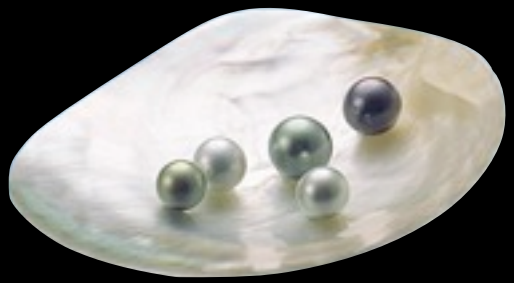
Optimization of medical therapy in HFrEF

Pearls and Pitfalls



Rungsrit Kanjanavanit MD.

Why HF is an important health problem ?

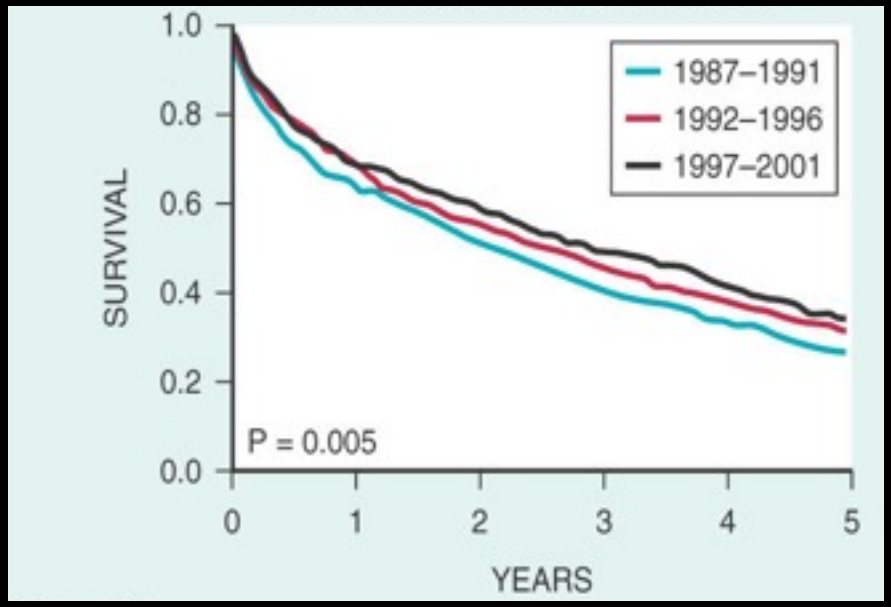
- Common
- Disabling
- Deadly
- Costly

But… treatable

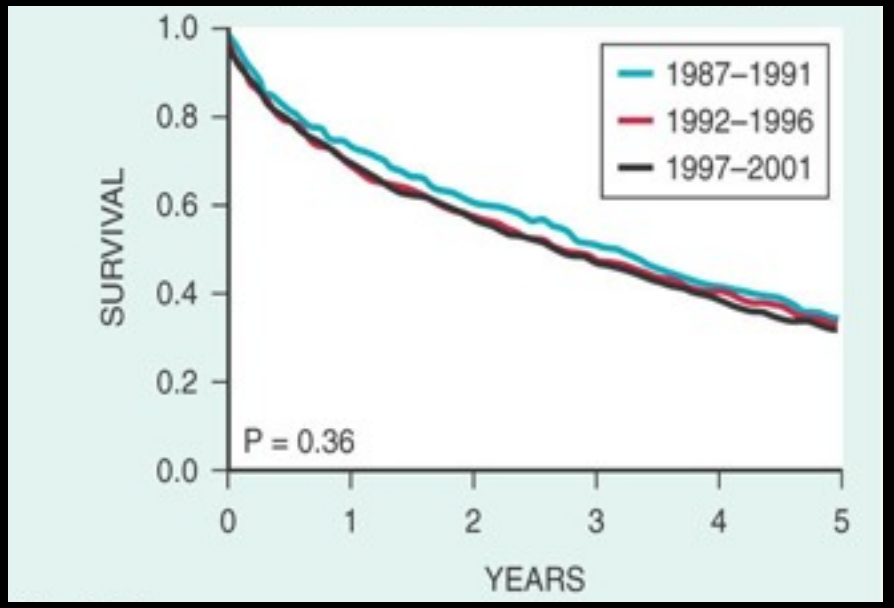
Evidences from large epidemiologic surveys suggested less than expected improvement in survival in patients with HF

why ?

HF reduced EF



HF preserved EF

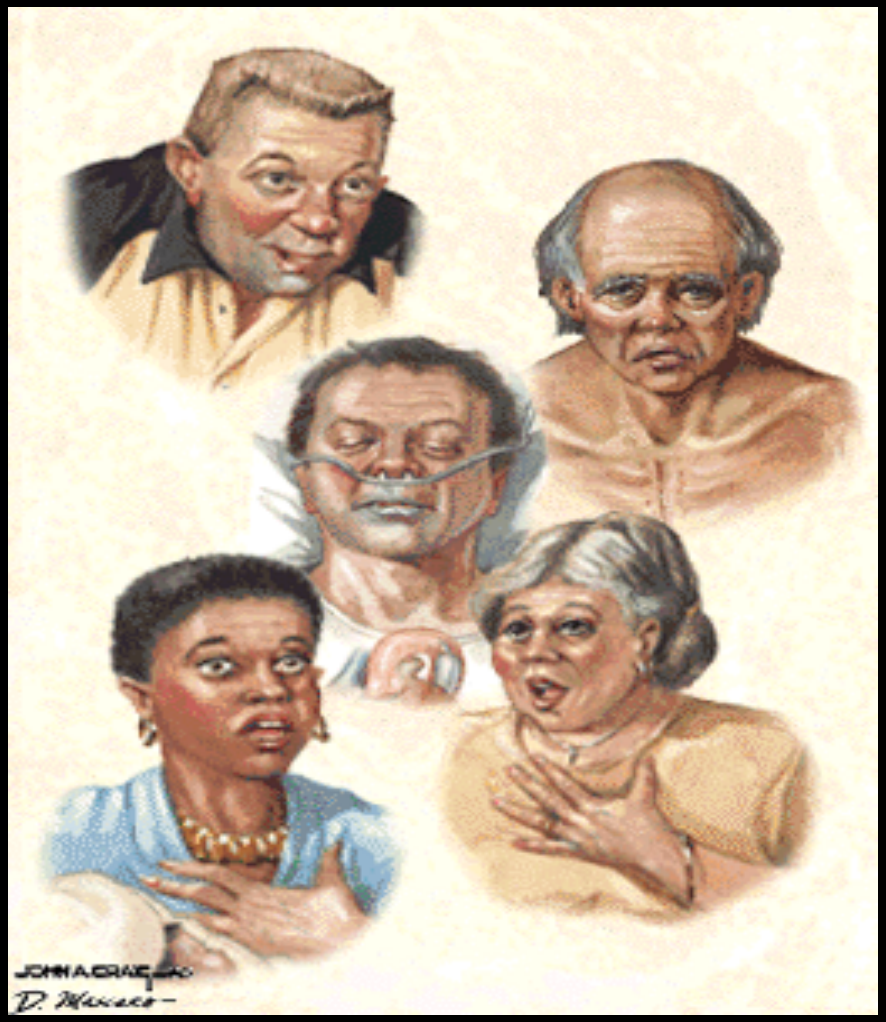


Survival curves for patients with heart failure
Olmsted County, Minnesota

Owan T et al N Engl J Med 355:308, 2006

Many faces of heart failure

Similar symptoms – Different pathology



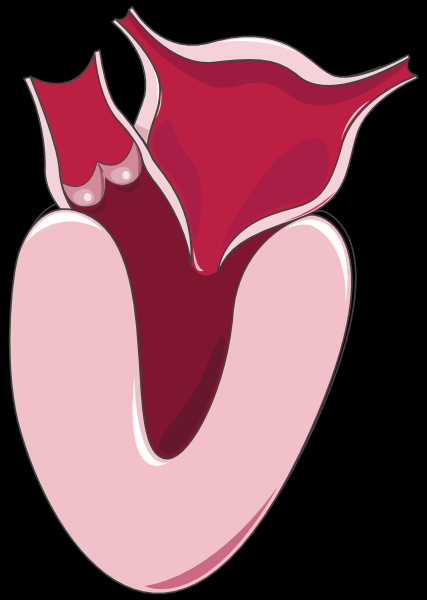
Classification of HF

Classification	EF (%)	Description
HFrEF	≤40	Sys HF Efficacious therapy demonstrated
HFpEF	≥50	"diastolic" HF
HFpEF, borderline	40-49	Characteristics treatment,outcomes similar to HFpEF
HFpEF, improved	>40	Previous HFrEF

ACC/AHA Guidelines 2013

Diastolic and systolic dysfunctions

Normal



Diastolic dysfunction

Sustained apex
S4

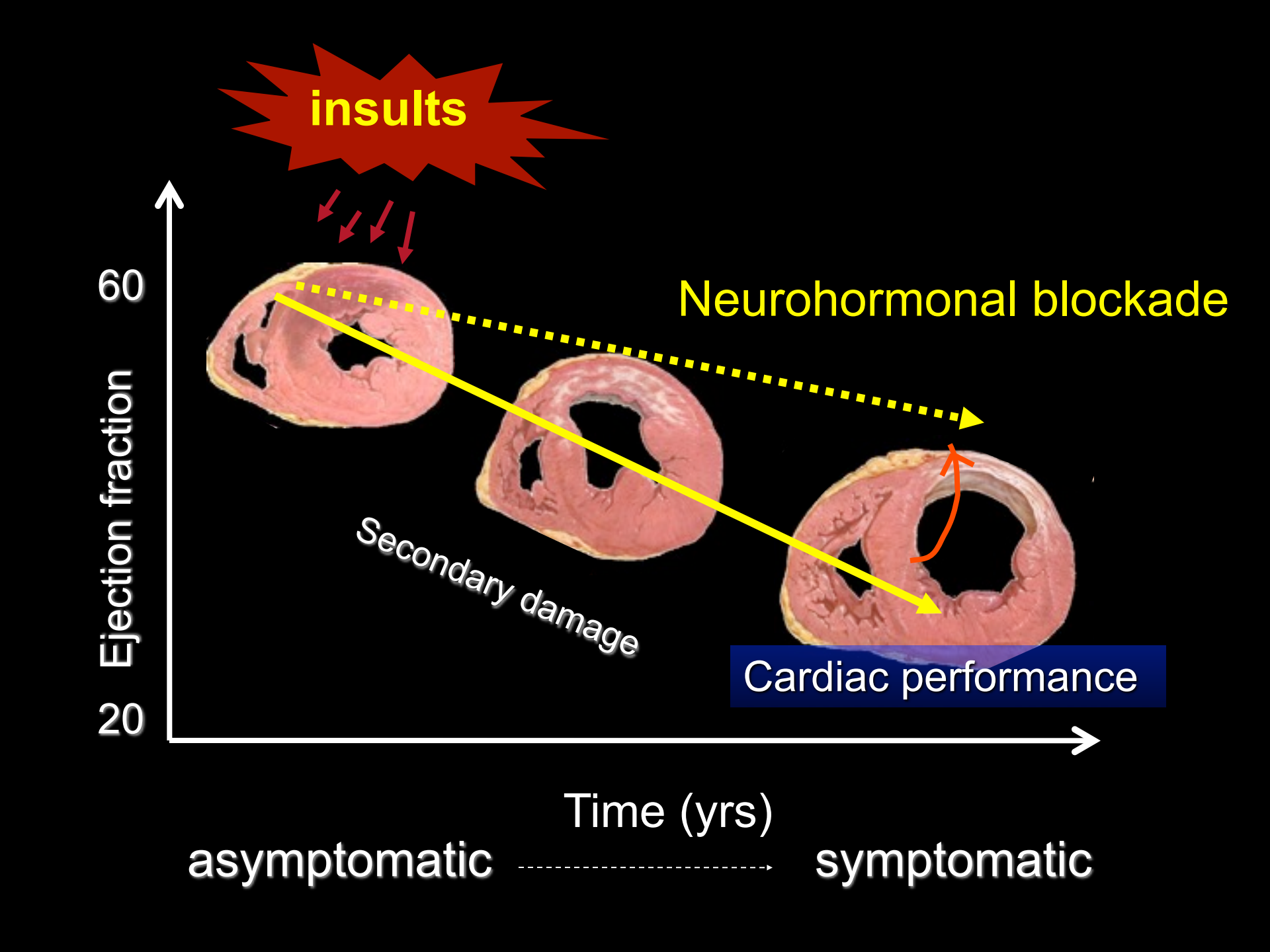
Systolic dysfunction

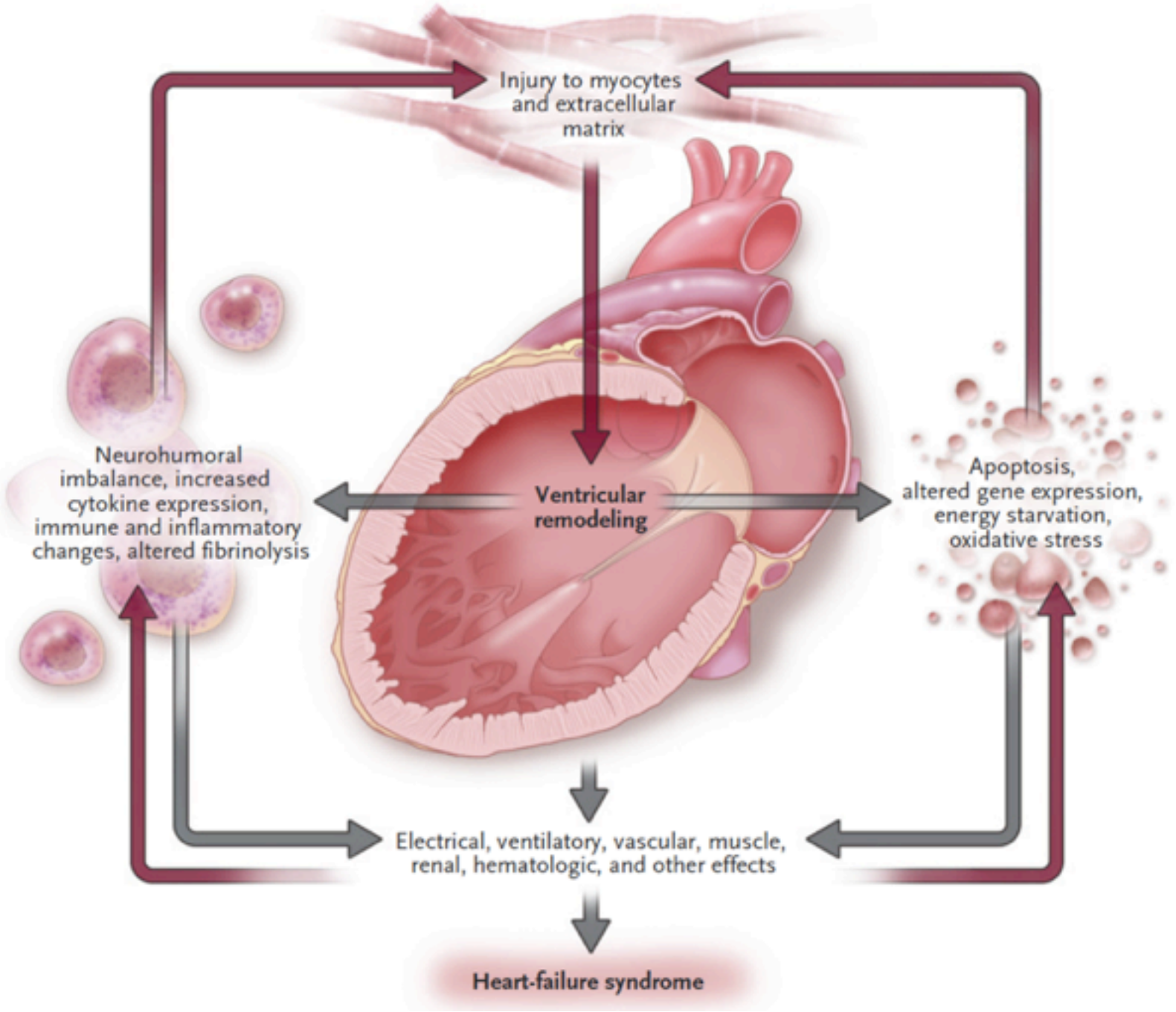
Diffused apex
S3


"Heart failure" should NEVER be
a final diagnosis.

Question to ask

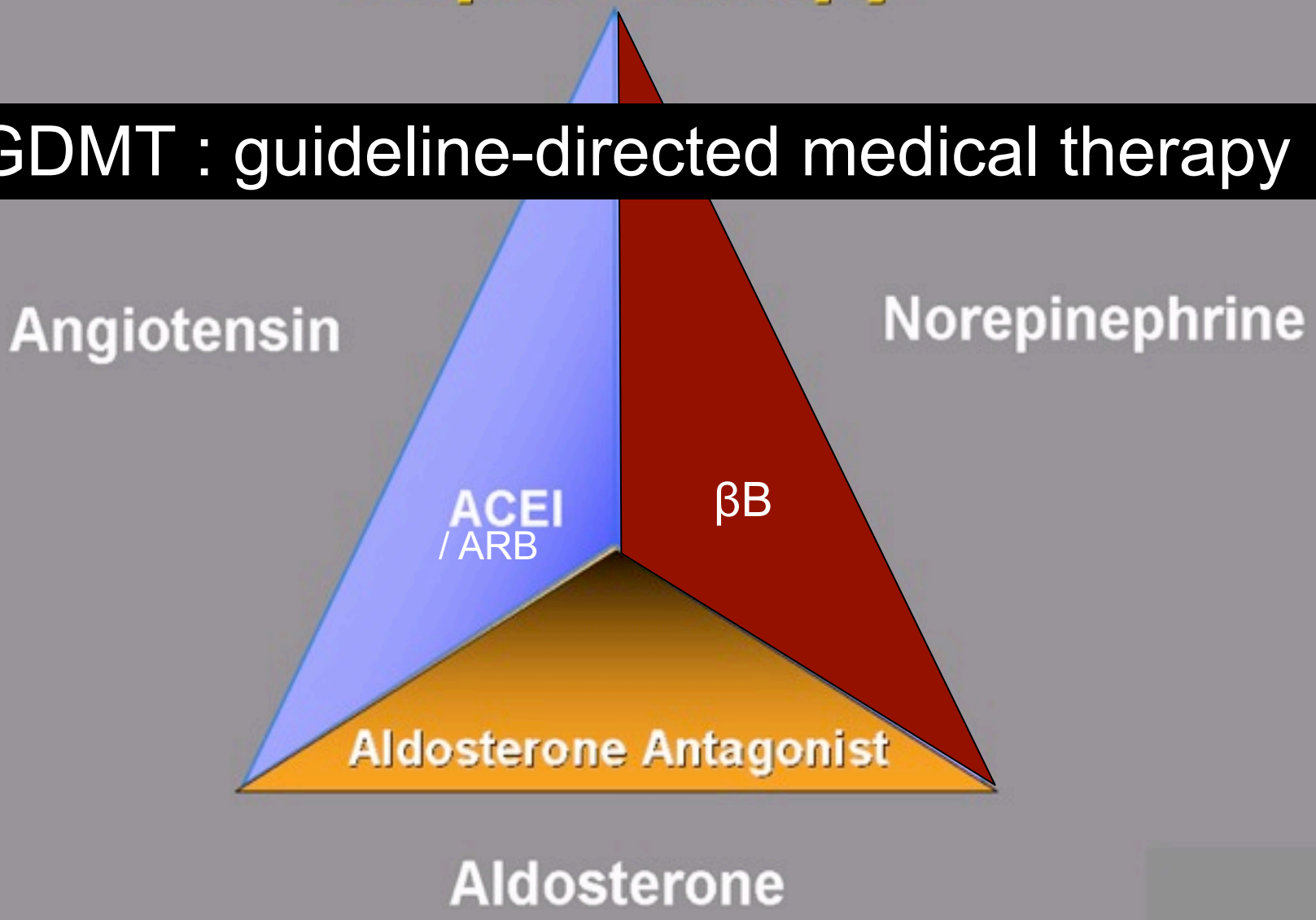
- Is it HF ?
- What is underlying cardiac pathology ?
- Does the the pathology responsible for HF signs and symptoms ?
- What is the cause of the cardiac pathology ?
- What is the precipitating cause of ADHF ?


insults
60
Ejection fraction
20
Neurohormonal blockade
Secondary damage
Cardiac performance
Time (yrs)
asymptomatic
symptomatic


Injury to myocytes and extracellular matrix
Neurohumoral imbalance, increased cytokine expression, immune and inflammatory changes, altered fibrinolysis
Ventricular remodeling
Apoptosis, altered gene expression, energy starvation, oxidative stress
Electrical, ventilatory, vascular, muscle, renal, hematologic, and other effects
Heart-failure syndrome

Triple Therapy

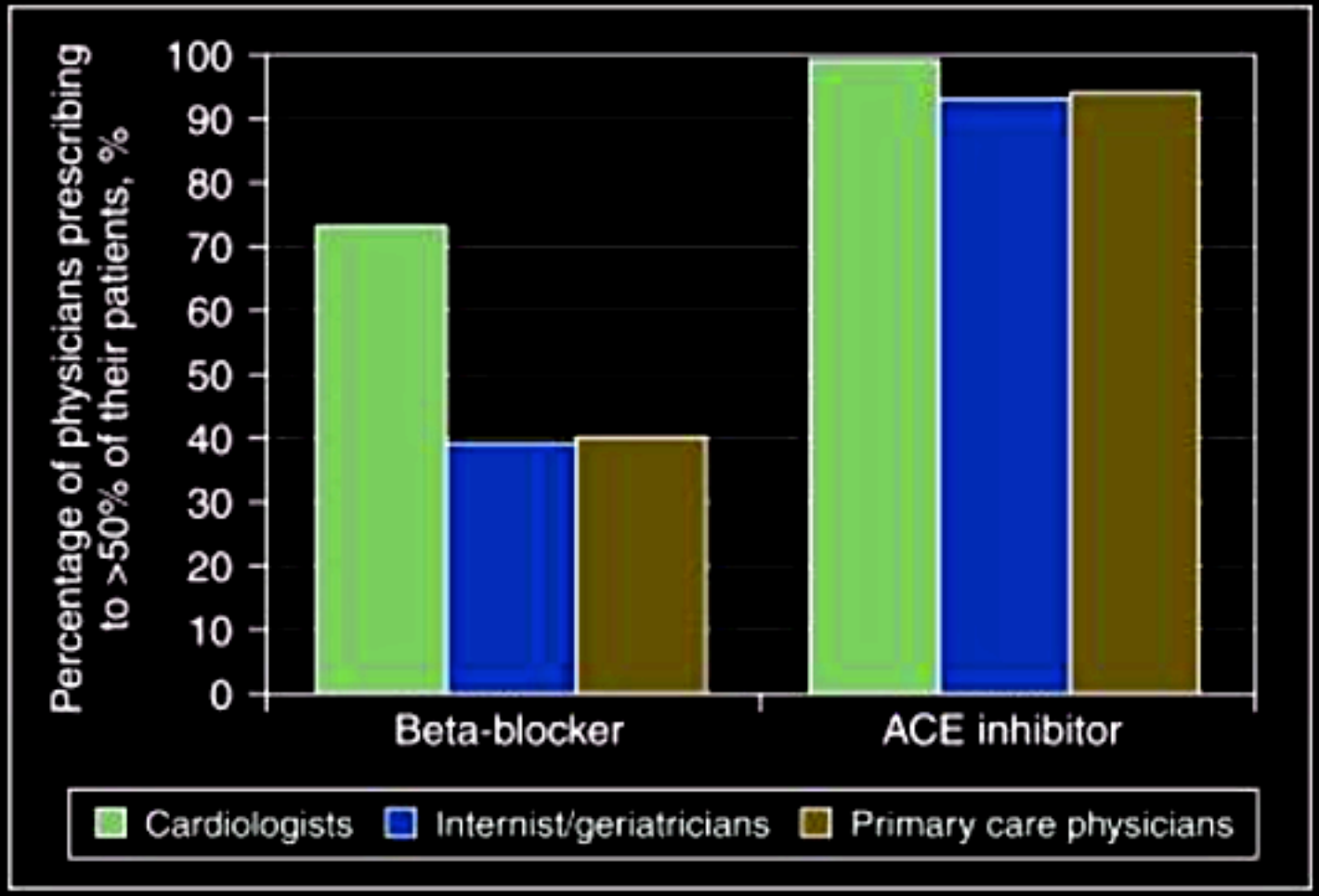
GDMT : guideline-directed medical therapy



ABCDE of HF

A. ACEI, AA, ARB
B. Beta blocker
C. CRT
D. Digitalis, Diuretics
E. Education

Physicians adherence to GDMT

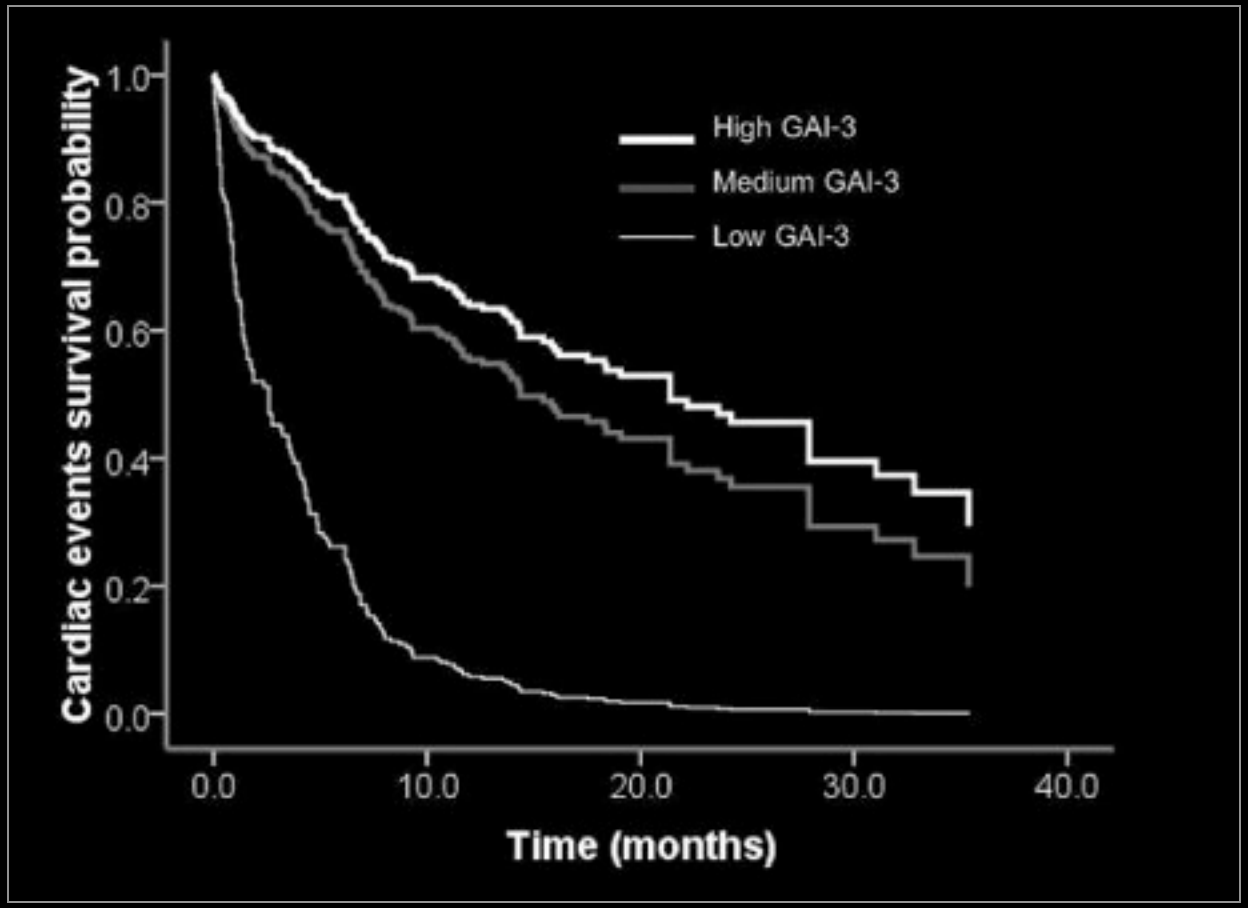


Eur Heart J 2008;29:1739-1752.)

Guideline adherence and cardiac events

(CVS death and rehospitalization)

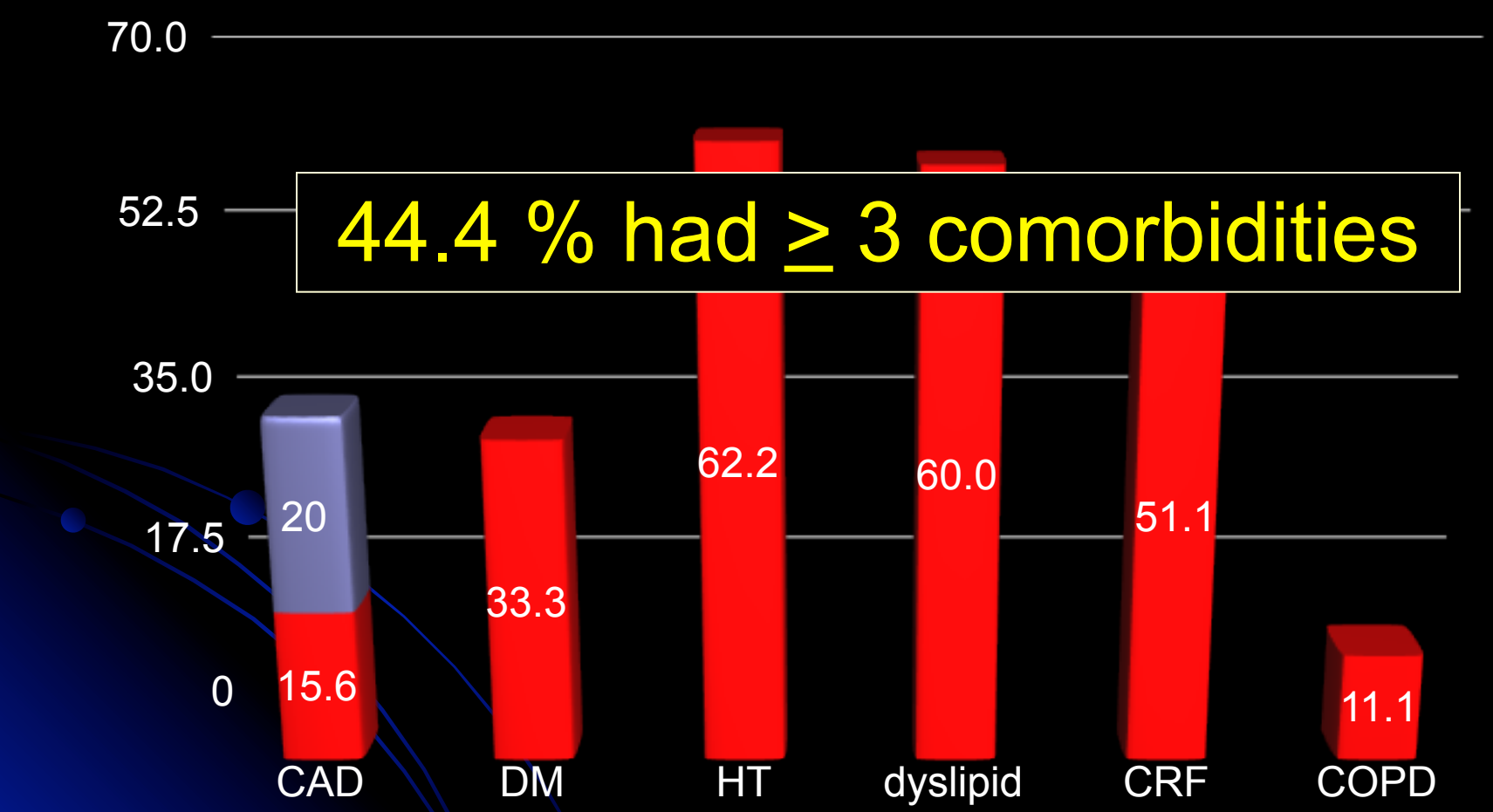
Nakornping Hospital Chiang Mai , Thailand



Multivariate analysis

Suntheep Batra, Surarong Chinwong. APCHF 2012

Co-morbidities CMU HF clinic



“optimized medical therapy”

Worsening renal function

- Some rise in BUN/Cr is to be expected and may actually be a marker of ACEi benefit
- An increase in Cr up to 50% above baseline or up to 3 mg% is acceptable
- K+ < 6 mmol/l is acceptable
- Stop NSAID's, other nephrotoxic drugs
- Avoid excessive diuresis
- Try lower the dose before discontinue permanently

Cough while taking ACEI

- Exclude pulmonary edema or bronchial diseases
- Rarely requires discontinuation
- Intolerable, disturbs sleep and proven to be due to ACEi (withdrawal/rechallenge)
  - substitute with A II receptor blockers

When to use Angiotensin Receptor Blockers

- ARB is ,at best, only as good as ACEI in treating HF
- Intolerant to ACE inhibitors *for reasons other than hyperkalemia or renal insufficiency*
- Do NOT use ARB instead of ACEI in patients who can tolerate ACEI
- Adding ARB to ACEI/ β-blocker can further reduce mortality and rehospitalization
- Angioedema has been reported with ARB

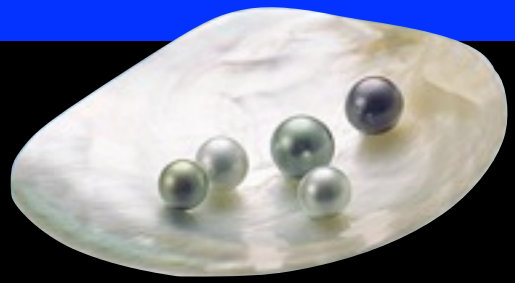
HFSA 2010 Practice Guideline ARBs

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose in Clinical Trials
Candesartan	Blopress	4-8 mg qd	32 mg qd	24 mg/day
Losartan	Cozaar	12.5-25 mg qd	150 mg qd	129 mg/day
Valsartan	Diovan	40 mg bid	160 mg bid	254 mg/day

Heart Failure Society of America

Lindenfeld J, et al. HFSA 2010 Comprehensive Heart Failure Guideline. J Card Fail 2010;16:e1-e194.

Implementation of β blocker therapy -When?



A simplified criteria

1. Edema free
2. Not requiring intravenous medication for HF

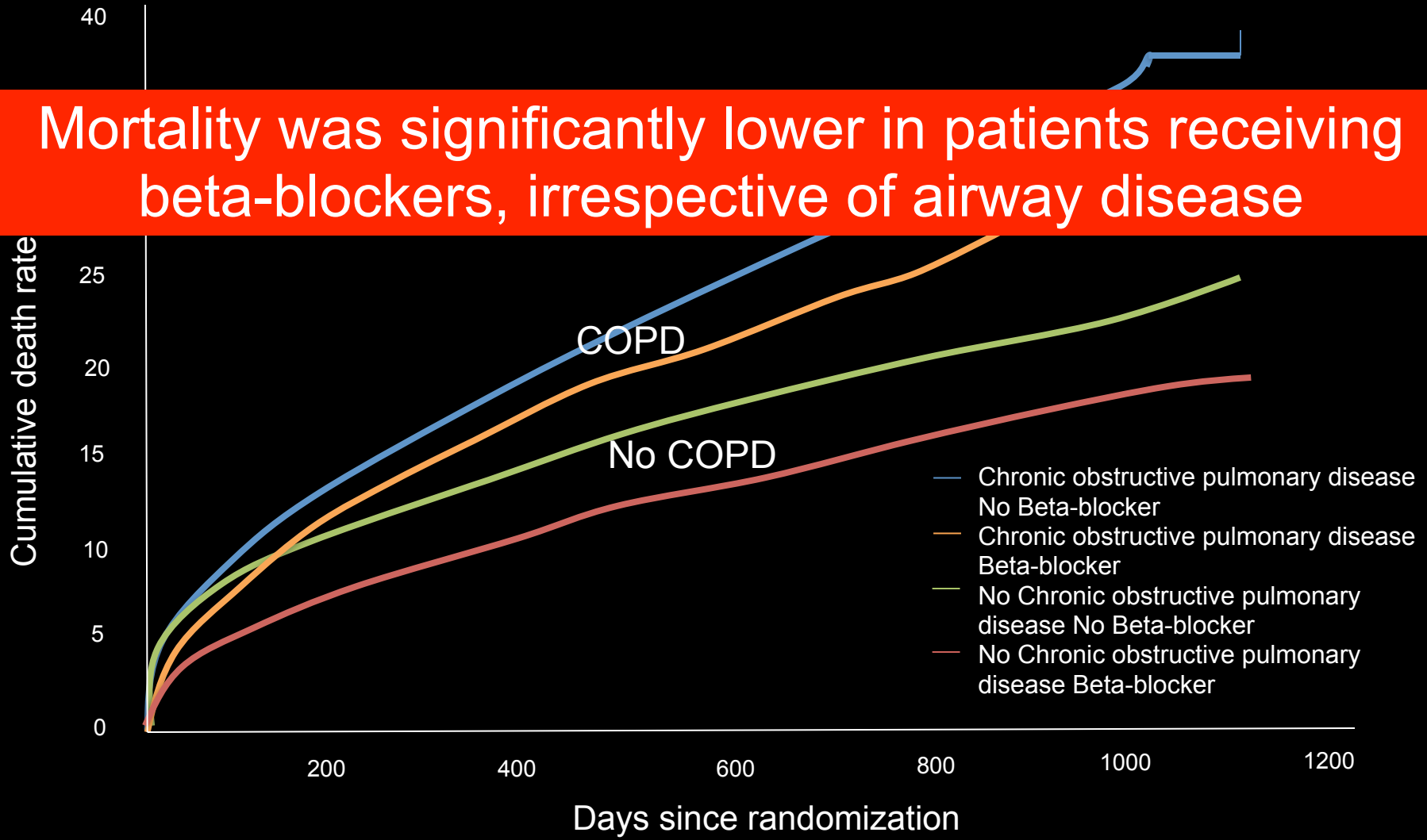
Which and what dose

	Starting dose(mg)	Target dose(mg)
Bisoprolol	1.25 od	10 od
Metroprolol CR/XL	12.5-25 od	200 od
Carvedilol	3.125 bid	25-50 bid
Nebivolol	1.25 od	10 od

Titration period – weeks to months

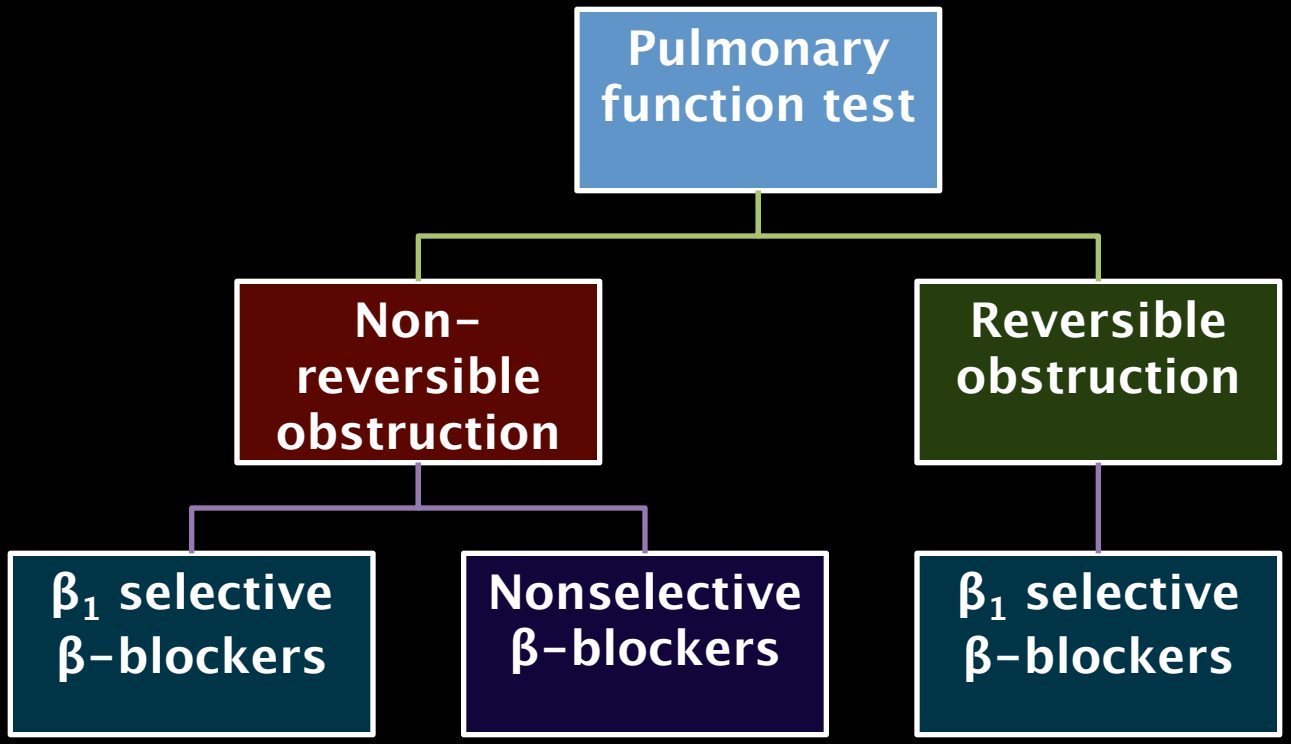
All-cause mortality rate by COPD status and β-blocker use

Mortality was significantly lower in patients receiving beta-blockers, irrespective of airway disease



Hawkins N M et al. Eur J Heart Fail 2009;11:292-298

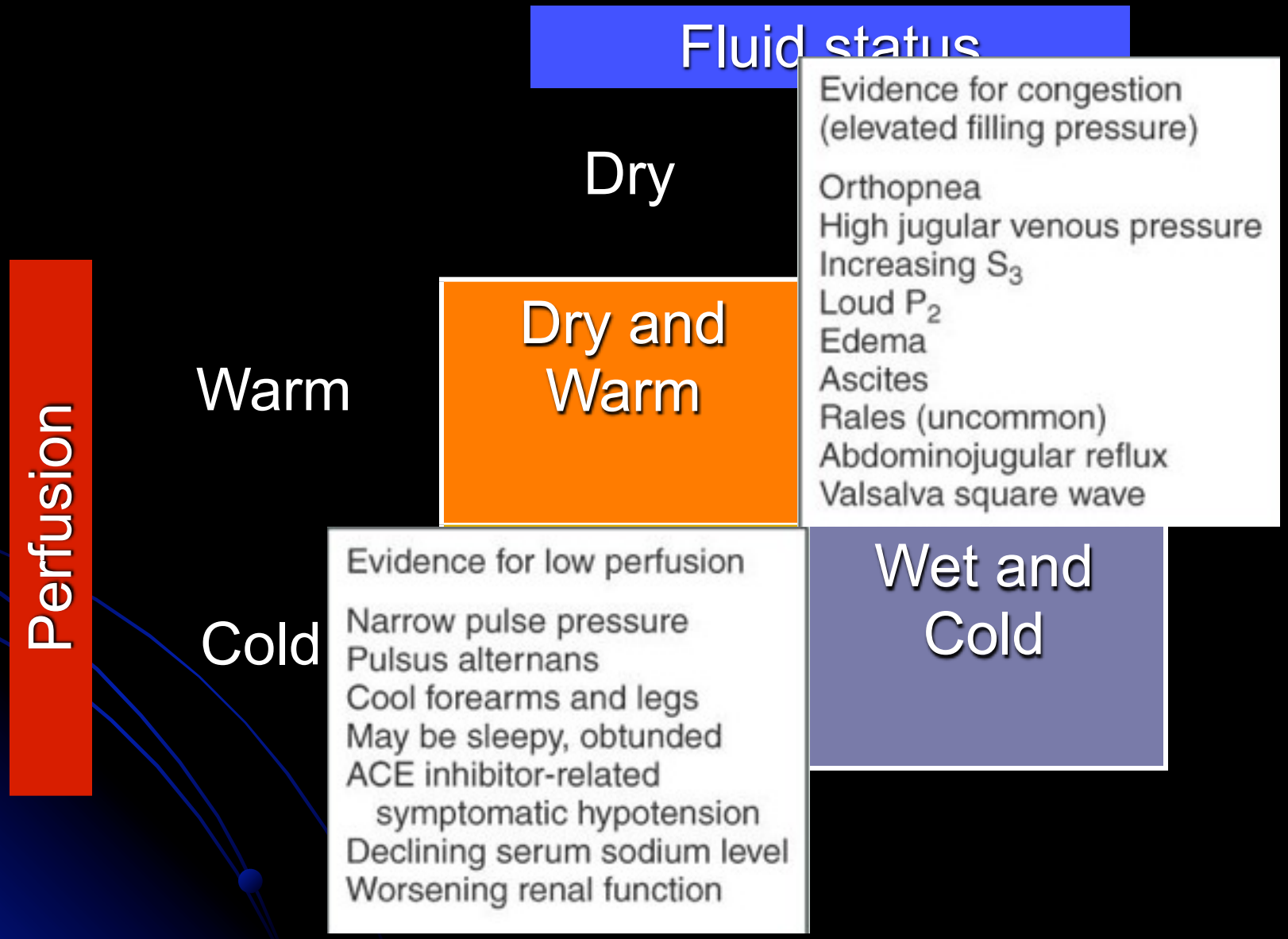
Beta-blockers should be attempted in CHF with coexistent COPD



Start with low dose, slowly titrate and closely monitor of symptoms, frequency of bronchodilator use, PFT

Patient came in with decompensated HF
What to do

- Wet and warm
  - IV diuretics
  - No need to decrease dose of β-blocker
  - Up-titrate dose of ACEi and β-blocker when stabilized
- Wet and cold
  - Positive inotropic support (PDE inhibitors)
  - Decrease the dose of β-blocker by 50%
  - Reintroduction or up-titrate β-blocker when stabilized

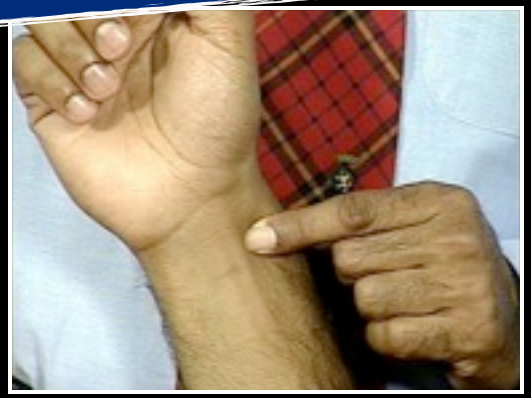

Fluid status
Dry
Warm
Perfusion
Cold
Dry and Warm
Wet and Cold
Evidence for congestion (elevated filling pressure)
Orthopnea
High jugular venous pressure
Increasing S_3
Loud P_2
Edema
Ascites
Rales (uncommon)
Abdominojugular reflux
Valsalva square wave
Evidence for low perfusion
Narrow pulse pressure
Pulsus alternans
Cool forearms and legs
May be sleepy, obtunded
ACE inhibitor-related symptomatic hypotension
Declining serum sodium level
Worsening renal function

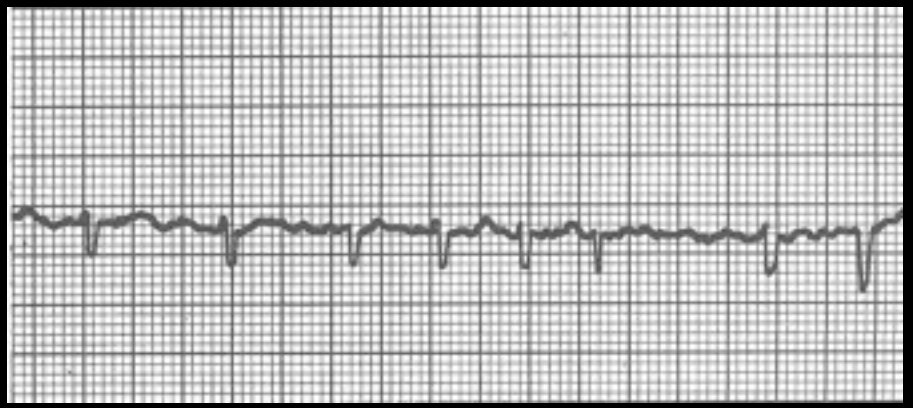
Dealing with low heart rate

- If < 50 bpm, halve dose of β-blocker
- Review other medications

- Drug interaction to look for :
  - Digitalis
  - Verapamil / diltiazem - should be discontinue
  - Amiodarone
  - Ivabradine ?

Do not rely on pulse rate in BB dose adjustment





Pulse rate ≠ Heart rate

PR 75/min VS. HR 96/min

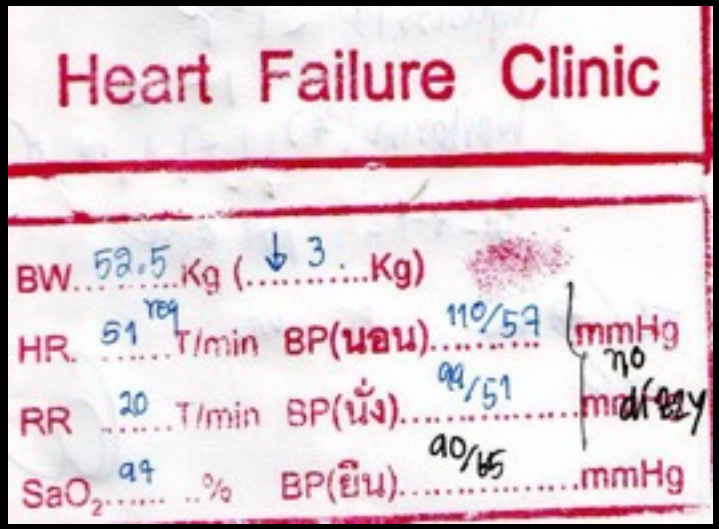
Problem solving : Hypotension

- Asymptomatic low BP does not require any change in therapy.
- HypoPERFUSION not hypoTENSION is the concern.
- Dizziness,light-headedness and confusion
  - D/C nitrates, CCB , other vasodilators
  - reducing dose of the diuretics if no signs/symptoms of congestion

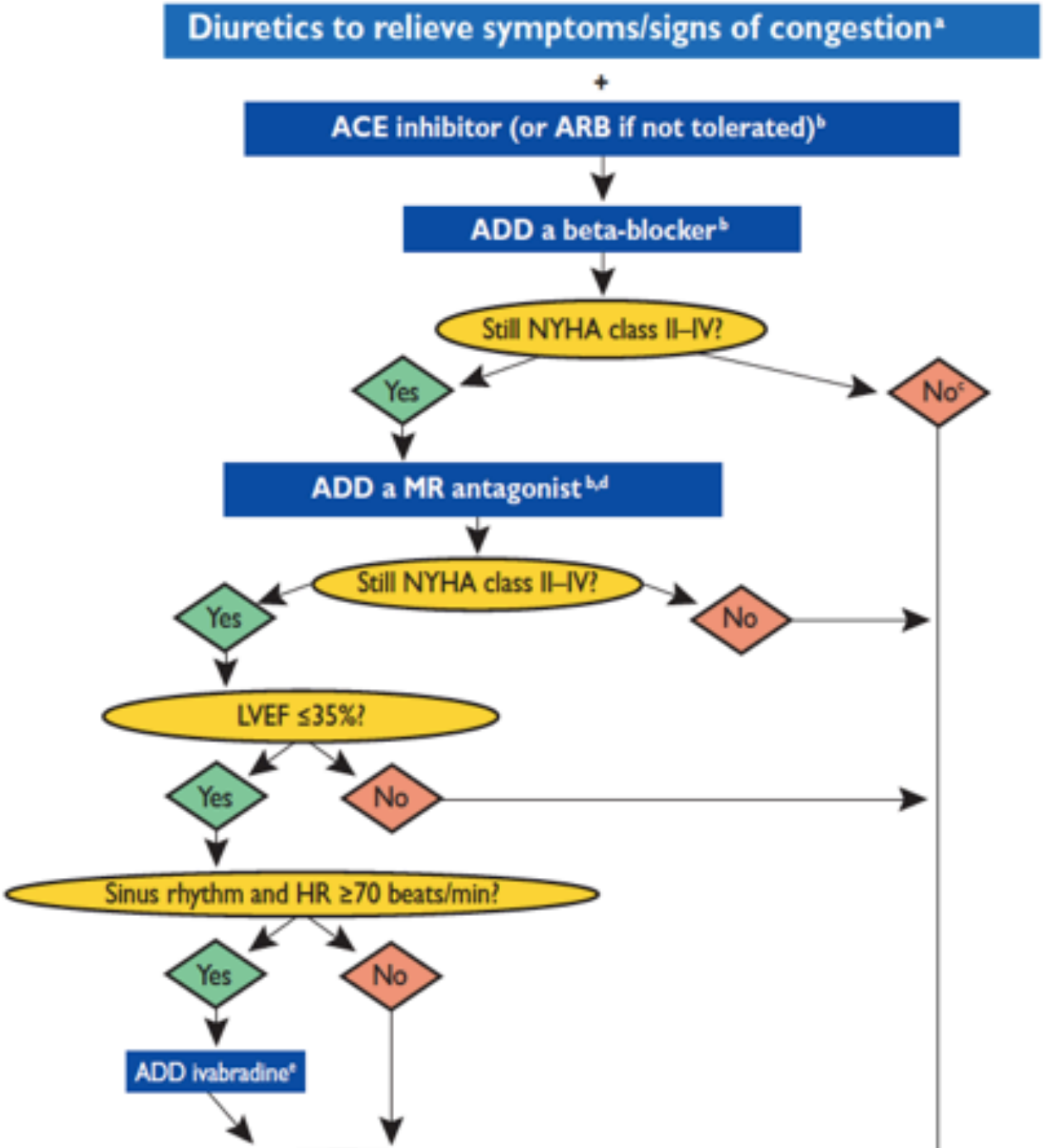
Overdiuresis

- RAAS stimulation
- Worsening renal function
- Electrolytes imbalance
- Barrier to GDMT optimization

Detection of orthostatic hypotension



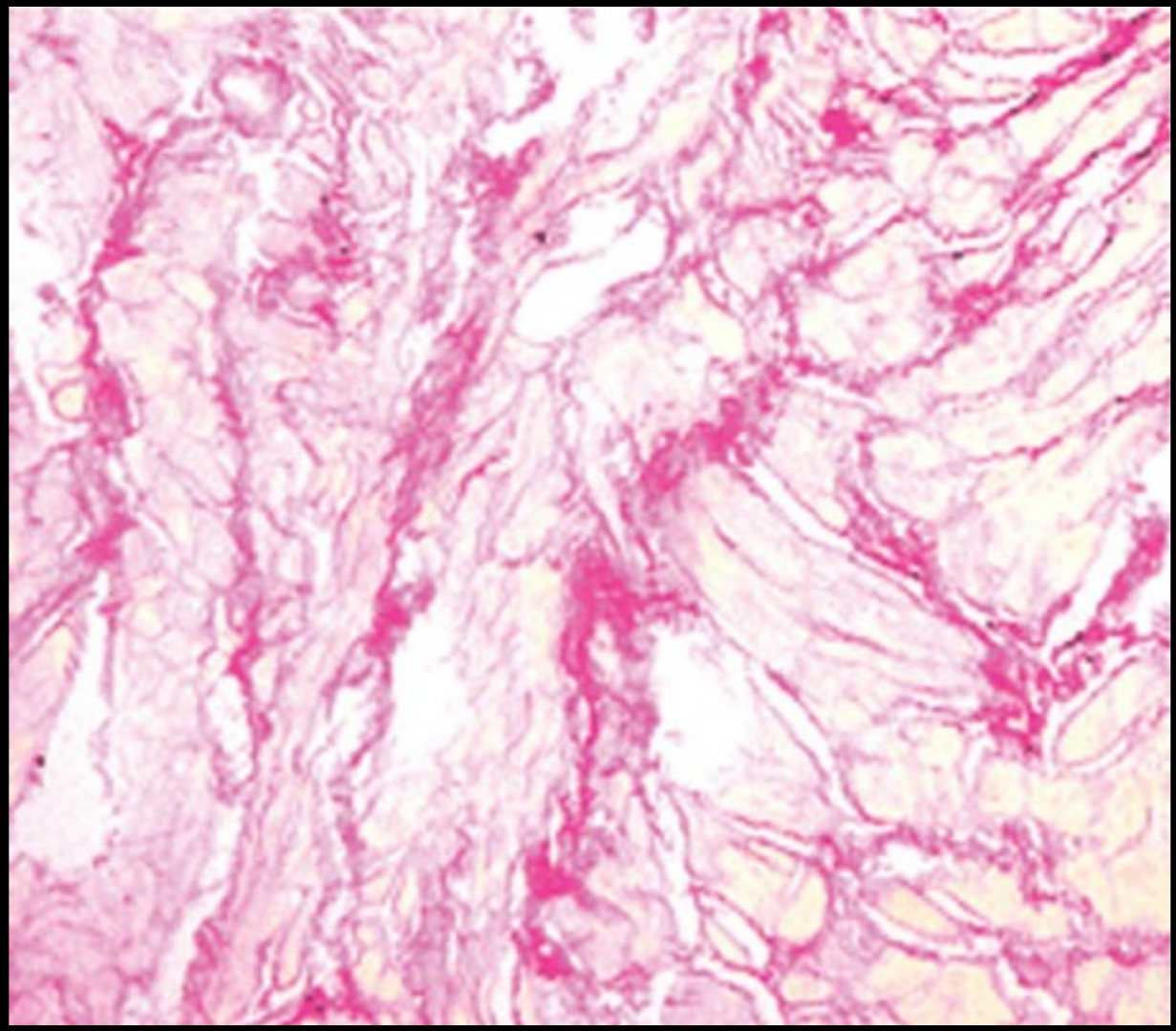
Always measure supine and upright BP in every HF patients at every visit


Diuretics to relieve symptoms/signs of congestion[a]
+
ACE inhibitor (or ARB if not tolerated)[b]
ADD a beta-blocker[b]
Still NYHA class II–IV?
Yes
No[c]
ADD a MR antagonist[b,d]
Still NYHA class II–IV?
Yes
No
LVEF ≤35%?
Yes
No
Sinus rhythm and HR ≥70 beats/min?
Yes
No
ADD ivabradine[e]

Magnitude of benefit seen in RCTs

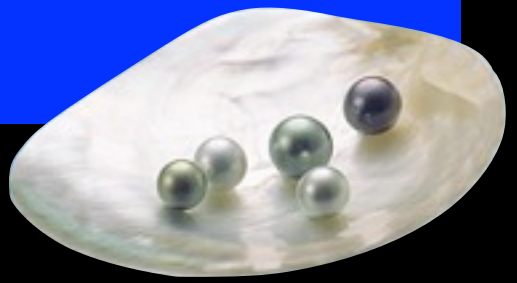
GDMT	RRR in mortality (%)	NNT to save one life (36 mo)	RRR HF hospitalizations
ACEi /ARB	17	26	31
β-blocker	34	9	41
AA	30	6	35
Hydralazine/ nitrate	43	7	33

Myocardial fibrosis

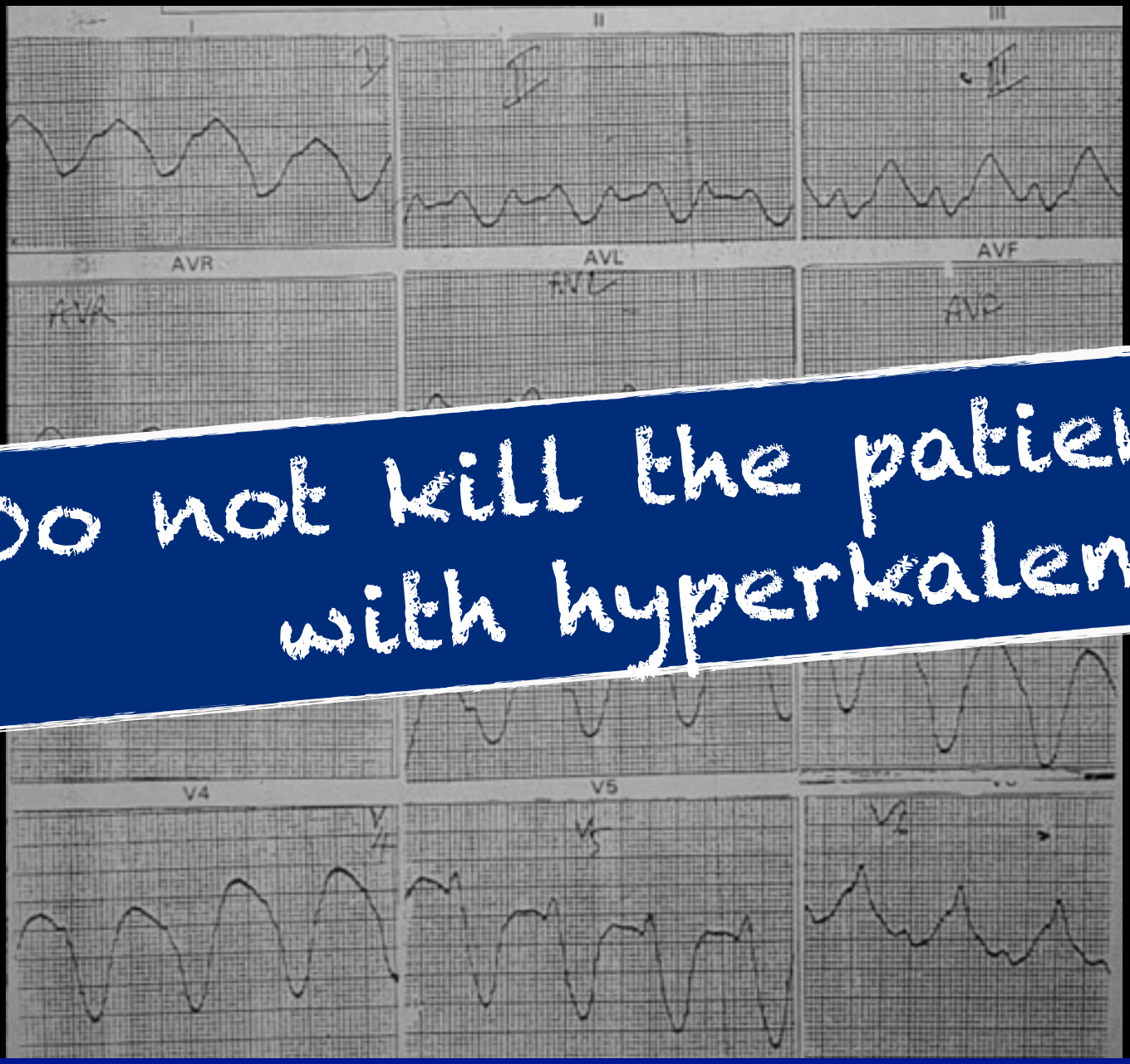


picrosirius red staining

Tip



Combined use of low doses of several drugs is preferred to a large dose of a single agent.



Do not kill the patients with hyperkalemia

Sine wave - Hyperkalemia : K^+= 8.2 mEq/L

How to avoid fatal hyperkalemia

HFSA 2010 Practice Guideline
Aldosterone Antagonists

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose in Clinical Trials
Spironolactone	Aldactone	12.5-25 mg qd	25 mg qd	26 mg/day
Eplerenone	Inspra	25 mg qd	50 mg qd	42.6 mg/day

Do not use high dose AA

Never use Triple A's combination (ACEi/ARB/AA)

Lindenfeld J, et al. HFSA 2010 Comprehensive Heart Failure Guideline. J Card Fail 2010;16:e1-e194.

Do not use aldosterone receptor antagonists when

Cr > 2.5 mg/dL in men or > 2.0 mg/dL in women

(GFR<30 mL/min/1.73 m2)

K^+> 5.0 mEq/L

K^+ monitoring should reflect protocols followed in clinical trials

- K^+ and Cr rechecked within 2 to 3 days and again at 7 days after initiation of AA
- Recheck *at least monthly for the first 3 months and every 3 months thereafter*
- The addition or an increase in dosage of ACE inhibitors or ARBs should trigger a new cycle of monitoring

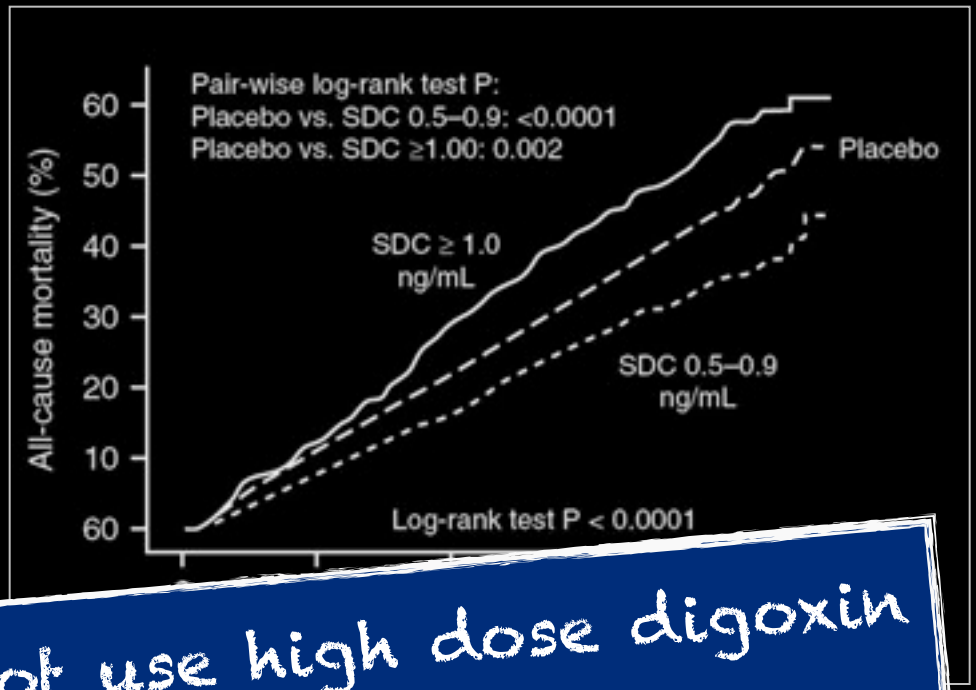
ACC/AHA HF Guidelines 2013


gold roast
SALT


No Sodium
No MSG
NoSalt
SALT ALTERNATIVE
Flavors like salt,
but is salt free!
NET WT. 11 OZ. (311g)
Do not use salt supplement

How to use digitalis

- A third-line drug
- If digoxin needed , use low dose.
- SDC >1.0 ng/ml may do harm
- Suggested new therapeutic level 0.5-0.9 ng/ml



Do not use high dose digoxin

Do not use digoxin in small old frail ladies

Ahmed A, et al. post hoc analysis of the DIG trial. *Eur Heart J.* 2006;27: 178–186.)

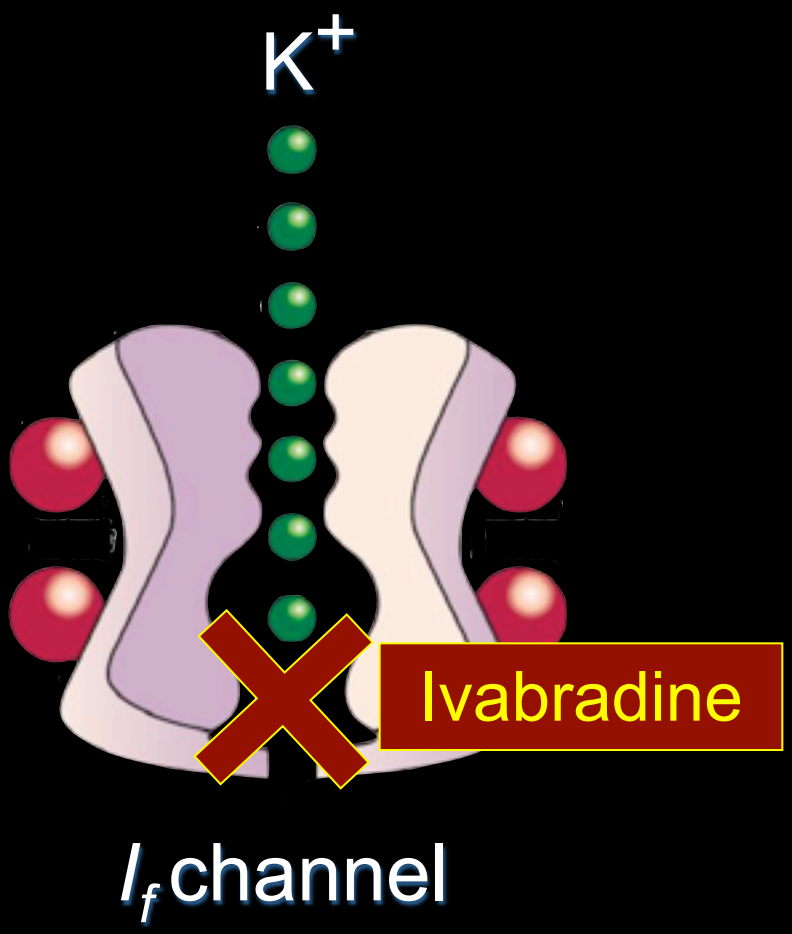
Current Guidelines for Digoxin

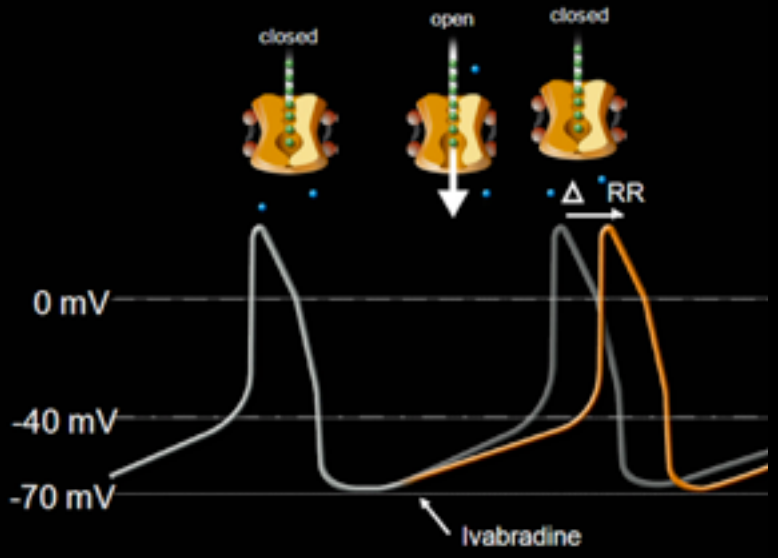
ACC/AHA 2013

ESC 2012

Recommend	Level of Evidence
IIa	B
IIb	B

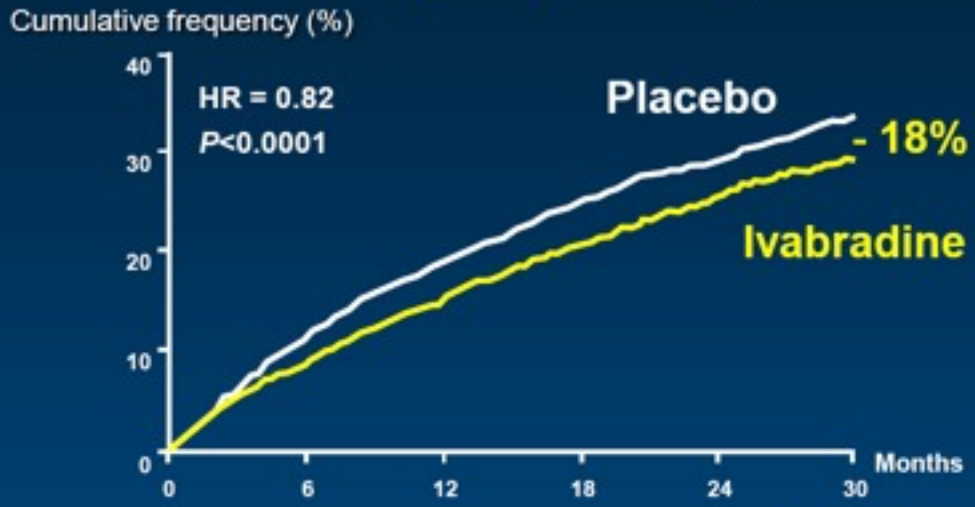
Ivabradine : Pure HR reduction



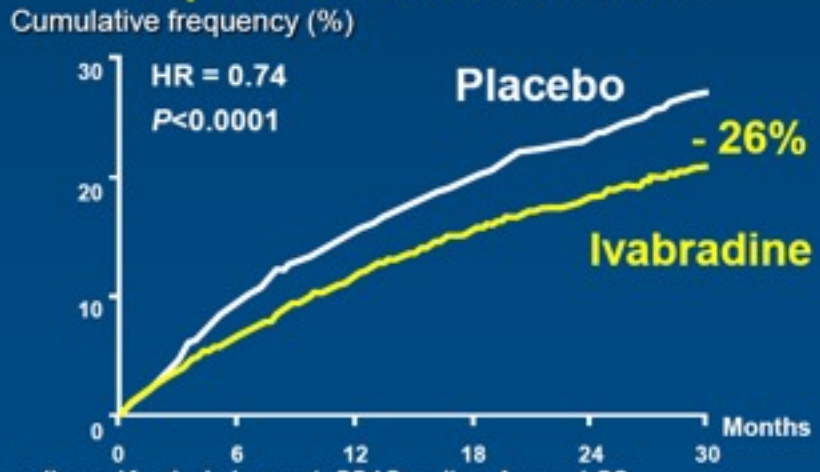


Ivabradine effect on outcomes

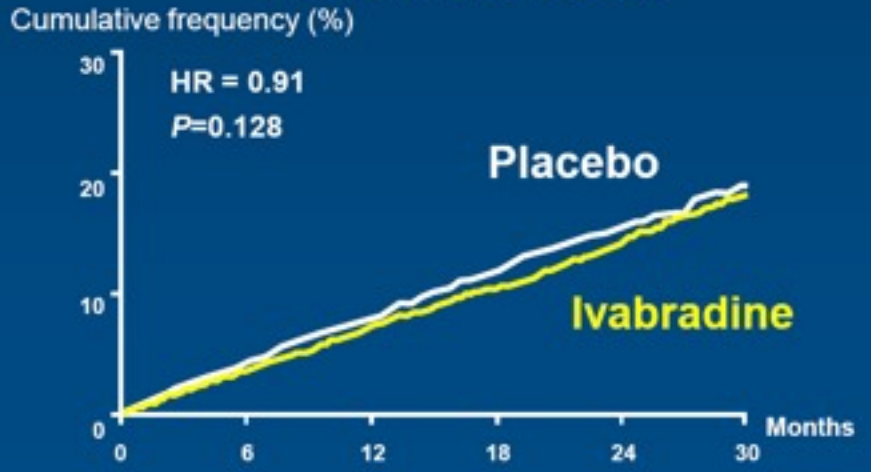
Primary composite endpoint



Hospitalization for heart failure



Cardiovascular death



Swedberg K, et al. *Lancet*. 2010;online August 29.

Role for Ivabradine

Sinus rhythm with an EF ≤35% and HR ≥70 /min

- Difficult to up-titrate β-blockers for other reasons other than bradycardia
  - Hypotension
  - Low output syndrome

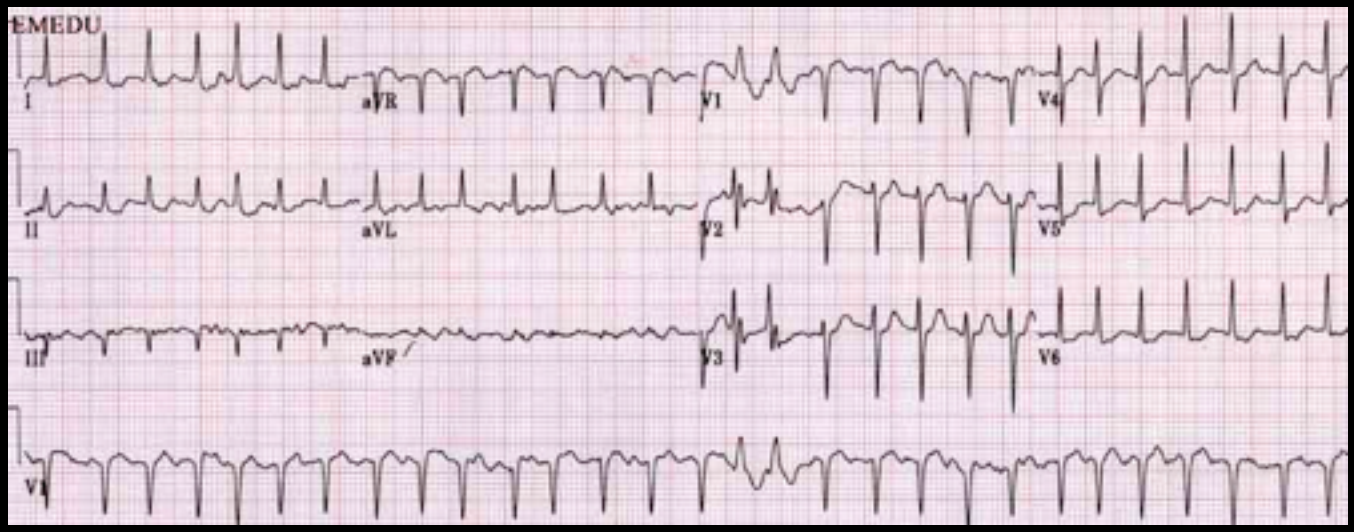
Class IIa B

Class IIb C

DO NOT substitute ivabradine for β blockers in patients with CHF who had not optimally up-titrated

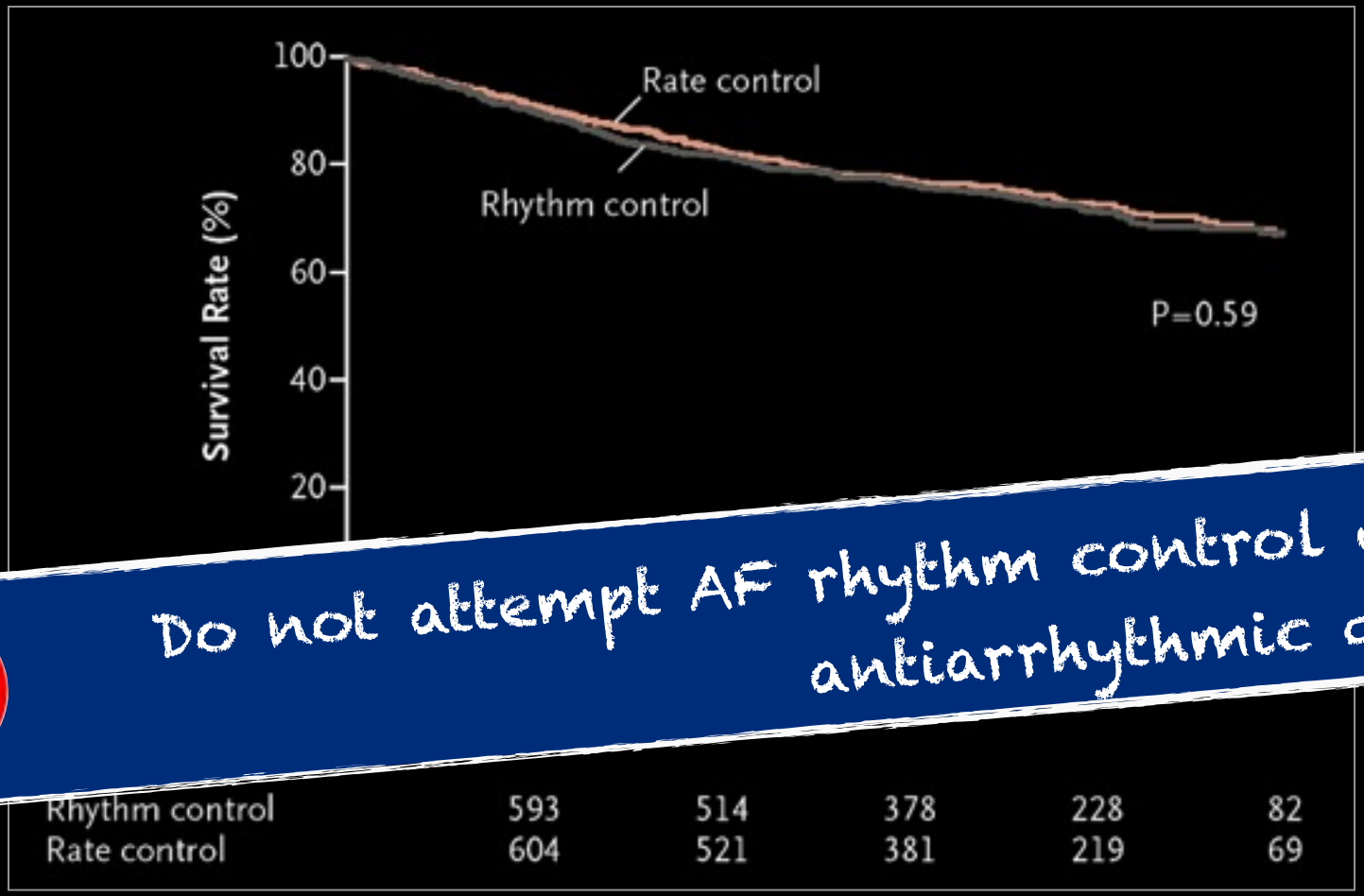
ESC Guidelines 2012

What to do with AF in HF



1. Rhythm control
2. Rate control

AF Rate control VS Rhythm control in HF



Do not attempt AF rhythm control with antiarrhythmic drug

AF HF. N Engl J Med 2008;358:2667–2677.

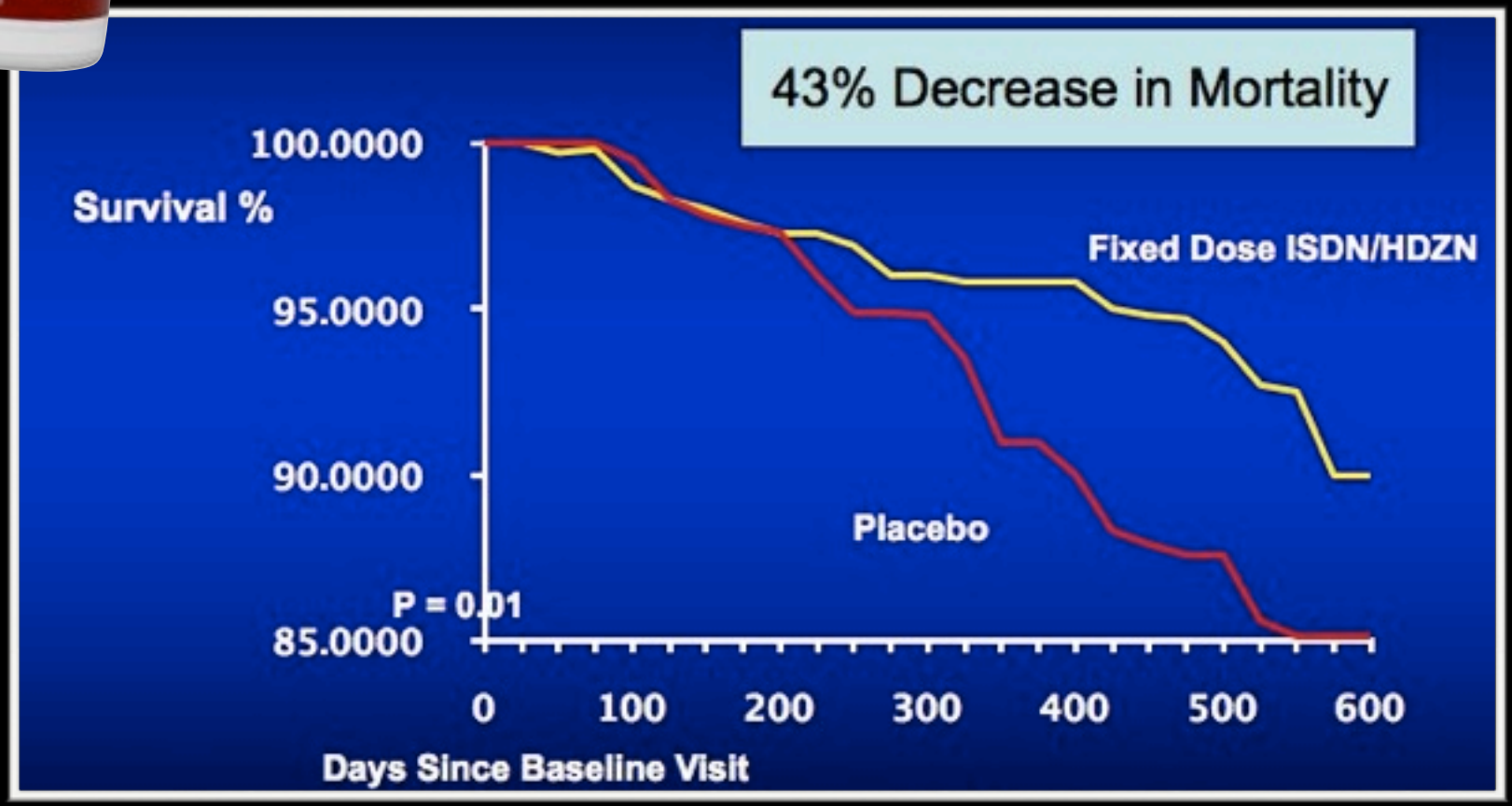
How to slow AF rate in HFREF?

- β-blocker
- Digoxin
- Amiodarone
- AV nodal ablation with CRT-P

No role of ivabradine

Non dihydropyridine CCB : absolute contraindication

Hydralazine / Nitrates



A-Heft N Engl J Med 2004:351:2049-57

LV dysfunction

Atria and ventricular stretches

Neurohormonal activation

Natriuretic peptides

Renin-Angiotensin-Aldosterone –System

Sympathetic nervous system

Endothelin

Compensatory mechanism for hemodynamic derangement

Prolonged stimulation

Apotosis

Myocyte hypertrophy

Interstitial fibrosis

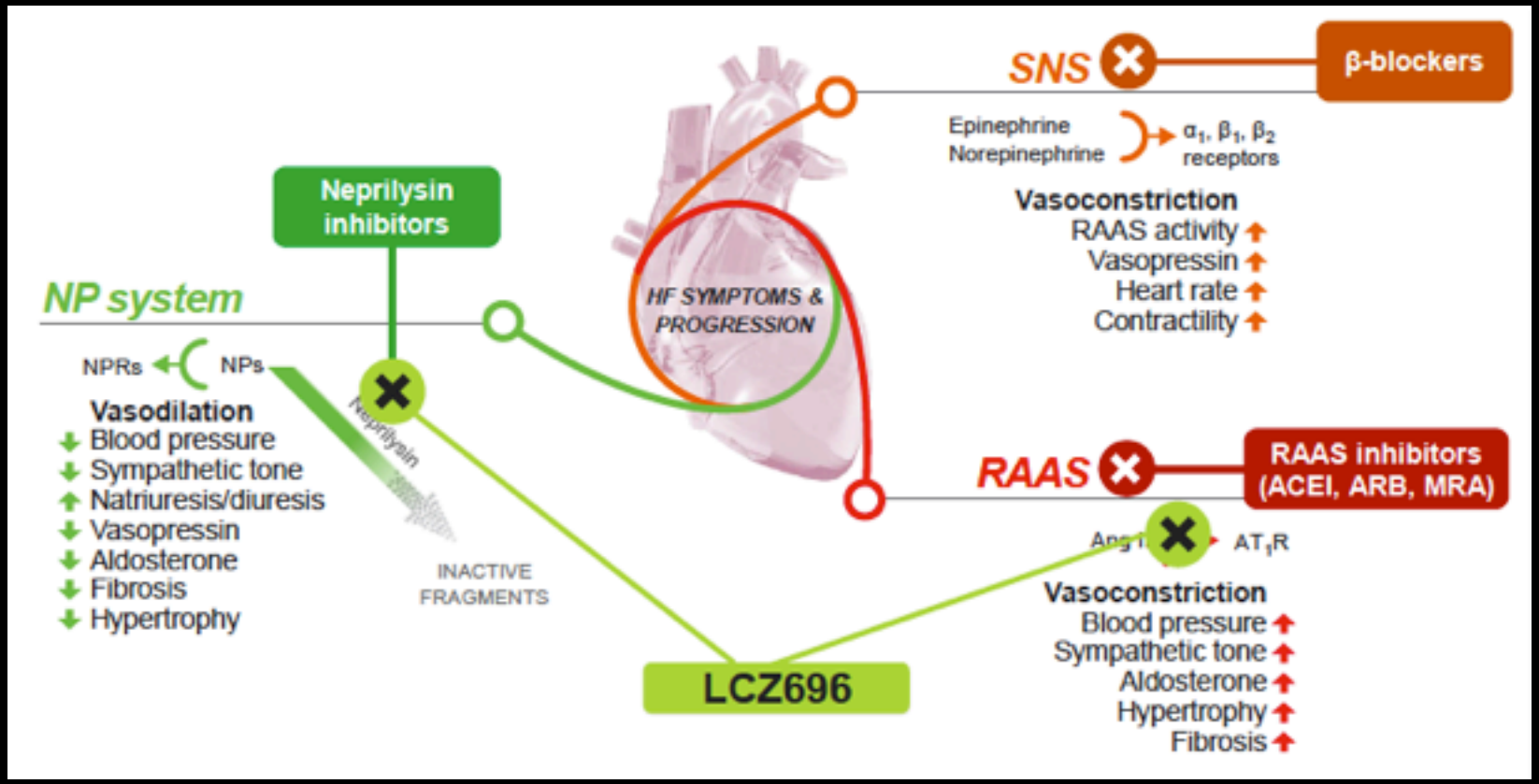
Cardiac remodeling

Diuresis

Vasodilation

Decrease salt appetite

neurohormonal modulation

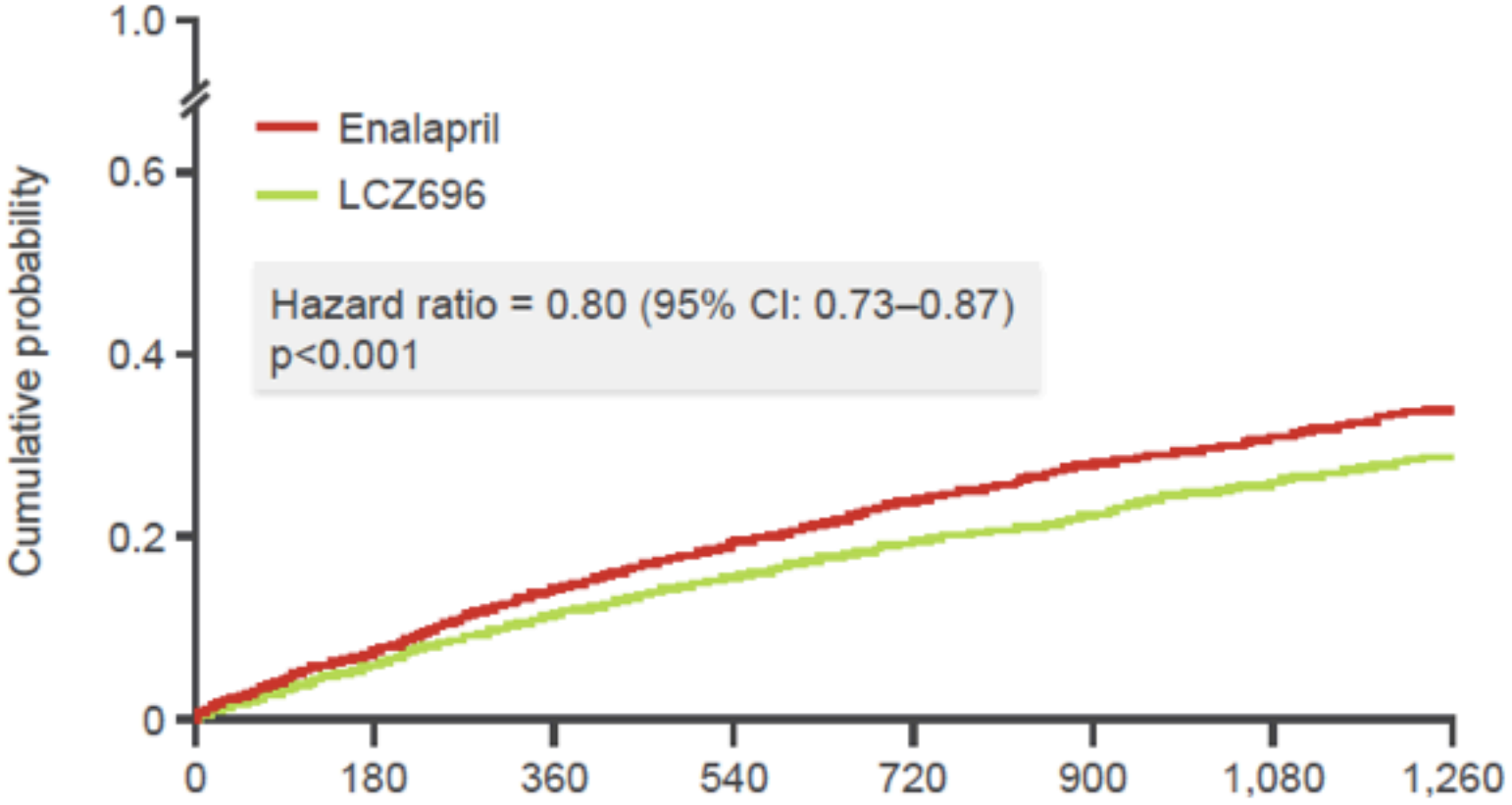


ARB + Neprilysin inhibitor
NI

= Angiotensin Receptor Neprilysin Inhibitor - ARNI

Primary endpoint:

Death from CV causes or first hospitalization for HF

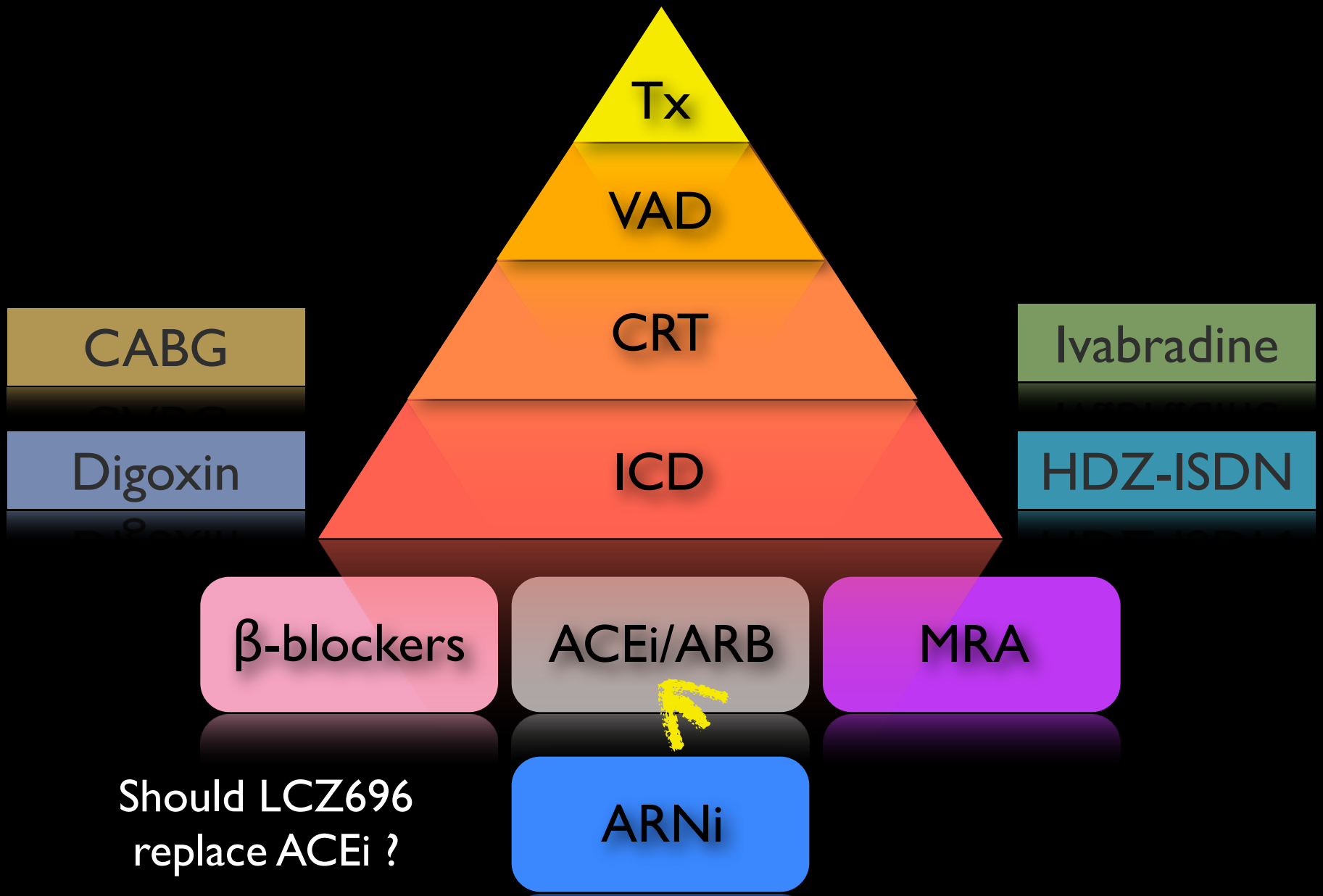


No at risk								
LCZ696	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

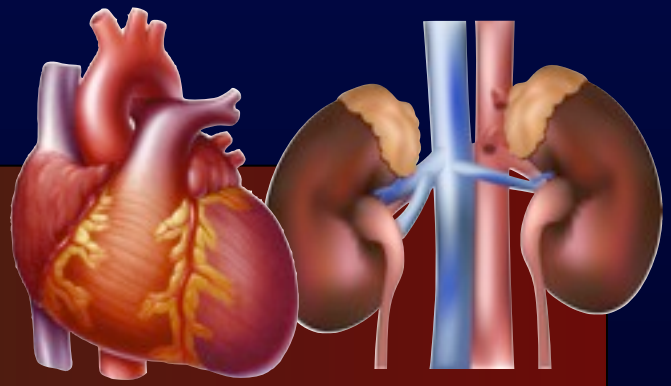
CI=confidence interval; CV=cardiovascular; HF=heart failure

McMurray et al. N Engl J Med 2014;371:993–1004

HFrEF : The building blocks of therapy



Cardiac / renal function



Acute cardiac event

congestion hypoperfusion

ADHF

ADHF

ADHF

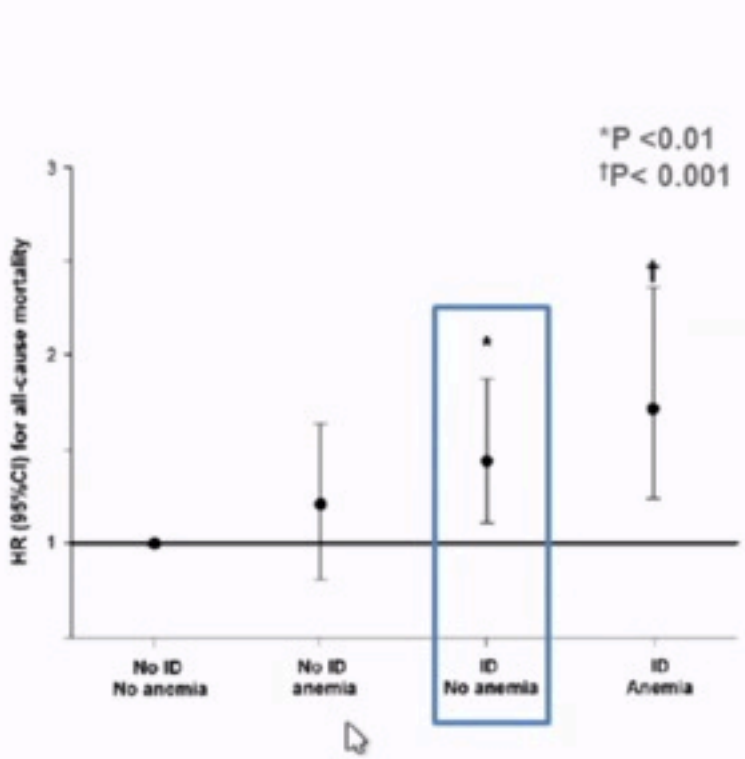
ADHF

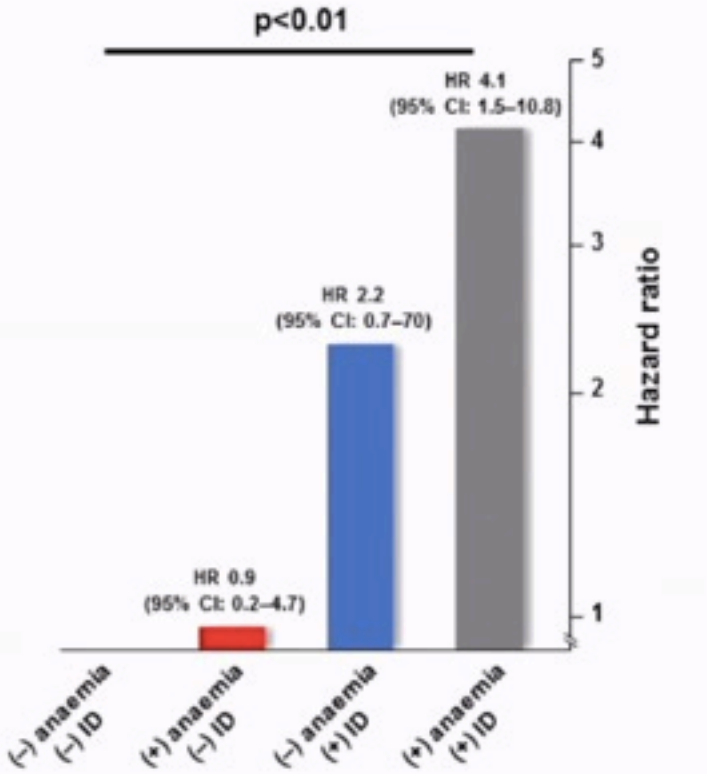
death

Refractory HF ?

- anemia
- concomitant valvular dysfunction
- ischemia / hibernation
- poorly controlled arrhythmias - AF
- thyroid dysfunction
- diuretic resistant
- large LV aneurysm
- ventricular dyssynchrony
- obstructive sleep apnea
- malnutrition
- physical deconditioning
- depression
- dietary and medication non adherence

Iron deficiency - beyond anaemia - is associated with increased all-cause mortality in systolic HF





Klip IT, et al. Am Heart J 2013;165:575-82.

Okonko DO, et al. JACC 2011;58:1241–51.

CONFIRM HF


European Heart Journal Advance Access published August 31, 2014

FASTTRACK ESC HOT LINE

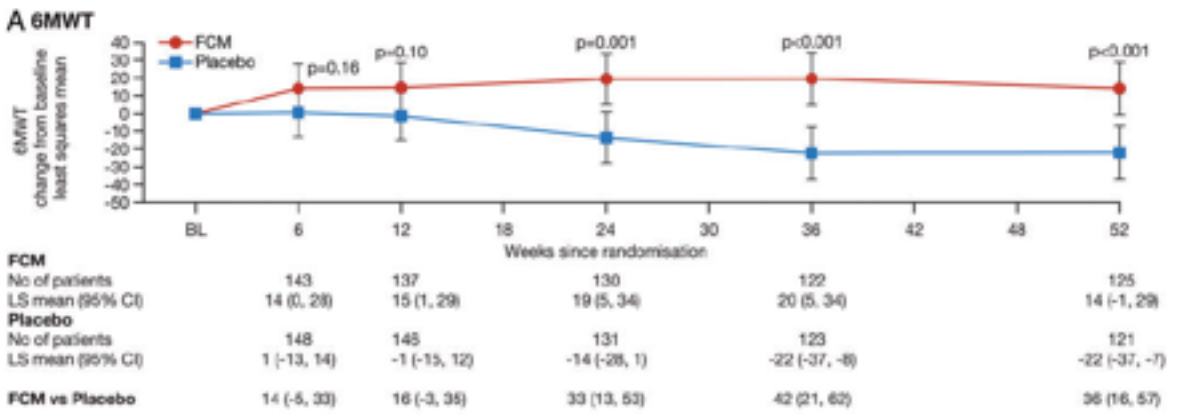
Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency

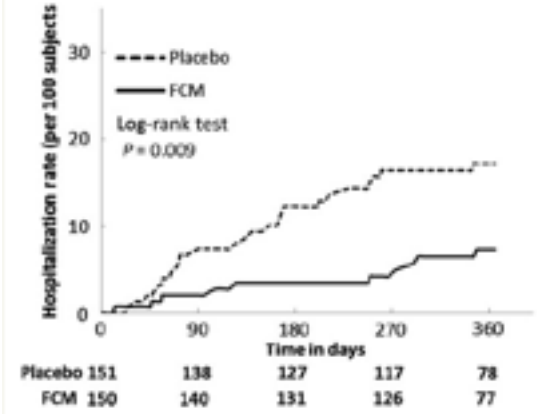
Piotr Ponikowski, Dirk J. van Veldhuisen, Josep Comin-Colet, Georg Ertl, Michel Komajda, Viacheslav Mareev, Theresa McDonagh, Alexander Parkhomenko, Luigi Tavazzi, Victoria Levesque, Claudio Mori, Bernard Roubert, Gerasimos Filippatos, Frank Ruschitzka, and Stefan D. Anker, for the CONFIRM-HF Investigators

304 ambulatory symptomatic HFrEF patients
- elevated BNP
- Fe deficiency
  - ferritin<100 ng/mL or
  - 100–300 ng/mL if transferrin saturation < 20%

i.v. ferric carboxymaltose VS placebo

Primary end-point : change 6MWT distance at Week 24.
Secondary end-points NYHA QoL, HF rehospitalization





P. Ponikowski et al. EHJ 2014

Problems and Pitfalls

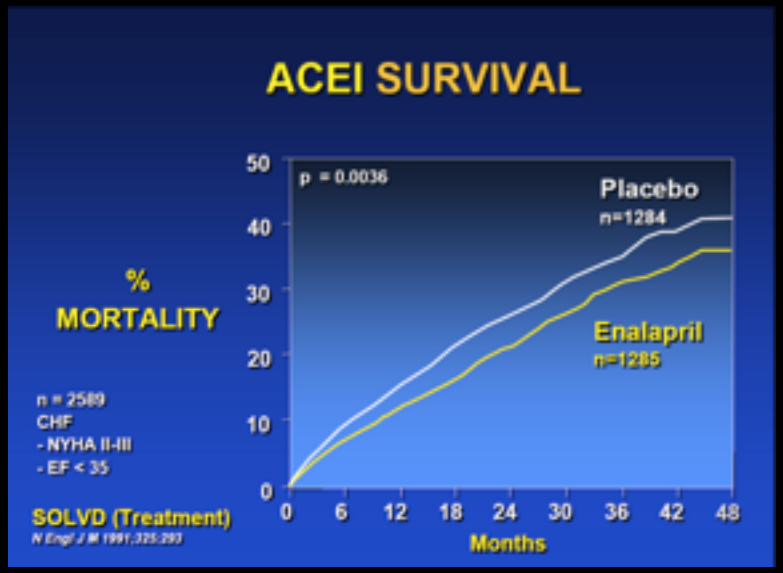
High readmission rate

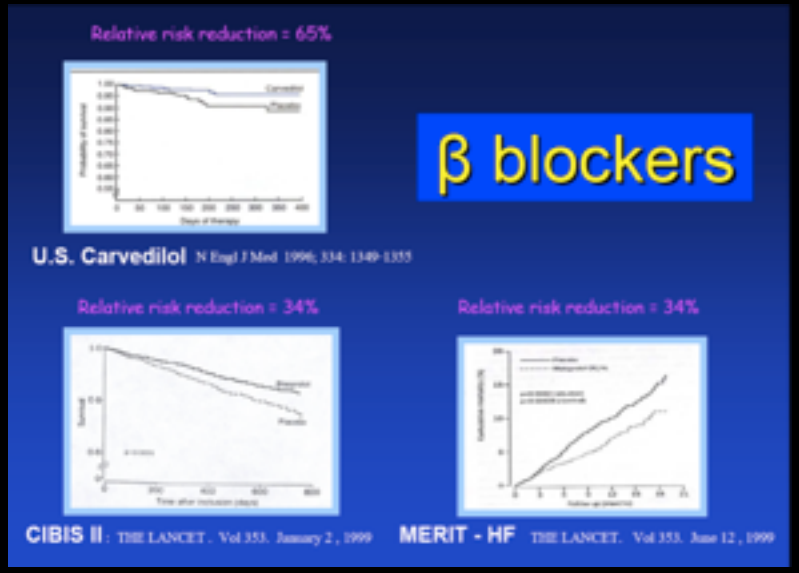
- 78% had at least two admission per year
- 40% within 3 months of discharge

Half of these readmissions may have been preventable !

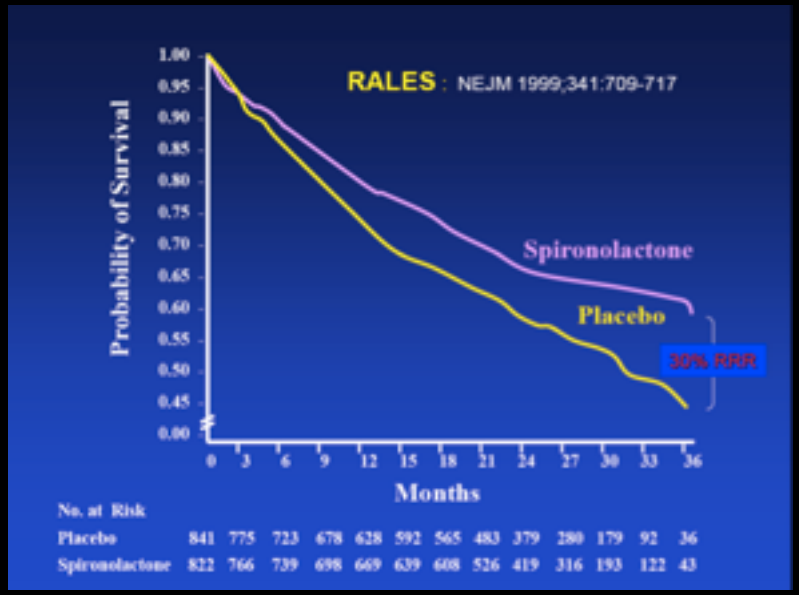
Precipitating causes of heart failure

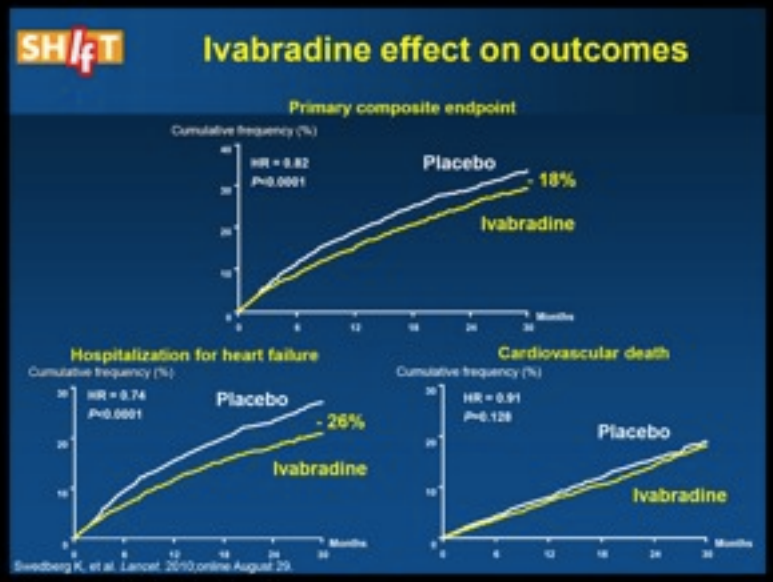
- Non compliance with medications
- Non compliance with dietary recommendations
- Inadequate diuretics programme
  - Increased cardiac demand
  - Concurrent illness
  - New cardiac event
- Use of new medications - NSAID's

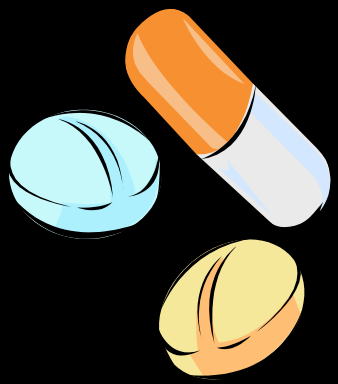




If the benefit seen in these clinical trials are to be replicated, patients must be prescribed treatment according to guidelines and patients must follow the prescribed treatment.







Rx

Enalapril 20 mg
1 tab bid
Carvedilol 25 mg
½ tab bid
Spironolactone 25 mg
½ tab od

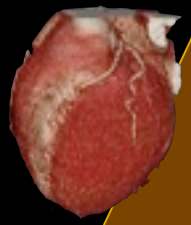
Mong

Do not stop @ prescribing GDMT

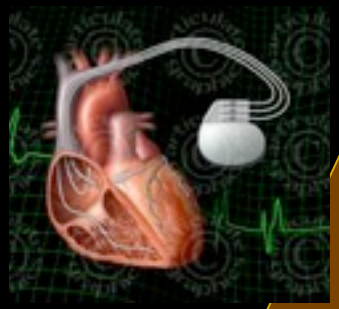
Drugs don't work in patients who don't take them.

C. Everett Koop, M.D.

Pyramid of HF care



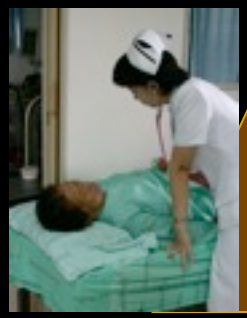
Heart transplant



Revascularization

Resynchronization Therapy

Pharmacologic Therapy



Patient education

Self management

Disease management program

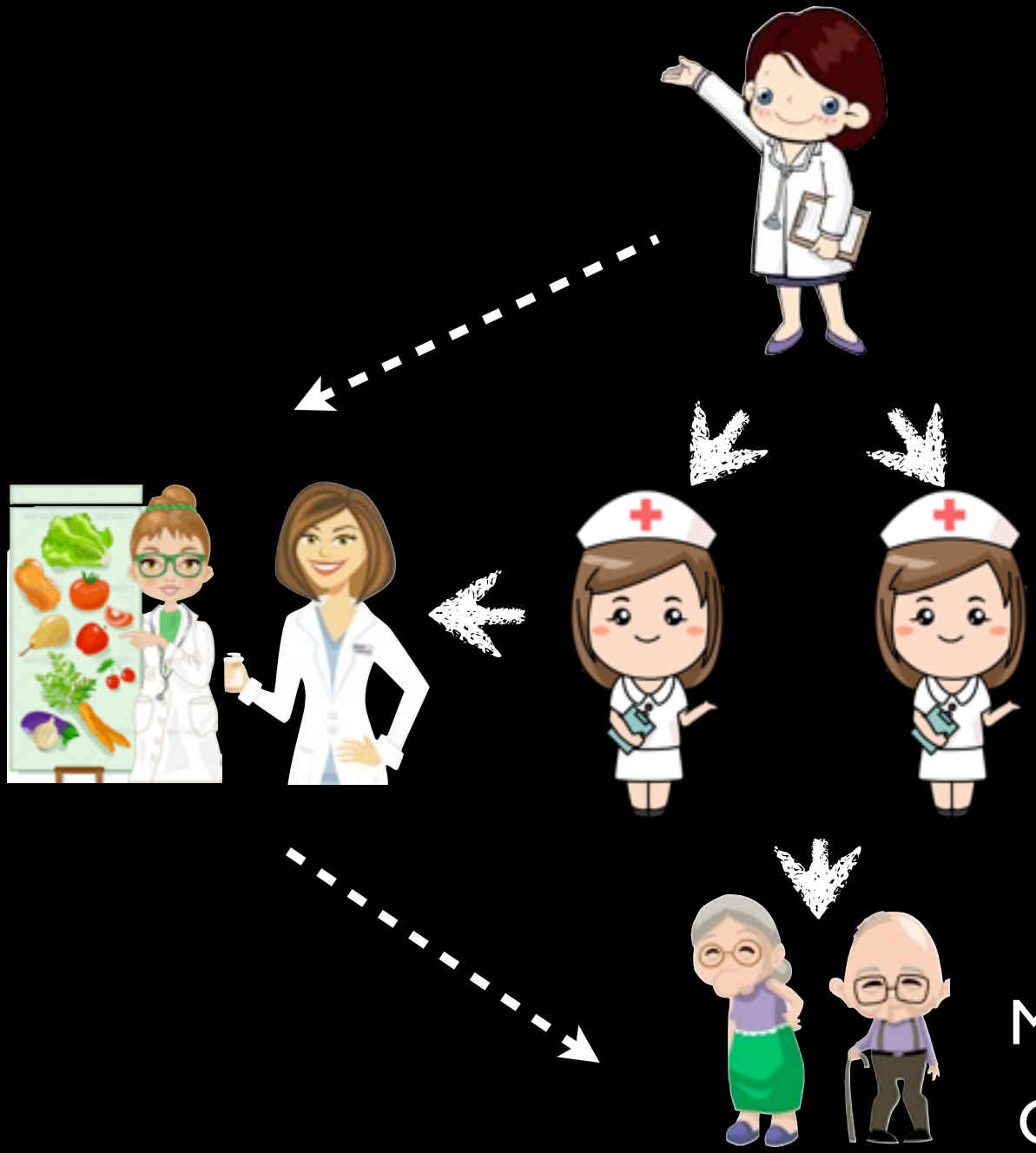
Low tech – high touch therapy

" filling the G A P in the care of chronic diseases "

Comprehensive Heart Failure Program

Keeping heart failure patients away from hospitals

Low Tech, High Touch, High Efficiency

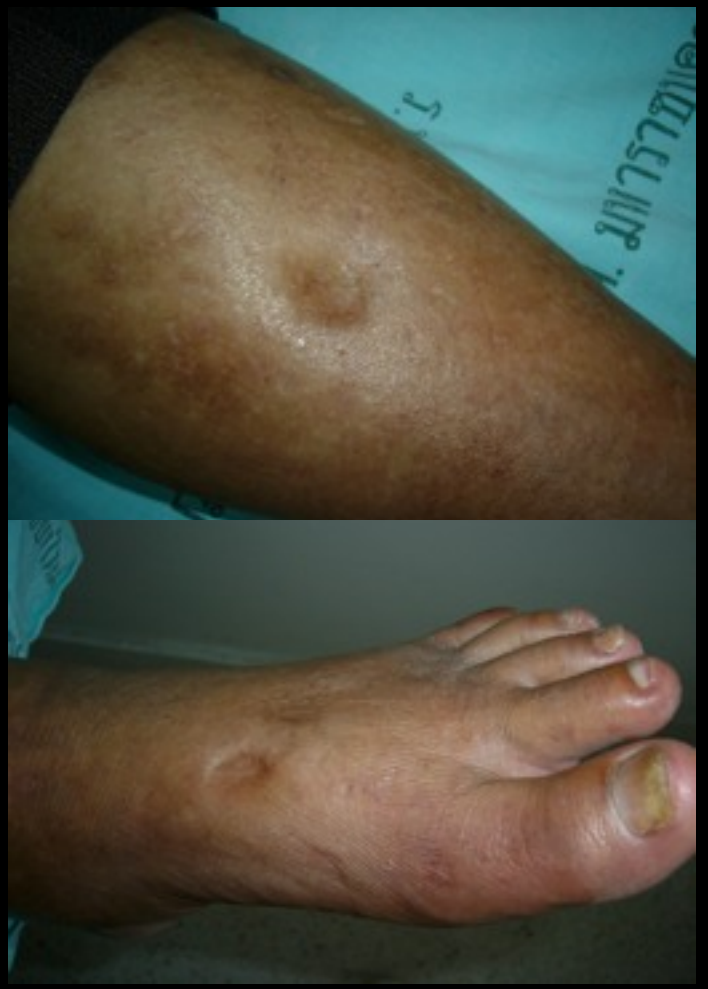


Multidisciplinary team

Case manager model

Education and Counseling

- General topics
  - Nature of heart failure
  - Be able to recognize early signs of worsening HF



The most important tool in HF management

Self daily weight monitoring :

If weight increases > 1 kg within 1 or 2 days

→ double the dose of diuretics , until returns to ideal BW

- ASA 100 mg od
- Ramipril 5 mg od
- ISDN 20 mg tid
- Carvedilol 12.5 mg bid
- Marforan 5 mg ½ tab od

- Caltrate
- Glakay
- Foscanet

POLYPHARMACY

- Seretide 1 puff bid
- Theodur 200 mg od
- Singulair

- Allopurinol 300 mg ½ tab od
- Colchicine 0.6 mg od

- Pletaal

- Prosac 20 mg od
- Ativan 1 mg hs

ยาจาก รพ. จังหวัด

- Enalapril 5 mg bid
- Orfarin 3 mg od
- Metformin 500 mg tid
- Digoxin 0.25 mg od
- Moduretic 1 tab od
- Senekot 2 tab o hs
- Bactrim forte 1 tab bid

Keys to HF clinic success

1. An ethusiastic and visionary physician champion
2. Interdisciplinary collaboration
   - An independent and professionally competent full-time staff
3. A holistic approach
4. Evidence based approach
5. Easy access to the specialist nurse
6. Facilitation of self management
7. Vigilant follow up

10 Practical Tips - Summary

1. HF should never be a final diagnosis -Identify treatable cause of HF
2. Give evidence based medication
3. Optimized HF medication
4. Know how to use diuretics effectively
    1. Flexible regimen
    2. Dealing with diuretic resistance

10 Practical Tips - Summary

5. Hypotension VS hypoperfusion
6. How to avoid fatal hyperkalemia
7. How to deal with acute decompensation
8. Intractable HF – always ask why? remind yourself of the frequently overlooked problems
9. Good drugs do not work on patients who do not take them
10. Nurses are doctor’s best friend