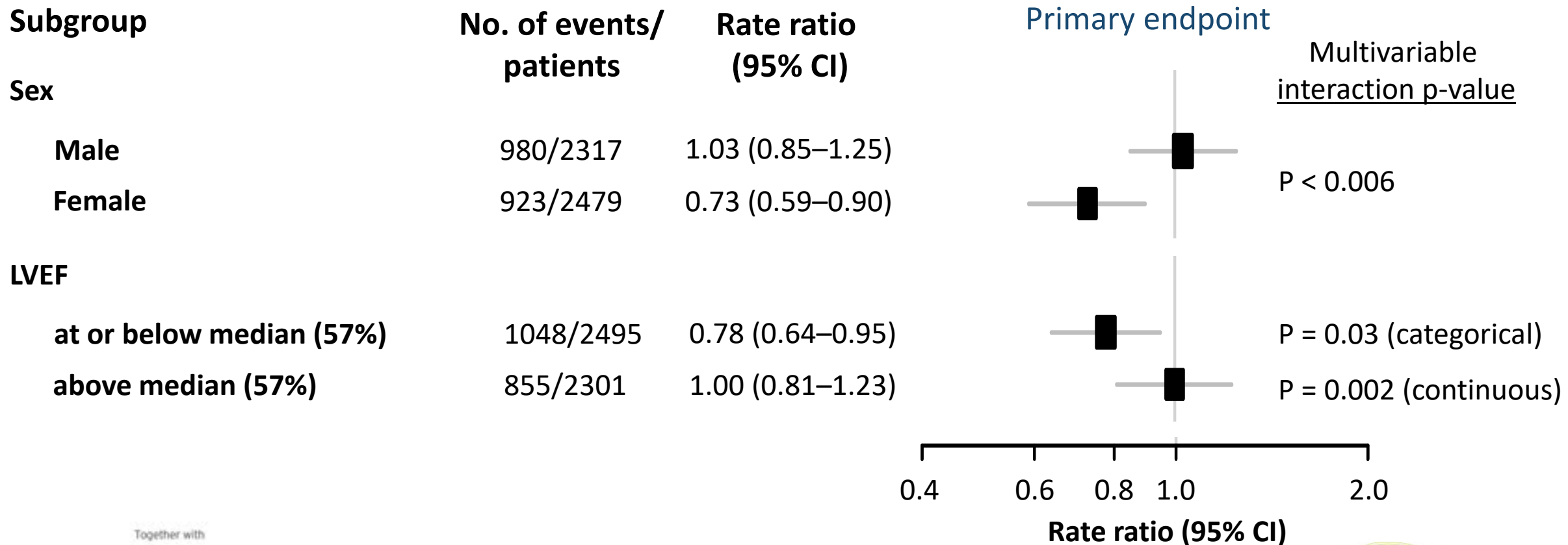
Recurrent event analysis of total HF hospitalizations and CV death*



*Semiparametric LWYY method.

Significant Heterogeneity in Multivariate Analysis by Ejection Fraction and Sex

Only interactions for sex and ejection fraction remained nominally significant



Congestive Heart Failure: Summary

- Heart failure is a clinical diagnosis
- BNP may be helpful when diagnosis of heart failure is uncertain but should not replace clinical assessment
- ACEi and Beta-blockers remain the cornerstone of HF therapy and should be titrated to goal carefully
- ARBs are useful in ACEi intolerant patients
- Substitution w/ ARNI should be considered in pts tolerant of ACEi or ARB to reduce HF mortality and hospitalization
- Beta blockers should not be started in acutely decompensated patients

Congestive Heart Failure: Summary

- Aldosterone antagonists are increasingly the favored 'second-line' after ACEi/ARB and beta-blocker
- Hydralazine/Isordil is an alternative for the ACEi/ARB intolerant and may be added for those still symptomatic on ACEi/Beta-blocker/aldosterone antagonist
- Dig and ivabradine can be considered to reduce HF hospitalization
- Device Therapy (ICD +/- CRT) is appropriate for many HF patients with LVEF $\leq 35\%$
- Heart failure with preserved EF remains a poorly understood, heterogeneous disorder with limited therapeutic options