Congestive Heart Failure Update 2023

Arash Karnama, D.O., FACC

Heart Failure

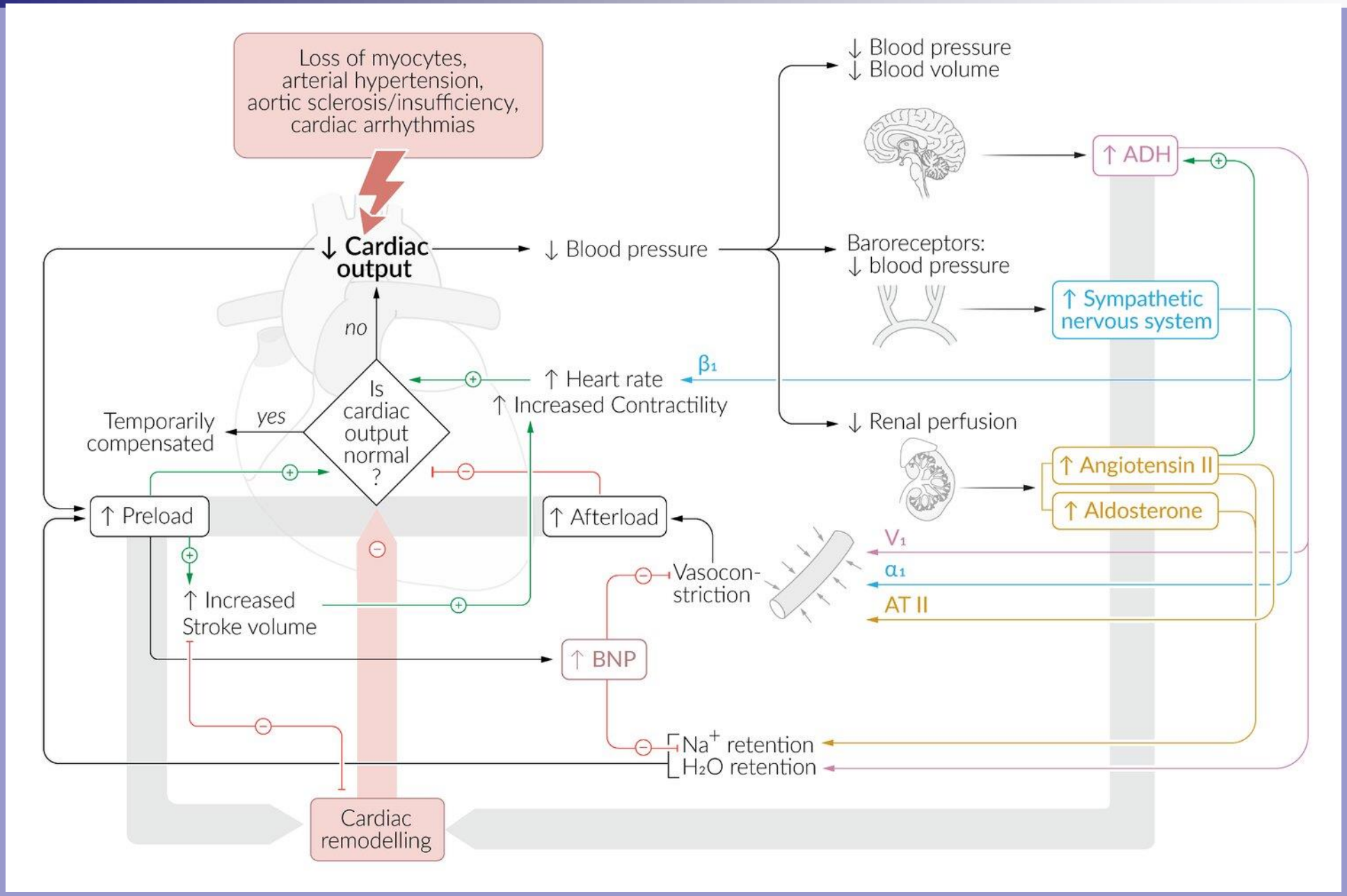
- Complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

Statistics

- Prevalence of 6.5 million people in the U.S. 960,000 new cases per year.
- Directly responsible for 8.5% of CV death per year.
- Contributes to 36% of CV death per year
- Most common Medicare diagnosis and also the most costly.

Pathophysiology

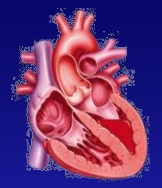
- Ischemia → infarction → poor pump function → poor tissue perfusion → compensatory increase in cardiac output caused by activation of neurohormonal axis (norepinephrine, arginine-vasopressin (AVP), angiotensin II, endothelin).


Loss of myocytes, arterial hypertension, aortic sclerosis/insufficiency, cardiac arrhythmias
↓ Cardiac output
↓ Blood pressure
↓ Blood pressure
↓ Blood volume
↑ ADH
Baroreceptors:
↓ blood pressure
↑ Sympathetic nervous system
β1
↑ Heart rate
↑ Increased Contractility
no
Is cardiac output normal ?
yes
Temporarily compensated
↓ Renal perfusion
↑ Angiotensin II
↑ Aldosterone
↑ Preload
↑ Afterload
V1
α1
AT II
Vasocon-striction
↑ Increased Stroke volume
↑ BNP
Na+ retention
H2O retention
Cardiac remodelling

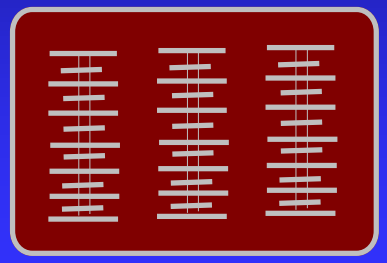
AMBOSS

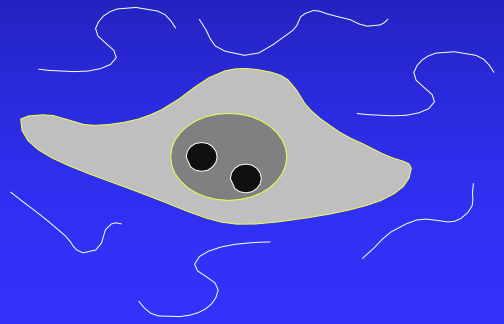
Pathophysiology

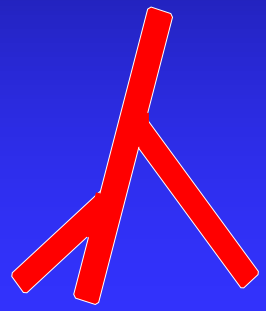
- Norepinephrine – increased contractility, rate, vasoconstriction, sodium retention.
- AVP – retention of water to expand plasma volume.
- Angiotensin II – vasoconstriction, sodium retention, pathologic remodeling of the myocardium.
- Endothelin – vasoconstriction, inotropic effects. Stimulates further secretion of AVP and aldosterone.

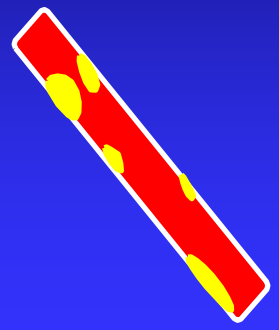


Maladaptive Effects of Epinephrine and Norepinephrine









Cardiac Myocyte

Hypertrophy
Apoptosis
Necrosis
Increased wall stress
Increased O_2 consumption
Impaired relaxation

Fibroblast

Hyperplasia
Collagen synthesis
Fibrosis

Peripheral Artery

Vasoconstriction
Endothelial dysfunction
Hypertrophy
Decreased compliance

Coronary Artery

Vasoconstriction
Endothelial dysfunction
Atherosclerosis
Thrombosis

Sackner-Bernstein JD, Mancini DM. *JAMA.* 1995;274:1462–1467.

Pathophysiology

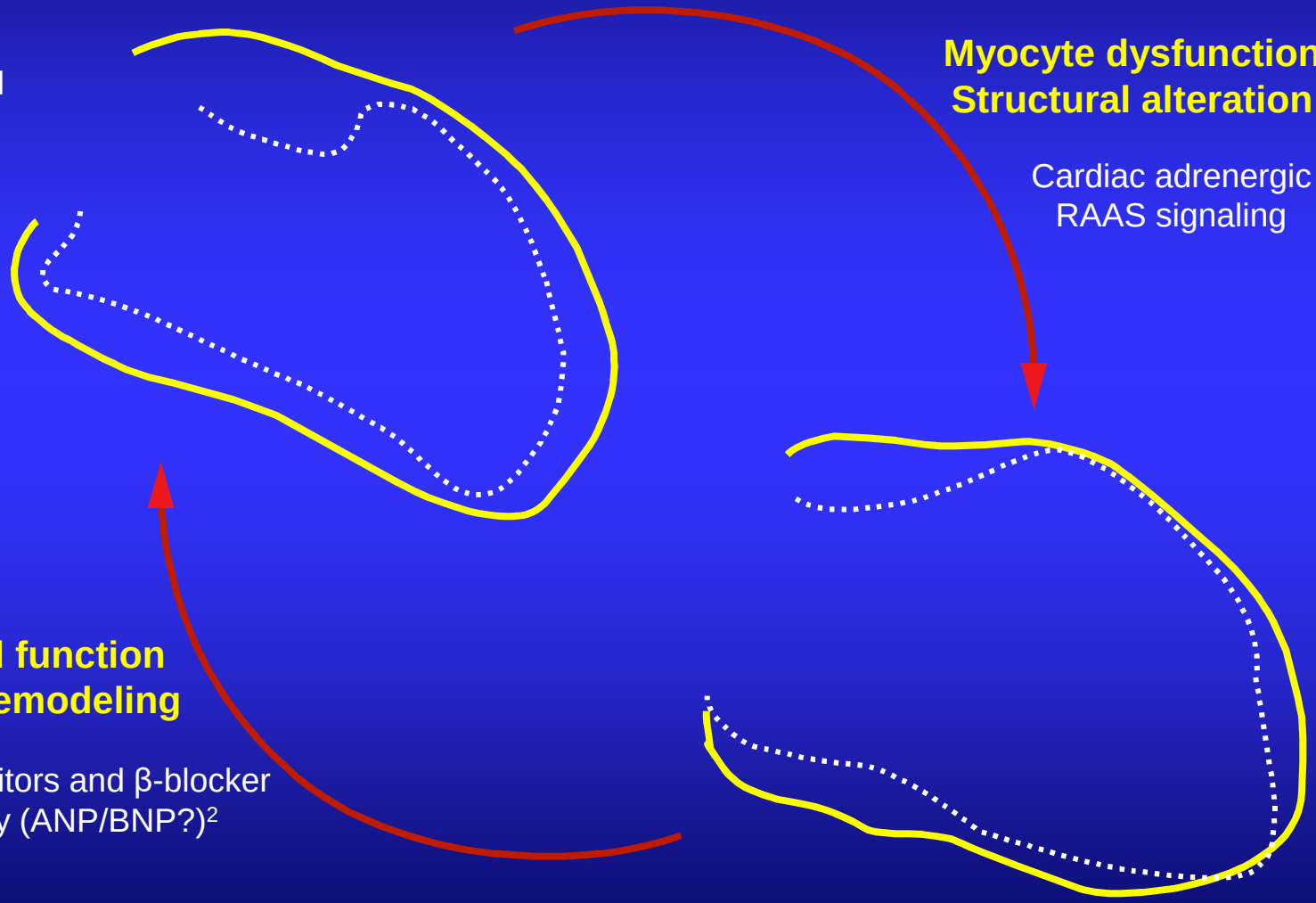
- When these neurohormones are expressed on a chronic basis, a maladaptive pattern emerges, perpetuating heart failure.
- Two leading cause of death in these patients are progressive inotropic failure and arrhythmia.

Relation of Neurohumoral Activation to Myocardial Remodeling

Relatively normal chamber size and geometry[1]

Myocyte dysfunction
Structural alteration

Cardiac adrenergic
RAAS signaling



Improved function
Reverse remodeling

ACE Inhibitors and β-blocker therapy (ANP/BNP?)[2]

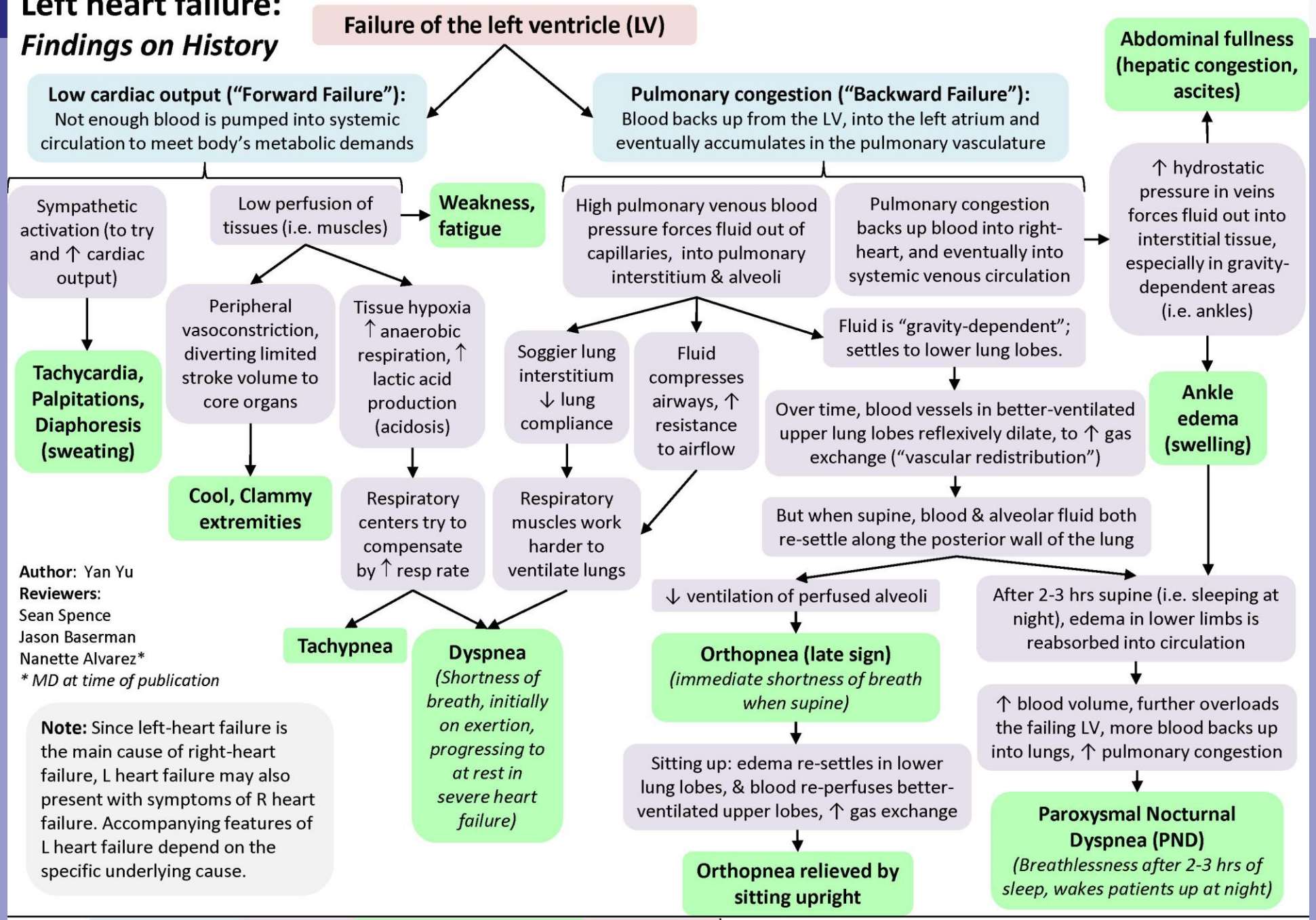
Remodeled Ventricle[1]

1. Cohn JN et al. *J Am Coll Cardiol.* 2000;35:569–582.
2. Burnett JC Jr. *J Hypertens.* 1999;17(suppl 1):S37–S43.

Diagnosis

- Clinical diagnosis – history and physical examination are key to making diagnosis.

Left heart failure:
Findings on History



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Jason Baserman
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** MD at time of publication*

Note: Since left-heart failure is the main cause of right-heart failure, L heart failure may also present with symptoms of R heart failure. Accompanying features of L heart failure depend on the specific underlying cause.

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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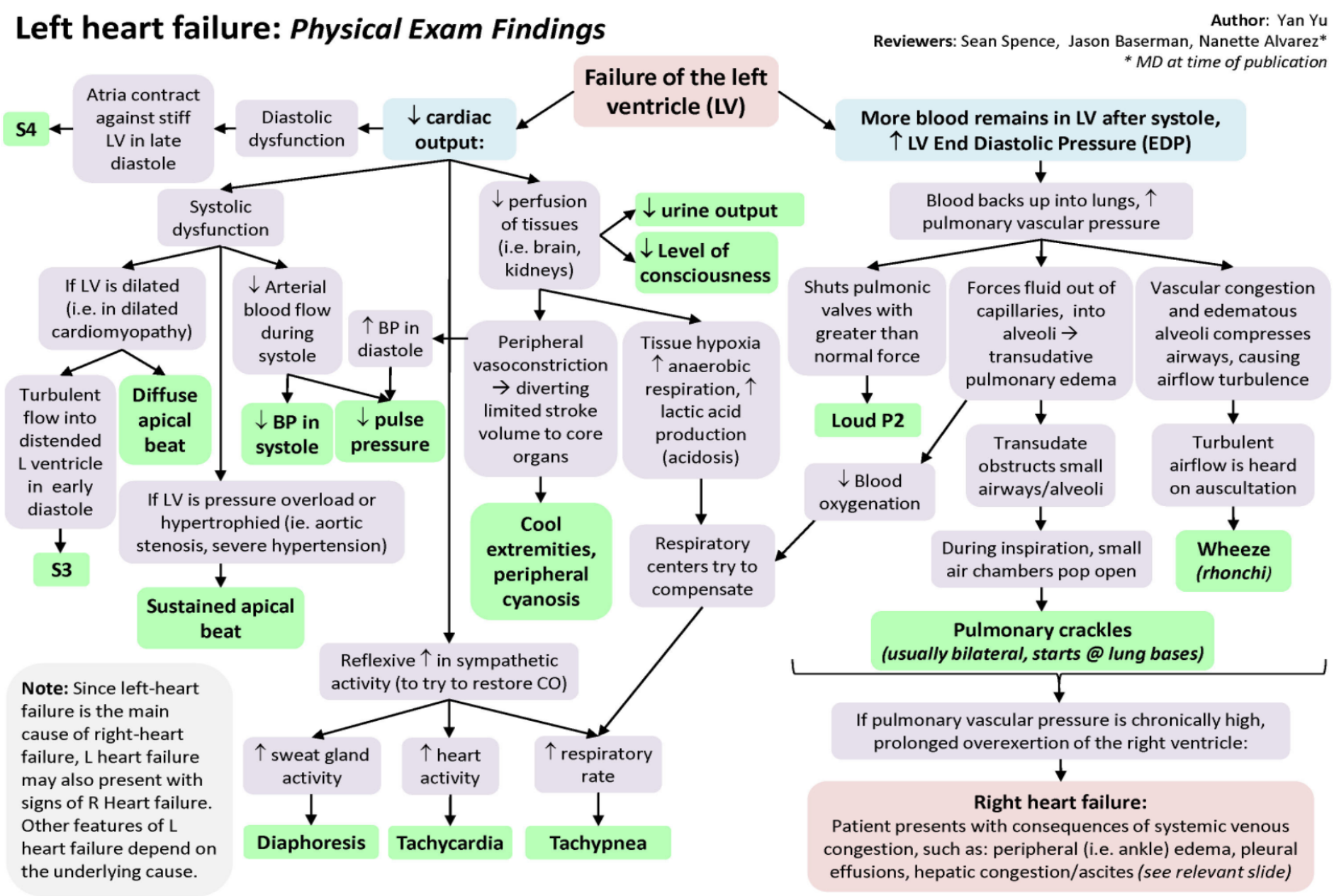
LEFT HEART FAILURE: PHYSICAL EXAM FINDINGS



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EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

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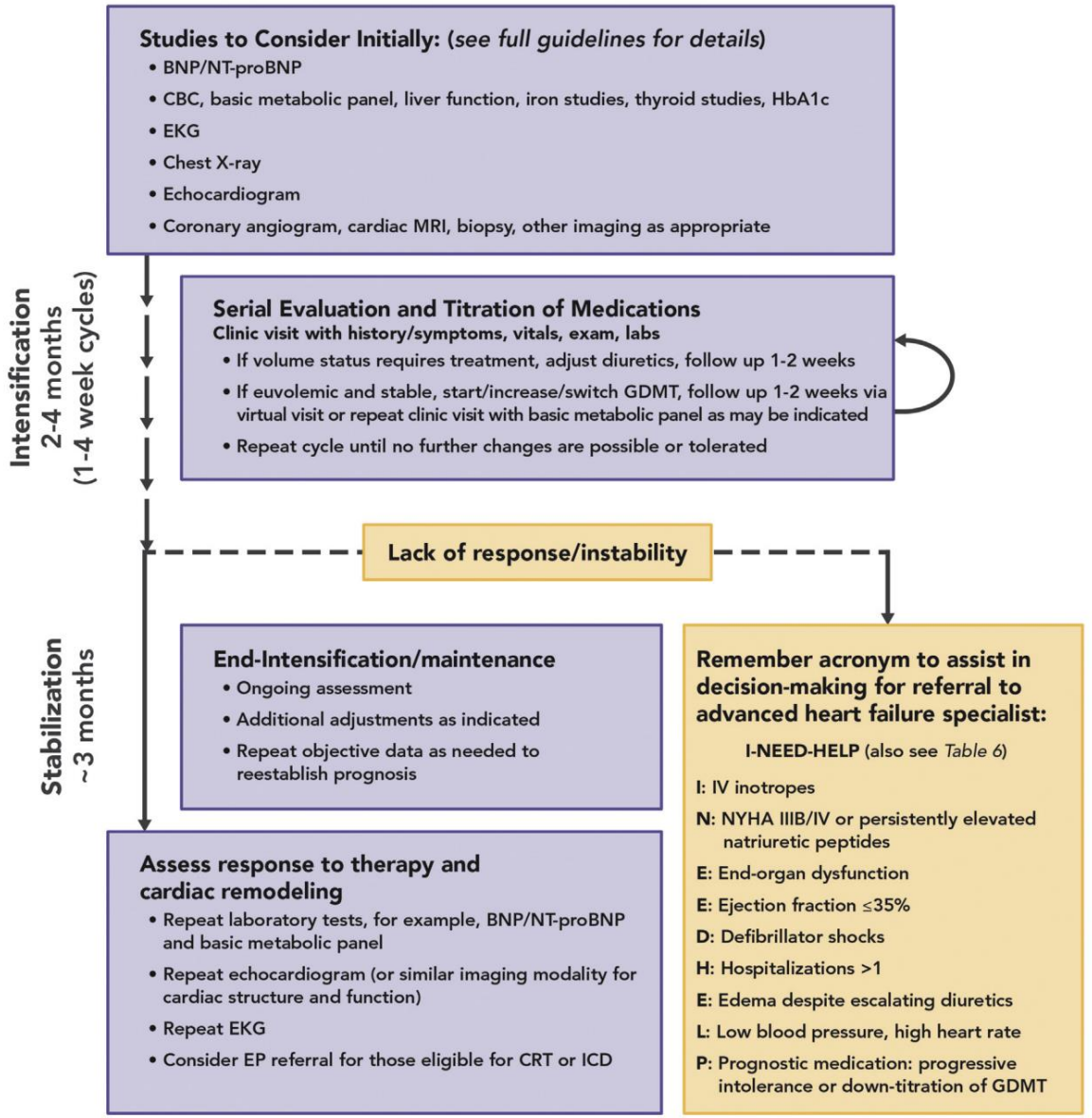
FIGURE 4 Testing and Medication Titration Following Diagnosis of HFrEF



BNP = B-type natriuretic peptide; CBC = complete blood count; CRT = cardiac resynchronization therapy; ECG= electrocardiogram; EP = electrophysiologist; GDMT = guideline-directed medical therapy; HbA1c = hemoglobin A1c; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; IV = intravenous; NT-proBNP = N terminal pro B-type natriuretic peptide); NYHA = New York Heart Association.

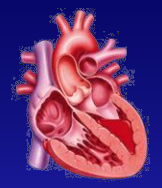
Diagnosis

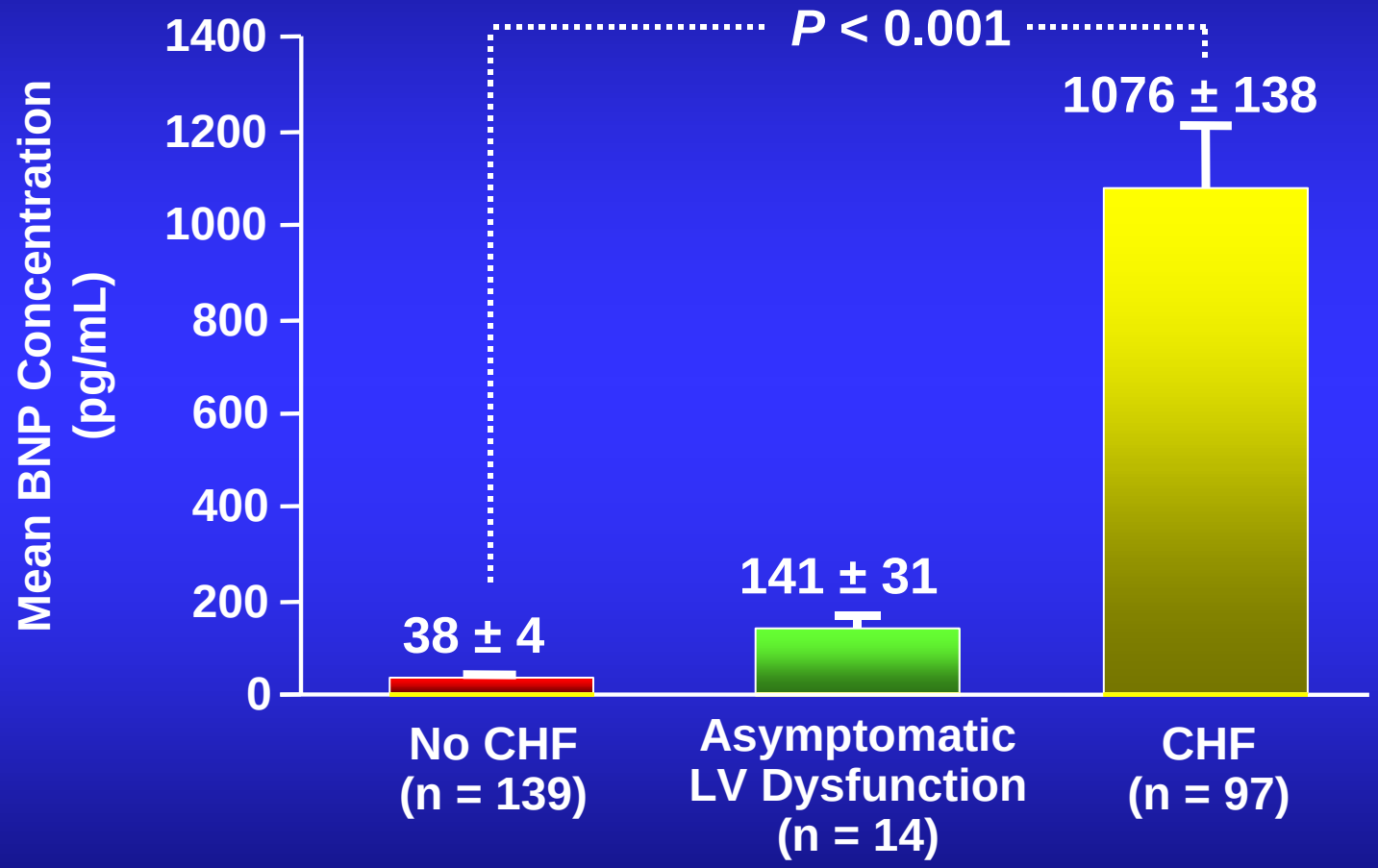
- BNP – 32 amino acid peptide secreted from ventricles of the heart.
- It is released in response to stretch and increased volume in the ventricles.
- Levels correlate with LVEDP and NYHA classification.

Diagnosis

- BNP- level of 100pg/ml has sensitivity of 90%, specificity of 76%, and accuracy of 83% of differentiating CHF from other causes of dyspnea.
- BNP level of 50pg/ml has negative predictive value of 96%.
- BNP level is more accurate than NHANES criteria (67%) and Framingham criteria (73%), the two criteria most commonly used to diagnose CHF.

BNP Levels of Patients Without CHF, With Baseline LV Dysfunction, and With CHF





Dao Q et al. *J Am Coll Cardiol.* 2001;37:379–385.

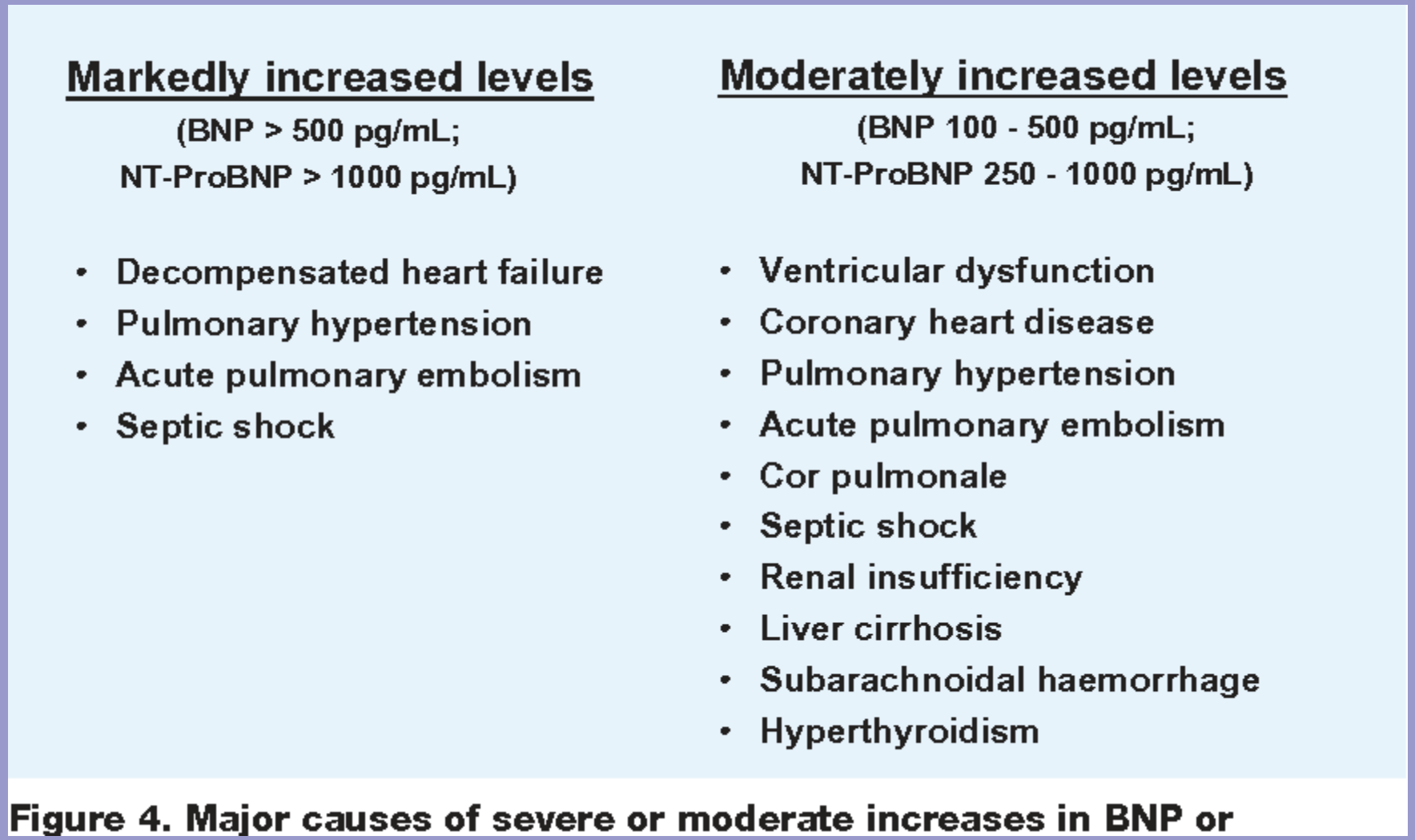


Figure 4. Major causes of severe or moderate increases in BNP or

Staging and classification

ACC/AHA staging system	NYHA functional classification system
A – At high risk for HF w/out structural heart disease or symptoms of HF	I – Cardiac disease but no symptoms of HF with ordinary activity
B – Structural heart disease w/out symptoms	II – Cardiac disease that limits function slightly. Symptoms with ordinary activity.
C – Structural heart disease with prior or current symptoms of HF	III – Cardiac disease that limits function significantly. Symptoms with less than ordinary activity.
D – Refractory HF requiring specialized interventions	IV – Symptoms with any physical activity and may occur at rest.

Universal Definition and Classification of Heart Failure (HF)

Definition

HF is a *clinical syndrome* with current or prior

- ***Symptoms and or signs caused by a structural and/or functional cardiac***

And corroborated by at least one of the following:

- ***Elevated natriuretic peptide levels***
- ***Objective evidence of cardiogenic pulmonary or systemic congestion***

Stages

AT RISK *(STAGE A)*	**Patients at risk for HF, but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease**
PRE-HF *(STAGE B)*	**Patients without current or prior symptoms or signs of HF with evidence of <u>one</u> of the following:** • *Structural Heart Disease* • *Abnormal cardiac function* • *Elevated natriuretic peptide or cardiac troponin levels*
HF *(STAGE C)*	**Patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality**
ADVANCED HF *(STAGE D)*	**Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT, requiring advanced therapies transplantation, mechanical circulatory support, or palliative care**

Classification By EF

HF with reduced EF (HFrEF)
- *HF with **LVEF < 40%***

HF with mildly reduced EF (HFmrEF)
- *HF with **LVEF 41-49%***

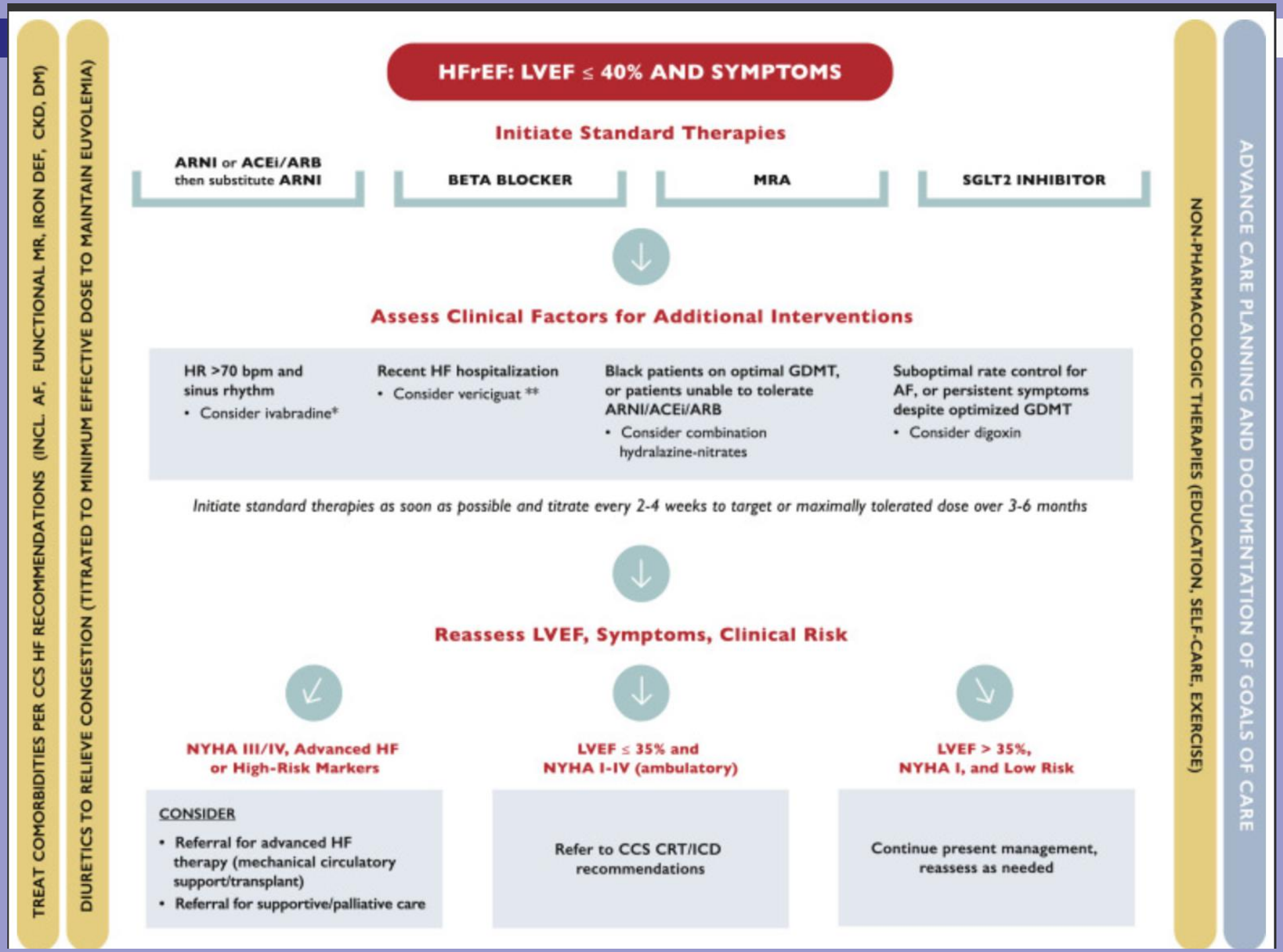
HF with preserved EF (HFpEF)
- *HF with **LVEF > 50%***

HF with improved EF (HFimpEF)
- *HF with a baseline LVEF of < 40%, a 10-point increase from baseline LVEF, and a second measurement of LVEF of > 40%*

Language matters! The new universal definition offers opportunities for *more precise communication* and description with terms including ***persistent HF*** instead of "stable HF," and ***HF in remission*** rather than "recovered HF."

TABLE 14 **Important Pathophysiological Targets in Chronic, Hemodynamically Stable HFrEF and Treatments**

Target	Therapy
Renin-angiotensin-aldosterone system	ARNIs/ACEIs/ARBs, aldosterone antagonists
Sympathetic nervous system	Beta-blockers
Natriuretic and other vasodilator peptides	Neprilysin inhibitor (ARNI)
Sodium-glucose cotransporter-2	SGLT2 inhibitors
Balanced vasodilation and oxidative stress modulation	HYD/ISDN
Elevated heart rate	Beta-blocker, ivabradine
Guanylyl cyclase	Soluble guanylyl cyclase stimulators
Relief of congestion	Diuretic agents
Ventricular arrhythmias	Implantable cardioverter-defibrillators
Ventricular dyssynchrony due to conduction abnormalities	Cardiac resynchronization therapy
Mitral regurgitation	Surgical or percutaneous mitral valve repair
Reduced aerobic capacity	Aerobic exercise training


TREAT COMORBIDITIES PER CCS HF RECOMMENDATIONS (INCL. AF, FUNCTIONAL MR, IRON DEF, CKD, DM)
DIURETICS TO RELIEVE CONGESTION (TITRATED TO MINIMUM EFFECTIVE DOSE TO MAINTAIN EUVOLEMIA)
HFrEF: LVEF ≤ 40% AND SYMPTOMS
Initiate Standard Therapies
ARNI or ACEi/ARB then substitute ARNI
BETA BLOCKER
MRA
SGLT2 INHIBITOR
Assess Clinical Factors for Additional Interventions
HR >70 bpm and sinus rhythm
• Consider ivabradine*
Recent HF hospitalization
• Consider vericiguat **
Black patients on optimal GDMT, or patients unable to tolerate ARNI/ACEi/ARB
• Consider combination hydralazine-nitrates
Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT
• Consider digoxin
Initiate standard therapies as soon as possible and titrate every 2-4 weeks to target or maximally tolerated dose over 3-6 months
Reassess LVEF, Symptoms, Clinical Risk
NYHA III/IV, Advanced HF or High-Risk Markers
CONSIDER
• Referral for advanced HF therapy (mechanical circulatory support/transplant)
• Referral for supportive/palliative care
LVEF ≤ 35% and NYHA I-IV (ambulatory)
Refer to CCS CRT/ICD recommendations
LVEF > 35%, NYHA I, and Low Risk
Continue present management, reassess as needed
NON-PHARMACOLOGIC THERAPIES (EDUCATION, SELF-CARE, EXERCISE)
ADVANCE CARE PLANNING AND DOCUMENTATION OF GOALS OF CARE

Management – Nonpharmacologic therapy

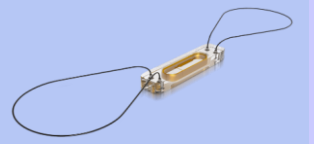
- Screen for htn, dm, dyslipidemia.
- Tobacco cessation, elimination of alcohol consumption.
- Exercise – in patients with symptomatic chronic heart failure, it has been linked to reduced mortality and hospital admission.
- Dietary sodium reduction – in patients with edema and/or hypertension.
- Daily Weights and diuretic adjustments.

cardiomems™ HF System:

Provides clarity in the management of heart failure

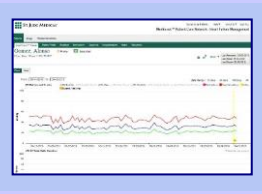
Delivers insight into the early onset of worsening HF to more proactively manage HF patients and improve outcomes

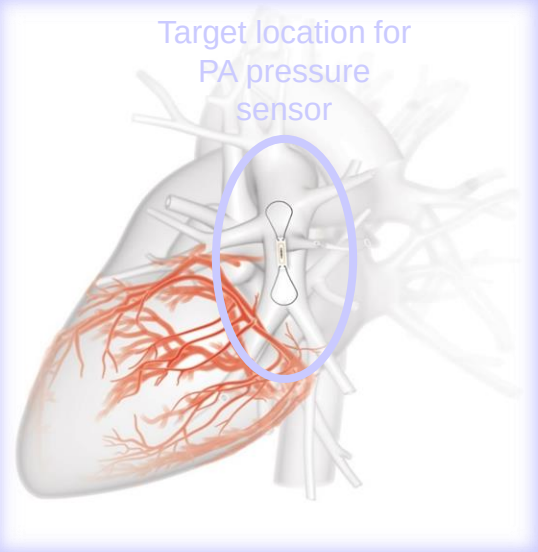
Pulmonary Artery Pressure Sensor



Patient Electronics System

Merlin.net™ PCN





Abraham WT, Lancet, 2011

GUIDE-HF: Hemodynamic-guided management of heart failure – randomized arm primary outcomes

Purpose: To evaluate whether pulmonary artery (PA) pressure-guided heart failure management leads to a clinical benefit in a broad range of heart failure patients (NYHA Class II, III, or IV), with either a recent hospitalization for heart failure or elevated natriuretic peptides.

Trial Design: Single blind, randomized controlled trial of PA pressure-guided therapy in NYHA class II-IV pts. (N=1000) with either HF hospitalization or elevated natriuretic peptide. Pts. received an implantable PA pressure sensor (CardioMEMS HF System) followed by randomization to either treatment group with provider remote access, or control group without provider access. Median follow-up 11.7 months.

Primary Endpoints: Composite of all-cause mortality and total heart failure events (heart failure hospitalizations and urgent heart failure hospital visits) at 12 months. The pre-COVID impact analysis included all primary endpoints up to March 13, 2020.

	Remote Hemodynamic Guided Care (n=497)	Standard Care (no access to PA pressures) (n=503)	HR (95%CI)	P value
Overall primary endpoint analysis	253	289	0.88 (0.74-1.05)	0.16
Components of overall primary endpoint				
HF events	213	252	0.85 (0.70-1.03)	0.096
Urgent HF hospital visits	28	27	1.04 (0.61-1.77)	0.89
HF hospitalizations	185	225	0.83 (0.68-1.01)	0.064
Death	40	37	1.09 (0.70-1.70)	0.71
Pre-COVID impact analysis-primary endpoint	177	224	0.81 (0.66-1.00)	0.049
Components of Pre-COVID impact analysis				
HF events	147	199	0.76(0.61-0.95)	0.014
Urgent HF hospital visits	23	23	1.02(0.57-1.82)	0.95
HF hospitalizations	124	176	0.72(0.57-0.92)	0.0072
Death	30	25	1.24(0.73-2.11)	0.42

Results:
Hemodynamic-guided management across the spectrum of ejection fraction and symptom severity was safe but did not reduce a composite of mortality and heart failure events.
COVID-19 pandemic impacted the outcomes of the trial. The pre-COVID impact analysis indicated a benefit of hemodynamic-guided management on the primary outcome in the pre-COVID-19 period, primarily driven by a lower HF hospitalization rate (28%) compared to control group

Results reflect the data available at the time of presentation.

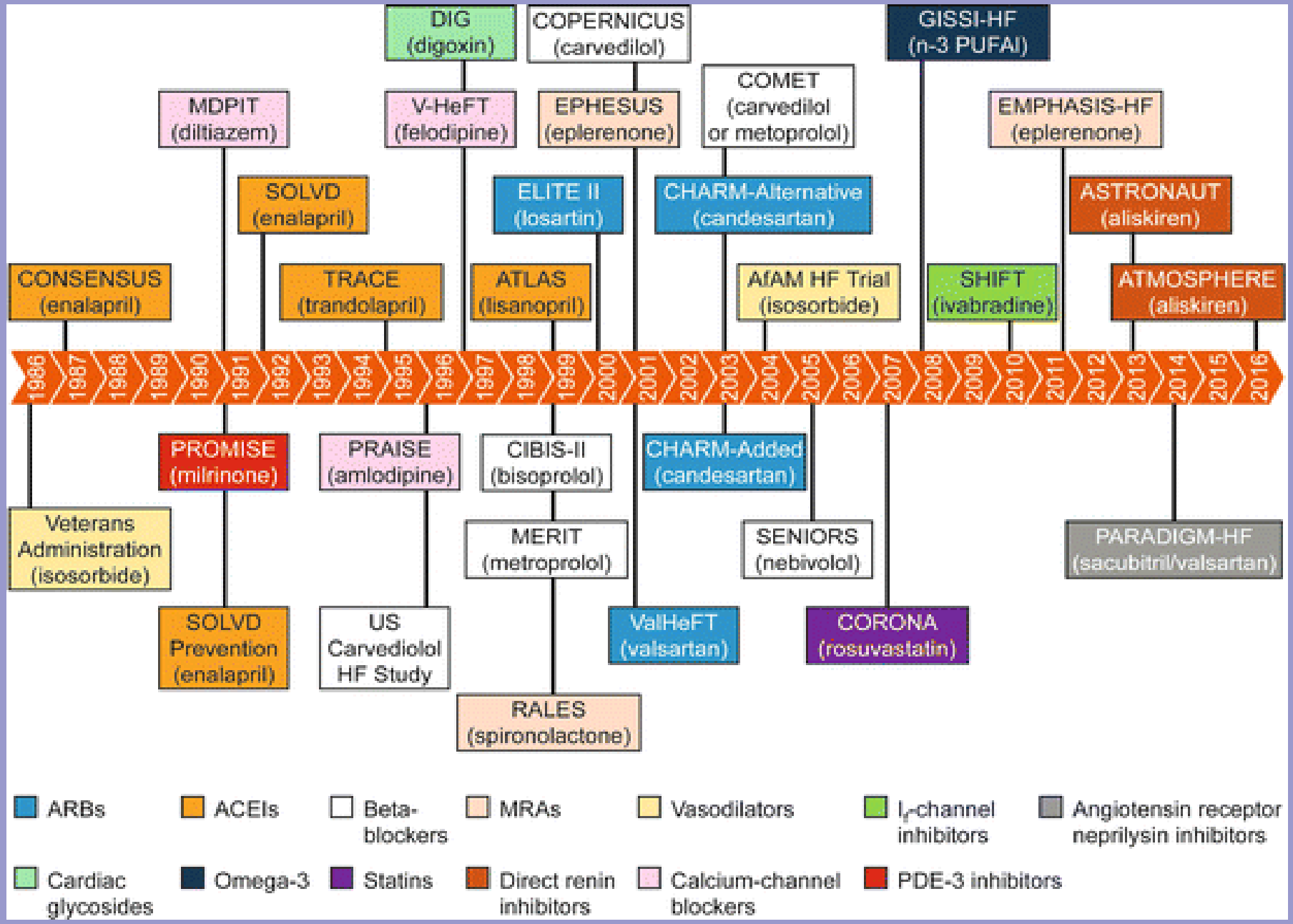
Presented by: Joann Lindefeld, ESC 2021, The Digital Experience

Pharmacologic therapy

- ACE-I/ARB
- Beta-Blocker
- Hydralazine/Nitrate
- Aldosterone inhibitor
- Diuretic
- Digoxin

Pharmacologic therapy

- Sacubitril/valsartan (Entresto)
- Vericiguat (Verguvo)
- Dapaglifozin (Farxiga), Empaglifozin (Jardiance)
- Ivabradine (Corlanor)


DIG (digoxin)
COPERNICUS (carvedilol)
GISSI-HF (n-3 PUFAI)
MDPIT (diltiazem)
V-HeFT (felodipine)
EPHESUS (eplerenone)
COMET (carvedilol or metoprolol)
EMPHASIS-HF (eplerenone)
SOLVD (enalapril)
ELITE II (losartin)
CHARM-Alternative (candesartan)
ASTRONAUT (aliskiren)
CONSENSUS (enalapril)
TRACE (trandolapril)
ATLAS (lisanopril)
AfAM HF Trial (isosorbide)
SHIFT (ivabradine)
ATMOSPHERE (aliskiren)
1986
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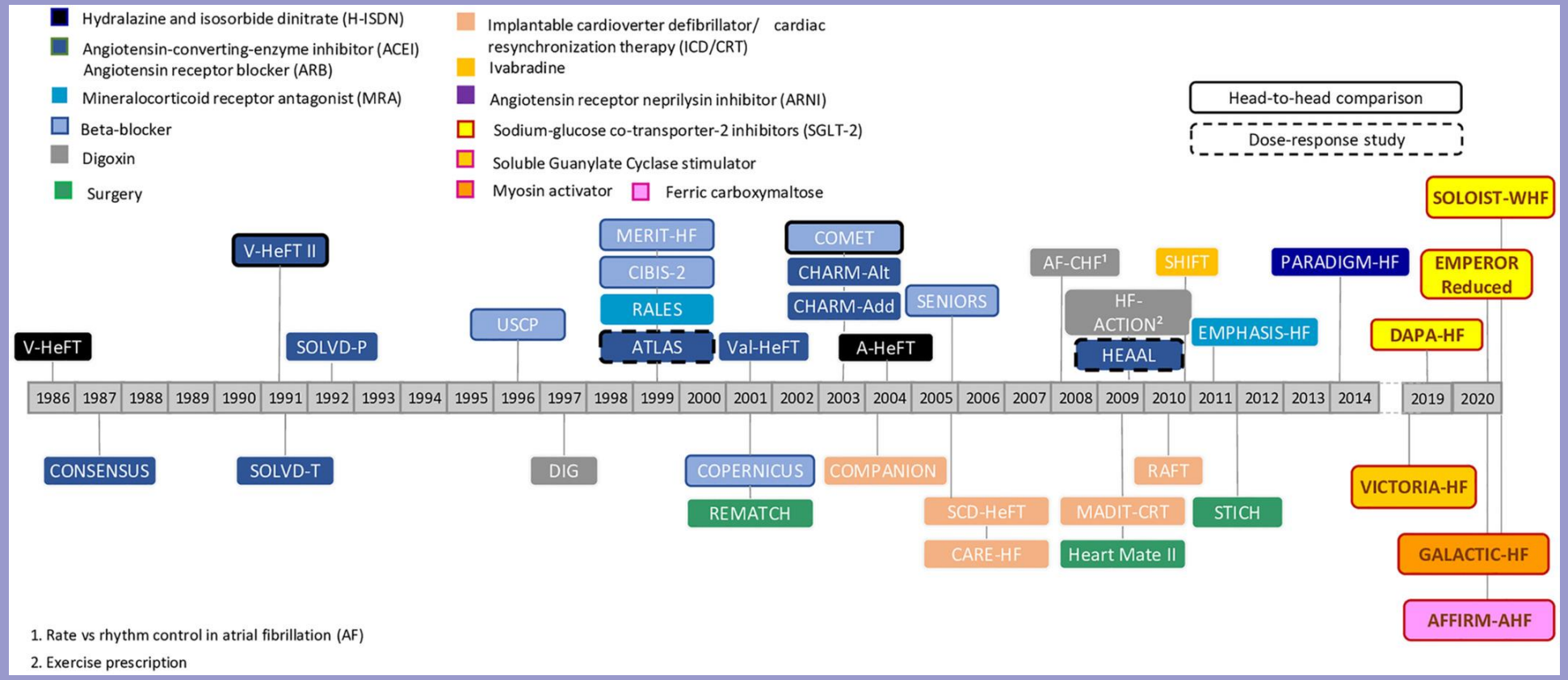
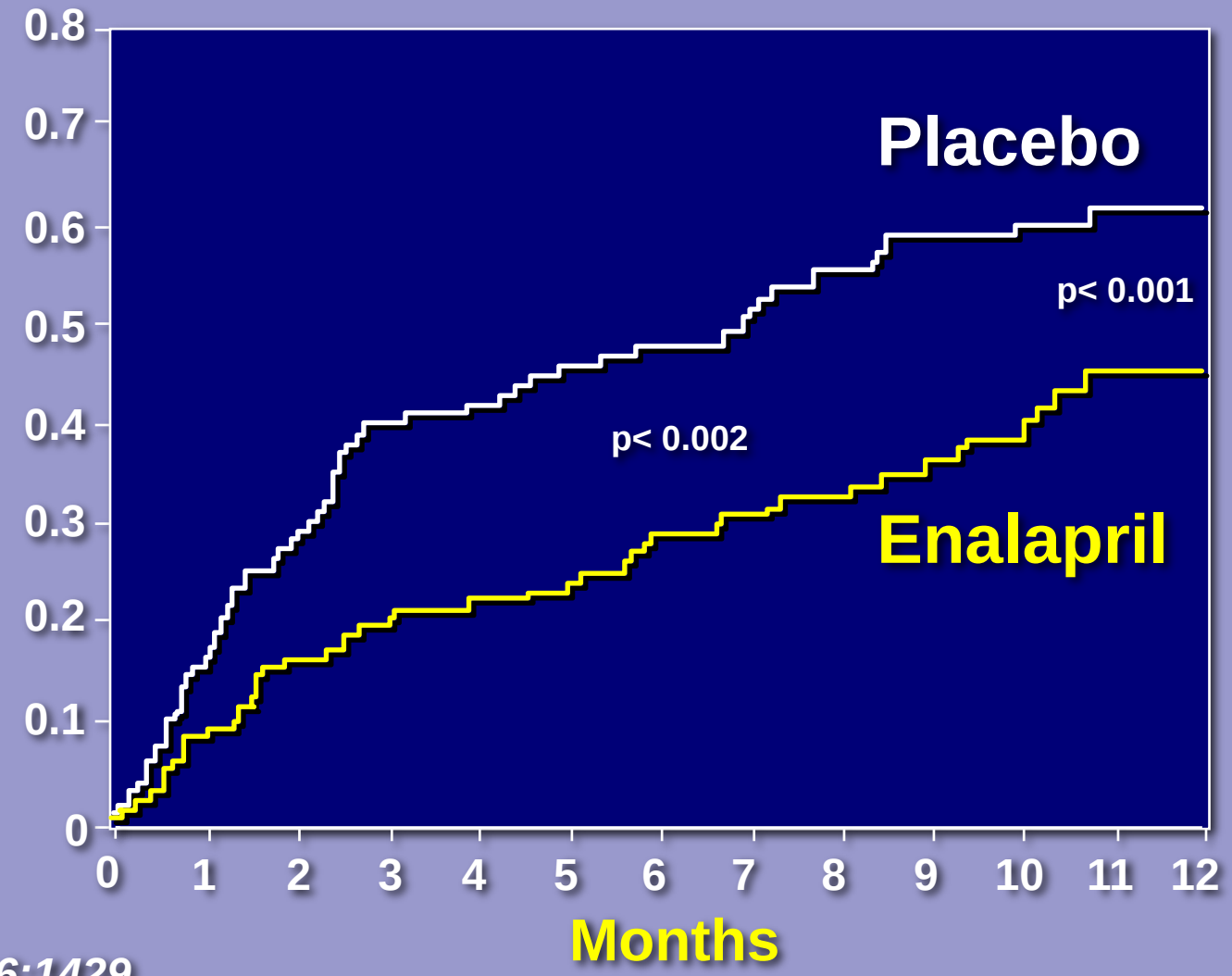
2016
PROMISE (milrinone)
PRAISE (amlodipine)
CIBIS-II (bisoprolol)
CHARM-Added (candesartan)
Veterans Administration (isosorbide)
MERIT (metroprolol)
SENIORS (nebivolol)
PARADIGM-HF (sacubitril/valsartan)
SOLVD Prevention (enalapril)
US Carvediolol HF Study
ValHeFT (valsartan)
CORONA (rosuvastatin)
RALES (spironolactone)
ARBs
ACEIs
Beta-blockers
MRAs
Vasodilators
I_f-channel inhibitors
Angiotensin receptor neprilysin inhibitors
Cardiac glycosides
Omega-3
Statins
Direct renin inhibitors
Calcium-channel blockers
PDE-3 inhibitors


Hydralazine and isosorbide dinitrate (H-ISDN)
Angiotensin-converting-enzyme inhibitor (ACEI)
Angiotensin receptor blocker (ARB)
Mineralocorticoid receptor antagonist (MRA)
Beta-blocker
Digoxin
Surgery
Implantable cardioverter defibrillator/ cardiac resynchronization therapy (ICD/CRT)
Ivabradine
Angiotensin receptor neprilysin inhibitor (ARNI)
Sodium-glucose co-transporter-2 inhibitors (SGLT-2)
Soluble Guanylate Cyclase stimulator
Myosin activator
Ferric carboxymaltose
Head-to-head comparison
Dose-response study
V-HeFT
V-HeFT II
SOLVD-P
USCP
MERIT-HF
CIBIS-2
RALES
ATLAS
Val-HeFT
COMET
CHARM-Alt
CHARM-Add
A-HeFT
SENIORS
AF-CHF1
HF-ACTION2
HEAAL
SHIFT
EMPHASIS-HF
PARADIGM-HF
DAPA-HF
EMPEROR Reduced
SOLOIST-WHF
1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2019 2020
CONSENSUS
SOLVD-T
DIG
COPERNICUS
REMATCH
COMPANION
SCD-HeFT
CARE-HF
MADIT-CRT
Heart Mate II
RAFT
STICH
VICTORIA-HF
GALACTIC-HF
AFFIRM-AHF
1. Rate vs rhythm control in atrial fibrillation (AF)
2. Exercise prescription

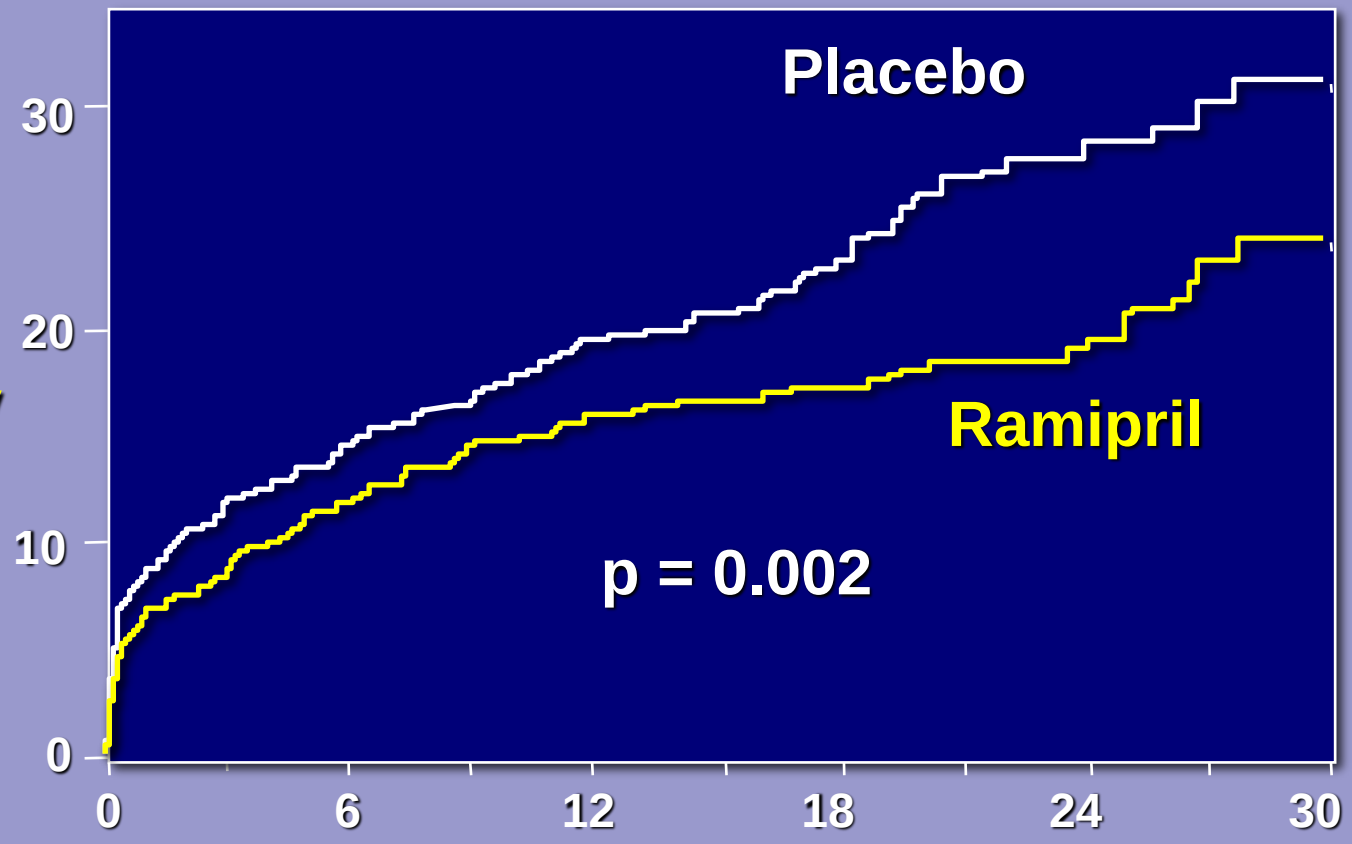
ACE-I



CONSENSUS

N Engl J Med 1987;316:1429

ACE-I

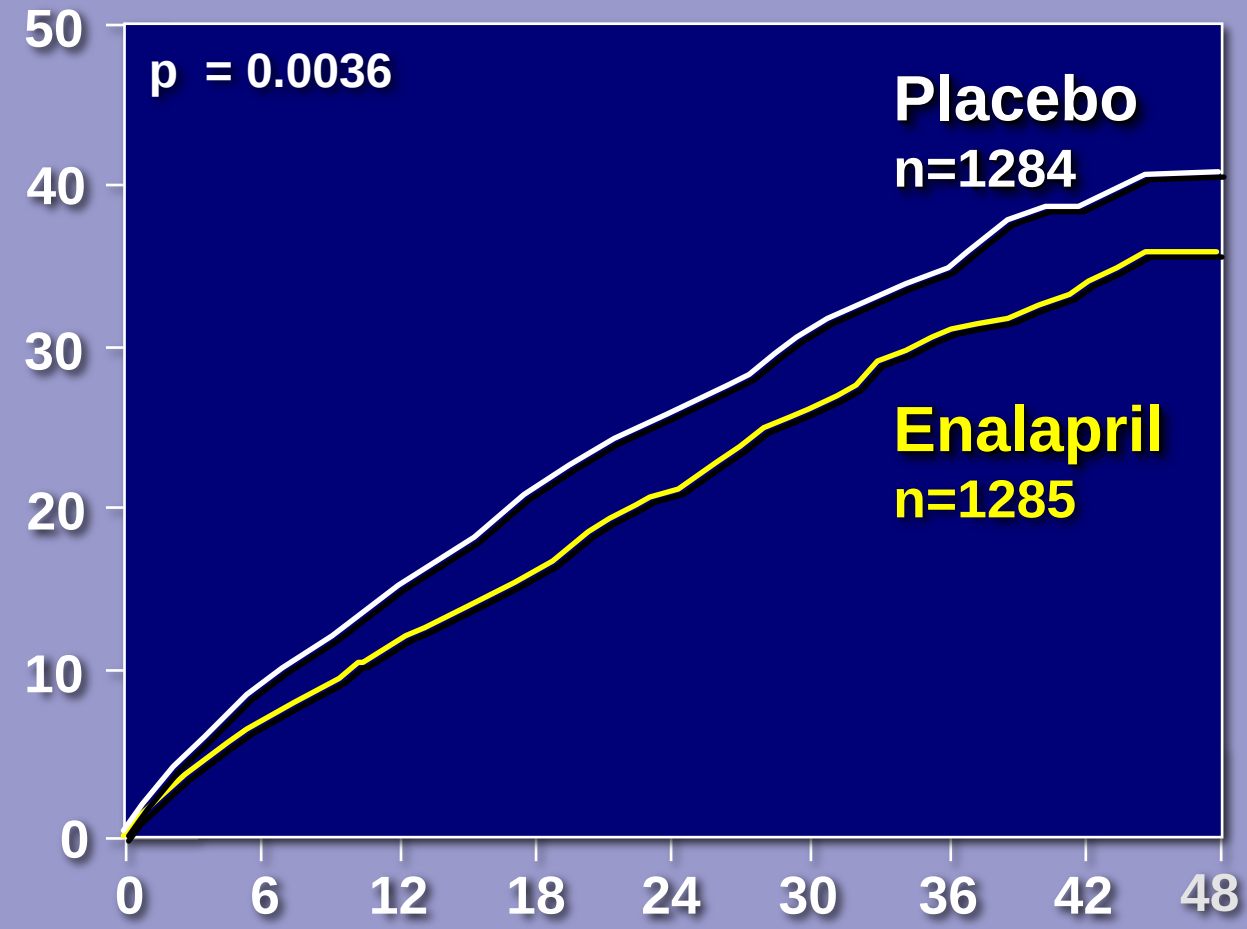


n = 2006
HF after AMI

AIRE

Lancet 1993;342:821

ACE-I



% Mortality

n = 2589
CHF
- NYHA II-III
- EF < 35

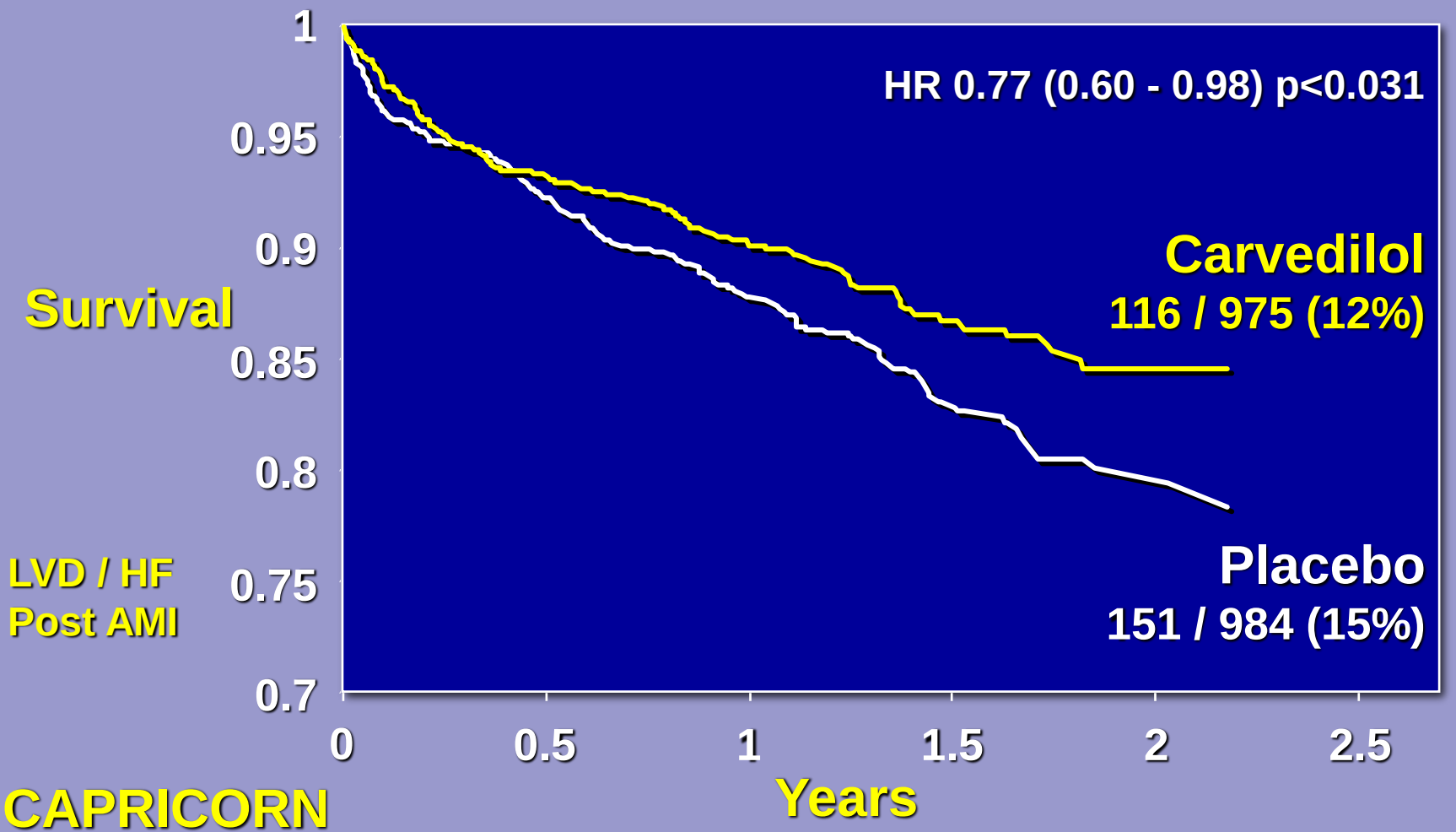
SOLVD (Treatment)

N Engl J M 1991;325:293

VALIANT

	Valsartan	Captopril	Combination
All cause mortality (n,%)	979(19.9)	958(19.5)	941(19.3)
CV Death	870(16.8)	830(16.9)	
CV Death or MI	1103(22.4)	1132(23.1)	
CV Death or HF	1326(27.0)	1335(27.1)	
CV Death, MI, or HF	1529(31.1)	1567(31.9)	

ß-Adrenergic Blockers

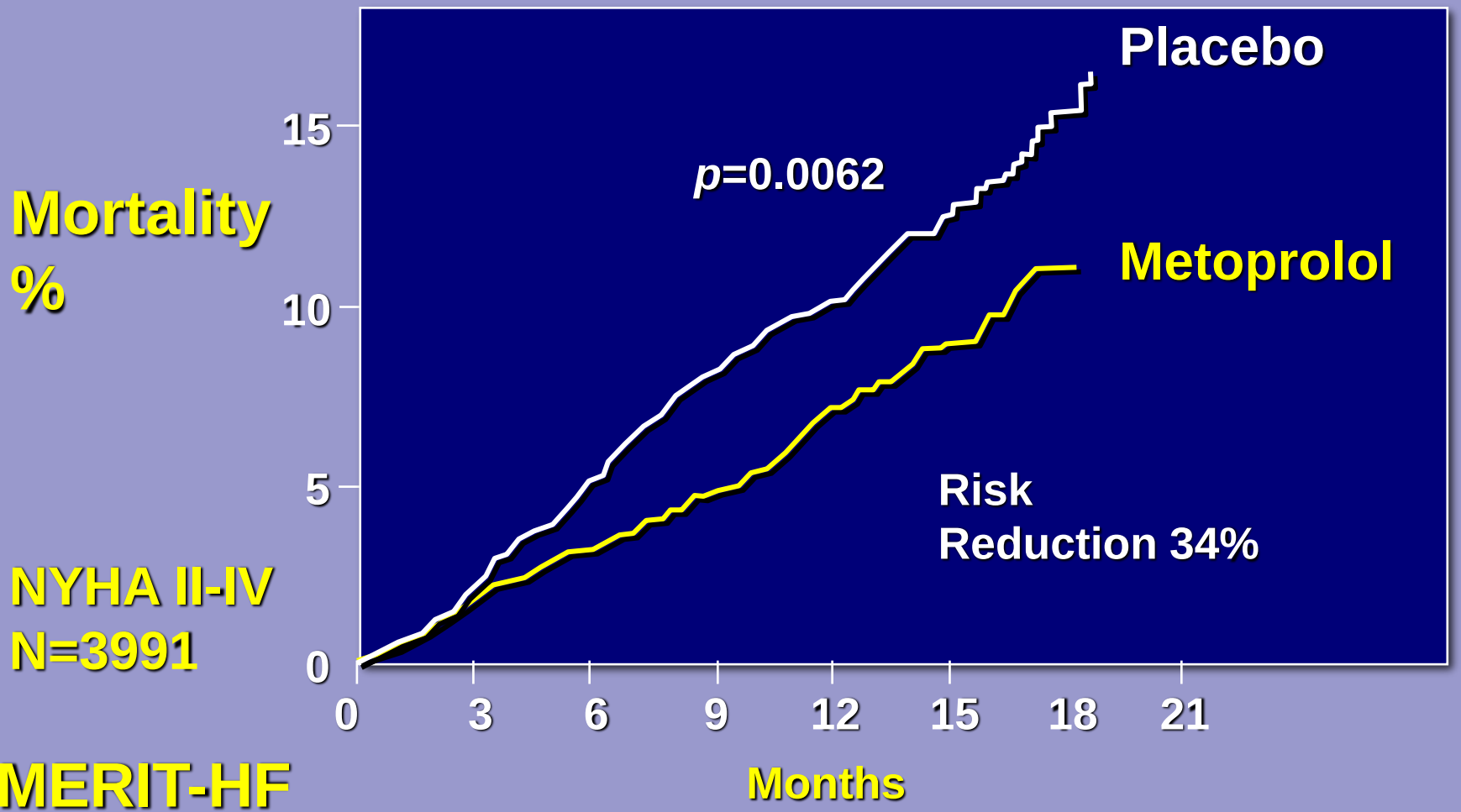


LVD / HF
Post AMI

CAPRICORN

Lancet 2001;357:1385

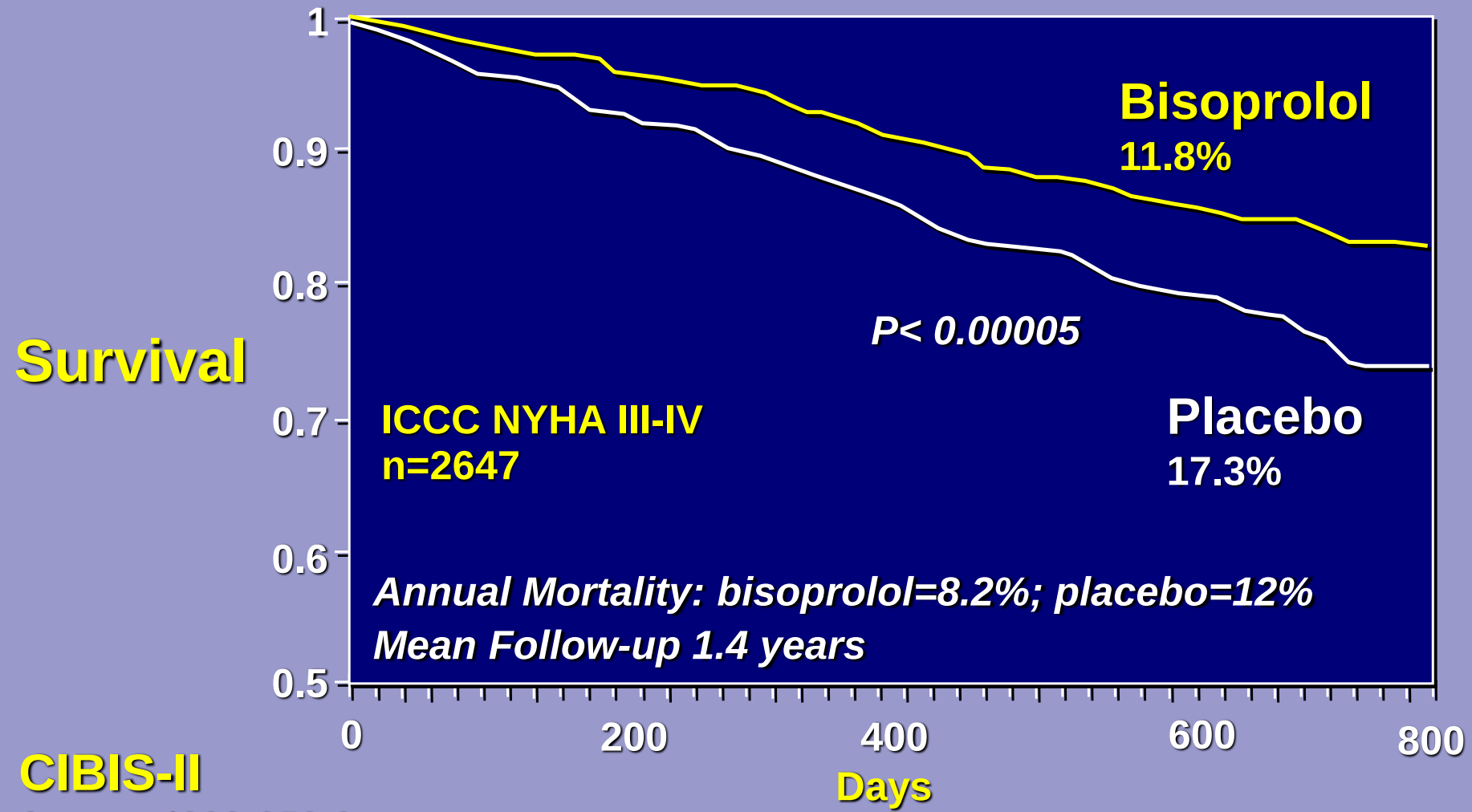
ß-Adrenergic Blockers



MERIT-HF

Lancet 1999; 353: 2001

ß-Adrenergic Blockers



CIBIS-II

Lancet 1999;353:9

COMET trial

End point	Carvedilol (n=1511) (%)	Metoprolol (n=1518) (%)	HR (95% CI)	p
All-cause mortality	33.9	39.5	0.83 (0.74-0.93)	0.0017
All-cause mortality or all-cause hospitalization	73.9	76.4	0.93 (0.86-1.10)	0.1222

ß-Adrenergic Blockers

Dose (mg)

	Initial	Target
Bisoprolol	1.25 / 24h	10 / 24h
Carvedilol	3.125 / 12h	25 / 12h
Metoprolol Succinate	12,5-25 / 24h	200 / 24h

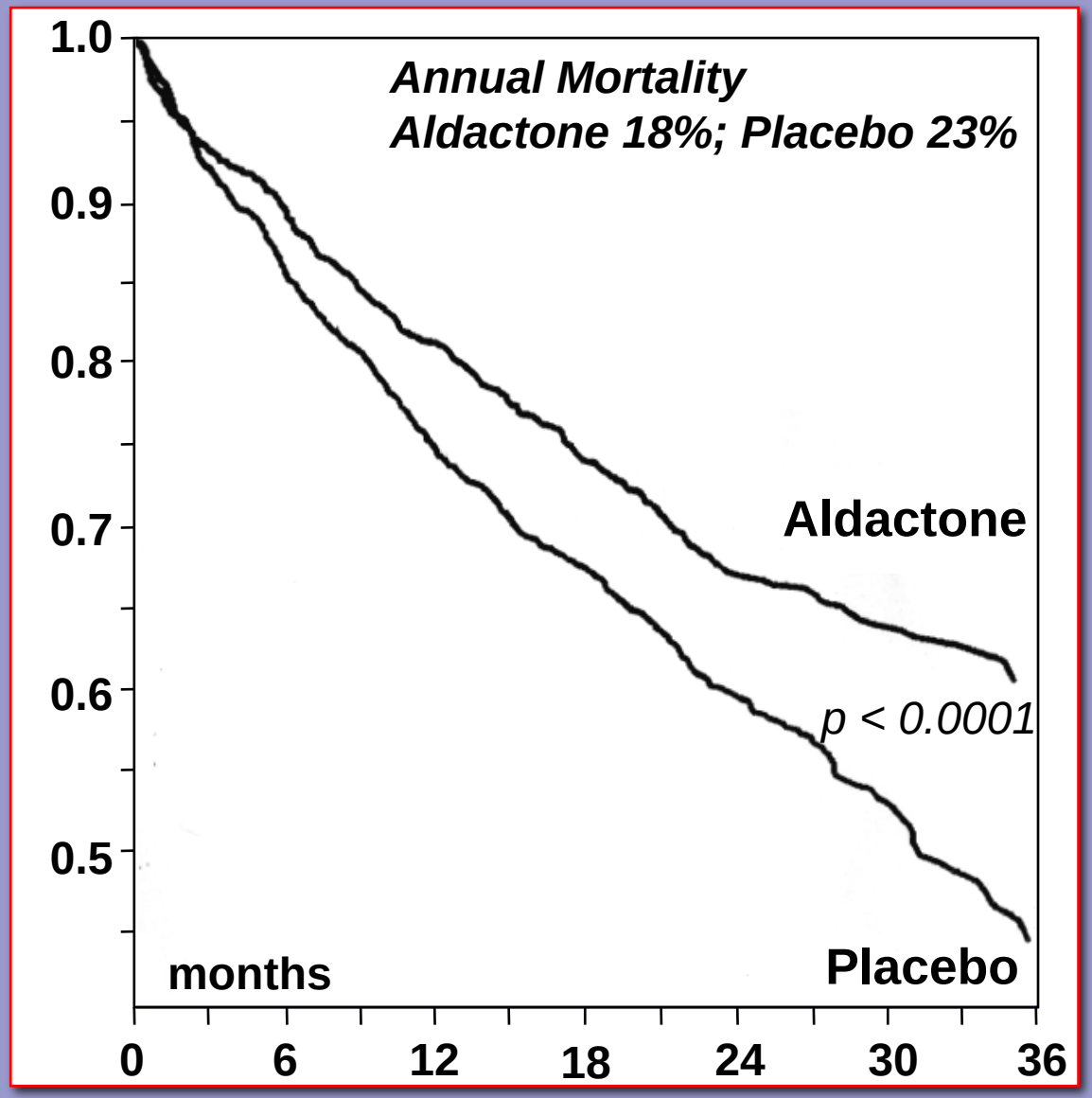
- **Start Low, Increase Slowly**
- Increase the dose every 2 - 4 weeks

Spironolactone

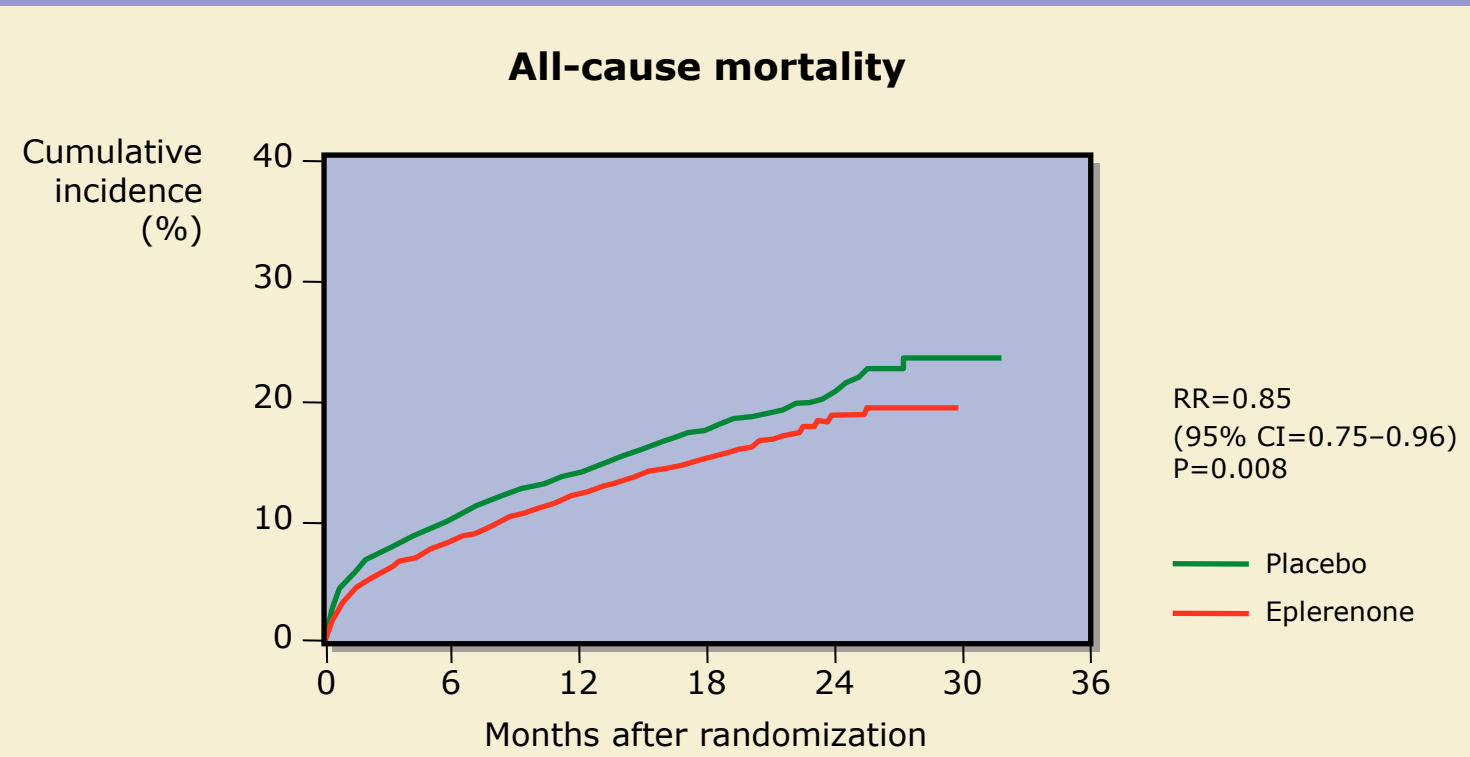
Survival

N = 1663
NYHA III-IV
Mean follow-up 2 y

RALES
NEJM 1999;341:709



EPHESUS: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

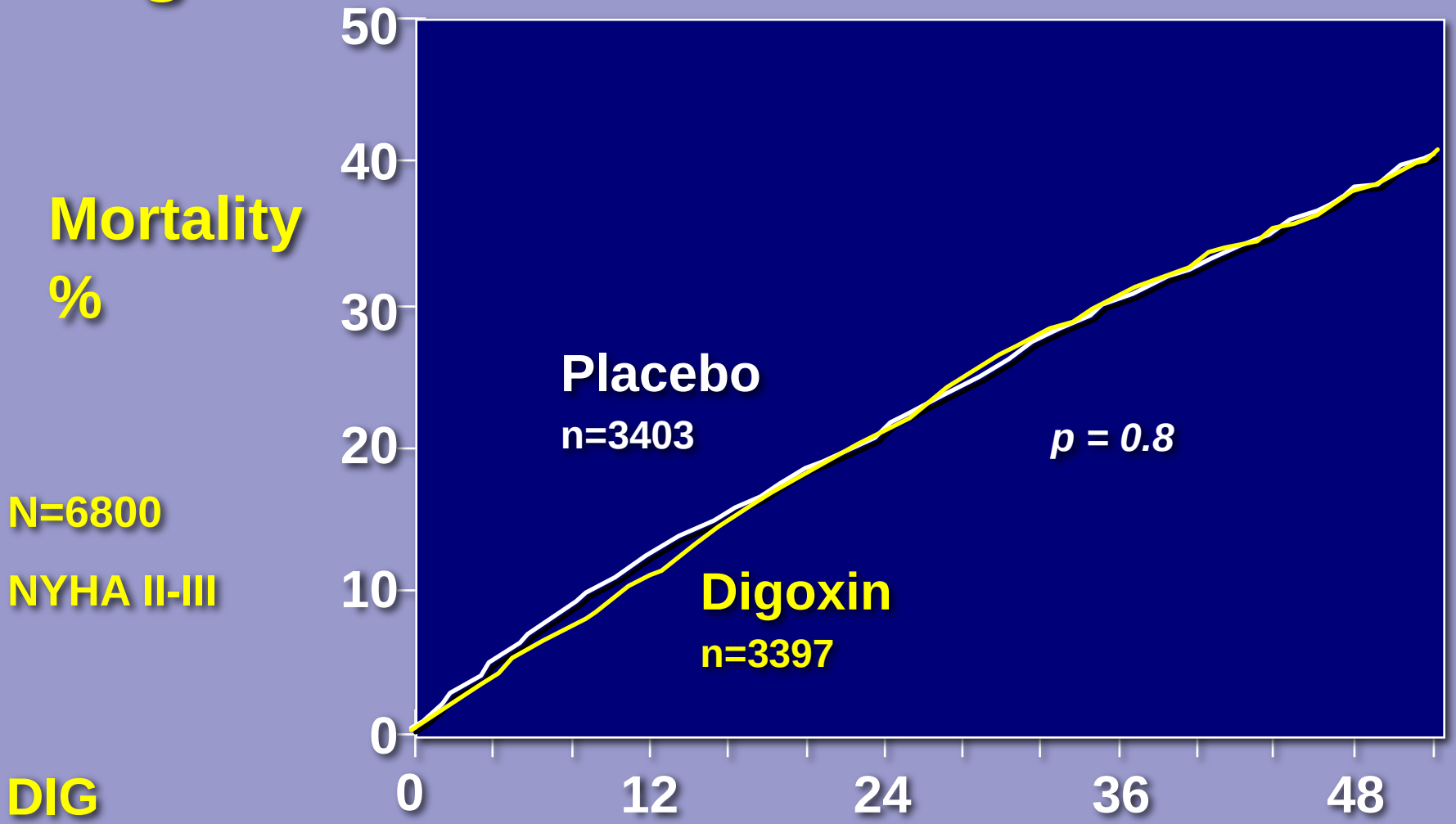


Pitt et al. *N Engl J Med* 2003;**348**:1309–21.

A-Heft

	ISDN + Hydralazine	Placebo	*P*
Primary composite score	-0.1	-0.5	.01
Components of primary composite score:			
All-cause mortality (%)	6.2	10.2	.02
First hospitalization for heart failure (%)	16.4	24.4	.001
Change in quality of life score at 6 mos	-5.6	-2.7	.02

Digitalis



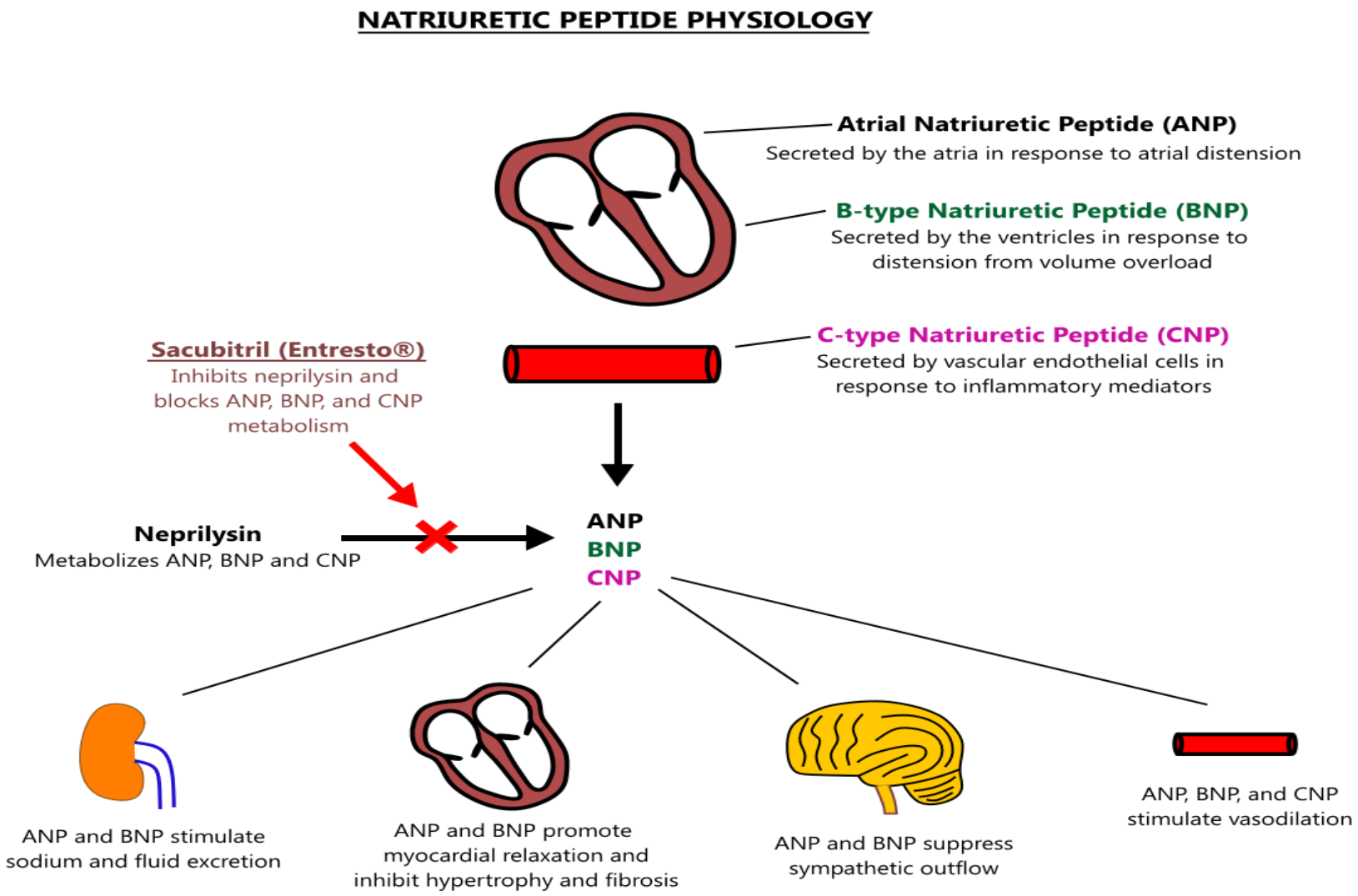
N=6800

NYHA II-III

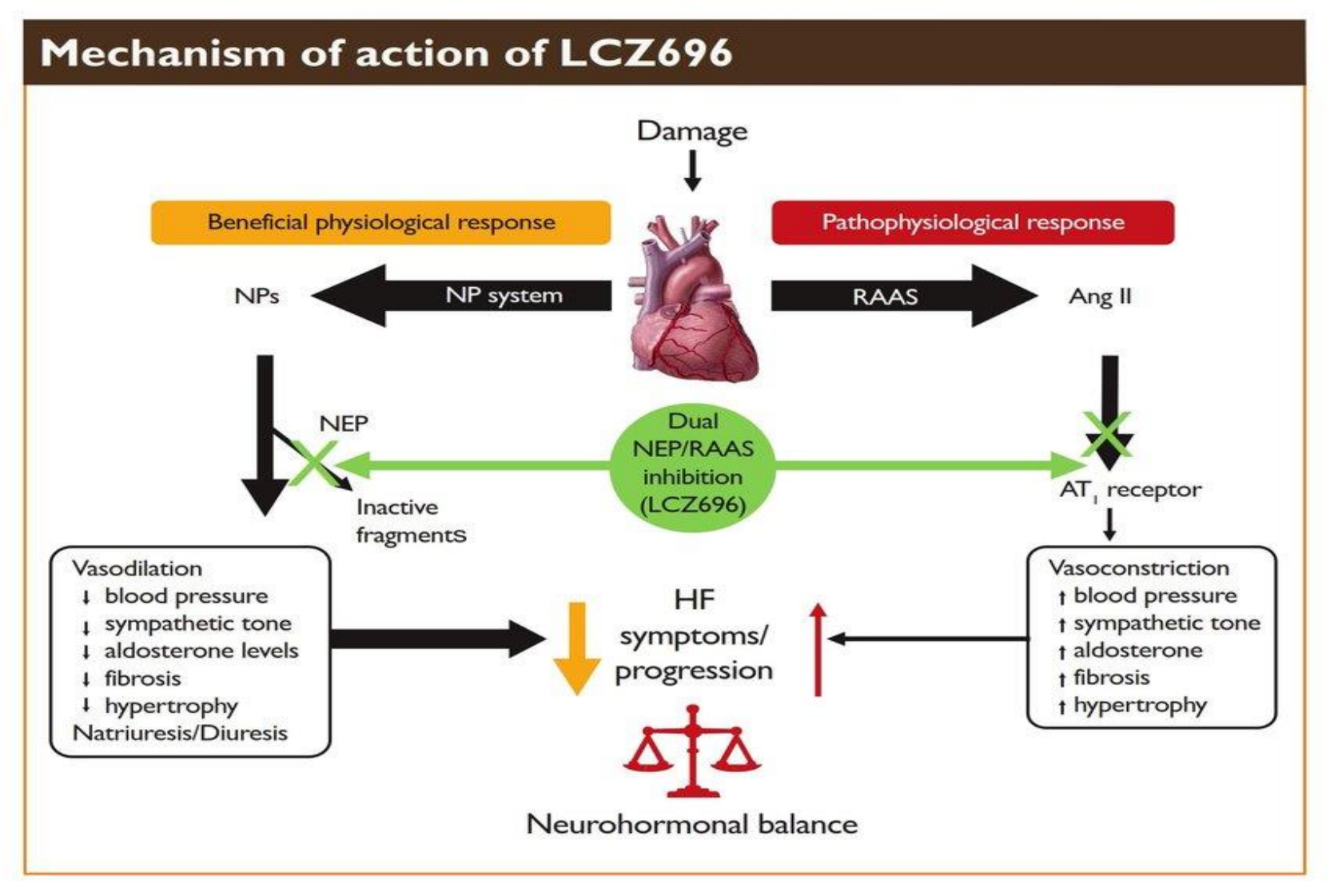
DIG

N Engl J Med 1997;336:525

Entresto


NATRIURETIC PEPTIDE PHYSIOLOGY
Atrial Natriuretic Peptide (ANP)
Secreted by the atria in response to atrial distension
B-type Natriuretic Peptide (BNP)
Secreted by the ventricles in response to distension from volume overload
C-type Natriuretic Peptide (CNP)
Secreted by vascular endothelial cells in response to inflammatory mediators
Sacubitril (Entresto®)
Inhibits neprilysin and blocks ANP, BNP, and CNP metabolism
Neprilysin
Metabolizes ANP, BNP and CNP
ANP
BNP
CNP
ANP and BNP stimulate sodium and fluid excretion
ANP and BNP promote myocardial relaxation and inhibit hypertrophy and fibrosis
ANP and BNP suppress sympathetic outflow
ANP, BNP, and CNP stimulate vasodilation

Entresto


Mechanism of action of LCZ696
Damage
Beneficial physiological response
Pathophysiological response
NPs
NP system
RAAS
Ang II
NEP
Dual NEP/RAAS inhibition (LCZ696)
Inactive fragments
AT1 receptor
Vasodilation
↓ blood pressure
↓ sympathetic tone
↓ aldosterone levels
↓ fibrosis
↓ hypertrophy
Natriuresis/Diuresis
HF symptoms/ progression
Vasoconstriction
↑ blood pressure
↑ sympathetic tone
↑ aldosterone
↑ fibrosis
↑ hypertrophy
Neurohormonal balance

Entresto

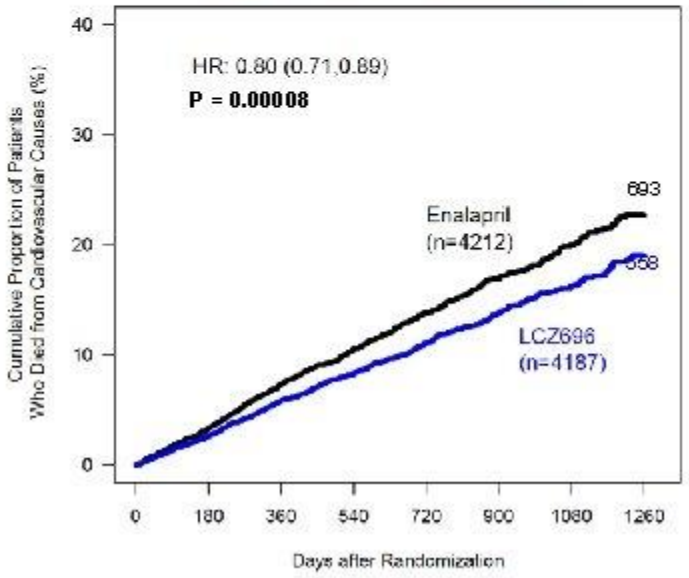

PARADIGMHF
A Comparison of Angiotensin Receptor-Neprilysin Inhibition (ARNI) With ACE Inhibition in the Long-Term Treatment of Chronic Heart Failure With a Reduced Ejection Fraction
Milton Packer, John J.V. McMurray, Akshay S. Desai, Jianjian Gong, Martin P. Lefkowitz, Adel R. Rizkala, Jean L. Rouleau, Victor C. Shi, Scott D. Solomon, Karl Swedberg and Michael R. Zile for the PARADIGM-HF Investigators and Committees

PARADIGM-HF

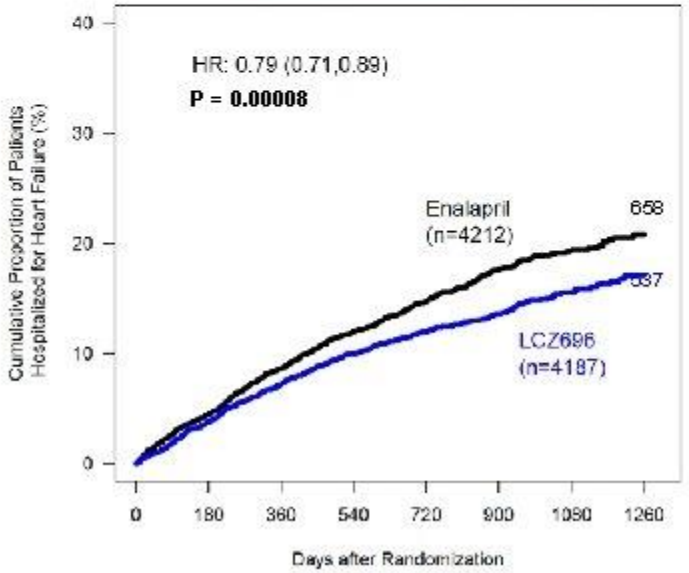
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Primary composite outcome
HR: 0.80 (0.73, 0.87) p = 0.0000004

Death from CV causes
20% risk reduction



HF hospitalization
21% risk reduction



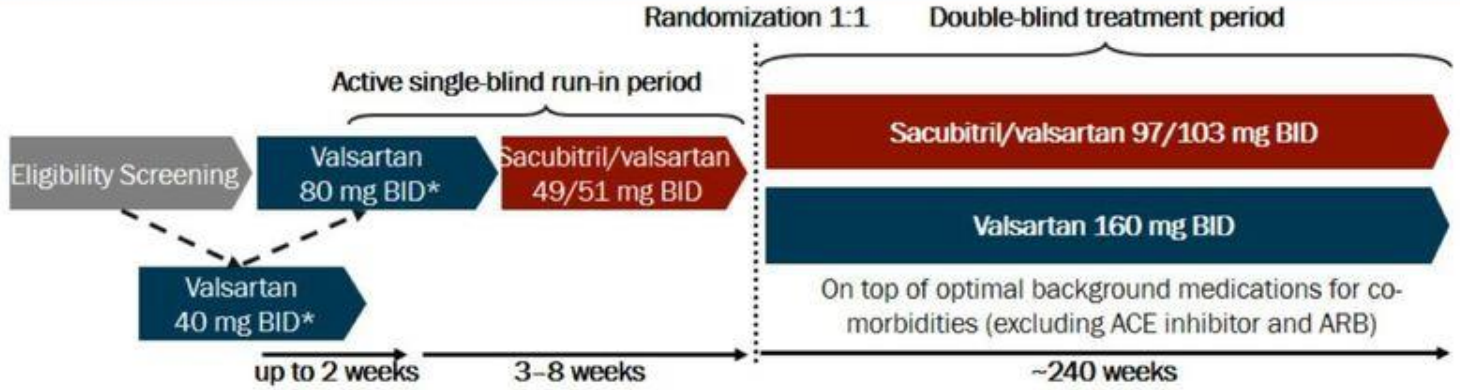
McMurray, Packer et al NEJM 2014

PARAGON-HF

Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction

PARAGON-HF Study Design

Randomized, double-blind, active comparator trial testing the hypothesis that sacubitril/valsartan, compared with valsartan, would reduce the composite outcome of total HF hospitalizations and CV death*



Primary Endpoint
Composite of total (first and recurrent) HF hospitalizations and CV death

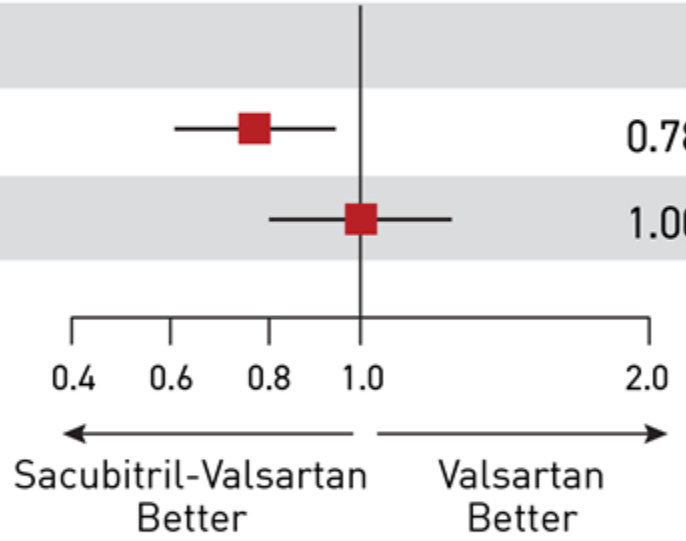
Secondary Endpoints:
- Improvement in NYHA functional classification at 8 months
- Changes in KCCQ clinical summary score at 8 months
- Time to first occurrence of worsening renal failure
- Time to all-cause mortality

* See publication for details.

Solomon SD, *et al. JACC-Heart Fail* 2017; 5:471-482.

PARAGON-HF: Primary Outcome in LVEF Subgroup

Subgroup	No. of Events/ No. of Patients	Rate Ratio (95% CI)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64-0.95)
>Median (57%)	855/2301	1.00 (0.81-1.23)

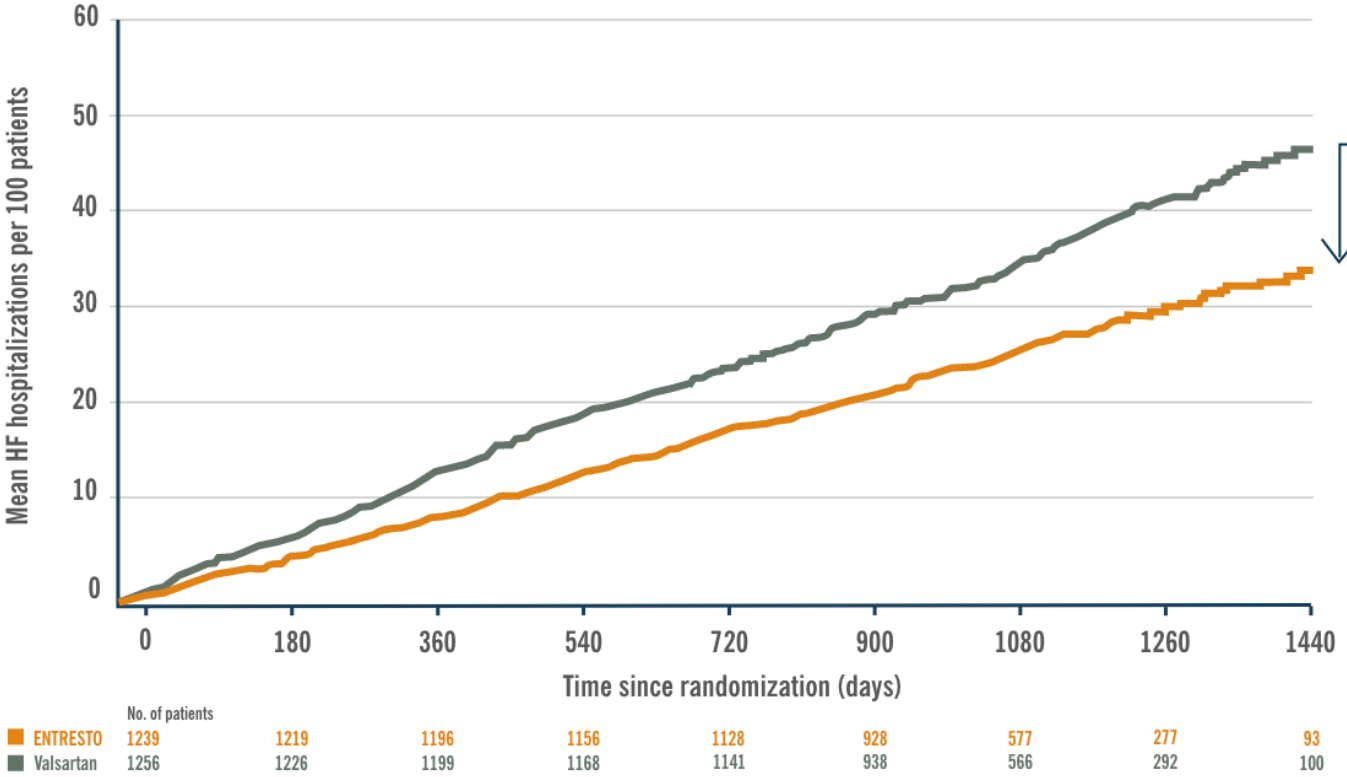


Adapted from Solomon SD et al. As presented during ESC Congress 2019, Abstract 2101.

PARAGON-HF: Secondary Endpoints

	Sacubitril/Valsartan N = 2316	Valsartan N = 2302	Effect size (95% CI)	Nominal *P*-value
NYHA functional classification at 8 months - Change from baseline (%)			OR for improvement 1.45 (1.13, 1.86)	0.004
Improved	15.0%	12.6%		
Unchanged	76.3%	77.9%		
Worsened	8.7%	9.6%		
Worsening Renal Function Composite of renal death, reaching ESRD, or ≥50% decline in eGFR relative to baseline	1.4%	2.7%	HR = 0.50 (0.33, 0.77)	0.002
All-cause mortality (%)	14.2%	14.6%	HR = 0.97 (0.84, 1.13)	0.68

Adapted from Solomon SD et al. As presented during ESC Congress 2019, Abstract 2101.



25% RRR

IN TOTAL HF HOSPITALIZATIONS

RR 0.75 (95% CI: 0.60, 0.95); ARR 3.6¶

CV death: HR 0.99 (95% CI: 0.77, 1.26); ARR 0.1¶

Entresto and BNP

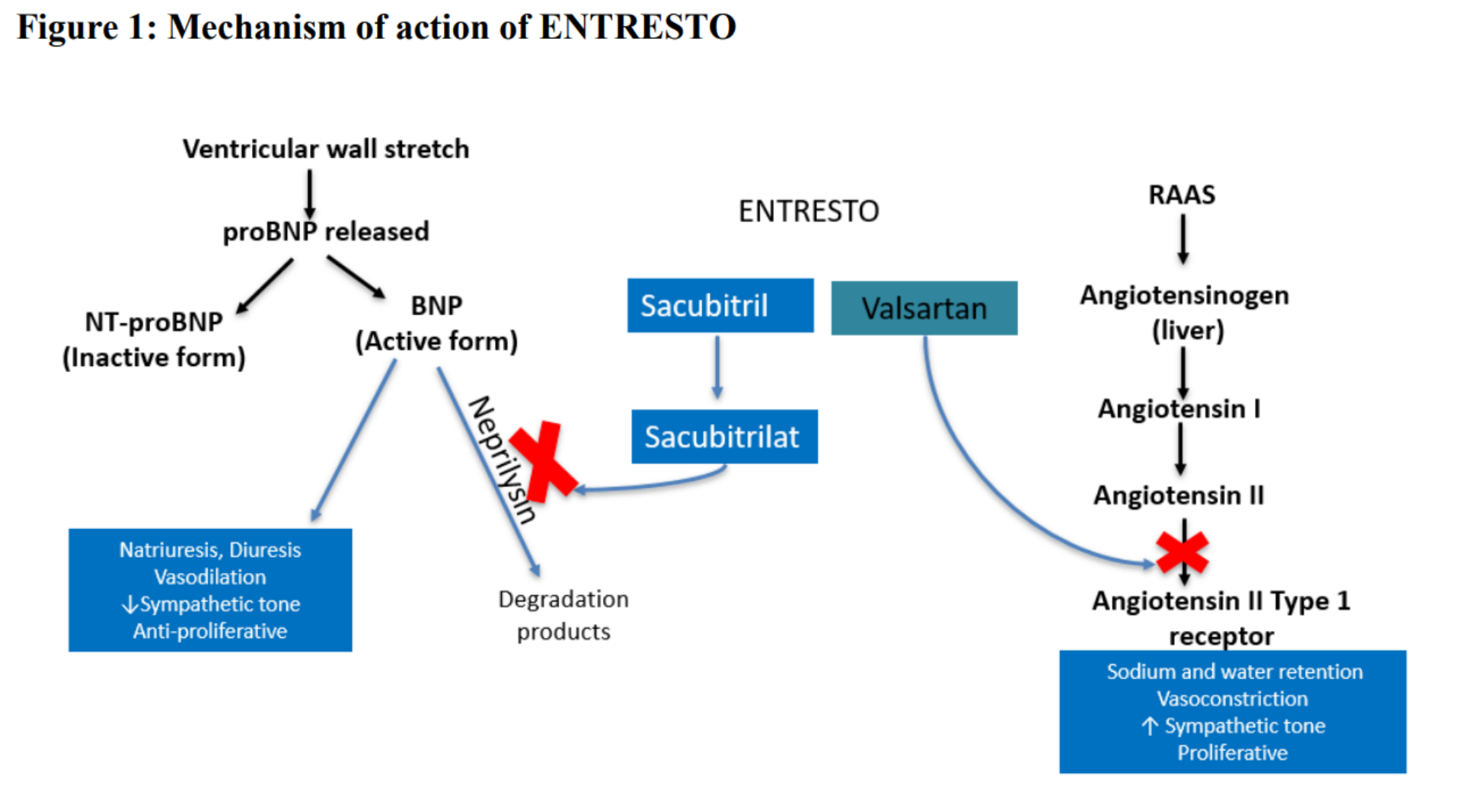


TABLE 3 Dose Adjustments of Sacubitril/Valsartan for Specific Patient Populations

Population	Initial Dose
High-dose ACEI *> Enalapril 10-mg total daily dose or therapeutically equivalent dose of another ACEI*	**49/51 mg twice daily**
High-dose ARB *> Valsartan 160-mg total daily dose or therapeutically equivalent dose of another ARB*	
De novo initiation of ARNI *Low- or medium-dose ACEI* *≤ Enalapril 10-mg total daily dose or therapeutically equivalent dose of another ACEI*	**24/26 mg twice daily**
Low- or medium-dose ARB *≤ Valsartan 160-mg total daily dose or therapeutically equivalent dose of another ARB*	
ACEI/ARB naive	
*Severe renal impairment** *(eGFR <30 mL/min/1.73 m^2)*	
Moderate hepatic impairment (Child-Pugh Class B)	
Elderly (age ≥75 years)	

*This population was not studied in the PARADIGM-HF trial. The statement is consistent with FDA-approved labeling indications.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI= angiotensin receptor-neprilysin inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF.

Corlanor

Blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I f current, which regulates heart rate.

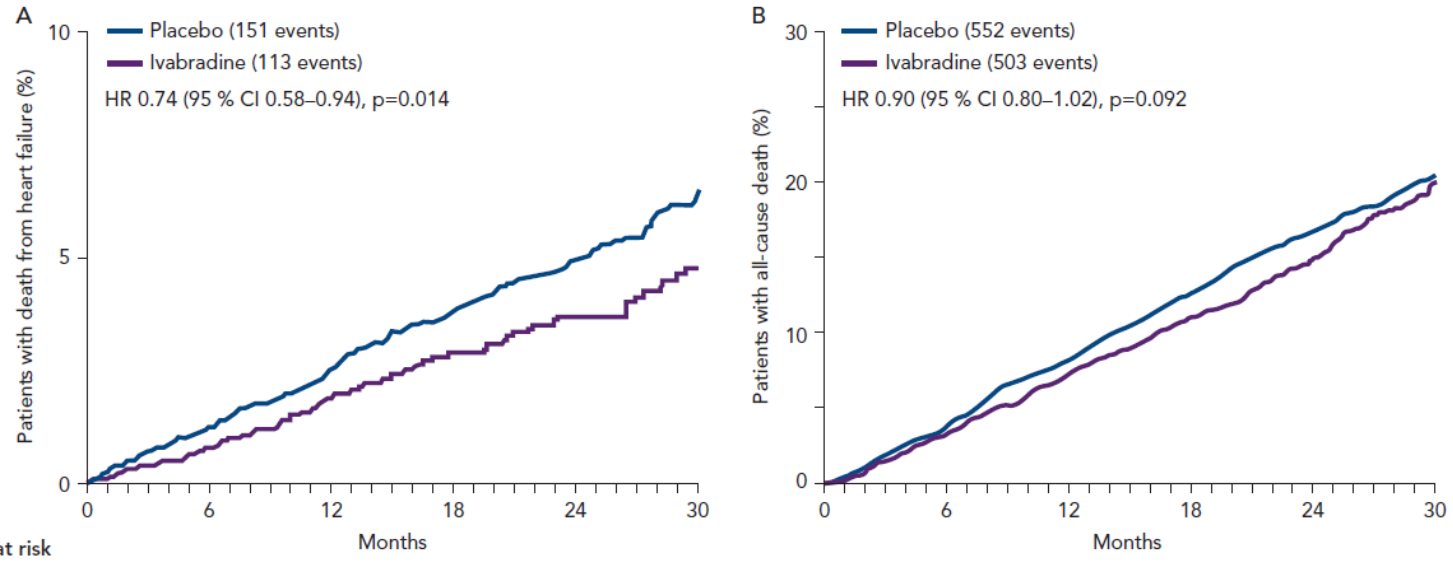
Corlanor

TABLE 5 **Recommended Starting Dose of Ivabradine**

Population	Initial Dose
Maximally tolerated beta-blocker dose with persistent resting heart rate ≥70 beats/min	5 mg twice daily with meals
History of conduction defects Age ≥75 years	2.5 mg twice daily with meals

Ivabradine (SHIFT Trial)

Figure 2: Kaplan–Meier cumulative event curves for death from heart failure (A) and all-cause death in the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine (SHIFT) trial (B). HR = hazard ratio. Source: Swedberg, et al., 2010.[14] Reprinted with permission from Elsevier.



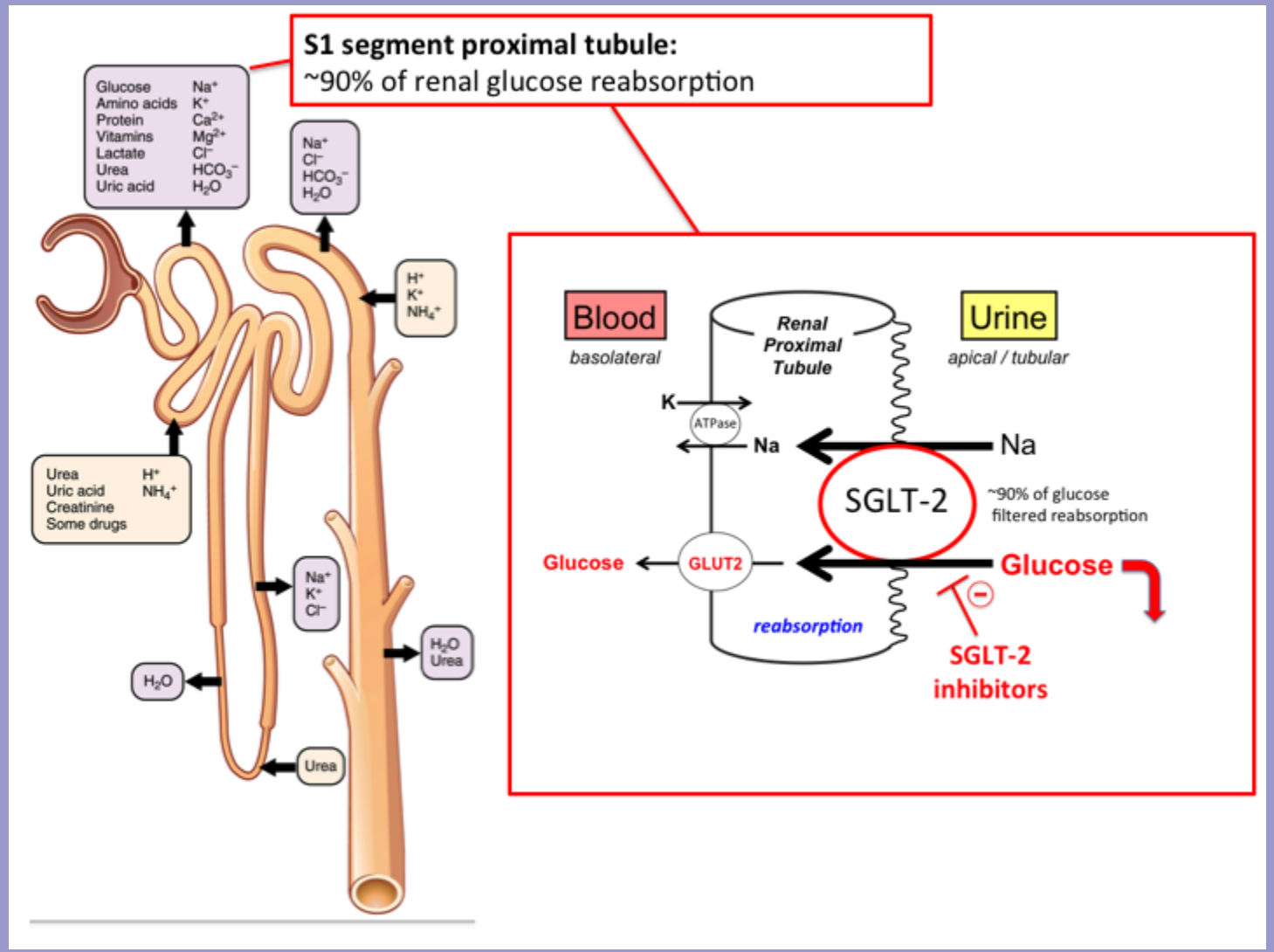
Number at risk						
Placebo group	3264	3094	2817	2391	1318	534
Ivabradine group	3241	3085	2818	2428	1376	531

3264	3094	2817	2391	1318	534
3241	3085	2818	2428	1376	531

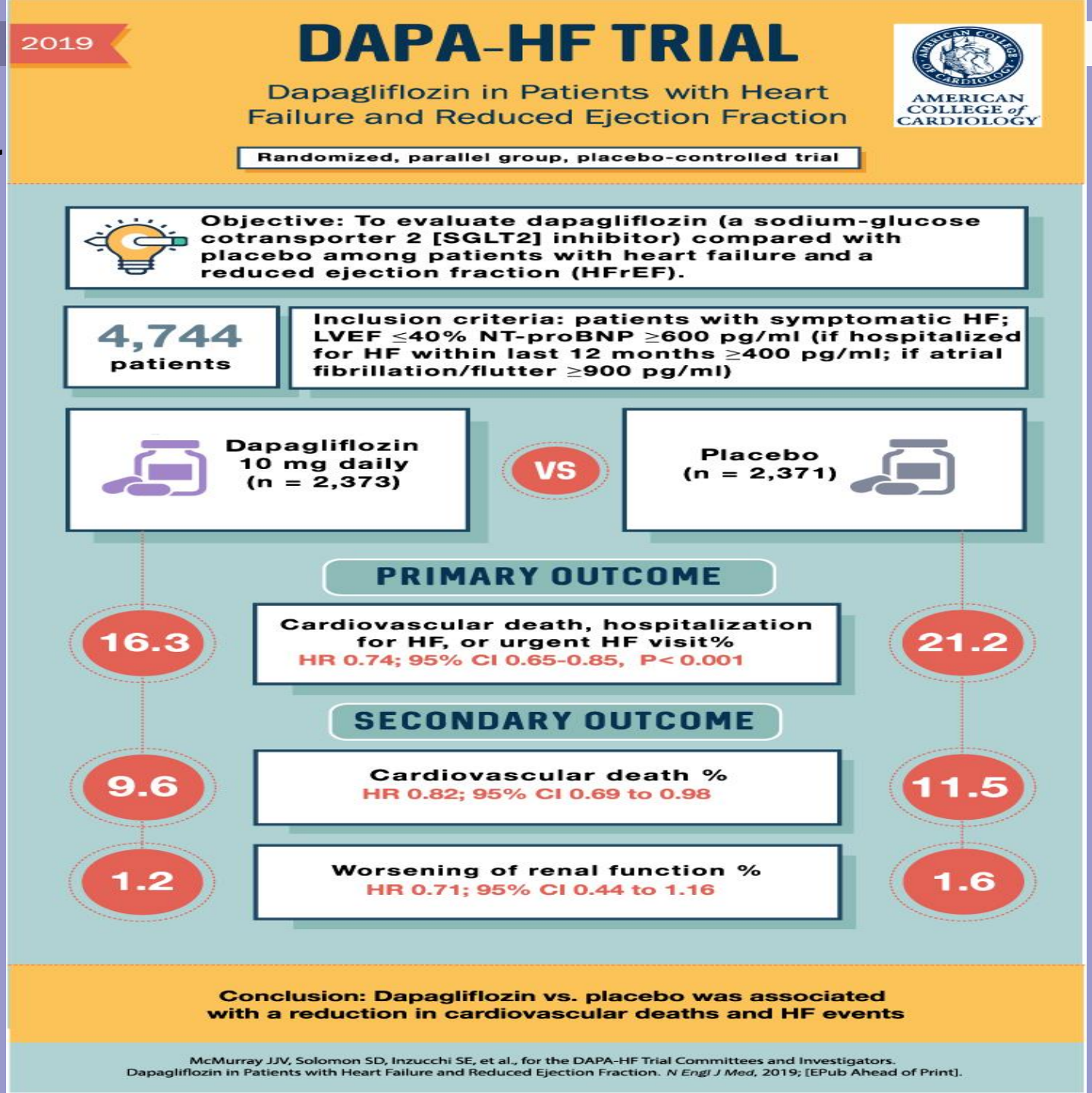
HR = hazard ratio. Source: Swedberg, et al., 2010.[14] Reprinted with permission from Elsevier

Farxiga(Dapagliflozin), Jardiance(Empagliflozin)

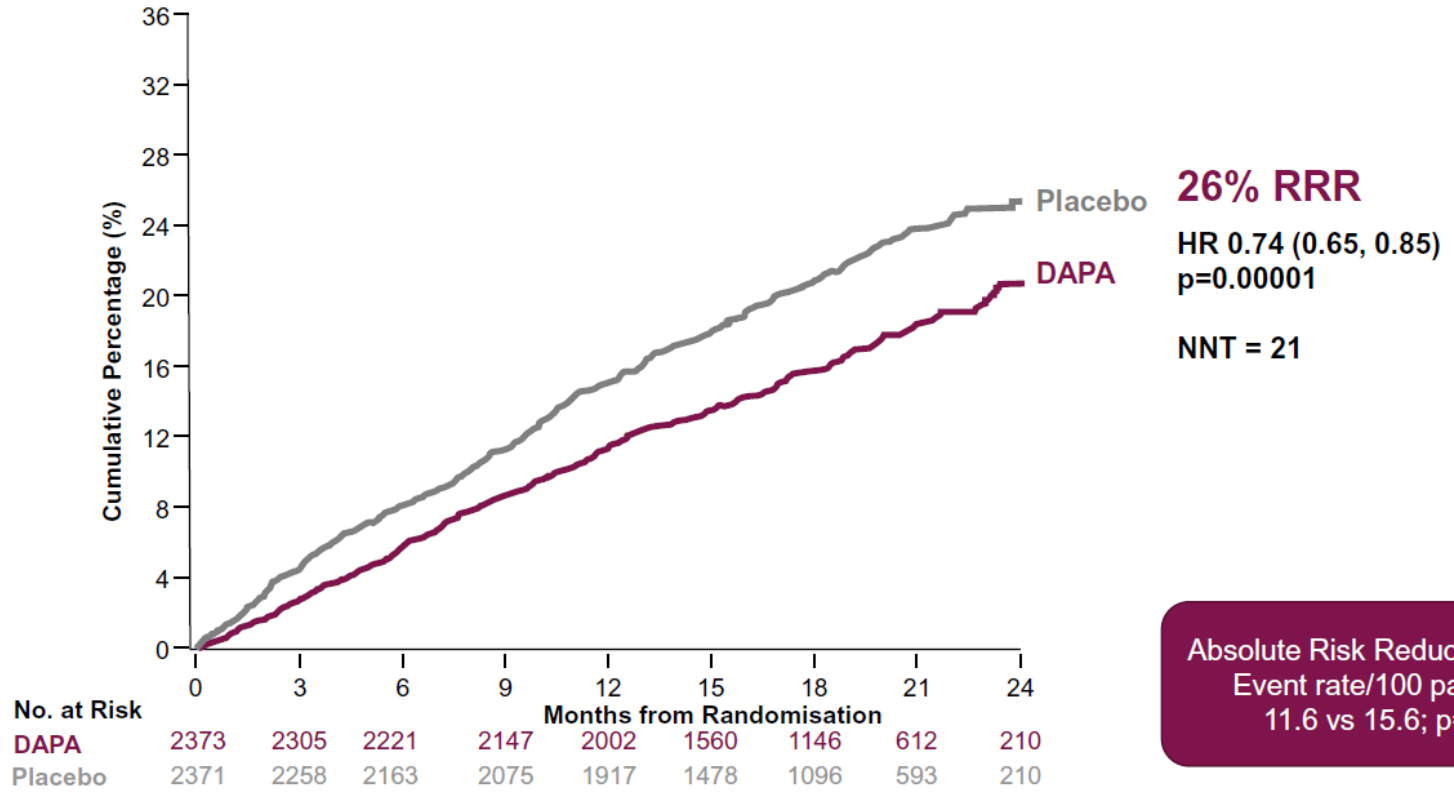
- SGLT2 inhibitors inhibit the coupled reabsorption of sodium and glucose from the proximal tubules, thereby increasing renal glucose and sodium excretion


S1 segment proximal tubule:
~90% of renal glucose reabsorption
Glucose
Amino acids
Protein
Vitamins
Lactate
Urea
Uric acid
Na+
K+
Ca2+
Mg2+
Cl−
HCO3−
H2O
Na+ Cl− HCO3− H2O
H+ K+ NH4+
Urea Uric acid Creatinine Some drugs
H+ NH4+
Na+ K+ Cl−
H2O Urea
H2O
Urea
Blood
basolateral
Renal Proximal Tubule
Urine
apical / tubular
K
ATPase
Na
Na
SGLT-2
~90% of glucose filtered reabsorption
Glucose
GLUT2
Glucose
reabsorption
SGLT-2 inhibitors

Farxiga


2019
DAPA-HF TRIAL
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction
Randomized, parallel group, placebo-controlled trial
AMERICAN COLLEGE of CARDIOLOGY
Objective: To evaluate dapagliflozin (a sodium-glucose cotransporter 2 [SGLT2] inhibitor) compared with placebo among patients with heart failure and a reduced ejection fraction (HFrEF).
4,744 patients
Inclusion criteria: patients with symptomatic HF; LVEF ≤40% NT-proBNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/ml; if atrial fibrillation/flutter ≥900 pg/ml)
Dapagliflozin 10 mg daily (n = 2,373)
VS
Placebo (n = 2,371)
PRIMARY OUTCOME
16.3
Cardiovascular death, hospitalization for HF, or urgent HF visit%
HR 0.74; 95% CI 0.65-0.85, P< 0.001
21.2
SECONDARY OUTCOME
9.6
Cardiovascular death %
HR 0.82; 95% CI 0.69 to 0.98
11.5
1.2
Worsening of renal function %
HR 0.71; 95% CI 0.44 to 1.16
1.6
Conclusion: Dapagliflozin vs. placebo was associated with a reduction in cardiovascular deaths and HF events
McMurray JJV, Solomon SD, Inzucchi SE, et al., for the DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med, 2019; [EPub Ahead of Print].

Primary Endpoint: CV Death or hHF or an Urgent HF Visit



26% RRR

HR 0.74 (0.65, 0.85)
p=0.00001

NNT = 21

Absolute Risk Reduction [ARR]=4%
Event rate/100 patient years:
11.6 vs 15.6; p=0.00001

DAPA = dapagliflozin; HF = heart failure; hHF = hospitalisation for heart failure; HR = hazard ratio; NNT = number needed to treat.

Jardiance

EMPEROR-Reduced Trial

Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

Milton Packer MD and Faiez Zannad MD, on behalf of the EMPEROR-Reduced Executive Committee, Trial Committees, Investigators and Coordinators

Baylor University Medical Center, Dallas TX, Imperial College, London UK
Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France

Disclosures for presenter: Abbvie, Actavis, Akcea, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Eli LillyJohnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance

2020

EMPEROR-REDUCED

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

AMERICAN COLLEGE of CARDIOLOGY

Double-blind, parallel-group, placebo-controlled trial

Objective: To evaluate the use of empagliflozin in patients with chronic heart failure and a reduced ejection fraction with or without diabetes.

3730 patients

Inclusion criteria: Adults (≥18 years of age) with or without diabetes who had chronic heart failure (functional class II, III, or IV) with a left ventricular ejection fraction of 40% or less on excellent baseline GDMT.

empagliflozin (N=1863)	vs	placebo (N=1867)

PRIMARY OUTCOME

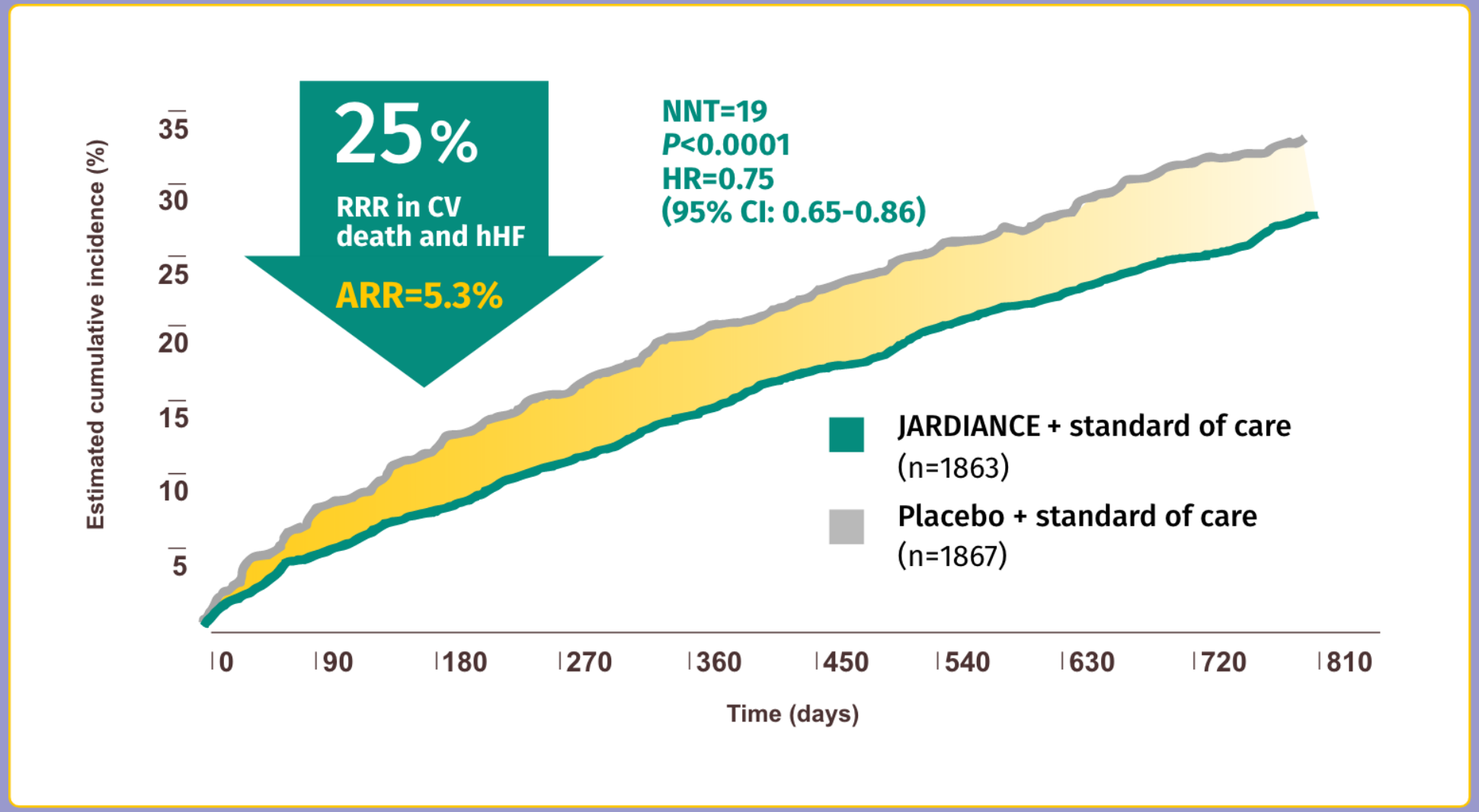
empagliflozin		placebo
19.4	Cardiovascular death or hospitalization for heart failure % HR 0.75; 95% CI, 0.65 to 0.86; P<0.001	24.7

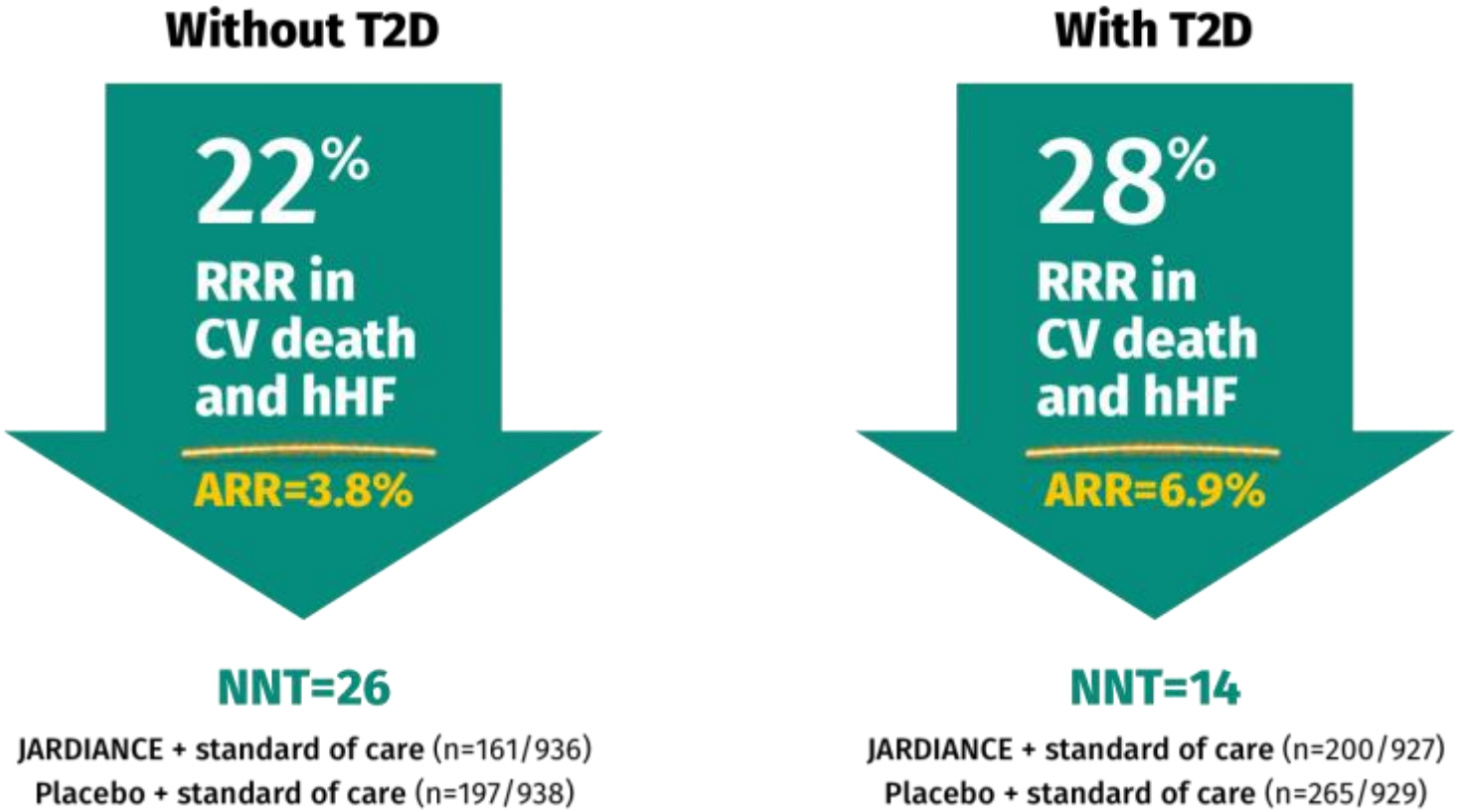
SECONDARY OUTCOME

empagliflozin		placebo
388	Total no. of hospitalizations for heart failure (N) HR 0.70; 95% CI, 0.58 to 0.85; P<0.001	553
-0.55	Mean change in eGFR per year HR 1.73 ; 95% CI, 1.10 to 2.37; P<0.001	-2.28

Conclusion: Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes.

Packer M, Anker SD, Butler J, et al., for the EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020;Aug 29:[Epub ahead of print].


25%
RRR in CV death and hHF
ARR=5.3%
NNT=19
P<0.0001
HR=0.75
(95% CI: 0.65-0.86)
Estimated cumulative incidence (%)
35
30
25
20
15
10
5
JARDIANCE + standard of care
(n=1863)
Placebo + standard of care
(n=1867)
0
90
180
270
360
450
540
630
720
810
Time (days)


Without T2D
22%
RRR in CV death and hHF
ARR=3.8%
NNT=26
JARDIANCE + standard of care (n=161/936)
Placebo + standard of care (n=197/938)
With T2D
28%
RRR in CV death and hHF
ARR=6.9%
NNT=14
JARDIANCE + standard of care (n=200/927)
Placebo + standard of care (n=265/929)

EMPEROR-PRESERVED

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Anker et al, Aug 27, 2021. NEJM.

QUESTION

In patients with heart failure and a preserved ejection fraction, does Empagliflozin improve outcomes?

INCLUDED

- 18 and older
- NYHA II-IV
- LVEF > 40%
- ntProBNP>300; or>900 if AFib
- Evidence of LAE or LVH
- Stable diuretic use
- BMI <45 kg/m2

5988 PATIENTS

EMPAGLIFLOZIN 10MG
(SGLT-2 INHIBITOR)

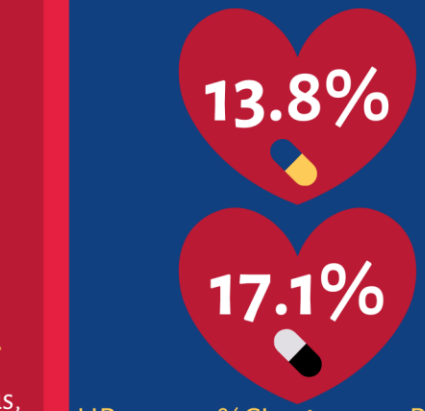
VS

PLACEBO

Stratified by region, diabetes status, eGFR of 50, and LVEF 50%

PRIMARY OUTCOME

CV Death*
HF Hospitalization



HR 0.79; 95%CI 0.69-0.90; P<0.001

*Mostly driven by HF hospitalizations

SECONDARY OUTCOMES

HF Hospitalization

↓ WITH EMPAGLIFLOZIN

HR 0.73; 95% CI, 0.61-0.88; P<0.001

Rate of GFR decline

E -1.25 vs. -2.62 P

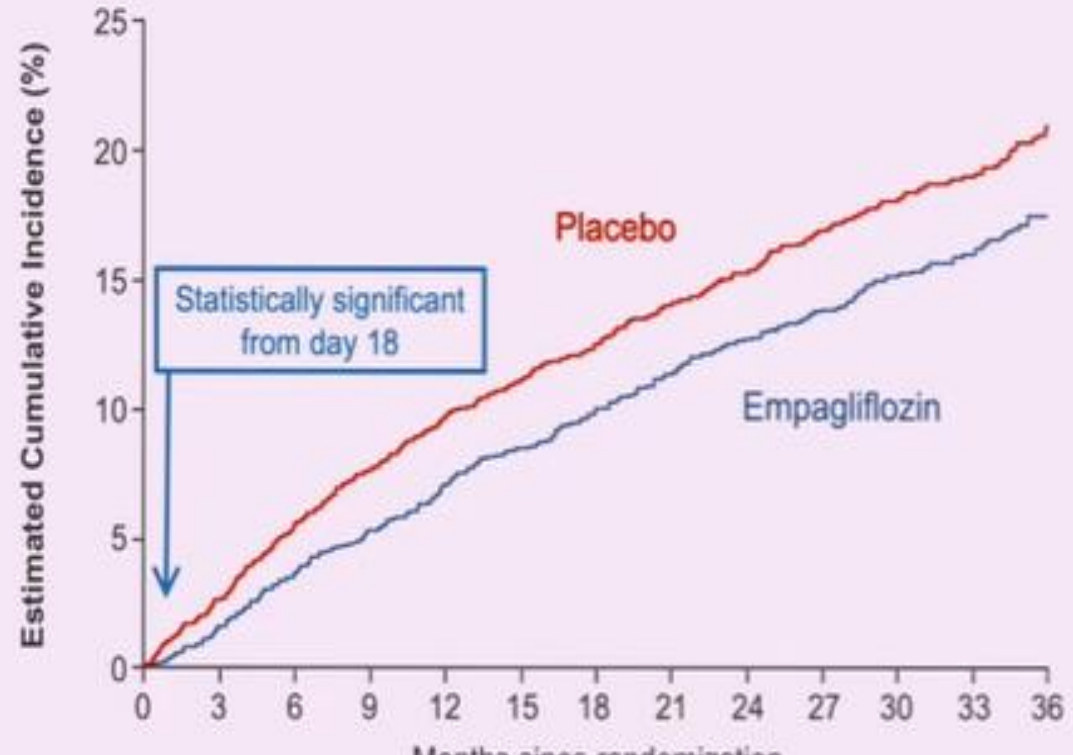
ml/min/1.73m2/year; P<0.001

CONCLUSION

Empagliflozin reduced the combined risk of cardiovascular death or heart failure hospitalization in patients with heart failure with preserved ejection fraction, regardless of the presence or absence of diabetes.

@IsaMathiasMD

Primary Endpoint – Composite of Cardiovascular Death or Heart Failure Hospitalization



Patients at risk

Placebo	2991	2786	2627	2066	1534	961	400
Empagliflozin	2997	2843	2708	2134	1578	1005	402

HR 0.79
(95% CI 0.69, 0.90)
P = 0.0003

Placebo:
511 patients with event
Rate: 8.7 per 100 patient-years

Empagliflozin:
415 patients with event
Rate: 6.9 per 100 patient-years

RRR 21%

NNT=31
During a median trial period of 26 months.

TABLE 2 Indications for ARNI, Ivabradine, and SGLT2 Inhibitor Use

Indications for Use of an ARNI

- HFrEF (EF ≤40%)
- NYHA class II-IV HF
- Administered in conjunction with a background of GDMT for HF in place of an ACEI or ARB

Indications for Use of Ivabradine

- HFrEF (EF ≤35%)
- On maximum tolerated dose of beta-blocker
- Sinus rhythm with a resting heart rate ≥70 beats/min
- NYHA class II or III HF

Indications for Use of an SGLT2 Inhibitor

- HFrEF (EF ≤40%) with or without diabetes
- NYHA class II-IV HF
- Administered in conjunction with a background of GDMT for HF

ACEI = angiotensin-converting-enzyme inhibitor; ARB= angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

TABLE 4 Contraindications and Cautions for Sacubitril/Valsartan, Ivabradine, and SGLT2 inhibitors

A) Sacubitril/Valsartan

Contraindications	Cautions
■ Within 36 hours of ACEI use ■ History of angioedema with or without an ACEI or ARB ■ Pregnancy ■ Lactation (no data) ■ Severe hepatic impairment (Child-Pugh C) ■ Concomitant aliskiren use in patients with diabetes ■ Known hypersensitivity to either ARBs or ARNIs	■ Renal impairment: – Mild-to-moderate (eGFR 30-59 mL/ min/1.73 m^2): no starting dose adjustment required – Severe* (eGFR <30 mL/min/ 1.73 m^2): reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated ■ Hepatic impairment: – Mild (Child-Pugh A): no starting dose adjustment required – Moderate (Child-Pugh B): reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated ■ Renal artery stenosis ■ Systolic blood pressure <100 mm Hg ■ Volume depletion

B) Ivabradine

Contraindications	Cautions
■ HFpEF ■ Presence of angina with normal EF ■ Hypersensitivity ■ Severe hepatic impairment (Child-Pugh C) ■ Acute decompensated HF ■ Blood pressure <90/50 mm Hg ■ Sick sinus syndrome without a pacemaker ■ Sinoatrial node block ■ 2nd or 3rd degree block without a pacemaker ■ Resting heart rate <60 beats/min ■ Persistent AF or flutter ■ Atrial pacemaker dependence	■ Sinus node disease ■ Cardiac conduction defects ■ Prolonged QT interval

C) SGLT2 Inhibitors

Contraindications	Cautions
■ Not approved for use in patients with type I diabetes due to increased risk of diabetic ketoacidosis ■ Known hypersensitivity to drug ■ Lactation (no data) ■ On dialysis	■ For HF care, dapagliflozin, eGFR <30 mL/min/1.73 m^2 ■ For HF care, empagliflozin, eGFR <20 mL/min/1.73 m^2 ■ Pregnancy ■ Increased risk of mycotic genital infections ■ May contribute to volume depletion. Consider altering diuretic dose if applicable ■ Ketoacidosis in patients with diabetes: ■ Temporary discontinuation before scheduled surgery is recommended to avoid potential risk for ketoacidosis ■ Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level ■ Acute kidney injury and impairment in renal function: consider temporarily discontinuing in settings of reduced oral intake or fluid losses ■ Urosepsis and pyelonephritis: evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated ■ Necrotizing fasciitis of the perineum (Fournier's gangrene): rare, serious, life-threatening cases have occurred in both female and male patients; assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise

*This population was not studied in PARADIGM-HF. The statement is consistent with FDA-approved labeling indications.

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FDA = Food and Drug Administration; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF; SGLT2 = sodium-glucose cotransporter-2.

Verquvo

- Verquvo is a soluble guanylate cyclase (sGC) stimulator that independently and synergistically with NO, vericiguat **increases intracellular cGMP levels**, causing smooth muscle relaxation and vasodilation.

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Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

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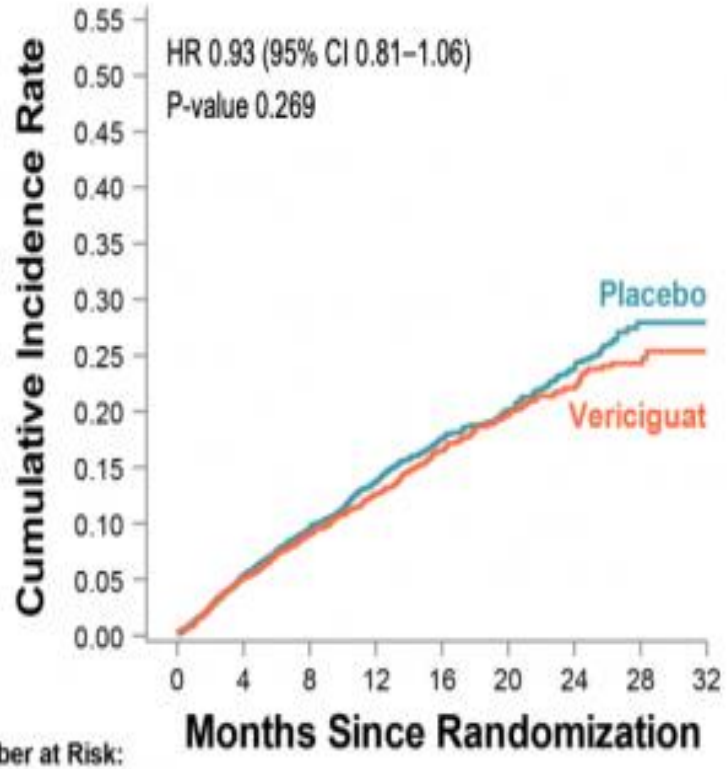
Table 1 VICTORIA trial inclusion criteria

Inclusion criteria
• Ejection fraction <45% assessed within 12 months prior to randomization
• Elevated natriuretic peptide levels within 30 days prior to randomization; for patients in sinus rhythm BNP ≥300 pg/mL and NT-proBNP ≥1000 pg/mL; for those in atrial fibrillation BNP ≥500 pg/mL and NT-proBNP ≥1600 pg/mL[a]
• Prior HF hospitalization within 6 months (those >3 months limited to 20%) or outpatient IV diuretic therapy for HF within 3 months prior to randomization

BNP, B-type natriuretic peptide; HF, heart failure; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[a]For those subjects receiving sacubitril/valsartan, NT-proBNP criteria will be applied.

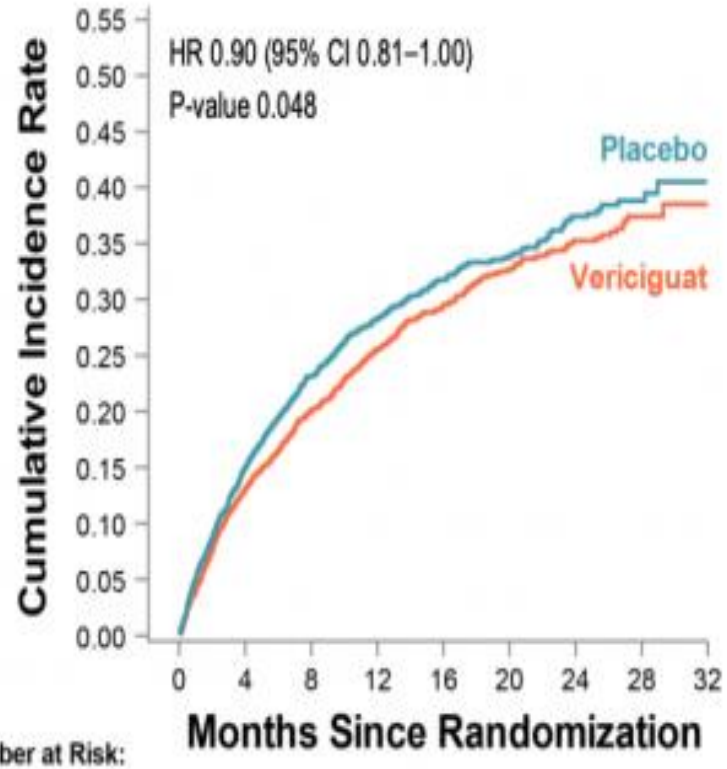
Cardiovascular Death



Number at Risk:

Vericiguat	2526	2376	1968	1468	1070	779	467	165	1
Placebo	2524	2370	1951	1439	1045	768	471	157	0

HF Hospitalization



Number at Risk:

Vericiguat	2526	2098	1620	1153	825	577	346	125	1
Placebo	2524	2052	1554	1096	771	558	323	110	0

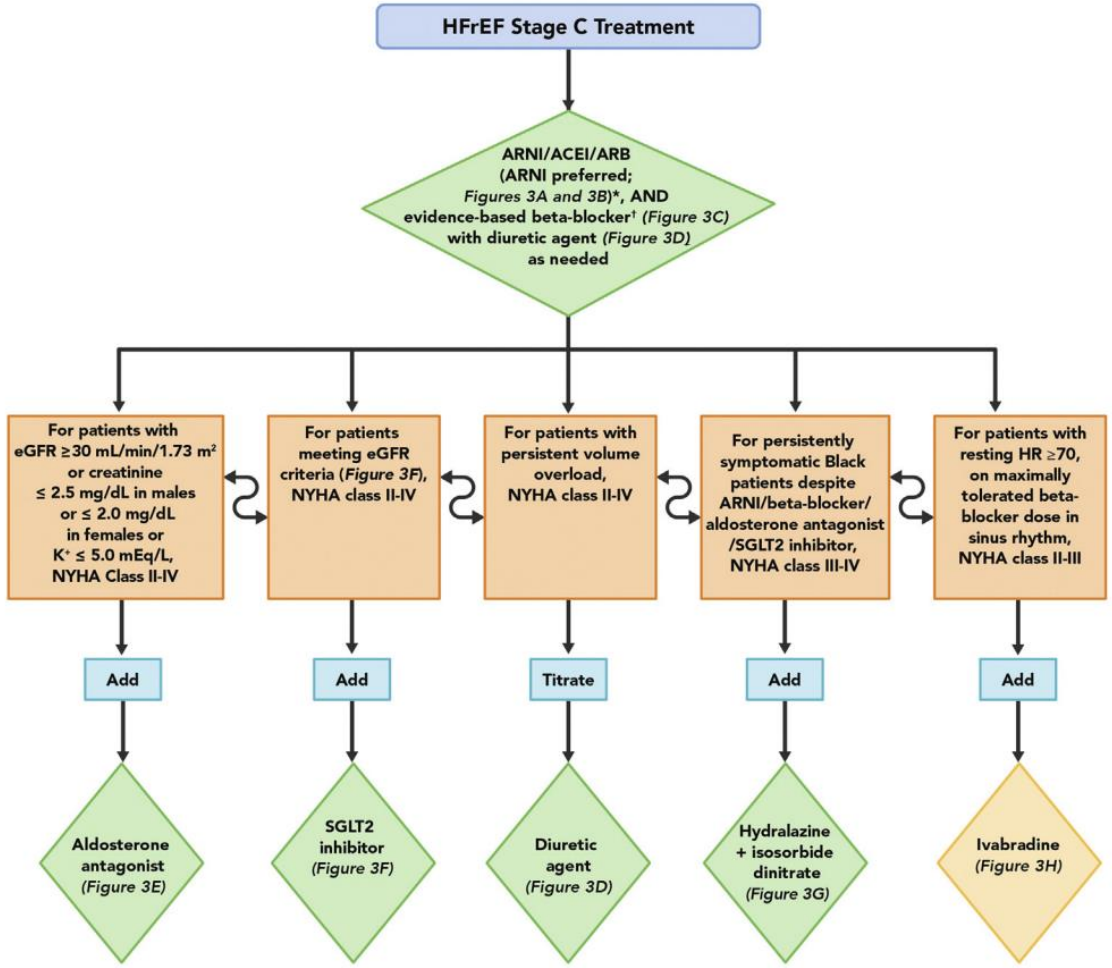
Canadian VIGOUR Centre
Bridging Hearts and Minds

Duke Clinical Research Institute

TABLE 1 Starting and Target Doses of Select GDMT and Novel Therapies for HF (choice and timing of each therapy and in whom they should be added discussed in the text)*

	Starting Dose	Target Dose
Beta-Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5–25 mg daily	200 mg daily
ARNIs		
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily
ACEIs		
Captopril	6.25 mg 3× daily	50 mg 3× daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5 mg daily	20–40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARBs		
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5–25 mg daily	25–50 mg daily
SGLT2 inhibitors		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily
Vasodilators		
Hydralazine	25 mg 3× daily	75 mg 3× daily
Isosorbide dinitrate†	20 mg 3× daily	40 mg 3× daily
Fixed-dose combination isosorbide dinitrate/hydralazine‡	20 mg/37.5 mg (1 tab) 3× daily	2 tabs 3× daily
Ivabradine		
Ivabradine	2.5–5 mg twice daily	Titrate to heart rate 50–60 beats/min. Maximum dose 7.5 mg twice daily

FIGURE 2 Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies



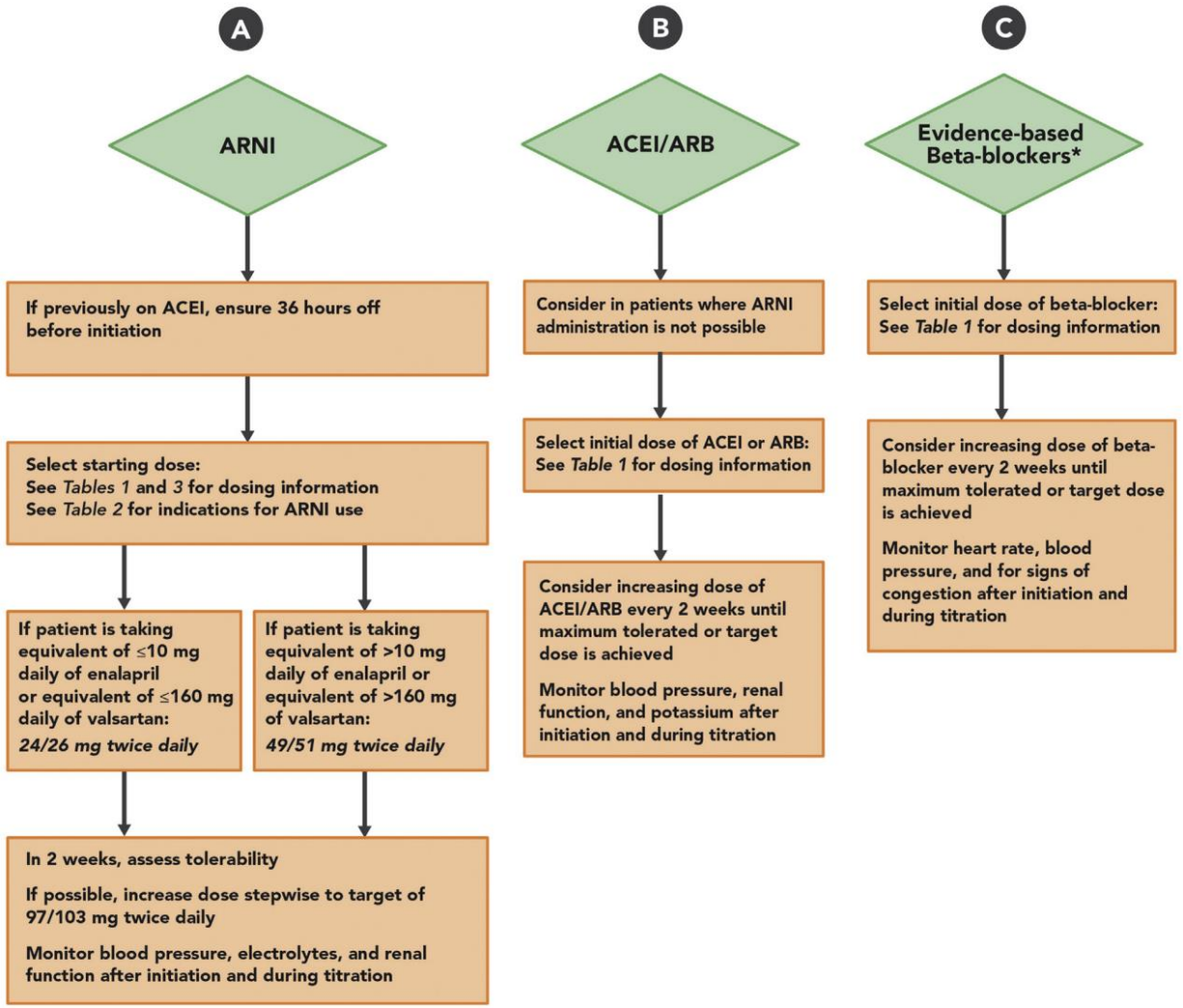
*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.

†Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K^+ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Green color identifies a Class I therapy from clinical practice guidelines, whereas yellow color indicates a Class II therapy.

FIGURE 3 Guideline-Directed Medical Therapy Including Novel Therapies in the Expert Consensus Decision Pathway for Chronic Heart Failure

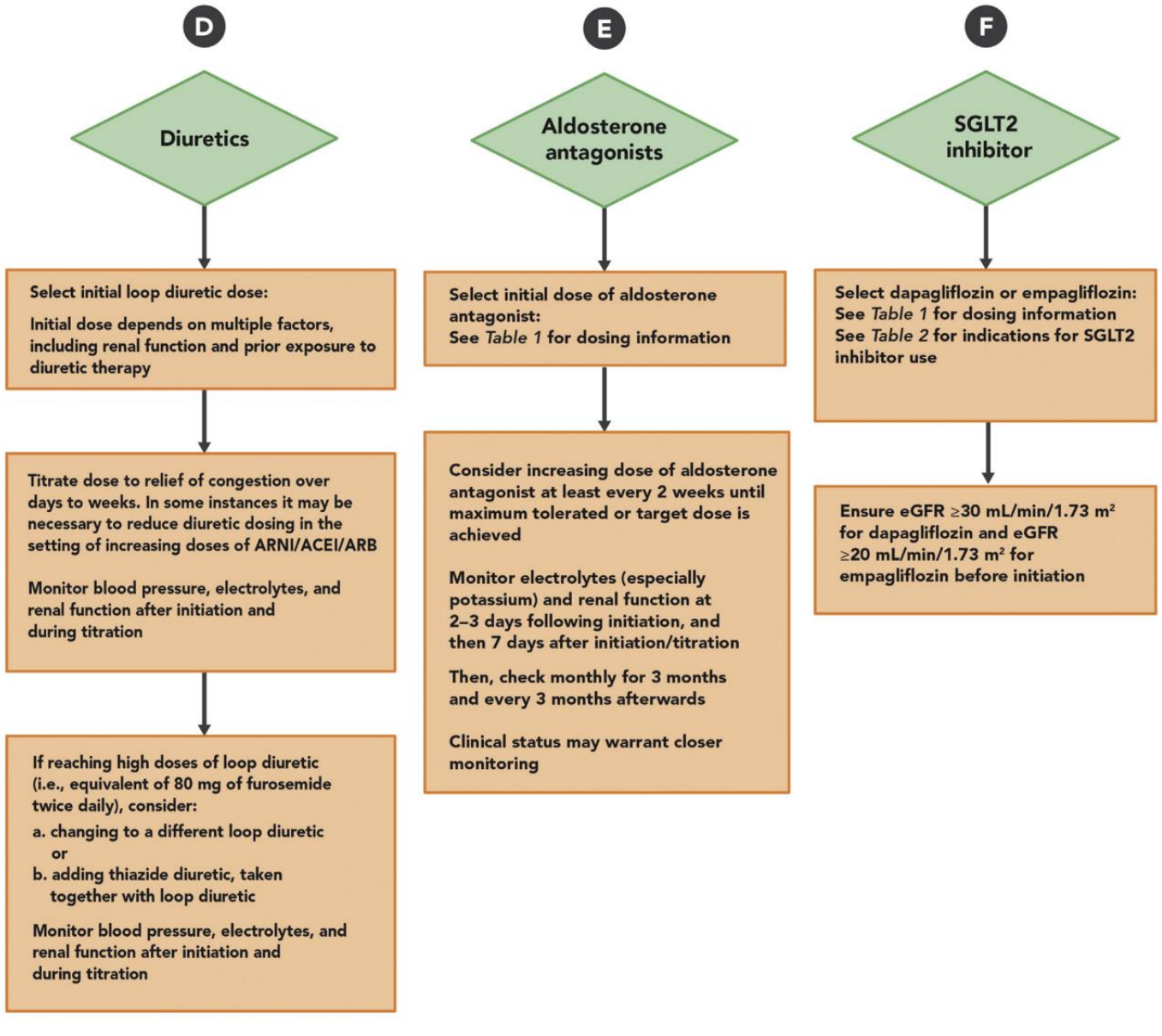


ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate.

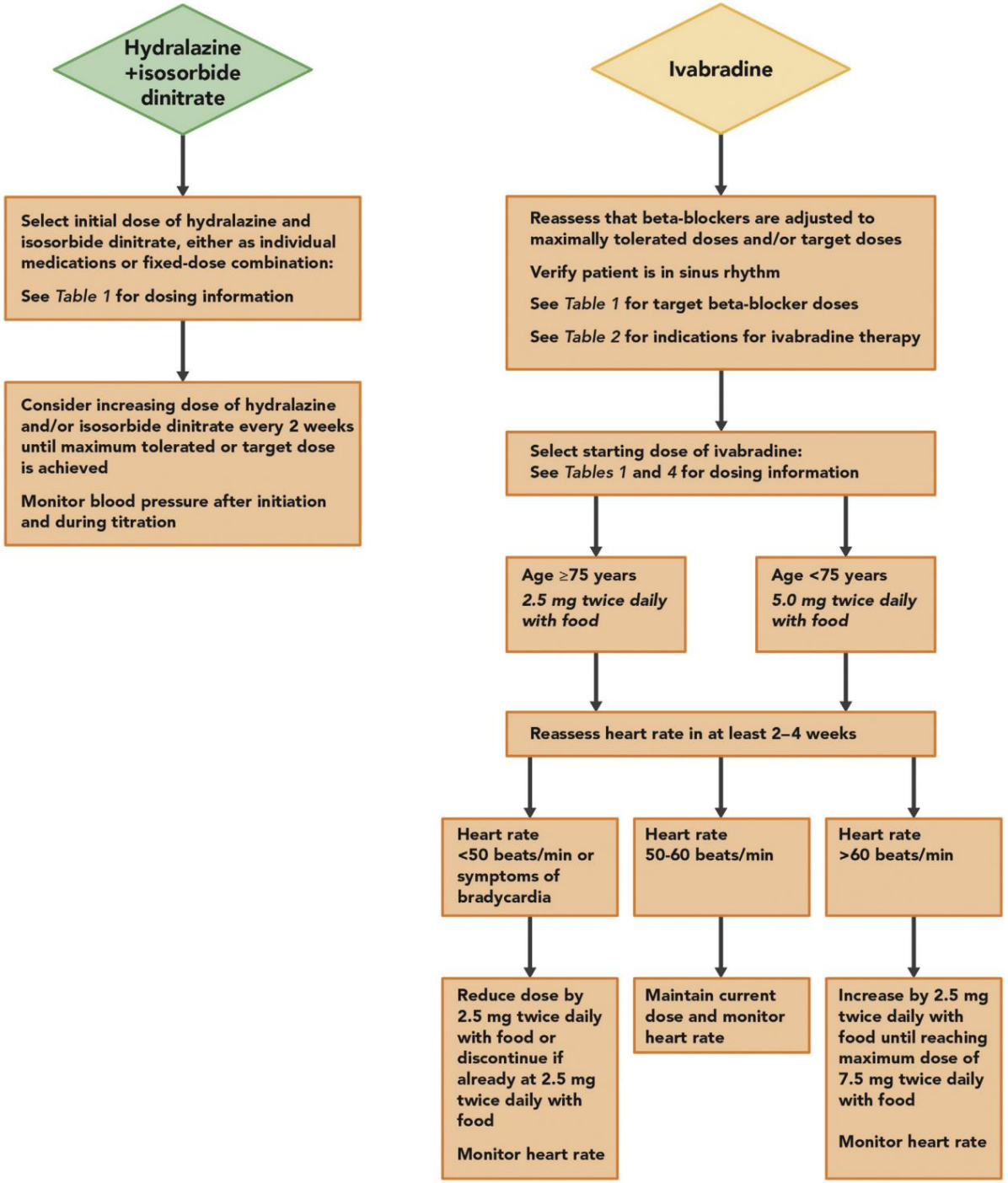
*Carvedilol, metoprolol succinate, or bisoprolol.

ARNIs are the preferred agents, but for patients in whom ARNI administration is not possible, an ACEI/ARB is recommended.

FIGURE 3 Continued



ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; SGLT2 = sodium-glucose cotransporter-2.

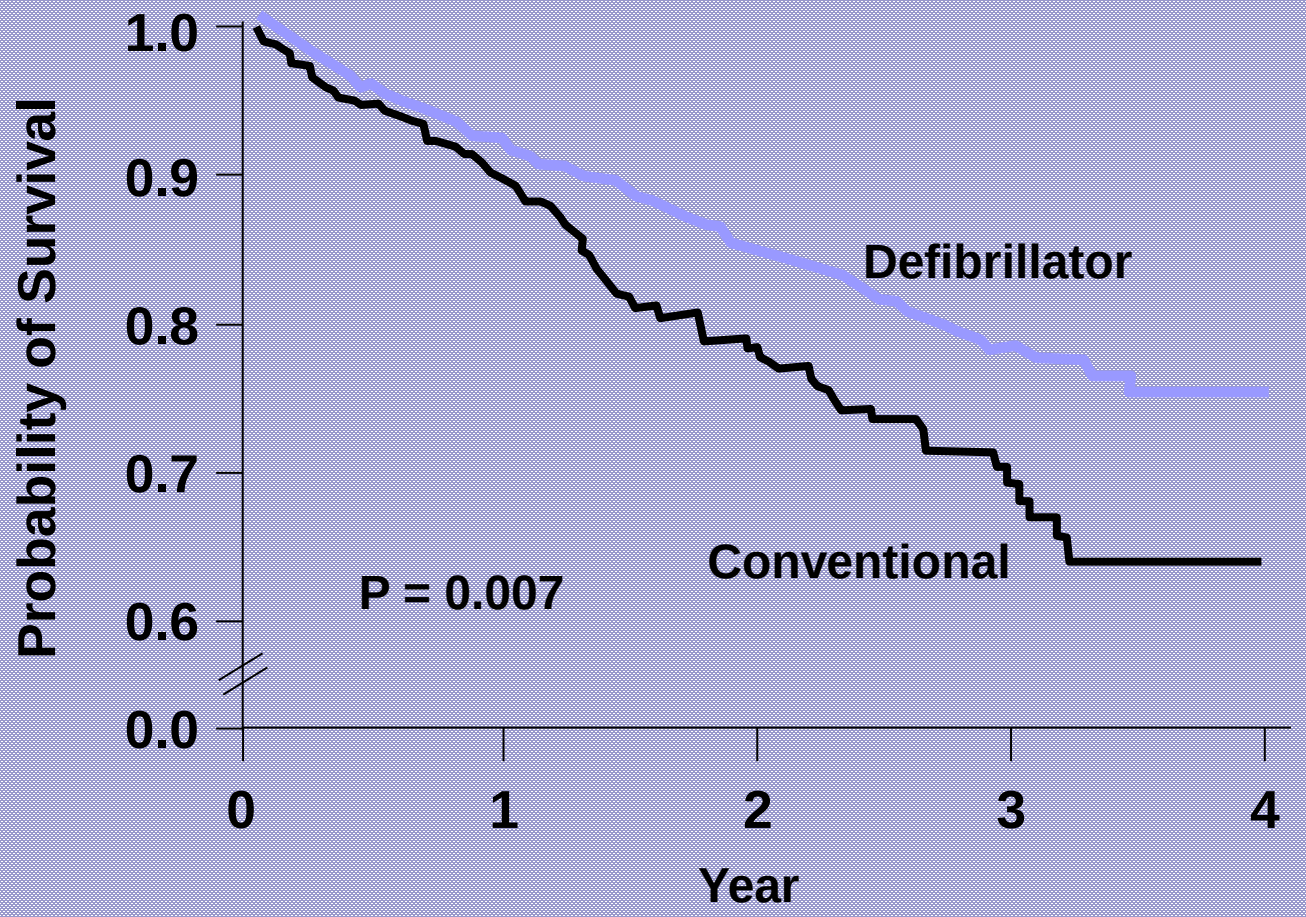

Hydralazine +isosorbide dinitrate
Select initial dose of hydralazine and isosorbide dinitrate, either as individual medications or fixed-dose combination:
See Table 1 for dosing information
Consider increasing dose of hydralazine and/or isosorbide dinitrate every 2 weeks until maximum tolerated or target dose is achieved
Monitor blood pressure after initiation and during titration
Ivabradine
Reassess that beta-blockers are adjusted to maximally tolerated doses and/or target doses
Verify patient is in sinus rhythm
See Table 1 for target beta-blocker doses
See Table 2 for indications for ivabradine therapy
Select starting dose of ivabradine:
See Tables 1 and 4 for dosing information
Age ≥75 years
2.5 mg twice daily with food
Age <75 years
5.0 mg twice daily with food
Reassess heart rate in at least 2–4 weeks
Heart rate <50 beats/min or symptoms of bradycardia
Heart rate 50-60 beats/min
Heart rate >60 beats/min
Reduce dose by 2.5 mg twice daily with food or discontinue if already at 2.5 mg twice daily with food
Monitor heart rate
Maintain current dose and monitor heart rate
Increase by 2.5 mg twice daily with food until reaching maximum dose of 7.5 mg twice daily with food
Monitor heart rate

Management – Nonpharmacologic therapy

- ICD/CRT-D therapy.

MADIT II

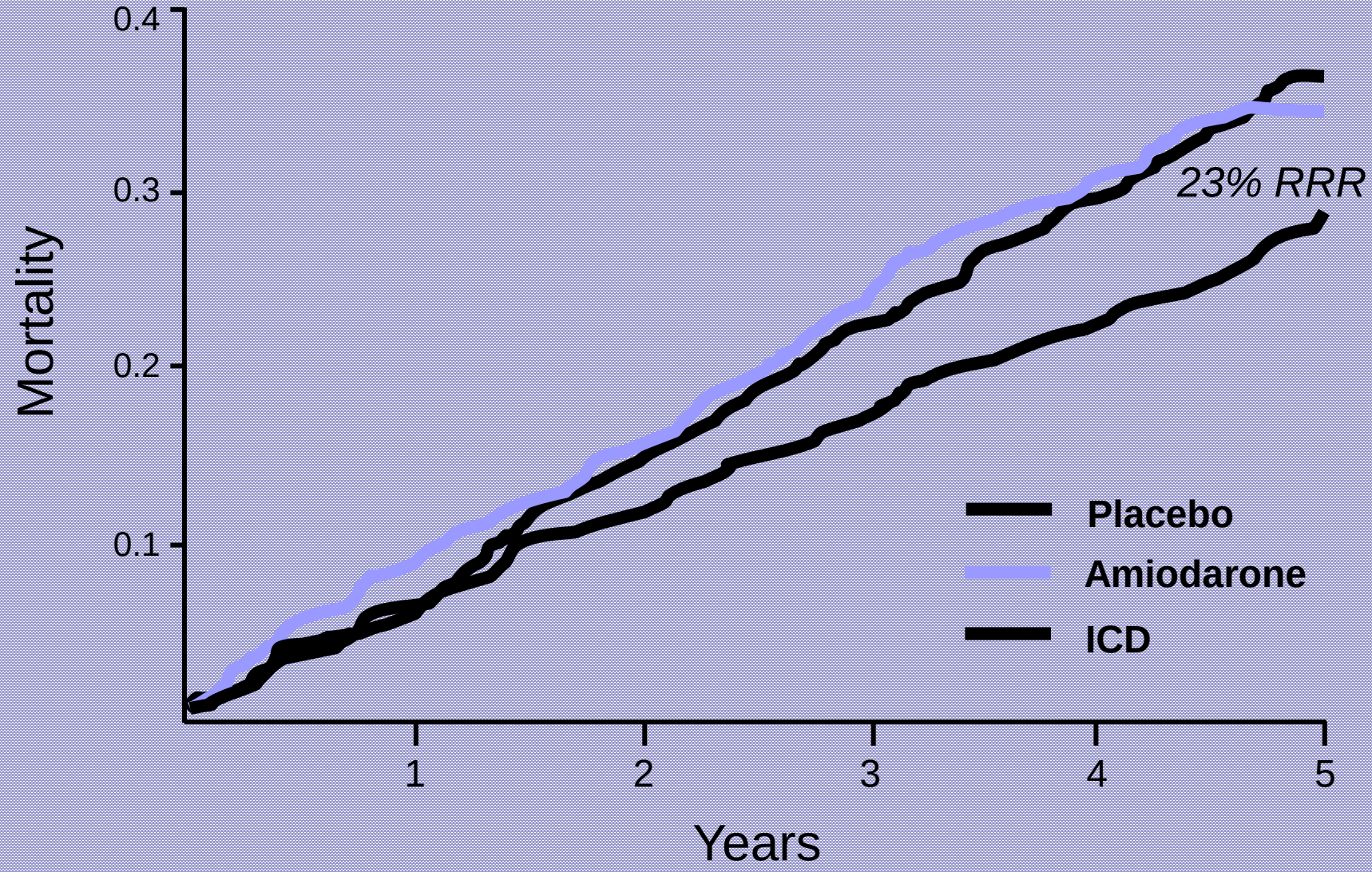
1232 patients with LVEF ≤ 30%, Prior MI



MADIT II - Moss AJ. *N Engl J Med*. 2002;346:877-83.

SCD-HeFT

2521 patients with LVEF ≤ 35%, NYHA II-III



2022 Update

Top 10 Take-Home Messages

•Guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF) now includes 4 medication classes that include sodium-glucose cotransporter-2 inhibitors (SGLT2i).

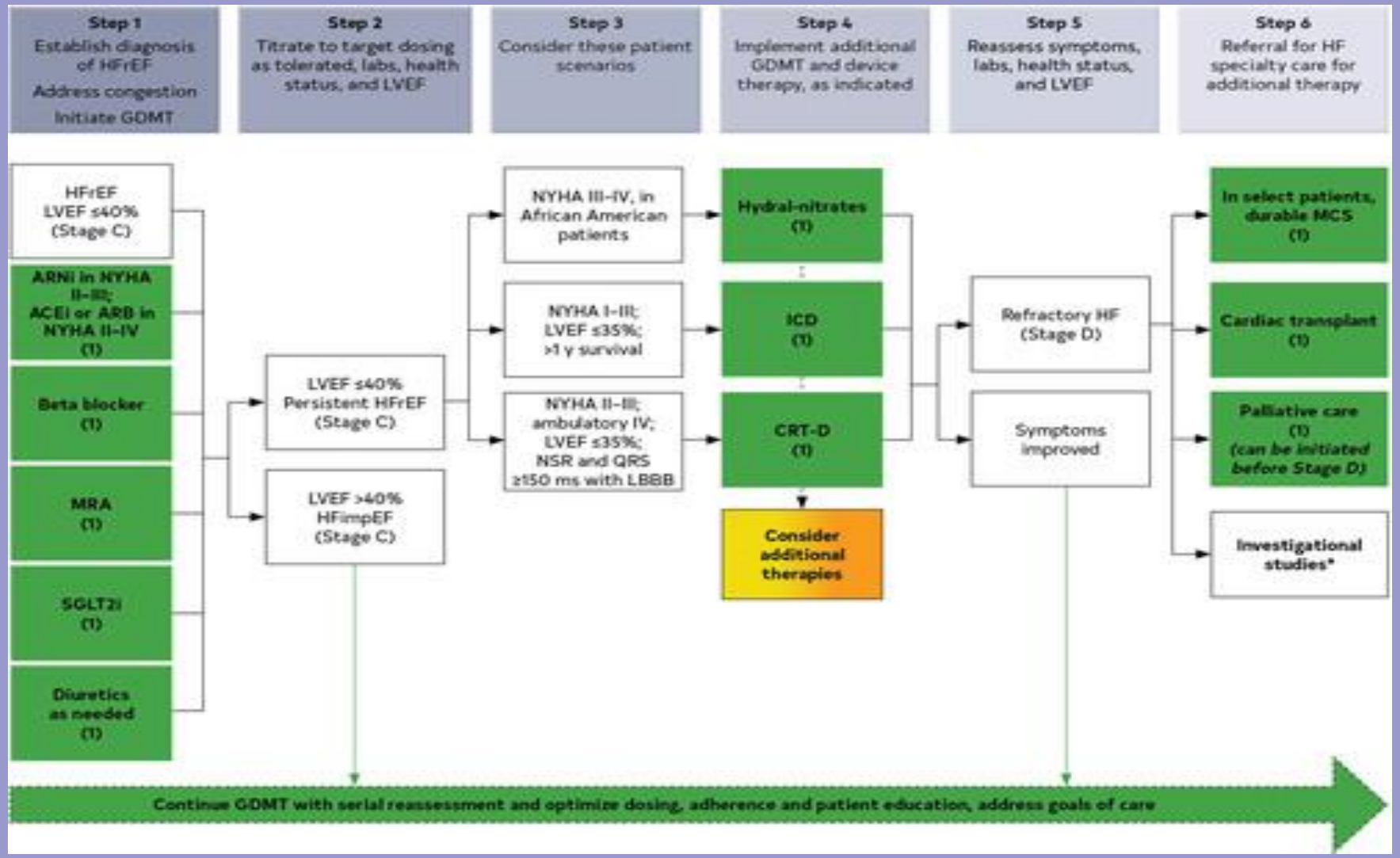
•SGLT2i have a Class of Recommendation 2a in HF with mildly reduced ejection fraction (HFmrEF). Weaker recommendations (Class of Recommendation 2b) are made for ARNi, ACEi, ARB, MRA, and beta blockers in this population.

•New recommendations for HFpEF are made for SGLT2i (Class of Recommendation 2a), MRAs (Class of Recommendation 2b), and ARNi (Class of Recommendation 2b). Several prior recommendations have been renewed including treatment of hypertension (Class of Recommendation 1), treatment of atrial fibrillation (Class of Recommendation 2a), use of ARBs (Class of Recommendation 2b), and avoidance of routine use of nitrates or phosphodiesterase-5 inhibitors (Class of Recommendation 3: No Benefit).

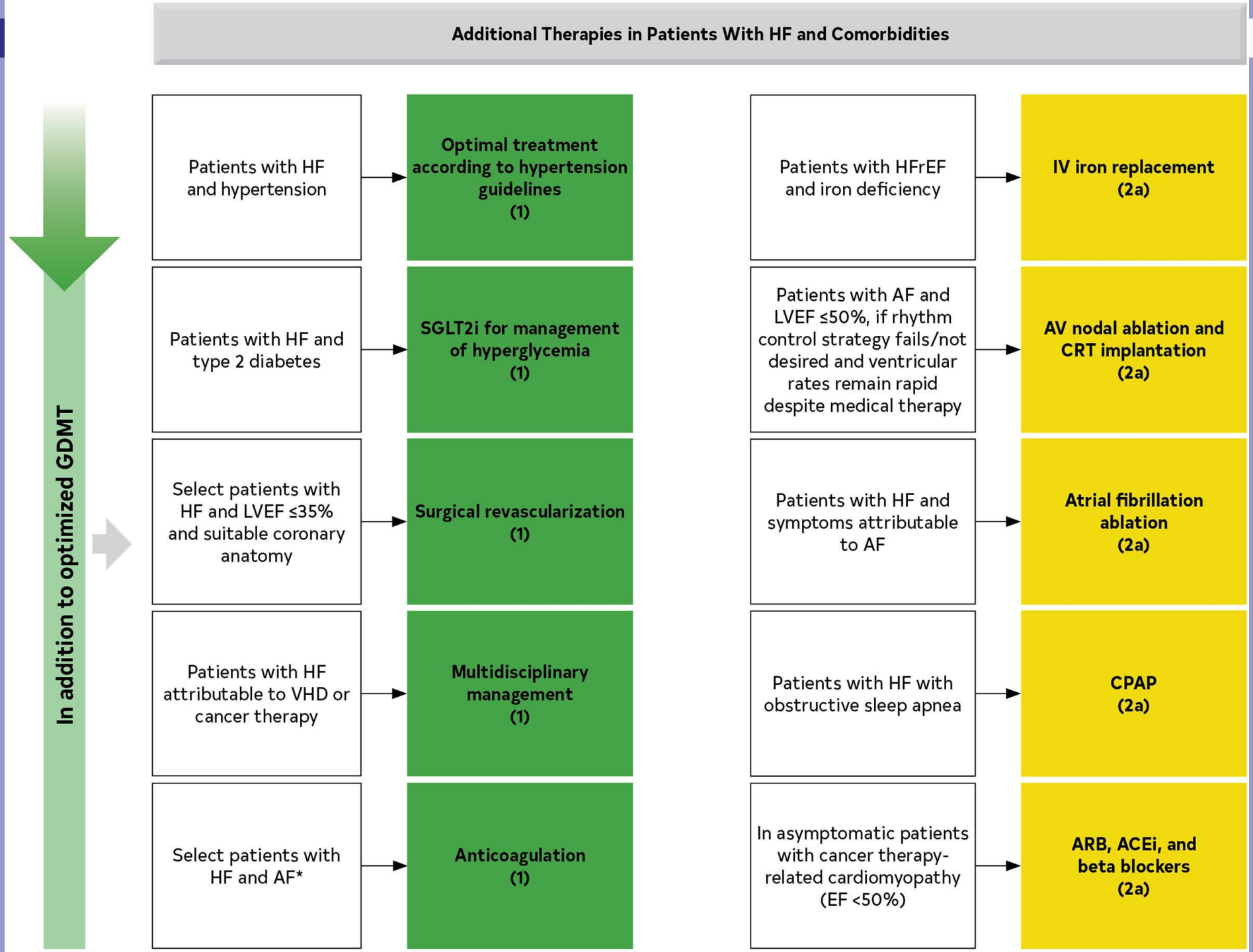
•Improved LVEF is used to refer to those patients with previous HFrEF who now have an LVEF >40%. These patients should continue their HFrEF treatment.

•Value statements were created for select recommendations where high-quality, cost-effectiveness studies of the intervention have been published.

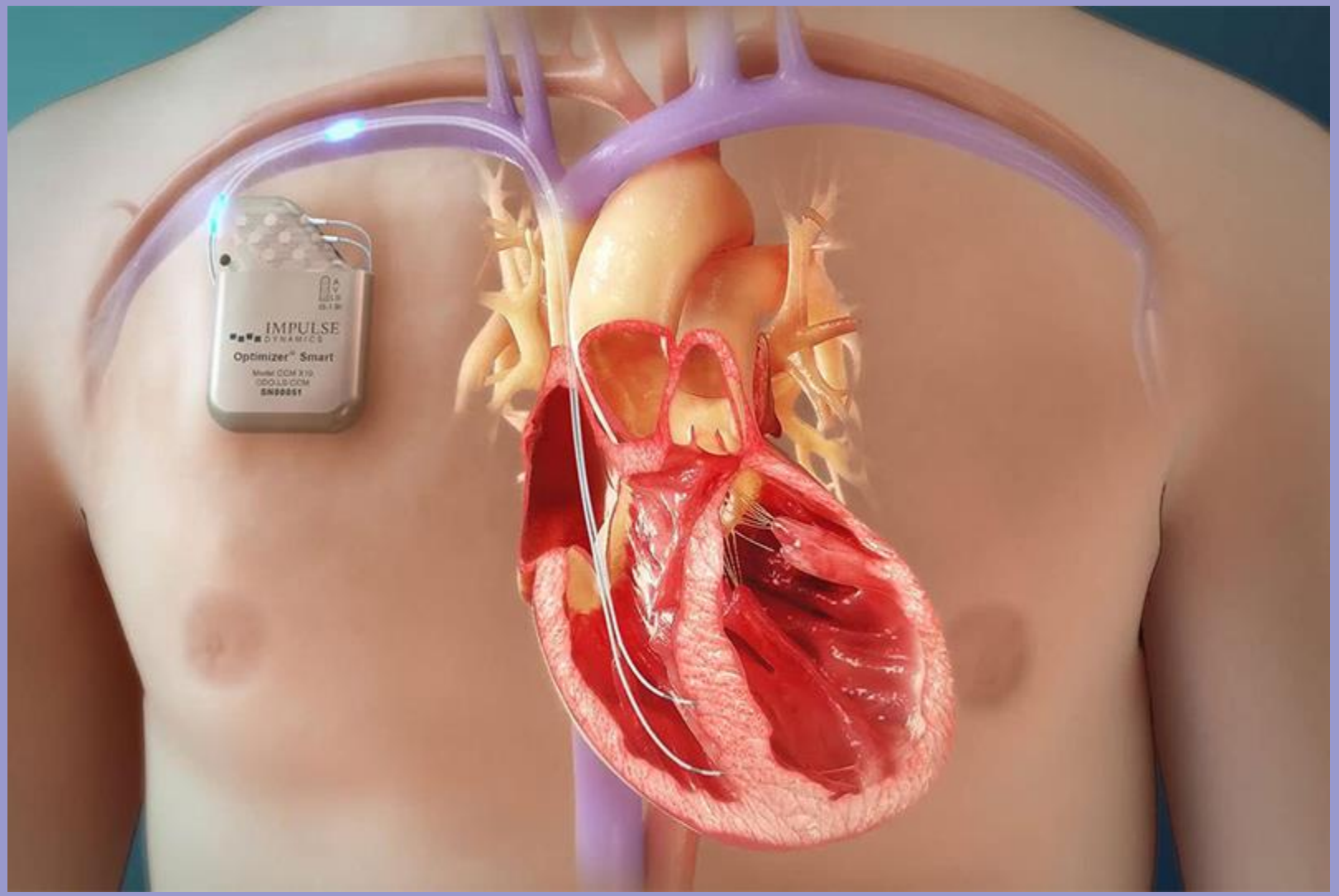
•Amyloid heart disease has new recommendations for treatment including screening for serum and urine monoclonal light chains, bone scintigraphy, genetic sequencing, tetramer stabilizer therapy, and anticoagulation.
•Evidence supporting increased filling pressures is important for the diagnosis of HF if the LVEF is >40%. Evidence for increased filling pressures can be obtained from noninvasive (eg, natriuretic peptide, diastolic function on imaging) or invasive testing (eg, hemodynamic measurement).
•Patients with advanced HF who wish to prolong survival should be referred to a team specializing in HF. A HF specialty team reviews HF management, assesses suitability for advanced HF therapies, and uses palliative care including palliative inotropes where consistent with the patient's goals of care.
•Primary prevention is important for those at risk for HF (stage A) or pre-HF (stage B). Stages of HF were revised to emphasize the new terminologies of "at risk" for HF for stage A and pre-HF for stage B.
•Recommendations are provided for select patients with HF and iron deficiency, anemia, hypertension, sleep disorders, type 2 diabetes, atrial fibrillation, coronary artery disease, and malignancy.



Paul A. Heidenreich. Circulation. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Volume: 145, Issue: 18, Pages: e876-e894, DOI: (10.1161/CIR.0000000000001062)


Additional Therapies in Patients With HF and Comorbidities
In addition to optimized GDMT
Patients with HF and hypertension
Optimal treatment according to hypertension guidelines (1)
Patients with HF and type 2 diabetes
SGLT2i for management of hyperglycemia (1)
Select patients with HF and LVEF ≤35% and suitable coronary anatomy
Surgical revascularization (1)
Patients with HF attributable to VHD or cancer therapy
Multidisciplinary management (1)
Select patients with HF and AF*
Anticoagulation (1)
Patients with HFrEF and iron deficiency
IV iron replacement (2a)
Patients with AF and LVEF ≤50%, if rhythm control strategy fails/not desired and ventricular rates remain rapid despite medical therapy
AV nodal ablation and CRT implantation (2a)
Patients with HF and symptoms attributable to AF
Atrial fibrillation ablation (2a)
Patients with HF with obstructive sleep apnea
CPAP (2a)
In asymptomatic patients with cancer therapy-related cardiomyopathy (EF <50%)
ARB, ACEi, and beta blockers (2a)

Cardiac Contractility Modulation



Thank you!