Reducing the Failure in Heart Failure

Pharmacological Treatment for Heart Failure

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DISCLOSURES

- I have no financial disclosures
- Everything discussed will be according to labeled packaging and/or primary literature

OBJECTIVES

1. List the key pharmacological treatments for HFrEF and their physiological purose

2. Classify heart failure patients into stages and apply treatments based on the 2013 ACCF/AHA and the 2017 Focused Updated Heart Failure Guidelines

COMPENSATORY PATHWAYS

↑ SNS

↑ RAAS

↑ADH

↑ Natriuretic Peptides

DEFINITIONS

Heart failure with reduced ejection fraction (HF*r*EF)	Heart failure with preserved ejection fraction (HF*p*EF)
EF ≤ 40%, also known as systolic heart failure	EF ≥ 50%, also known as diastolic heart failure

ACC/AHA Stages	
A	High risk of developing HF but without structural heart disease or HF symptoms
B	Presence of structural heart disease but without HF symptoms
C	Presence of structural heart disease with prior/current HF symptoms
D	Refractory HF requiring specialized interventions

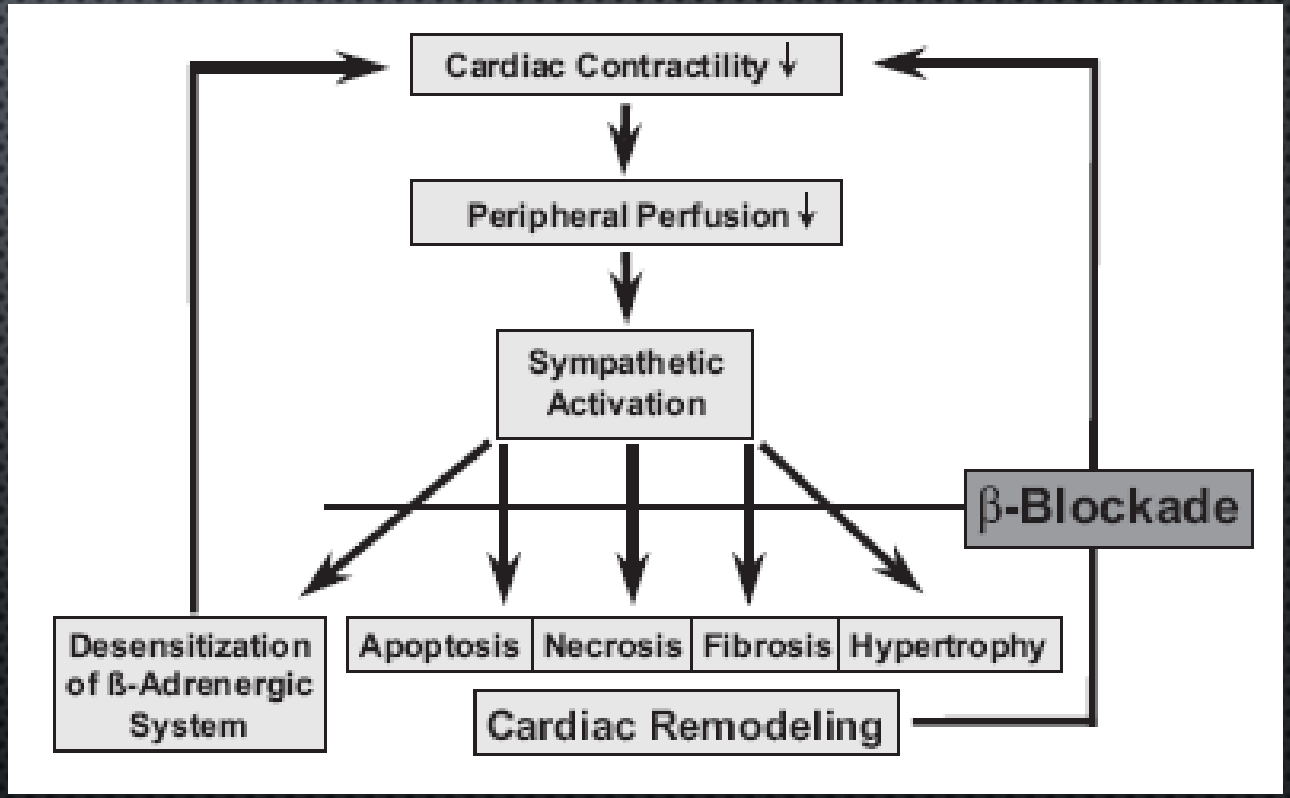
NYHA Functional Classes	
I	No limitation of physical activity. Ordinary activity does not cause HF symptoms.
II	Slight limitation of physical activity. Ordinary activity results in HF symptoms.
III	Marked limitation of physical activity. Less than ordinary activity results in HF symptoms.
IV	Any physical activity results in HF symptoms. HF symptoms also occur at rest.

Circulation. 2013;128:e240 e327

TREATMENTS

Beta-blocker

- Carvedilol (Coreg®)
- Metoprolol Succinate (Toprol XL®)
- Bisoprolol (Zebeta®)



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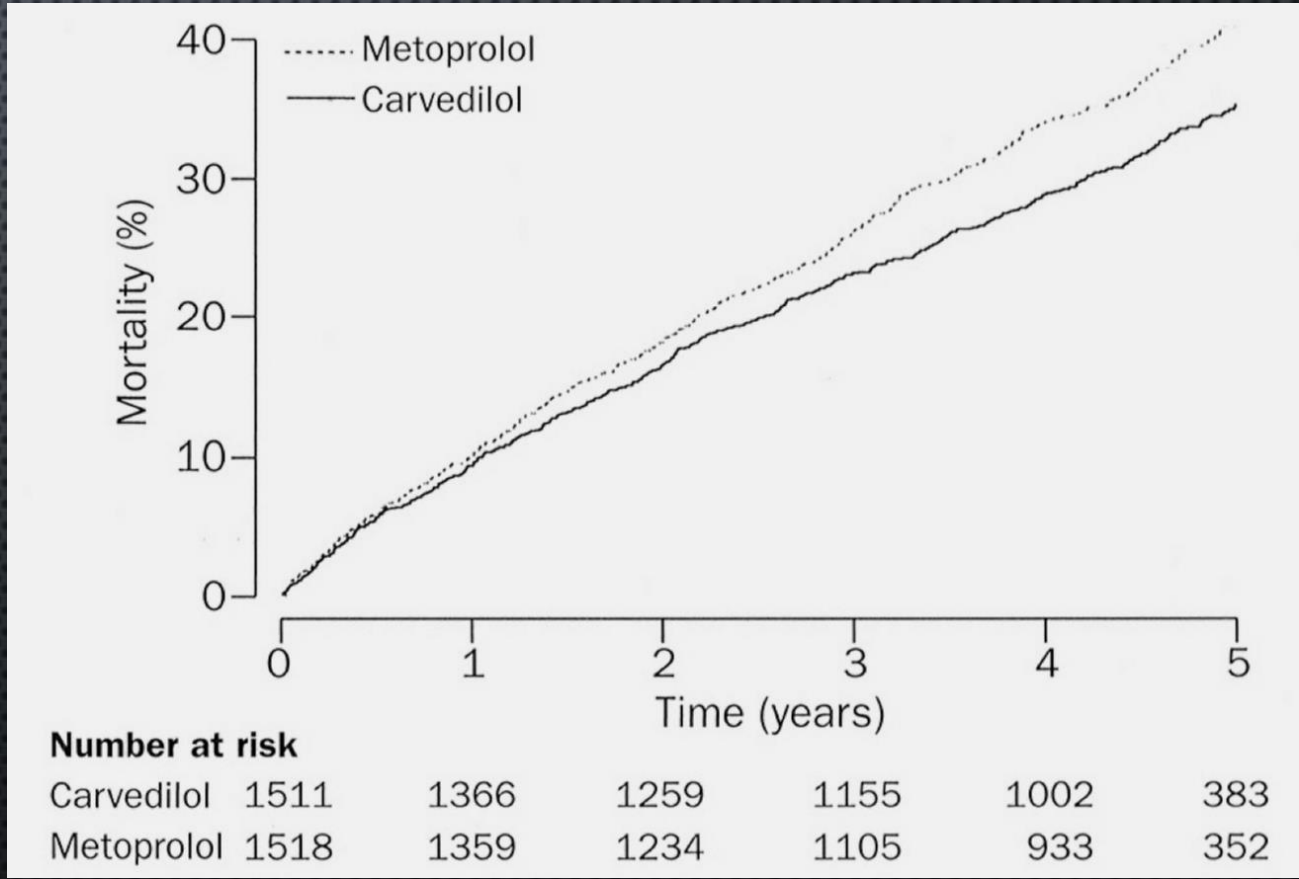
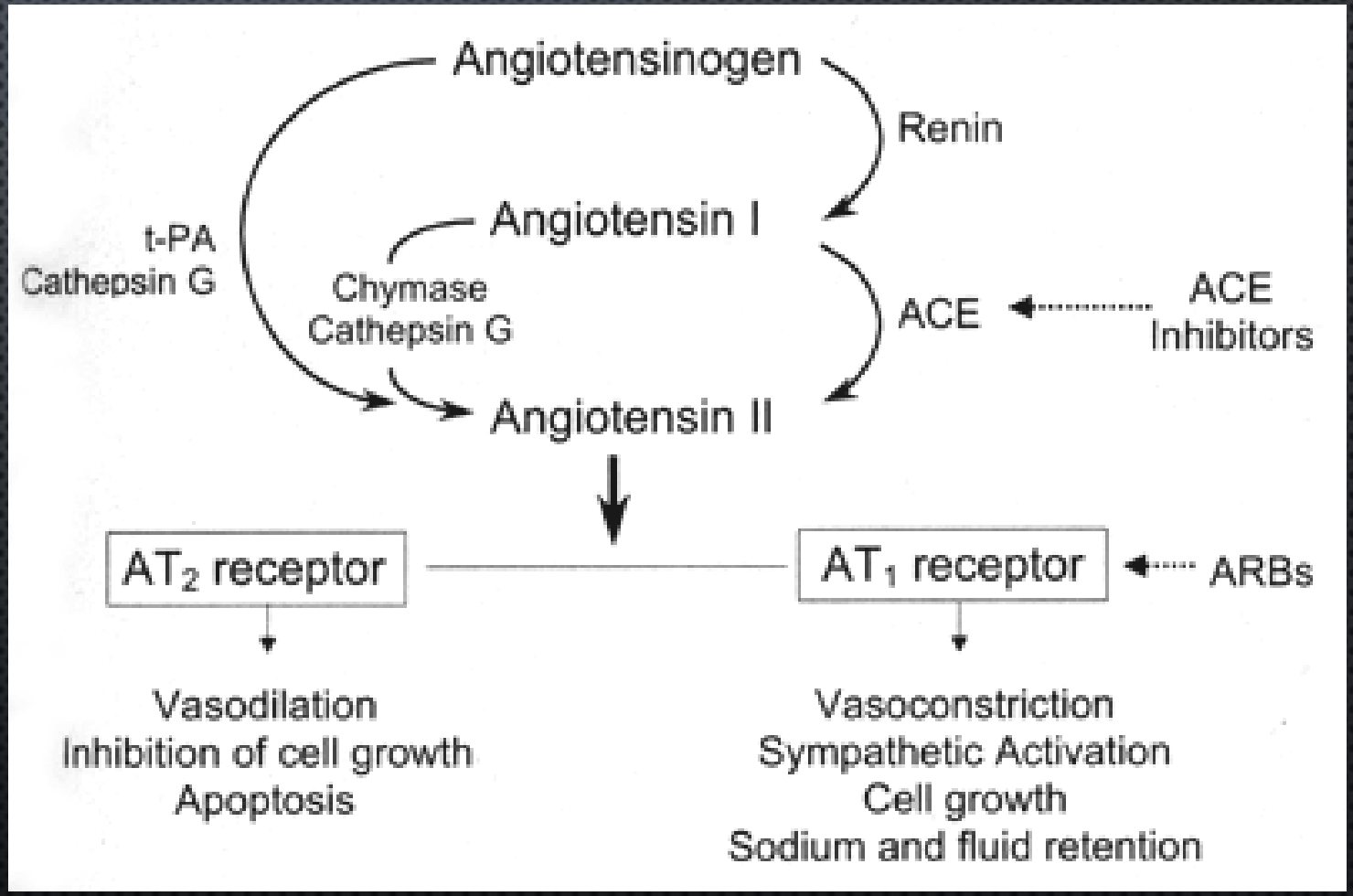


Lancet. 2003;362(9377):7

TREATMENTS

ACE-I/ARB

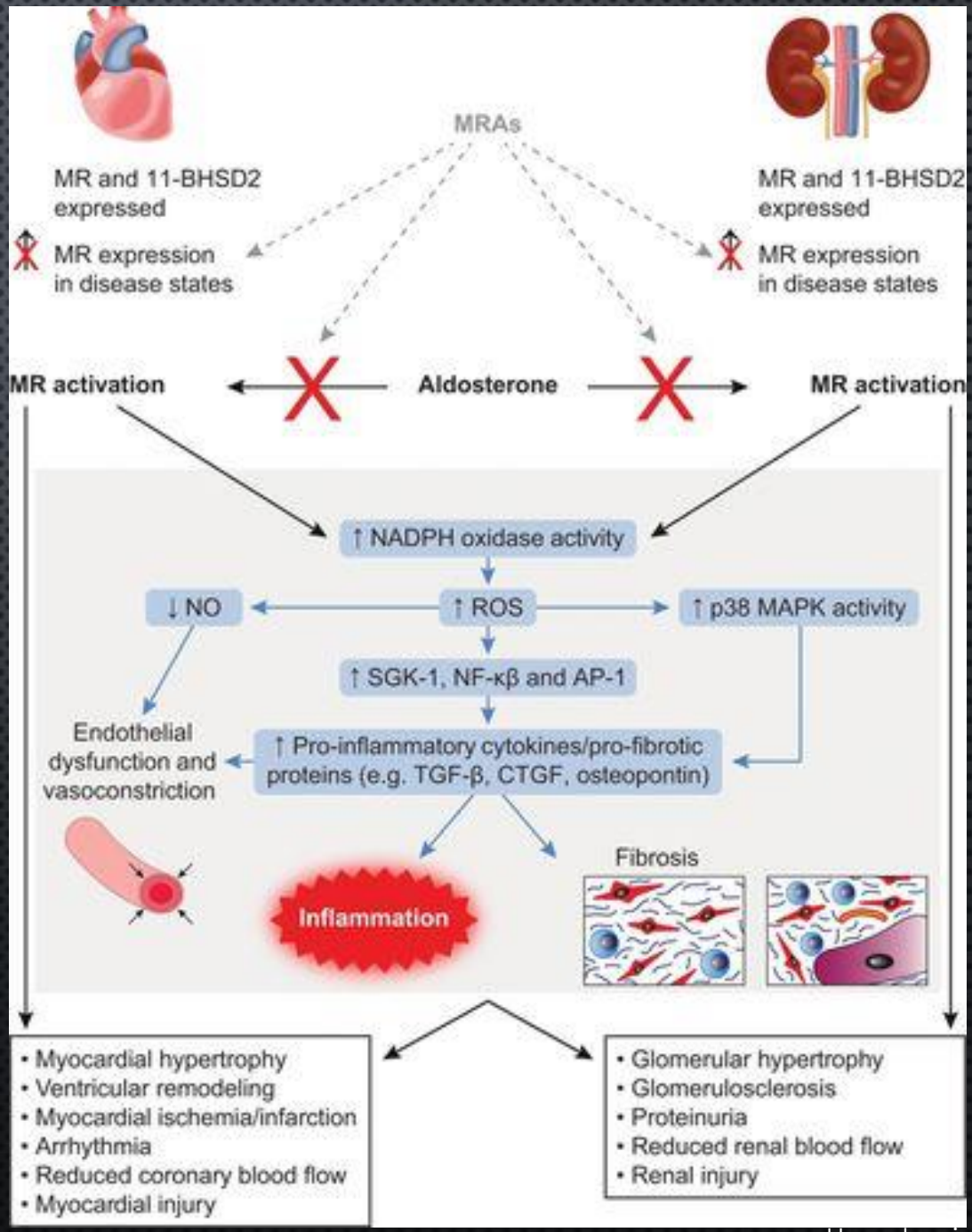
- Class Effect



TREATMENTS

MRA

- Spironolactone (Aldactone®)
- Eplerenone (Inspra®)



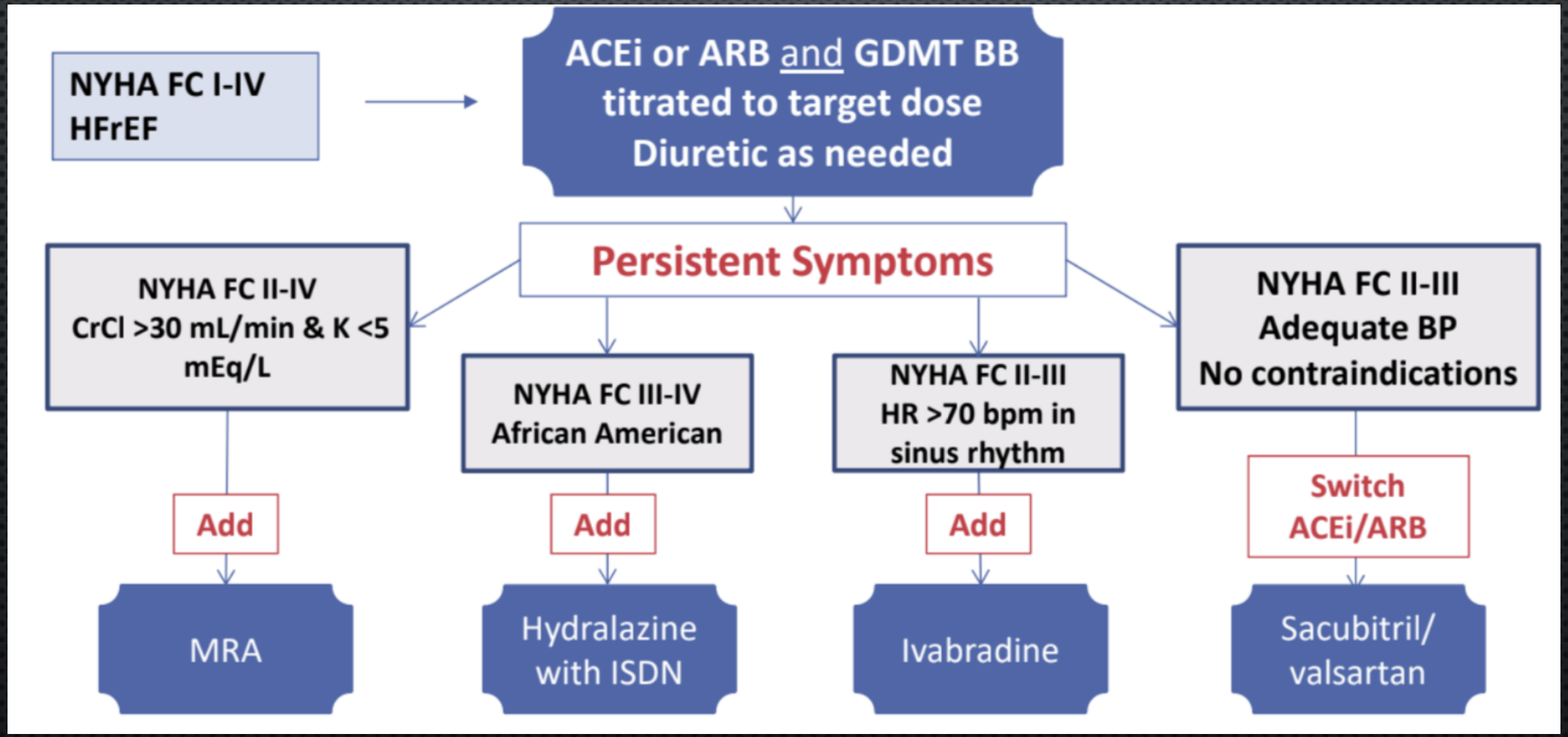
Hypertension. 2015;65:257 263

GUIDELINE DIRECTED MEDICAL MANAGEMENT

Therapy	RR Reduction in Mortality	NNT (Standardized to 36 mo)	RR Reduction in HF Hospitalizations
ACE-I or ARB	17%	26	31%
Beta Blocker	34%	9	41%
Aldosterone Antagonist	30%	6	35%
Hydralazine/Nitrate	43%	7	33%

Circulation. 2017;136:e137 e161

2017 ACC/AHA/HFSA GUIDELINES



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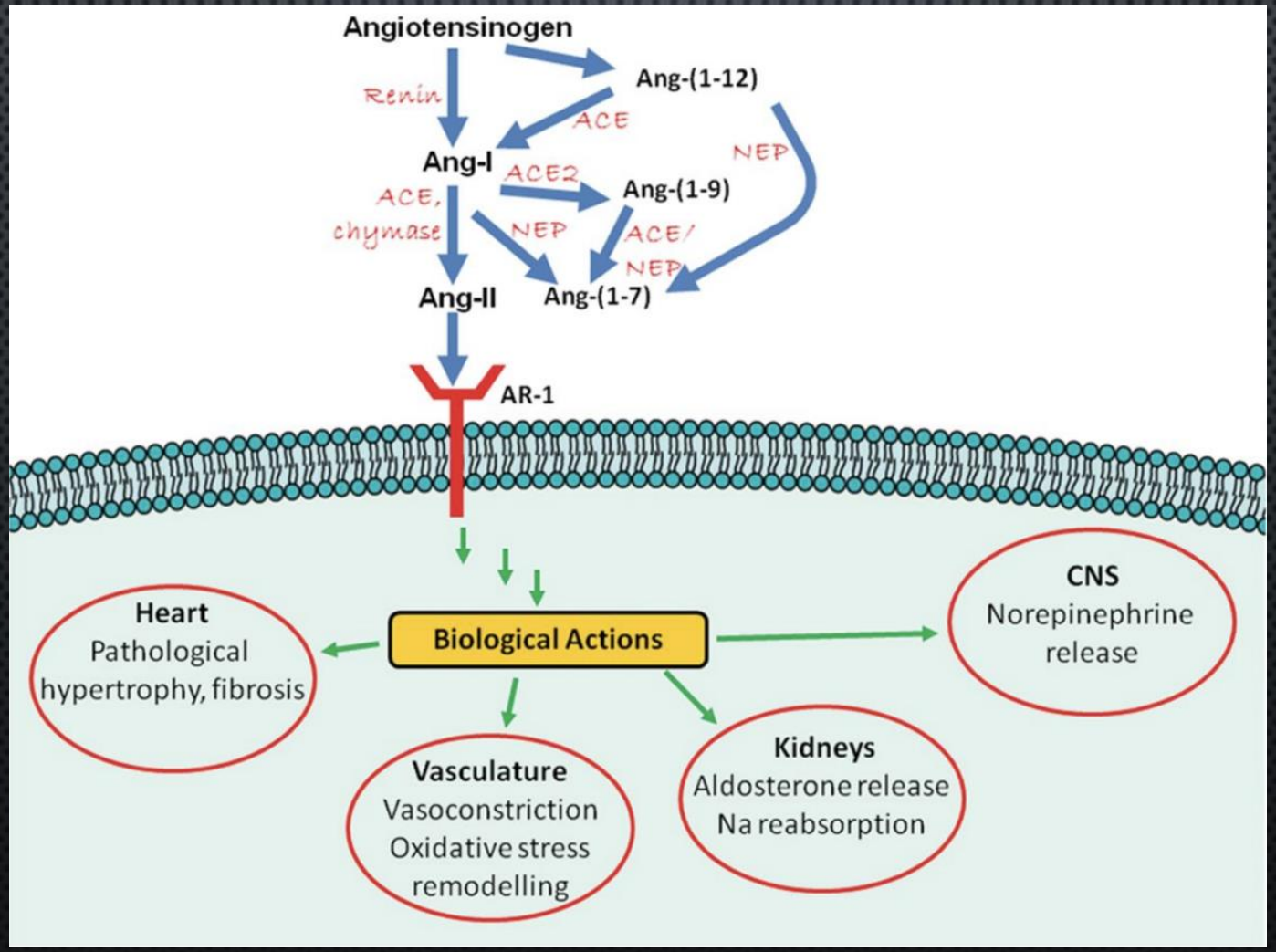
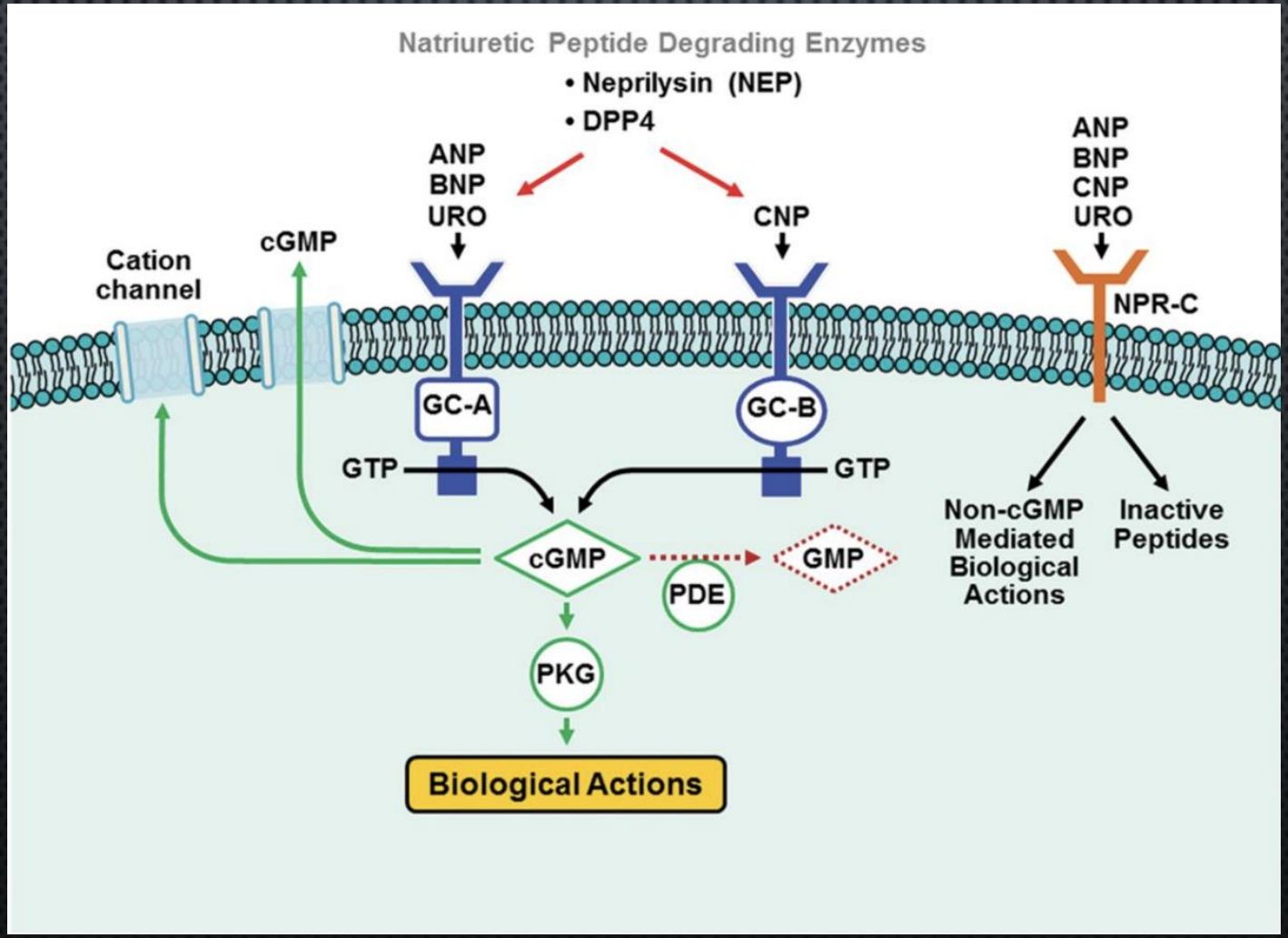
RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)



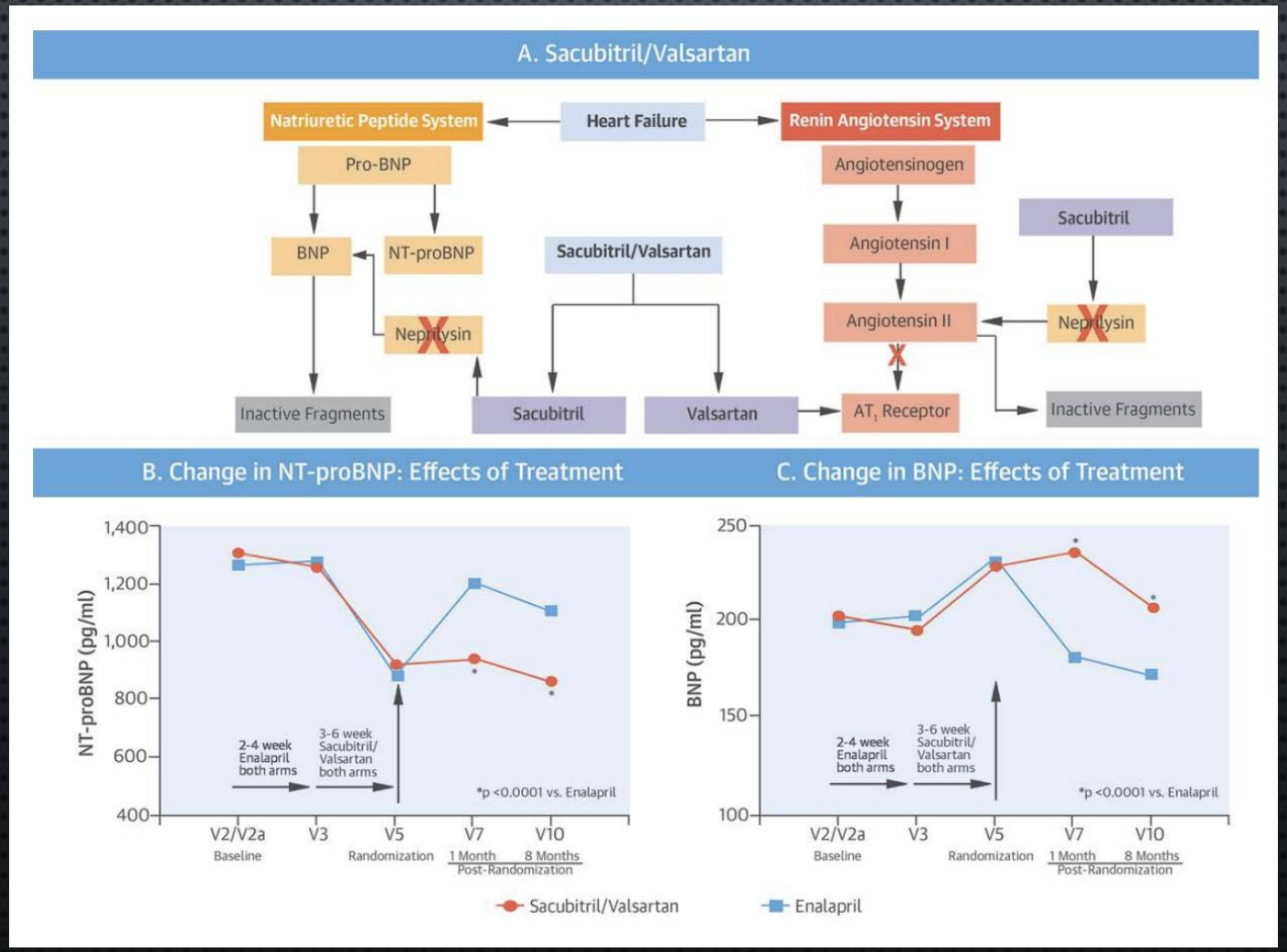
Circ Heart Fail. 2013;6:594 605

NATRIURETIC PEPTIDE SYSTEM (NPS)

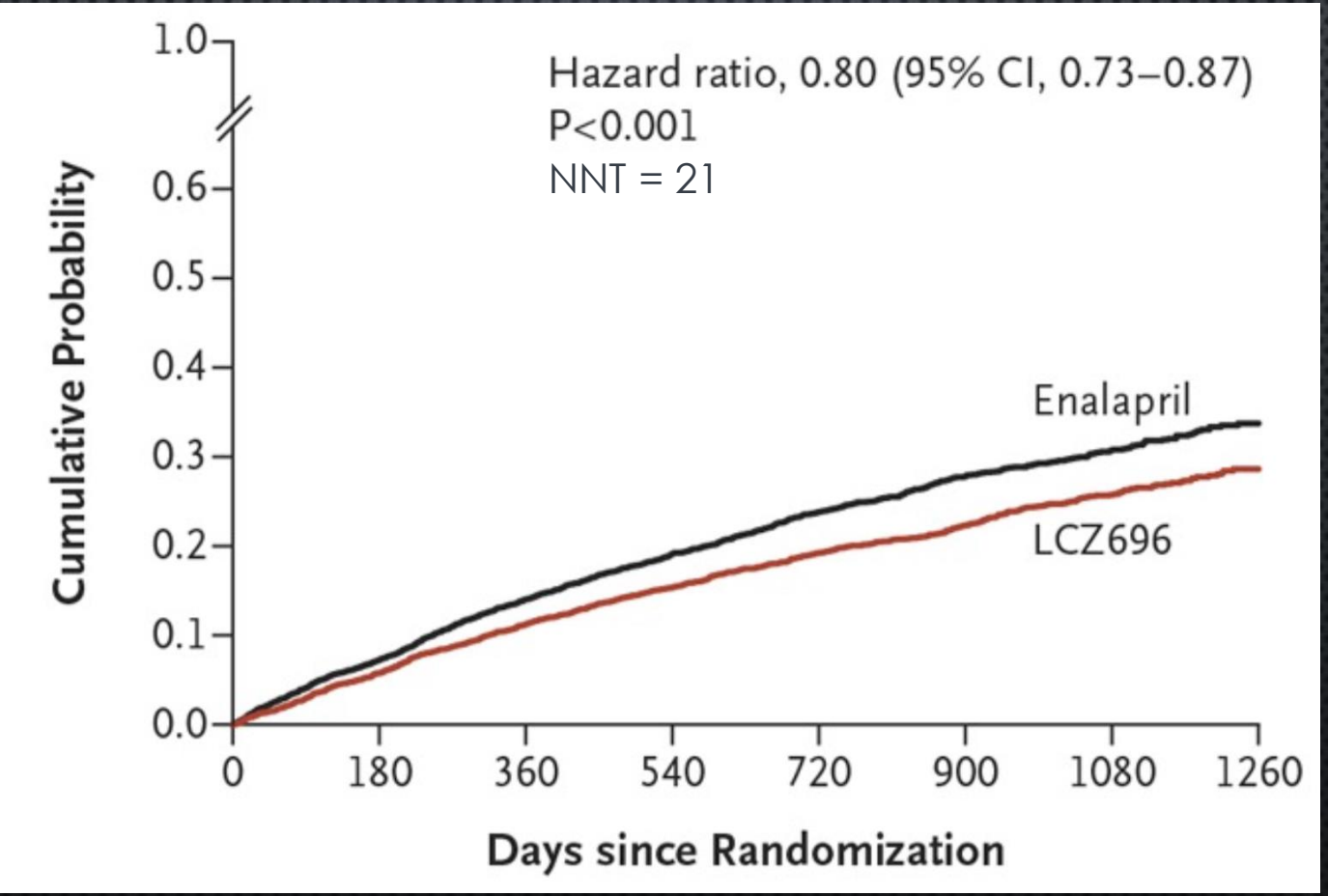


Circ Heart Fail. 2013;6:594 605

ENTRESTO®


A. Sacubitril/Valsartan
Natriuretic Peptide System
Heart Failure
Renin Angiotensin System
Pro-BNP
Angiotensinogen
Sacubitril
BNP
NT-proBNP
Sacubitril/Valsartan
Angiotensin I
Neprilysin
Angiotensin II
Neprilysin
Inactive Fragments
Sacubitril
Valsartan
AT1 Receptor
Inactive Fragments
B. Change in NT-proBNP: Effects of Treatment
C. Change in BNP: Effects of Treatment
NT-proBNP (pg/ml)
1,400
1,200
1,000
800
600
400
BNP (pg/ml)
250
200
150
100
2-4 week Enalapril both arms
3-6 week Sacubitril/ Valsartan both arms
*p <0.0001 vs. Enalapril
V2/V2a
Baseline
V3
V5
Randomization
V7
1 Month
V10
8 Months
Post-Randomization
Sacubitril/Valsartan
Enalapril

PARADIGM-HF



N Engl J Med 2014; 371:993 1004

PEARLS FOR ARNI DOSING

ACEi or ARB Dose	Sacubitril/valsartan Initial Dose
None or low dose	24/26 mg BID
Target or maximum dose	49/51 mg BID
Clinical Characteristics	
Severe renal impairment Moderate hepatic impairment	24/26 mg BID
History of angioedema	Contraindicated
Double every 2-4 weeks to target of 97/103 mg BID	

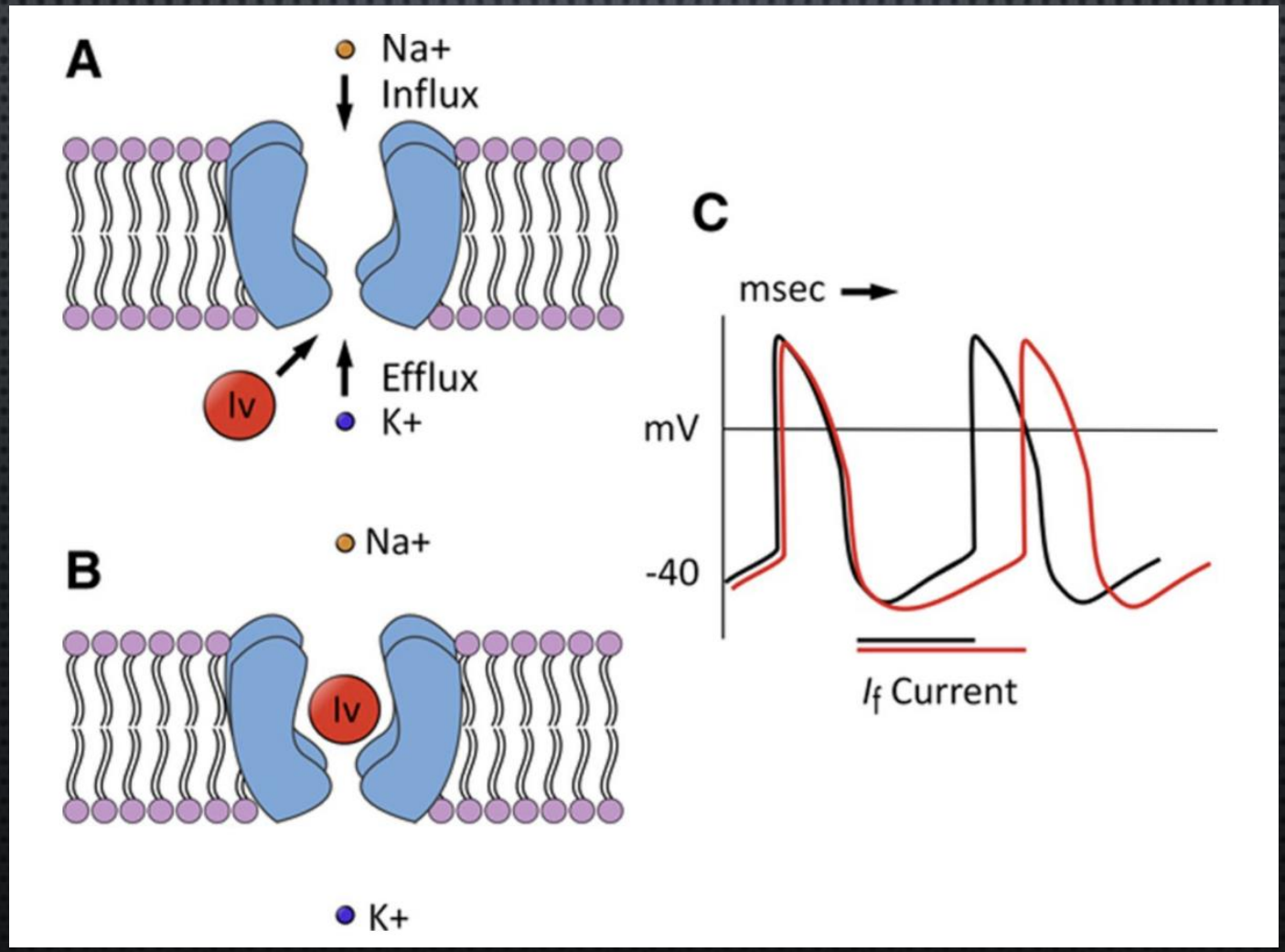
ACEi to ARNI:

- **36 hour washout**
- Cancel ACEi prescription at the pharmacy

ARB to ARNI:

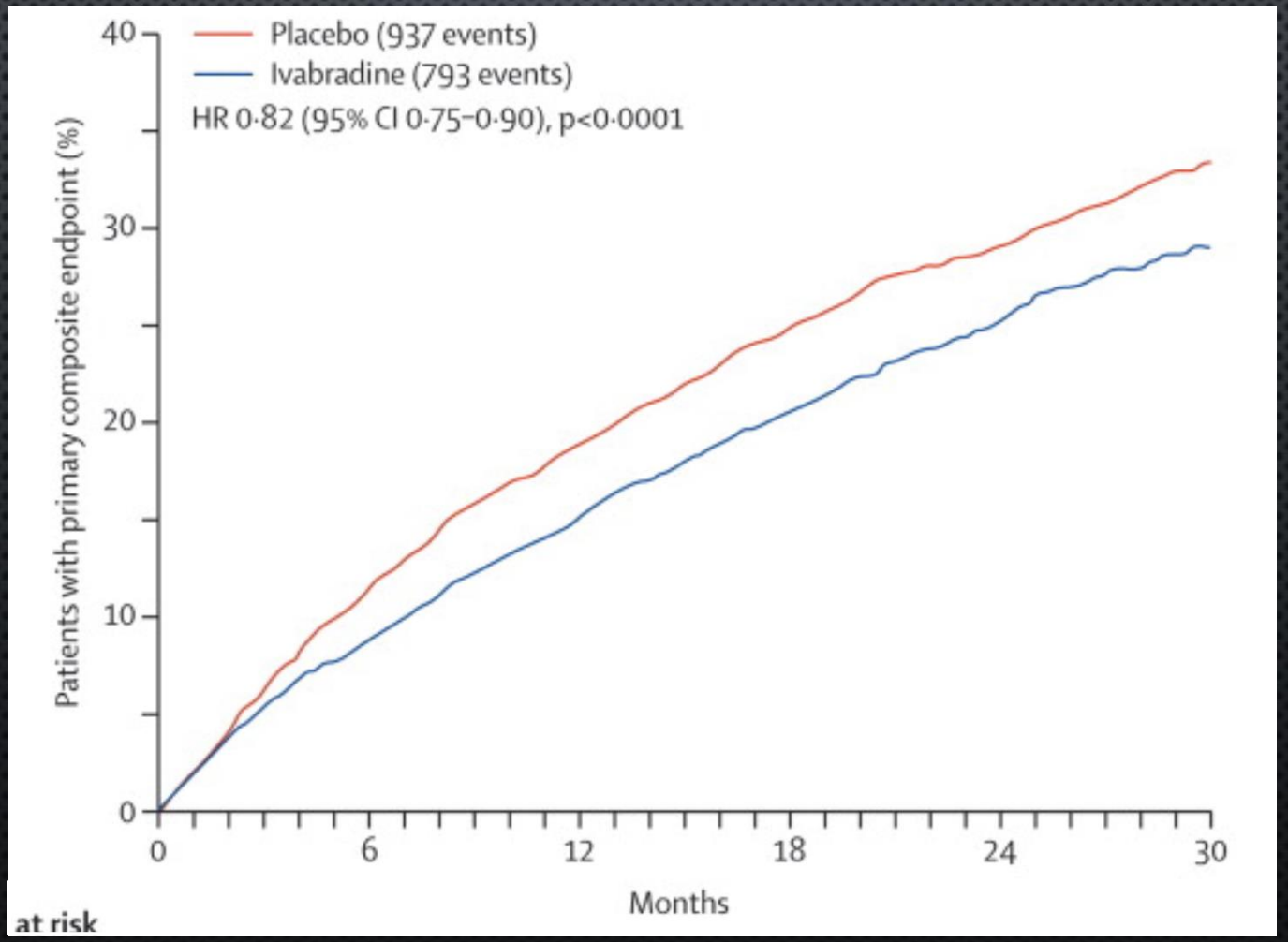
- Start when next dose normally due

INHIBITION OF HCN CHANNELS



Circulation. 2016;133:2066 2075

IVABRADINE (CORLANOR®) – SHIFT TRIAL



Lancet 2010; 376: 875 85

IMPACT OF GDMT ON ALL CAUSE MORTALITY

	Relative Risk	2 Year Mortality
None	--	35%
ARNI	↓ 28%	25.2%
Beta Blocker	↓ 35%	16.4%
Aldosterone Antagonist	↓ 30%	11.5%
SGLT2 Inhibitor	↓ 17%	9.5%

Cumulative risk reduction in mortality if all evidence-based medical therapies are used:
Relative risk reduction: 72.9%, Absolute risk reduction: 25.5%, NNT = 3.9

NEJM. 2014;371(11):993 1004

PATIENT CASE

AB is a 67 yo Hispanic female with long-standing HTN presents with cough, SOB when dressing/showering, PND, 8-lb weight gain, decreased appetite, and lower extremity edema.

Meds:
Diltiazem Er 240 mg daily
HCTZ 50 mg daily
Ibuprofen 200 mg TID

Vital Signs:
BP: 150/94 mmHg
HR: 92 bpm

Diagnostics:
EF = 20%
CXR: vascular congestion
ECG: left ventricular hypertrophy

LABS:
Na/K WNL
BUN/SCr 38/1.5 mg/dL
BNP 1200 pg/mL

In addition to discontinuing diltiazem, what is your plan for treating her HF?

a. Add furosemide, lisinopril, and carvedilol
b. Change HCTZ to furosemide and add lisinopril and carvedilol
c. Add furosemide and lisinopril
d. Change HCTZ to furosemide and add lisinopril

PATIENT CASE

3 months later AB returns to clinic. In the interim she has been titrated to goal doses of carvedilol and lisinopril. She was hospitalized 2 weeks ago for acute HF but now is feeling much better. Currently has stable "2 pillow" orthopnea and dyspnea after walking 3 blocks. NYHA FC II

Meds:
Carvedilol 25 mg BID
Furosemide 20 mg daily
Lisinopril 20 mg daily

Vital Signs:
BP: 135/84 mmHg
HR: 74 bpm

Diagnostics:
EF = 30-35%
CXR: cardiomegaly

LABS:
Na/K WNL
BUN/SCr 22/1.5 mg/dL
BNP 500 pg/mL

What is you next step for treating her HF?

a. Continue present management
b. Add hydralazine/isosorbide 37.5mg/20 mg TID
c. Add ivabradine 5 mg BID
d. Add spironolactone 25 mg daily
e. Change lisinopril to sacubitril/valsartan 97/103 mg BID

SUMMARY

Drug		Place in Therapy	Mortality Benefit?
ACE Inhibitors	enalapril, lisinopril, quinapril, or ramipril	All patients with HF*r*EF	Yes
ARBs	candesartan, losartan, or valsartan	HF*r*EF who are intolerant to ACEI	Yes
Beta Blockers	bisoprolol, carvedilol, or metoprolol succinate	All stable patients	Yes
Diuretics	typically bumetanide, furosemide, or torsemide	HF*r*EF with fluid retention	No
ARAs	eplerenone or spironolactone	NYHA class II-III and LVEF ≤ 35% or post MI/LVEF ≤ 40%/symptomatic or DM	Yes
ARNI	sacubitril/valsartan (Entresto)	Alternative to ACEI/ARB in NYHA class II-III with chronic symptomatic HFrE	Yes
Ivabradine (Corlanor)		NYHA class II-III with LVEF ≤ 35%, normal sinus rhythm, on max tolerated BB or BB CI, and have resting HR ≥ 70	No
Hydralazine/isosorbide dinitrate (BiDil)		African Americans with NYHA class III-IV HF*r*EF	Yes (specific patients)
Digoxin		Symptomatic patients on optimized therapy	No

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QUESTIONS?