The Management of Heart Failure – A PARADIGM Shift?

Richard Clarens, PharmD

UND School of Medicine & Health Sciences

Altru Family Medicine Residency

NDSU College of Pharmacy, Nursing, & Allied Sciences

OBJECTIVES

- Explain the neurohormonal pathophysiology of heart failure and the mechanism of action of the various agents used to manage HF.
- Review the therapeutics of HFrEF and compare the recently FDA-approved medications to the existing medications.
- Identify changes in the updated HFrEF guidelines and the potential for applying them to your patients.

RESOURCES

- 2013 ACCF/AHA Guideline for the Management of Heart Failure
  - Circulation 13;128:e240-e327
- 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
  - http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=2016&t=

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**

(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:

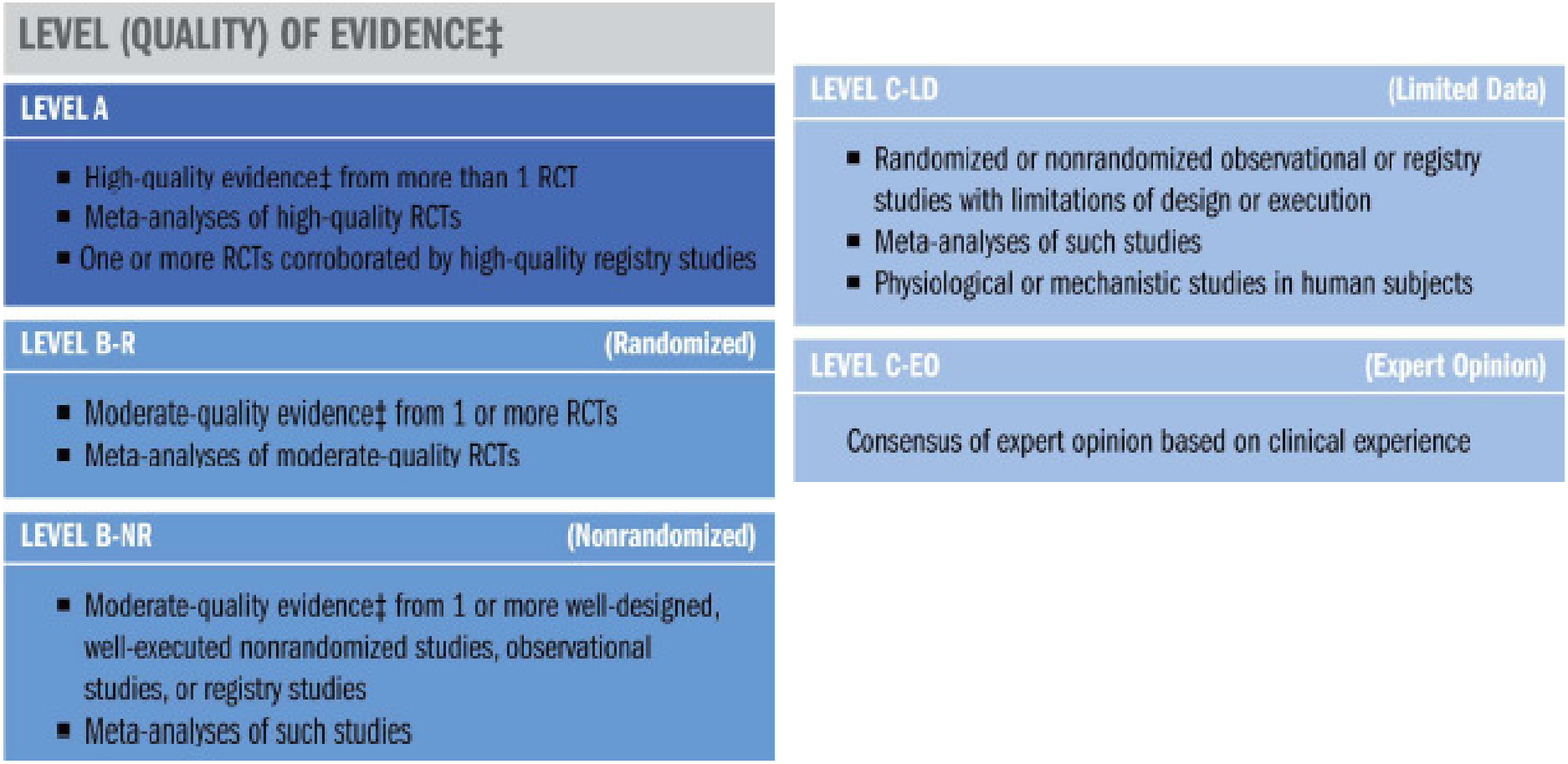
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

AHA/ACC Applying Class of Recommendation



AHA/ACC Applying Level of Evidence

HF STATISTICS

- Affects 5.7 million US residents
  - May increase 46% from 2012-2013 – >8M
  - 915,000 new cases/y
  - Causes or contributes to ~ 300,000 deaths/y
- Annual impact on health care resources
  - ~1 mill hospitalizations/y
    - ~4.3 d/stay with > 4% mortality
  - ~ $31 billion/y for direct/indirect costs
  - Number 1 cause of hospitalizations in the elderly
    - Medicare –> cost than on any other diagnosis & treatment

Heart Disease & Stroke Stats – 2016. AHA. Circ 16;133:338-360
J Am Col Card 12;59:1449-50 J Am Coll Cardiol HF 2013;1:1-20

PATHOPHYSIOLOGY

- Myocardial injury – Progressive disease

Cardiol Clin 32 (2014) 47–62

- Adaptive mechanisms to maintain perfusion
  - Increased preload to maintain CO
  - Activation of neurohumoral systems
    - **NE release – maintain contractility**
    - **Activation RAAS (& other systems) – maintain arterial pressure & perfusion of vital organs**
  - **Myocardial remodeling** – mass of contractile tissue is augmented
- May be adequate initially
  - Chronic becomes maladaptive

BIOLOGICALLY ACTIVE TISSUE & CIRCULATING SUBSTANCES

- Renin–angiotensin–aldosterone system (RAAS)
- Sympathetic nervous system (norepinephrine)
- Vasopressin (ADH)
- Vasoactive peptides: natriuretic peptides (NP), bradykinin, adrenomedullin, substance P, calcitonin gene-related peptide, angiotensin 1-7
- NO, prostaglandins
- Many proinflammatory cytokines

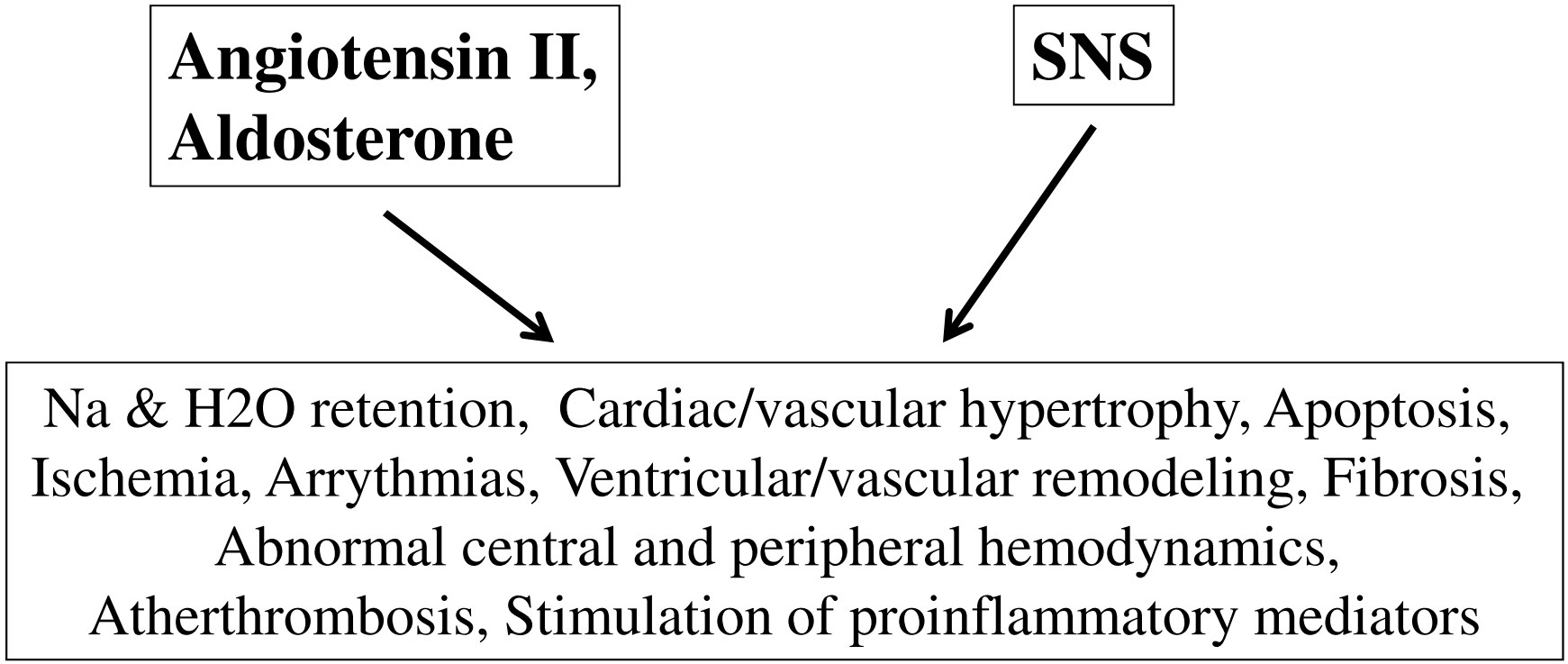
NEJM 03;348:2007-18 Heart 16;102:1342-7 Circulation 16;133:1115-24
Lancet. Published online December 2, 2016 http://dx.doi.org/10.1016/S0140-6736(16)30969-2

Neurohormones in HF

- SNS – epinephrine, NE
  - Vasoconstriction
  - Increase HR, contractility, RAAS activity, vasopressin
- RAAS – angiotensin II
  - Vasoconstriction
  - Increase BP, SNS, aldosterone, hypertrophy, fibrosis
- NP peptides
  - Vasodilation
  - Decrease BP, SNS, vasopressin, aldosterone, hypertrophy, fibrosis
  - Increase natriurersis, diuresis

Clinical Therapeutics 15;37:2199-2205 Circ 16;133:1115-24

ADVERSE EFFECTS OF NEUROHORMONES



Crit Care Med 08;36[Suppl.]:S44-S51 Heart 16;102:1342-7

Circulation 16;133:1115-24

Lancet. Published online December 2, 2016 http://dx.doi.org/10.1016/S0140-6736(16)30969-2 1

NEUROHORMONES IN HF

- Development and progression of HF
  - Progressive loss of compensatory vasoactive peptides to counter the actions of vasoconstrictor neurohormonal systems – RAAS and SNS
- Effects of vasoactive natriuretic peptides (NP) are blunted in HF
  - Reduced ability of the circulation to counter the maladaptive actions of RAAS & NE

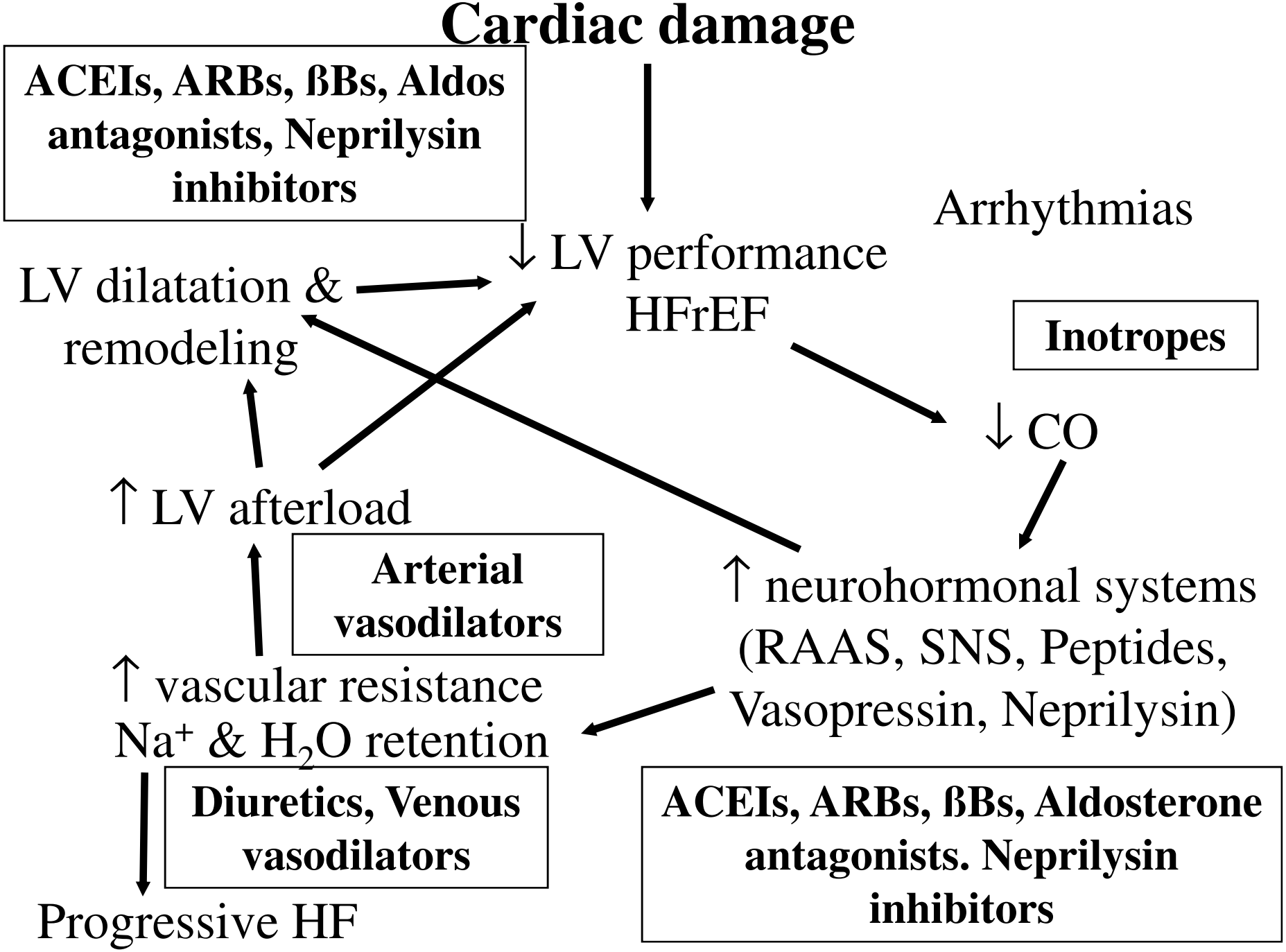
Lancet. Published online December 2, 2016 http://dx.doi.org/10.1016/S0140-6736(16)30969-2
Circulation 16;133:1115-24

NEUROHORMONES IN HF

- Neprilysin
  - Degrades NPs, bradykinin and adrenomedullin
  - Levels increase in HF
  - Resistance to compensatory vasoactive peptides
- Neprilysin inhibition
  - Enhances effects of NP, bradykinin, adrenomedullin and angiotensin (1-7) on heart, renal and adrenal
  - Counter maladaptive effects of RAAS, NE

Lancet. Published online December 2, 2016 http://dx.doi.org/10.1016/S0140-6736(16)30969-2

Circulation 16;133:1115-24


Cardiac damage
ACEIs, ARBs, ßBs, Aldos antagonists, Neprilysin inhibitors
↓ LV performance HFrEF
Arrhythmias
LV dilatation & remodeling
Inotropes
↓ CO
↑ LV afterload
Arterial vasodilators
↑ neurohormonal systems (RAAS, SNS, Peptides, Vasopressin, Neprilysin)
↑ vascular resistance
Na+ & H2O retention
Diuretics, Venous vasodilators
ACEIs, ARBs, ßBs, Aldosterone antagonists. Neprilysin inhibitors
Progressive HF

WHY SYMPTOM RELIEF IS NOT ENOUGH – HFrEF

- Symptomatic disease
  - Symptoms limit functional capacity & affedt quality of life
- A progressive disease
  - Worsening symptoms & clinical deterioration
    - **Repeated hospitalization & death**
- Therapy to manage symptoms, slow/reverse progression and decrease mortality

Cardiol Clin 32 (2014) 47–62

SYSTOLIC DYSFUNTION
Decreased Contractility

- Heart failure with reduced EF < 40% (HFrEF)
- Increased preload – congestion
- Diastolic function normal or impaired
- Neurohormonal activation
- LV wall thickness is decreased
- **RCTs showing efficacy with drugs only in these patients**

ACC/AHA HF Guideline 2013

HEART FAILURE (HFrEF)

- Conventional therapy – relief of symptoms
  - Diuretics, digoxin
- **Reduction in morbidity & mortality therapy**
  - Hydralazine/Isosorbide (early 1980s)
  - ACEIs (late 1980s)
  - ß-blockers (mid 1990s)
  - Aldosterone antagonists (late 1990s)
  - ARBs (early 2000s)
  - Neprilysin inhibitors (2016)

DIURETICS

- Must reach the site of action
  - Organic acid secretory pathway secrete drug into the tubule lumen fluid
  - Action at thick ascending limb of loop of Henle
  - Must attain a threshold level for diuresis to occur
- Duration of action ~ 6h, torsemide up to 12h
  - Na+ is reabsorbed when diuretic concentration falls below threshold
    - Rebound Na+ retention
    - $\geq$ 1xd of an effective dose to maintain response

Sem Neph 11;31:483-94 J Cardiovasc Pharm Ther 14;19:5-13 NEJM 98;339:387-95

IV DOSING OF LOOP DIURETICS

	Moderate – Severe Renal	**Heart Failure**
Mechanism of diminished response	Impaired delivery to site of action	Diminished nephron response
Strategy for dosing	↑ dose to ↑ level at ascending limb	↑ frequency of effective dose
Ceiling IV dose, mg		
Furosemide, bioavailability (F) 50% (10-100%)	80-200	40-80
Bumetanide, F 80-100%	4-10	1-2
Torsemide, F 80-100%	20-100	10-20

Sem Neph 11;31:483-94 NEJM 98;339:387-95

RELIEF OF SYMPTOMS
DIURETICS

- Relieve fluid retention signs/symptoms
  - Reduces preload without increasing CO
- **Individualize dosage**
  - Normalize JVP
  - Maintain dry weight
  - Prevent fatigue, hypotension, azotemia
    - Follow K+ and renal function
    - Too much diuresis
  - Furosemide – need to individualize dose because of wide variation in absorption

DIGITALIS INVESTIGATION GROUP STUDY (DIG)

- Randomized controlled trial in CHF & NSR
  - Dig vs. placebo plus ACEI (90%) & diuretics (80%)
- Digoxin has additional benefits to ACEIs & diuretics
  - **Reduced heart failure signs/symptoms and hospitalizations**
  - **Did not reduce mortality**

NEJM 97;336:525-33

EFFECTS OF DIGOXIN IN HF

- **Decreases s/s of HF**
- Improved NYHA classification
- Increased exercise time
- Modestly increased LVEF
- Increased CO
- **Decreased heart failure hospitalizations**
- **Does not improve survival in CHF**

DIG study NEJM 97;336:525-33. Hurst's the Heart. 13e. 2011

DIGOXIN SERUM LEVELS

- Narrow therapeutic window
- **"Therapeutic range"** about 0.5-2 ng/ml
  - Not helpful for efficacy or defining toxicity
- Low serum conentrations (< 1 ng/ml) are as beneficial as higher concentrations (1-1.5 ng/ml)
  - Additional benefits not seen at higher concentrations
- Higher concentrations increase risk of toxicity

DIGOXIN DOSES AND SERUM LEVELS

- **No target dose**
  - **Low doses (e.g., ≤ 0.125 mg/d for most)**
    - **Sufficient to achieve beneficial outcomes**
  - High doses increase risk of toxicity
- **Serum levels < 0.9 ng/ml** (e.g. 0.5-0.8 ng/ml)
  - Check to minimize risk of toxicity
  - **Decrease dose for higher levels**
  - **Do not increase dose for low levels**

Mayo Clin Proc 10;85:180-95 HFSA Guidelines 2010 J Am Geriatr Soc 12;60:616-31
Med Clin N Am 15;99:863-76

Digoxin for patients with AF and HF: paradise lost or not?

- **"achieving an SDC ≥ 1 ng/ml should no longer be recommended."**
  - "If lower SDCs can be achieved and maintained, digoxin could still be of use in HF … as a neurohormonal modulator"

Veldhuisen DJ. Editorial. Europ H J 13;34:1468-70

DIG CASE

- 85 y/o female with increasing confusion
  - Increasing weakness last few days with a fall
- PMH:
  - DM, AF, CVA 3 mon ago, PMR 2 mon ago, LDL
- Meds:
  - Prednisone, Dipyridamole/ASA, Metformin 500 mg/d, Furosemide 20 mg/d, KCl 20 mEq/d, Verapamil 80 mg TID, Digoxin 0.25 mg/d, Valsartan 160 mg/d, Metoprolol XL 50 mg/d, Ca++

DIG CASE

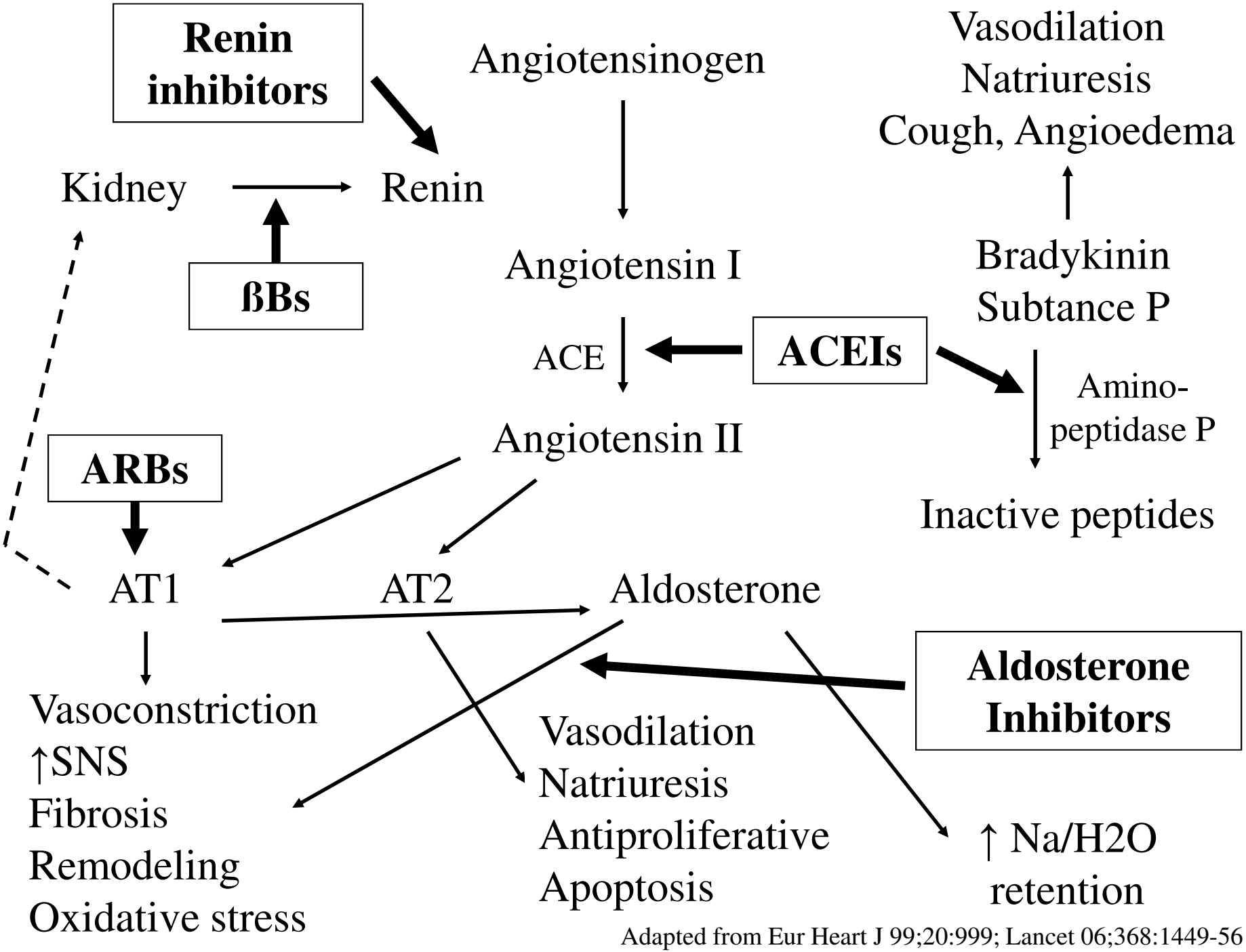
- 120s/50s, HR 60-75, wt. 66 kg
  - Lungs clear, Irregular/irregular
- BUN 19, SCr 0.7, K 4.4, Na 138, CO2 27
  - Tn WNL
- Dig level 2.7 (1 month ago 0.6) – confusion?
- Why dig level increased?
  - Verapamil reduces renal excretion
  - Verapamil increases digoxin bioavailability
  - Elderly, female, renal impairment, 0.125 mg/d more appropriate – Dose was increased 1 month prior

Circulation 06;113:2556-64

"Without question, the greatest advance in the treatment of chronic HF has been the application of agents that inhibit harmful neurohormonal systems that are activated to support the failing heart."

- **Adrenergic & Renin Angiotensin Aldosterone activation**
  - **Harmful effects**
  - **Inhibitors have beneficial effects**

Braunwald: Heart Disease: A Textbook of CV Medicine, 6th ed



Adapted from Eur Heart J 99;20:999; Lancet 06;368:1449-56

ACEI
CLINICAL EFFECTS

- **Improve symptoms**
  - ↓ preload
  - ↓ SVR and BP (afterload)
  - ↑ CO and exercise tolerance
- **Inhibit LV remodeling post-MI**
- Modify progression of chronic CHF
  - **↑ Survival – RRR ~28%, NNT 7-22 over 41 mon**
  - **↓ Hospitalizations – RRR ~26%**
  - Improve quality of life

CONSENSUS NEJM 87;316:1429-35 SOLVD NEJM 91;325:293-302

ACEI USE

- Start with **very low dose**
- **Increase dose as tolerated to HF target dose**
  - Dose shown to reduce CV events in studies
  - Try to attain at least intermediate dosages
  - "Do not delay the institution of ß blockers in patients because of a failure to reach target ACEI doses"
- **Monitor SCr & serum K+** after 1-2 wks
- Avoid fluid retention/hypovolemia
  - Adjust diuretic dose

ACC/AHA Guidelines 2005

Attempts Should Be Made to Attain Doses of Drugs Studied in Clinical Trials, and Rapid Outpatient Titration of Drugs Is Feasible

Mayo Clin Proc 10;85:180-95

TARGET ACEI DOSE FOR HF

	Initial (mg)	**Target (mg)**
Captopril	6.25 tid	50 tid
Enalapril	2.5 bid	10-20 bid
Lisinopril	2.5-5 qd	20-40 qd
Ramipril	2.5 qd	10 qd
Trandolapril	0.5 qd	4 qd

ACC/AHA Guidelines 2013. HFSA Guidellines 2010. NEJM 10;362:228-38

ARBs IN HF

- "benefit of ARBs in HF is generally regarded as a class effect … no head-to-head RCTs have been performed" (JAMA 12;307:1506-12)
- **Valsartan** – Initial dose 20-40 mg BID
  - Double dose ~q2wk to **target dose 160 mg BID**
- **Candesartan** – Initial dose 4-8 mg/d
  - Double dose ~q2wk to **target dose 32 mg/d**
- Losartan – Initial dose 50 mg/d
  - Increase dose to **target of 150 mg/d**

ACC/AHA Guidelines 2009. HFSA Guidelines 2010. NEJM 10;362:228-38

EFFICACY OF ACEI/ARB IN HF

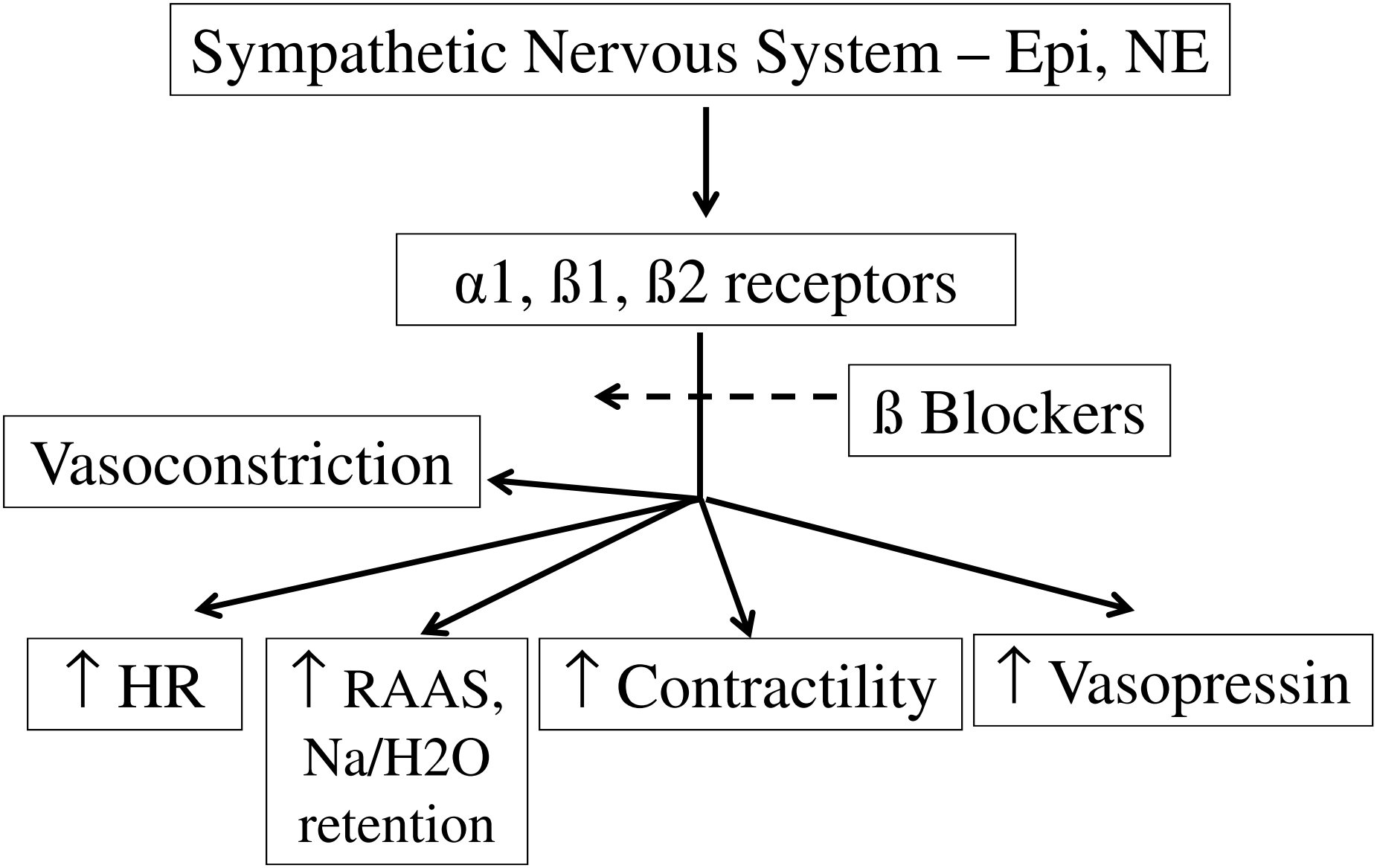
- Mortality efficacy
  - ACEIs effect is modest (RR 16-27%, p=0.003) vs. other agents (eg, ßB, aldosterone inhibitors)
  - ARBs have less benefit
- Symptom benefit
  - Modest long-term effects
  - Lower efficacy vs. other agents
- Do not fully block angiotensin II and escape of RAS from inhibition with long-term therapy

ESC HF 2016..

Lancet. Published online December 2, 2016 http://dx.doi.org/10.1016/S0140-6736(16)30969-2

ß BLOCKERS AND CHF

- Historically are contraindicated
  - Negative inotropic acitivity & slow HR
- Metoprolol, carvedilol, bisoprolol
- Increased sympathetic activation in the pathophysiology of CHF
  - Chronic cardiac NE – maladaptive
  - Hypertrophy, ischemia, & myocyte damage
- ß blockers inhibit negative actions of chronic increased sympathetic stimulation on failing heart


Sympathetic Nervous System – Epi, NE
α1, ß1, ß2 receptors
ß Blockers
Vasoconstriction
↑ HR
↑ RAAS, Na/H2O retention
↑ Contractility
↑ Vasopressin

ß BLOCKERS CLINICAL EFFECTS

- More RCTs with ßBs than with ACEIs
- In RCTs most patients on ACEI or ARB, diuretic
- **Improve symptoms (only long term)**
- **Improve survival – RRR ~34% within 1 y**, NNT 14-23 for 1 y
- Reduce remodeling/progression LV dysfunction
- Reduce hospitalization
- Reduce SCD

CIBIS-II Lancet 99;353:9-13 MERIT-HF JAMA 00;283:1295-1302 CHARM Lancet 03;362:767-71
COPERNICUS Circ 02;106:2194-99

ß BLOCKERS DOSING FOR HF

	Initial (mg)	**Target (mg)**
Bisoprolol* (Zebeta)	1.25 qd	10 qd
Carvedilol* (Coreg)	3.125 bid	25 bid (>85kg 50 bid)
Carvedilol CR* (Coreg CR)	10 qd	80 qd
Metoprolol succinate* (Toprol XL)	12.5-25 qd	200 qd

* FDA approved

ALDOSTERONE RECEPTOR ANTAGONISTS

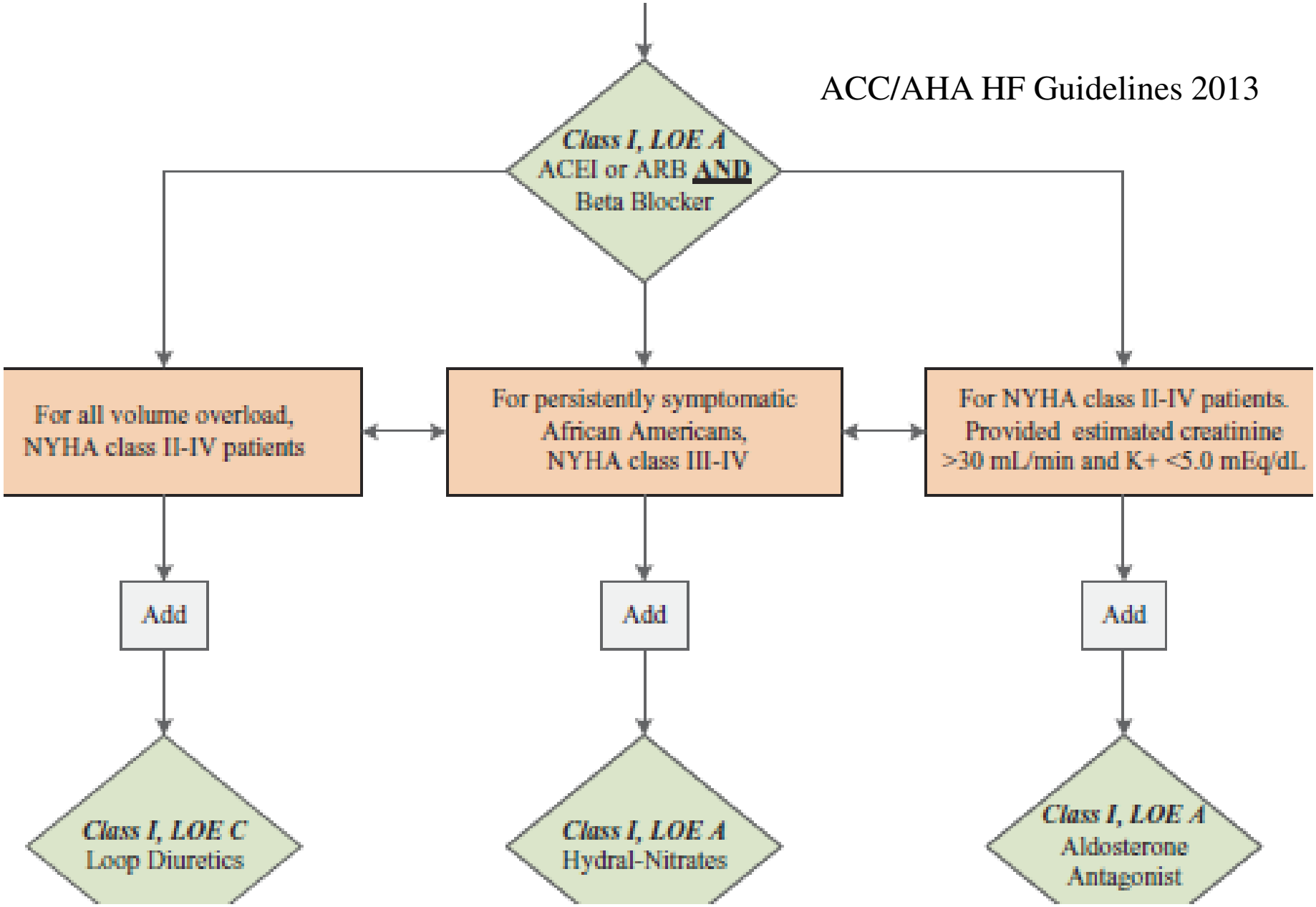
- Spironolactone
  - **NOT FDA**-approved for HF
  - Initial dose 12.5-25 mg/d; Max dose 25 mg 1-2xd
  - **RALES** study – Recent or current class IV HF
    - 12.5-50 mg/d vs. placebo
    - 30% decrease death, 35% decrease hospitalization
- Eplerenone (Inspra) **FDA-approved**
  - Improve survival of stable patients with LVSD (EF < 40%) & clinical evidence of CHF **after an acute MI**
  - Selective aldosterone blocker
  - Initial dose 25 mg/d; Max dose 50 mg/d

ACC/AHA HF 2013 – Stage B HFrEF Class I

- **All with history of MI or ACS and reduced EF**
  - **ACEIs** (or ARBs if intolerant) to prevent symptomatic HF and reduce mortality (LOE:A)
  - Evidence-based **ßBs** to reduce mortality (LOE: B)
  - **Statins** for secondary CV prevention. (LOE: A)
- **All with reduced EF** even if no MI history to prevent symptomatic HF
  - **ACEIs** (LOE: A)
  - **ßBs** (LOE: C)

HFrEF Stage C

ACC/AHA HF Guidelines 2013



ACC/AHA HF 2013 – Stage C HFrEF Drugs for Use in Selected Patient

- Hydralazine/isosorbide dinitrate
  - Reduce morbidity/mortality in self-described African Americans with NYHA III–IV receiving optimal ACEIs and ßBs, unless contraindicated (Class I, LOE: A)
- Digoxin
  - Can be beneficial, unless contraindicated, to decrease hospitalizations for HF (Class IIa, LOE: B)

DIGOXIN

- “Studies have suggested no benefit but rather increased mortality among patients taking digoxin even in the presence of atrial fibrillation. But digitalis has been declared dead many times and further retrospective analyses or registries add only weak evidence to weak evidence.”

Eur Heart J 14;35:470-3

"Triple Therapy" of HF With ACEI, ßB, and Aldosterone Antagonist May Triple Survival Time. Shouldn't We Tell Patients?

- Prescription and adherence to medical therapy for HF failure are disappointing despite convincing RCT evidence for ACEI, ßB, and aldosterone antagonism.
- Only one-half of clinicians mention increased lifespan, and very few suggest to the patient how large this gain might be
- **For patients whose lifespan is limited by HF, triple therapy triples lifespan**

J Am Coll Cardiol HF 14;2:545-8

IS THERE AN UPCOMING PARADIGM SHIFT IN THE MANAGEMENT OF HFrEF??

PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in HF)

- 8442 with NYHA II to IV with EF $\leq$ 40%
  - 72% Class II
  - BNP $\geq$ 150 (or NT-proBNP $\geq$ 600) or hospitalized within 1 y and BNP $\geq$ 100
  - Sacubitril/Valsartan 97/103 mg 2xd vs. Enalapril 10 mg 2xd
    - Most were also on recommended HF therapy
- The primary outcome a composite of death from CV causes and HF hospitalization

NEJM 14;371:993-1004

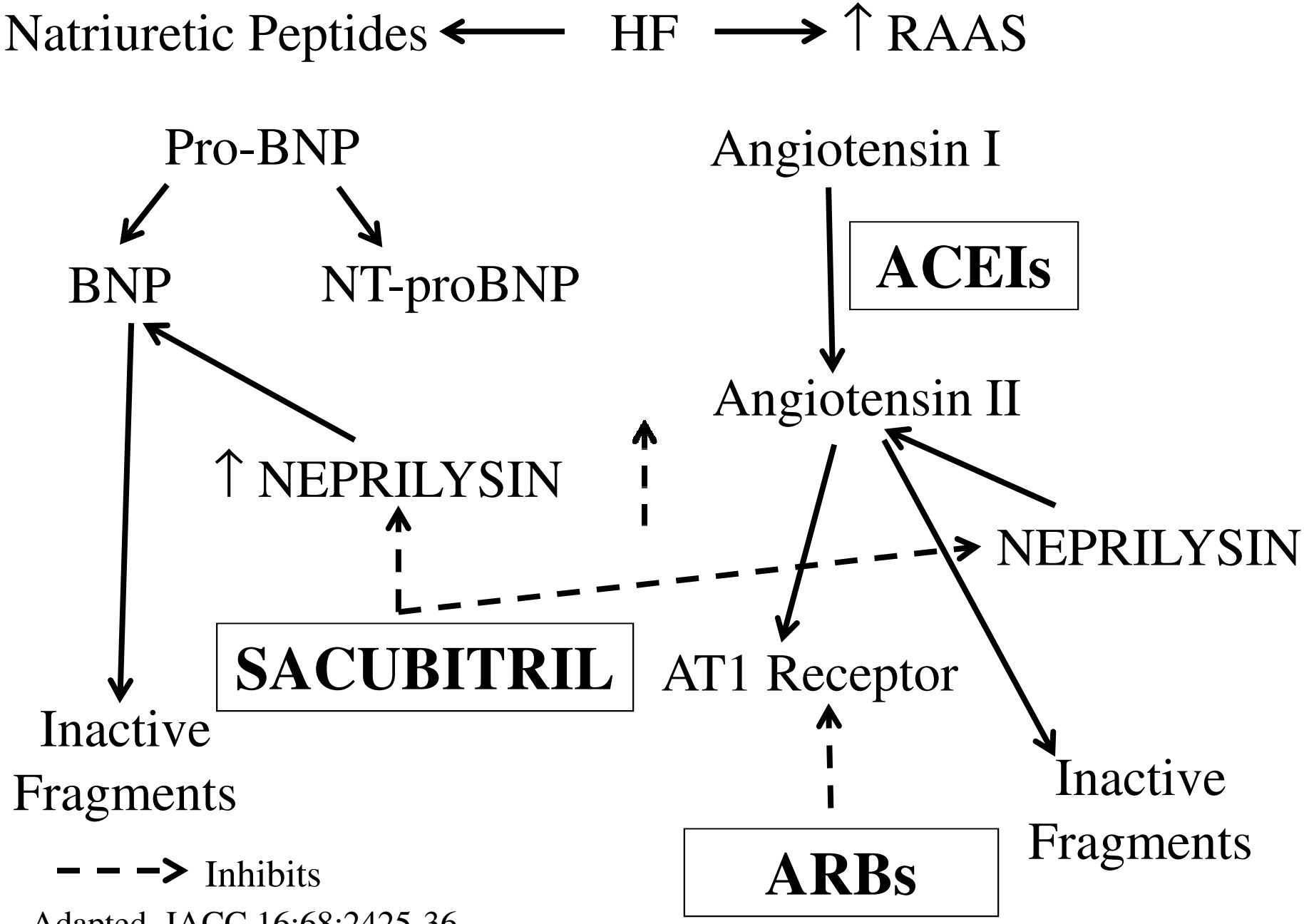
PARADIGM-HF

- Stopped early at median of 27 months due to overwhelming benefit
- Death/hospitalization
  - Sacubitril/Valsartan 21.8% vs Enalapril 26.5% (HR 0.80; p=<0.001) – NNT 21 over ~ 2 years
- CV Mortality 13.3% vs. 16.5% (HR 0.80, p<0.001)
- Superior to inhibition of the RAAS alone

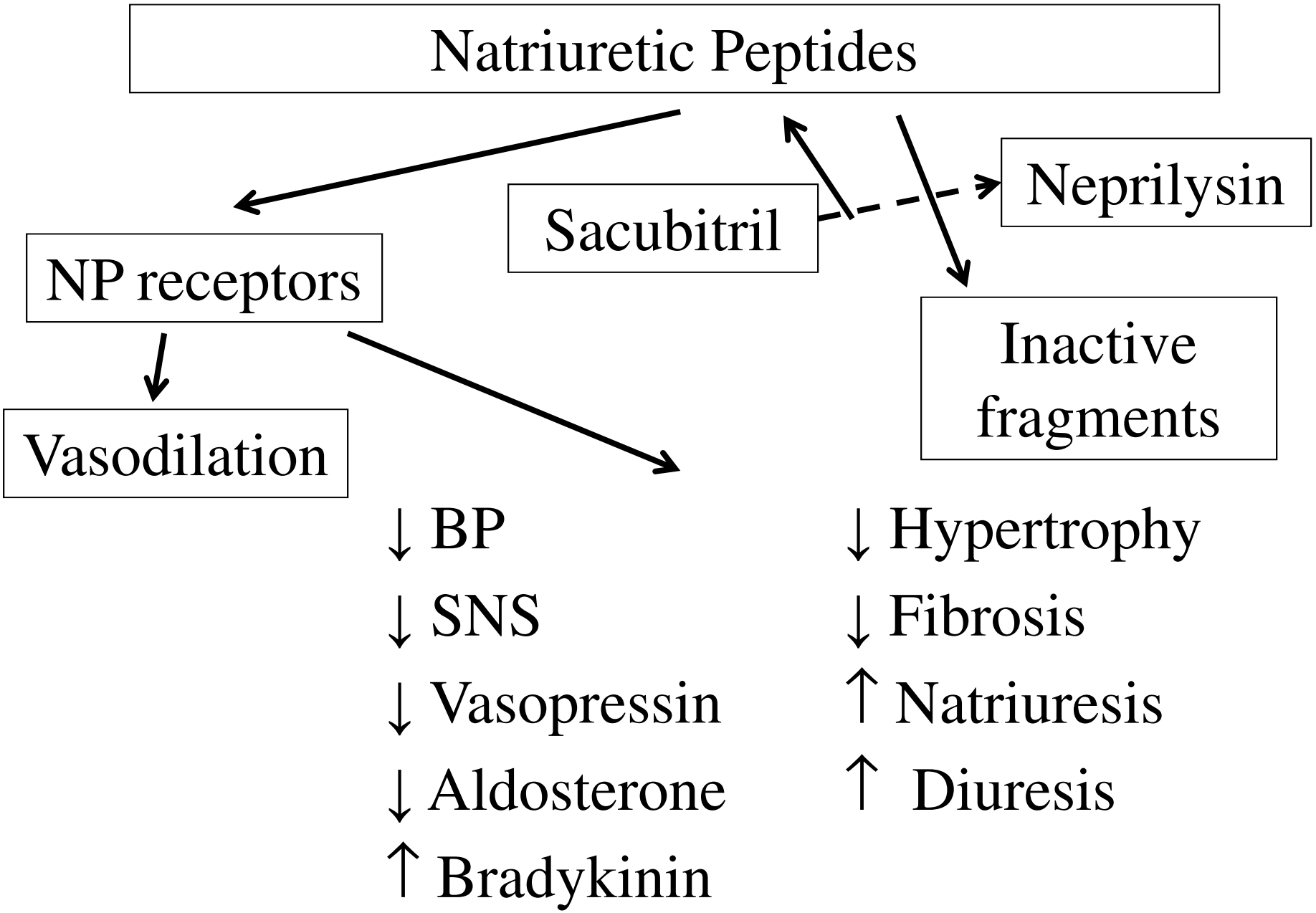
NEJM 14;371:993-1004

	Sacubitril/ ARB	Enalapril	P
Hypotension			
Symptoms	14%	9.2%	<0.001
Symptoms, SBP <90	2.7%	1.4%	<0.001
SCr Increased			
≥ 2.5	3.3%	4.5%	0.007
≥ 3	1.5%	2%	0.10
K Increased			
> 5.5	16.1%	17.3%	0.15
> 6	4.3%	5.6%	0.007
Cough	11.3%	14.3%	<0.001

NEJM 14;371:993-1004



Adapted. JACC 16;68:2425-36


Natriuretic Peptides
Neprilysin
Sacubitril
NP receptors
Inactive fragments
Vasodilation
↓ BP
↓ SNS
↓ Vasopressin
↓ Aldosterone
↑ Bradykinin
↓ Hypertrophy
↓ Fibrosis
↑ Natriuresis
↑ Diuresis

NEUROHORMONES IN HF

- Combined use of RAAS inhibitors and neprilysin inhibitors
  - Increased cardiac and vascular benefits vs. monotherapy
  - Potentiation of vasoactive peptides reduces adverse renal perfusion effects of ACEIs/ARBs

Lancet. Published online December 2, 2016 http://dx.doi.org/10.1016/S0140-6736(16)30969-2

Circulation 16;133:1115-24

NEUROHORMONES IN HF

- ACEIs plus neprilysin inhibition (omapatrilat)
  - May have > efficacy on cardiac function, BP, mortality, and decrease hospitalization than ACEI monotherapy
  - < renal adverse effect than ACEI alone
  - Significantly increases bradykinin
    - Increased risk of angioedema
  - Studies were stopped

OVERTURE. Circ 02;106:920-26

Sacubitril/Valsartan (Entresto)

- Angiotensin Receptor Neprilysin Inhibitor (ARNI)
- Neprilysin degrades vasoactive peptides
  - Neprilysin may be increased in HF (part of pathophys maladaptation in HF)
- Sacubitril is a neprilysin inhibitor
- Valsartan is an ARB

Pharmacist's Letter/Prescriber's Letter. September 2015.

Sacubitril/Valsartan (Entresto)

- **FDA-approved indication**
  - **Reduce risk of CV death & hospitalization for HF in NYHA Class II-IV HF & decreased EF**
- When used will be **in place of ACEI or ARB**

PL Detail-Document, New Drug: Entresto (Sacubitril/Valsartan). Pharmacist's Letter/Prescriber's Letter. September 2015

Sacubitril/Valsartan (Entresto)

- **ADE**
  - **Hypotension, hyperkalemia, cough, dizziness, angioedema and renal failure**
- **Contraindicated**
  - **h/o angioedema with previous ACEI/ARB**
  - **Concomitant with ACEI – ↑ risk angioedema**
- **Precautions**
  - **Monitor for s/s angioedema/ hypotension**
  - **SCr & serum K should be monitored periodically**

PL Detail-Document, New Drug: Entresto (Sacubitril/Valsartan). Pharmacist's Letter/Prescriber's Letter. September 2015

Sacubitril/Valsartan (Entresto)

- Sacubitril/Valsartan 24/26 mg, 49/51 mg, 97/103 mg tabs
- Initial dose is 49/51 mg 2xd
  - Start with 24/26 mg 2xd if: no h/o of ACEI or ARB, on low-dose ACEI or ARB, eGFR < 30, or moderate liver disease – start 24/26 mg 2xd
- Increase q2-4wk as tolerated to target dose of 97/103 mg 2xd

PL Detail-Document, New Drug: Entresto (Sacubitril/Valsartan). Pharmacist's Letter/Prescriber's Letter. September 2015

Neprilysin Inhibition – A Novel Therapy for HF

- "The beneficial results seen in PARADIGM-HF may apply to a wide spectrum of patients, even those who are currently receiving the best possible therapy."

Jessup M. edit NEJM 14;371:1062-4

Number of trials with p <0.05 to provide the same level of evidence as PARADIGM-HF on the primary outcome and CV death

Number trials p<0.05	P required by 1 trial to provide same evidence	PARADIGM-HF p for primary endpoint	PARADIGM-HF p for CV death
1	0.05		
2*	0.00125*		0.00008 (equiv 2-3 trials)
3	0.00003125		
4	0.00000078	0.0000004 (equiv 4-5 trials)	
5	0.0000000195		

* Usual regulatory requirement – 2 trials at p<0.05 or 1 trial at p<0.00125

Heart 2016;102:1342–1347

AHA 2016 Stage C HFrEF Recommendations – **Class I**

- **Clinical strategy of inhibition of RAAS with:**
  - **ACEIs (LOE A) OR**
  - **ARBs (LOE A) OR**
  - **ARNI (LOE B-R)**
- **<u>IN CONJUNCTION WITH</u>**
  - **Evidence-based BBs AND**
  - **Aldosterone antagonists in selected patients**
- Is recommended to **reduce morbidity and mortality**

Circulation. Ahead of print May 20, 2016

AHA 2016 Stage C HFrEF Recommendations – **Class I**

- **ACEIs beneficial with prior or current symptoms of chronic HFrEF to reduce morbidity/mortality (LOE A)**
  - **Class effect**
  - Although the use of an **ARNI in lieu of an ACEI has been found to be superior, for those patients for whom ARNI is not appropriate, continued use of an ACEI for all classes of HFrEF remains strongly advised**

AHA 2016 Stage C HFrEF Recommendations – Class I

- **ARBs** to reduce morbidity& mortality **recommended** with prior or current symptoms of chronic HFrEF who are **intolerant to ACEIs because of cough or angioedema** (LOE A)
  - **Head-to-head comparisons of an ARB vs. ARNI do not exist.**
  - **For patients for whom an ACEI or ARNI is inappropriate, use of an ARB remains advised.**

AHA 2016 Stage C HFrEF Recommendations – Class I

- **Chronic symptomatic HFrEF NYHA II/III who tolerate ACEI or ARB, replacement by an ARNI recommended to further reduce morbidity/mortality** (LOE B-R)
  - **Should not be administered concomitantly with ACEIs or within 36 h of the last dose of an ACEI (Class III Harm, LOE B-R)**
  - **Should not be administered with h/o angioedema (Class III Harm, LOE C-EO)**

2016 ESC HF Guidelines

- Sacubitril/valsartan is recommended as a replacement for an ACEI to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEI, a ßB and an MRA

Eur H J 16;37:2129-2200

NEW PARADIGM?

- "The newly available valsartan/sacubitril … promises to disrupt this stack of therapies [ACEI, ßB, spironolactone]"
- "… this agent is anticipated to displace the cornerstone of ACEi/ARB, on top of which the other therapies have been tested."

Udelson JE, Stevenson JW. Circ 16;133:2671-86

WHEN TO USE SACUBITRIL/VALSARTAN

- PARADIGM-HF trial did not include ACEI or ARB naïve with newly diagnosed HFrEF
- Should ACEIs/ARBs be used for awhile before switch to sacubitril/valsartan?
- FDA includes dosing start in ACEI/ARB-naïve patients
- Conducting a trial in ACEI/ARB-naïve probably will not occur

Heart 2016;102:1342–1347

USE OF SACUBITRIL/VALSARTAN

- New diagnosis of NYHA class II-IV HFrEF
  - Use ACEI (or ARB) rather than sacubitril-valsartan for initial therapy (Grade 2C)
  - Some have suggested sacubitril-valsartan as initial therapy for HFrEF
    - "we feel that at this time there is insufficient clinical experience to recommend its use as initial therapy"

Use of angiotensin II receptor blocker and neprilysin inhibitor in heart failure with reduced ejection fraction. UpToDate. Updated 10/25/16

USE OF SACUBITRIL/VALSARTAN

- Stable mild-moderate HFrEF with all of the following, "we suggest use of sacubitril-valsartan in place of ACEI/ARB (Grade 2B)"
  - BNP ≥150 or NT-proBNP ≥600 or hospitalized for HF within previous 12 mon
  - BNP ≥100 or NT-proBNP ≥400, SBP ≥100, eGFR ≥30, and tolerance to ACEI or ARB (eg, enalapril 10 mg 2xd for ≥4 wks)
  - Other factors: patient acceptance/tolerance of drug changes, limited experience with sacubitril-valsartan outside of controlled trials, and cost

Use of angiotensin II receptor blocker and neprilysin inhibitor in heart failure with reduced ejection fraction. UpToDate. Updated 10/25/16

HF BIOMARKERS AS A MANAGEMENT TOOL

- BNP and NT-proBNP should decrease after several days of effective diuresis
- Increased risk of death and readmit if discharge levels are not < admit – not euvolemic
- Discharge "dry" level may be useful to judge future decompensated HF ("baseline" BNP)
- May be useful to help titrate therapy
  - ↑ levels may suggest need for increasing therapy

AJM 16;129:560-7 JACC 16;68:2690-707

EFFECTS OF NEPRILYSIN INHIBITION ON SERUM PEPTIDES

- May be prognostic benefit to biomarker-guided therapy – ongoing study GUIDE-IT
- Decreases breakdown of BNP
  - **Increase in serum BNP**
  - ACEIs & ARBs improve hemodynamics and LV function leading to decrease in serum BNP
- Increased BNP
  - Decreases stimulus for natriuretic peptide synthesis
  - **Decrease in serum NT-proBNP**

J Am Coll Cardiol 16;68:2425-36

Prognostic Implications of Changes in NT-proBNP in Patients With HF

- Subanalysis of PARADIGM-HF data
  - 2,080 had NT-proBNP measured, 62% >1000 pg/ml
- At 1 month in 24% the level was $\leq$ 1000
  - 59% lower risk of HF hospitalization & CV death vs. >1000
  - 31% on combination $\leq$ 1000 vs 17% on enalapril
- Decrease in NT-proBNP – lower risk of CV death or HF hospitalization regardless of treatment group

JACC 16;68:2425-36

IVABRADINE (CORLANOR)

- Slows HR by inhibiting I(f) the funny current
  - No effect on contractility
- Reduces risk of hospitalization for worsening HF with EF < 35% who are in sinus rhythm with resting HR > 70/min & on max doses of ßBs or a contraindication to ßB
  - Has not been shown to reduce mortality
- Expensive ~$375/month

Med Lett Drugs Ther. 15;57:75-6

AHA 2016 Stage C HFrEF Recommendations – Class IIa

- **Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a ßB at max tolerated dose, and who are in NSR ≥ 70 at rest (LOE B-R)**

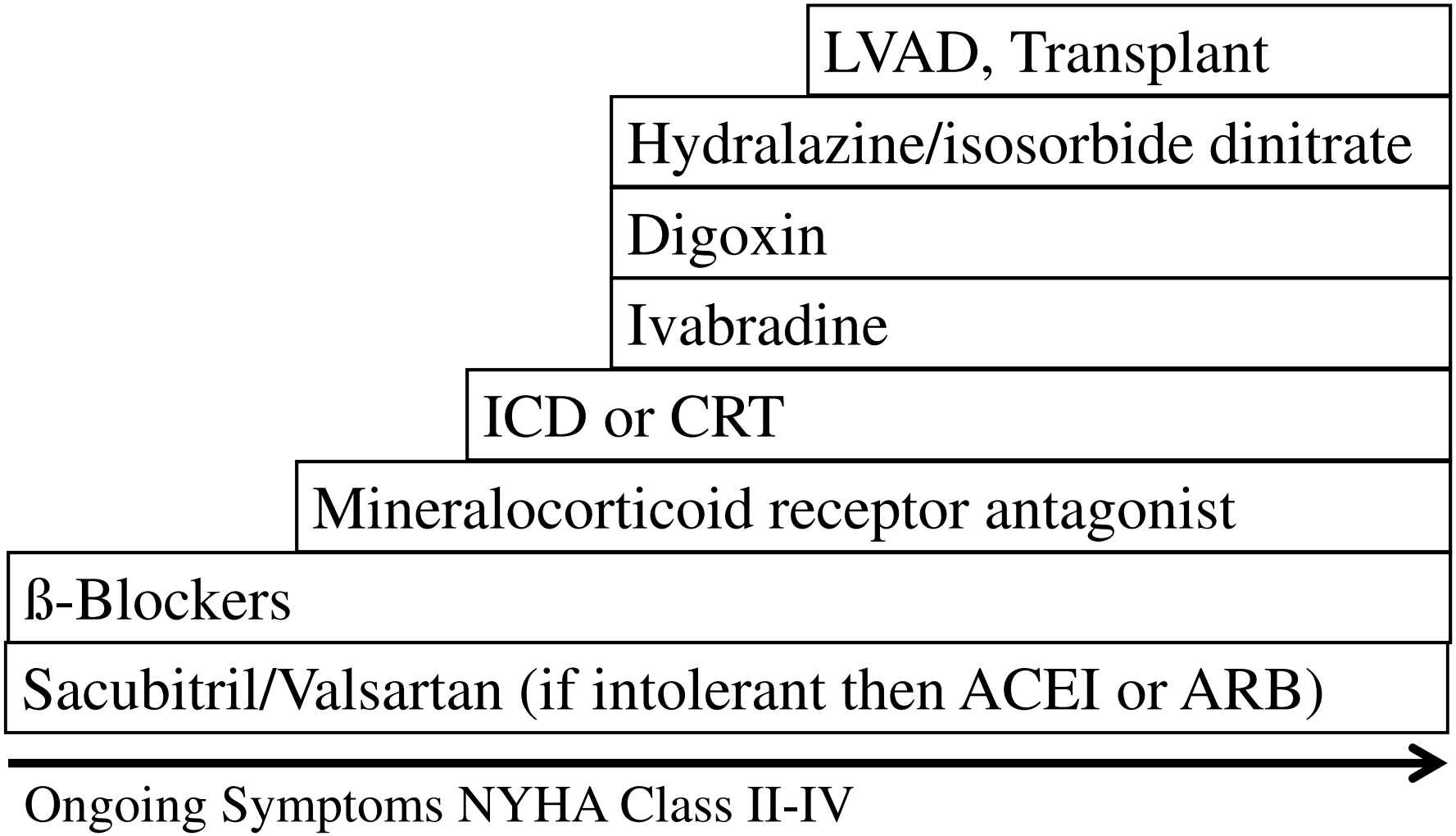
Benefits of Evidence-Based Therapies In HFrEF

	RR all-cause mortality (%)	**NNT over time**	**NNT over 12 mo**
ACEI/ARB	17	22 over 42 mo	77
ARNI	16	36 over 27 mo	80
ßB	34	28 over 12 mo	28
Aldo antag	30	9 over 24 mo	18
Hydralazine/ nitrate	43	25 over 10 mo	21
CRT	36	12 over 24 mo	24
ICD	23	14 over 60 mo	70

ARNI, angiotensin receptor neprilysin inhibitor; CRT cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator

JAMA Cardiol 16;1:714-7

WILL THIS BE THE PARADIGM SHIFT IN THE MANAGEMENT OF HFrEF?



Heart 2016;102:1342–1347