OPTIMAL MEDICAL THERAPY IN HEART FAILURE- A BRIEF OVERVIEW

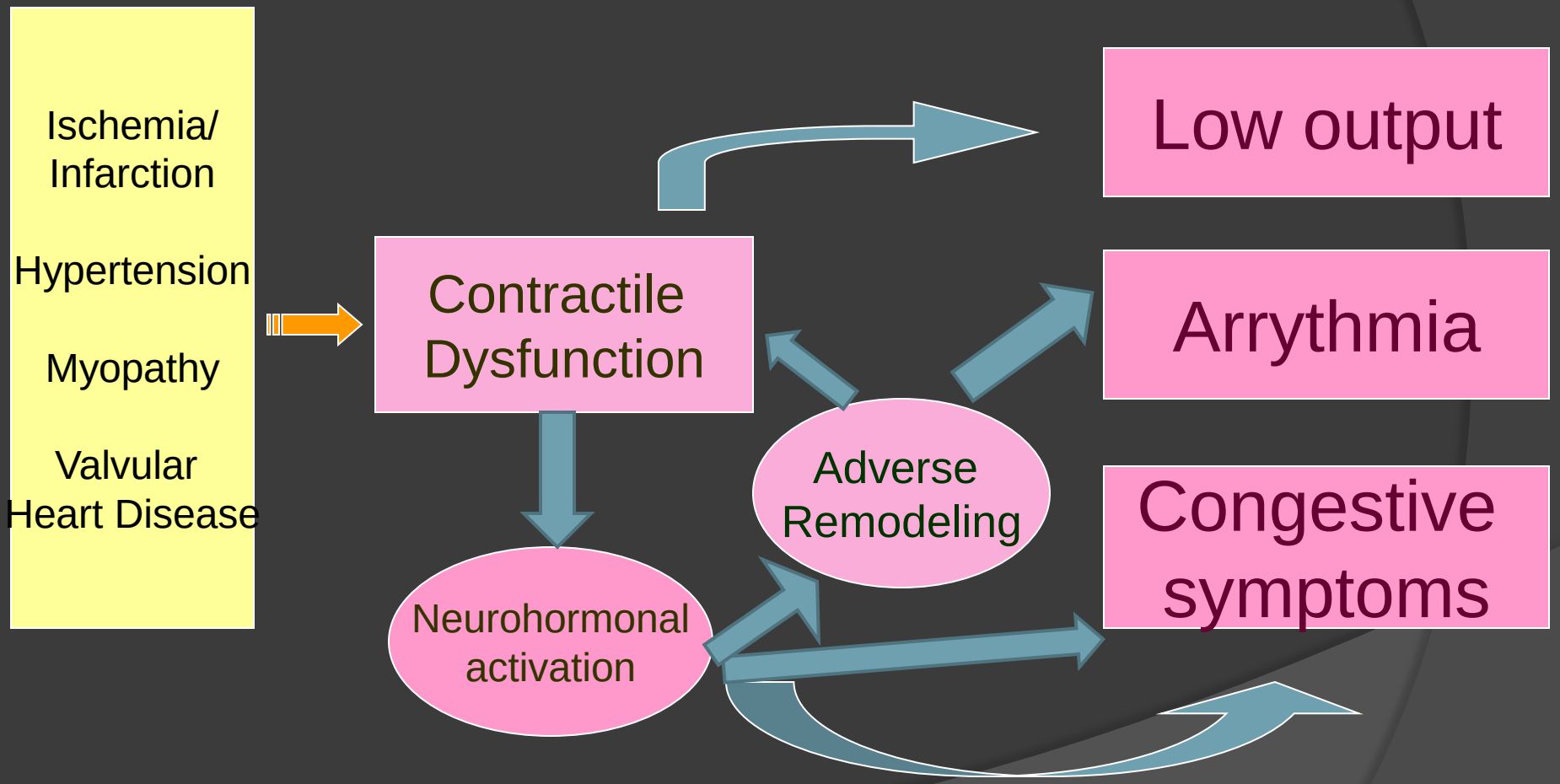
Heart Failure ----- Not a single disease

- clinical syndrome
- impaired cardiac pump function
- inadequate systemic perfusion
- unable to meet the body's metabolic demands

Changing classifications…

- Left Heart vs Right Heart
- Systolic vs Diastolic
- Forward vs Backward
- Low output vs High output

- Heart Failure with reduced ejection fraction
  Heart Failure with normal ejection Fraction


Ischemia/
Infarction
Hypertension
Myopathy
Valvular
Heart Disease
Contractile
Dysfunction
Low output
Arrythmia
Adverse
Remodeling
Congestive
symptoms
Neurohormonal
activation

New Classification of Heart Failure
ACC/AHA Staging v/s NYHA Functional Class

ACC/AHA HF Stage[1]	NYHA Functional Class[2]
A At high risk for heart failure but without structural heart disease or symptoms of heart failure (eg, patients with HTN or coronary artery disease)	
B Structural heart disease but without symptoms of heart failure	**I** Asymptomatic
C Structural heart disease with prior or current symptoms of heart failure	**II** Symptomatic with moderate exertion
	III Symptomatic with minimal exertion
D Refractory heart failure requiring specialized interventions	**IV** Symptomatic at rest

[1]Hunt SA et al. J Am Coll Cardiol. 2001;38:2101–2113

[2]New York Heart Association/Little Brown and Company, 1964. Adapted from: Farrell MH et al.JAMA.2002;287:890–897.

Non-Pharmacologic Therapy

Dietary restrictions…

- Dietary restriction of sodium (2 to 3 g daily).
- Further restriction (<2 g daily) may be considered in moderate to severe HF.

- Fluid restriction is generally unnecessary unless the patient is hyponatremic (<130 mEq/liter)
- Fluid restriction (<2 liters/day) should be considered in hyponatremic patients and those whose fluid retention is difficult to control despite high doses of diuretics and sodium restriction.

- Caloric supplementation is recommended for patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia)

- Stop smoking and to limit daily alcohol consumption to two standard drinks in men or one standard drink in women.
- Patients suspected of having an alcohol-induced cardiomyopathy should be advised to abstain from alcohol consumption indefinitely.
- Excessive temperature extremes and heavy physical exertion should be avoided.
- Certain drugs like (NSAIDs), including COX-2 inhibitors, are not recommended

- Treat aggressively comorbidities such as hypertension and diabetes
- Monitor weight gain
- Adjust the diuretic dose in the case of a sudden unexpected weight gain of more than 3 to 4 pounds over a 3-day period.
- Consider recommending influenza and pneumococcal vaccines

Diuretics- Loop diuretics

- Inhibit the action of the Na^+,K^+-$2Cl^-$ cotransporter, thereby preventing salt transport in the thick ascending loop of Henle.

- Also inhibits Ca^{2+} and Mg^{2+} resorption by abolishing the transepithelial potential difference

- Reduce the driving force for water resorption in the collecting duct, even in the presence of AVP

Other effects of loop diuretics...

- Loop diuretics acts as a venodilator and reduces right atrial and pulmonary capillary wedge pressure within minutes when given intravenously.
- An acute rise in systemic vascular resistance has been attributed to the transient activation of the systemic or intravascular renin-angiotensin system (RAS).

Class I indication for diuretics

Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention. *(Level of Evidence: C)*

How much diuretics?

DRUG	INITIAL DAILY DOSAGE	MAXIMUM TOTAL DAILY DOSAGE	DURATION OF ACTION (hr)
Loop diuretics*			
Bumetanide	0.5-1.0 mg qd or bid	10 mg	4-6
Furosemide	20-40 mg qd or bid	600 mg	6-8
Torsemide	10-20 mg qd	200 mg	12-16
Ethacrynic acid	25-50 mg qd or bid	200 mg	6
Thiazide diuretics [†]			
Chlorothiazide	250-500 mg qd or bid	1000 mg	6-12
Chlorthalidone	12.5-25 mg qd	100 mg	24-72
Hydrochlorothiazide	25 mg qd or bid	200 mg	6-12
Indapamide	2.5 mg qd	5 mg	36
Metolazone	2.5-5 mg qd	20 mg	12-24

- Once a diuretic effect is achieved with short-acting loop diuretics, increase frequency to 2-3 times a day if necessary, rather than increasing a single dose. *Strength of Evidence = B*
- Oral torsemide **may be considered** in patients exhibiting poor absorption of oral medication or erratic diuretic effect. *Strength of Evidence = C*
- IV administration of diuretics may be necessary. *Strength of Evidence = A*

Angiotensin Converting Enzyme Inhibitors

- ↓ Angiotensin II
  - ↑ vasodilation
  - ↓ ventricular remodeling and cardiac hypertrophy
  - ↓ myocyte apoptosis
  - ↓ sympathetic nervous system activation by ↓ NE release
- ↓ Aldosterone
  - ↓ sodium and water retention
- ↑ Bradykinin
  - ↑ vasodilation
  - ↓ ventricular remodeling and cardiac hypertrophy

Efficacy of ACEI

- Consistently shown in different trials
- In asymptomatic patients
  (e.g. SOLVD, SAVE, TRACE trials)
- In symptomatic patients
  (e.g.CONSENSUS, SOLVD-Rx trials)
- Effective across a wide range of patients with different causes and severity of LV dysfunction.
- Reduces Mortality, Symptoms, Hospitalisation

ACE Inhibitors in Heart Failure: From Asymptomatic LVD to Severe HF

SOLVD Prevention (Asymptomatic LVD)

20% ↓ death or HF hosp.

29% ↓ death or new HF

SOLVD Treatment (Chronic Heart Failure)

16% ↓ mortality

CONSENSUS (Severe Heart Failure)

40% ↓ mortality at 6 mos.

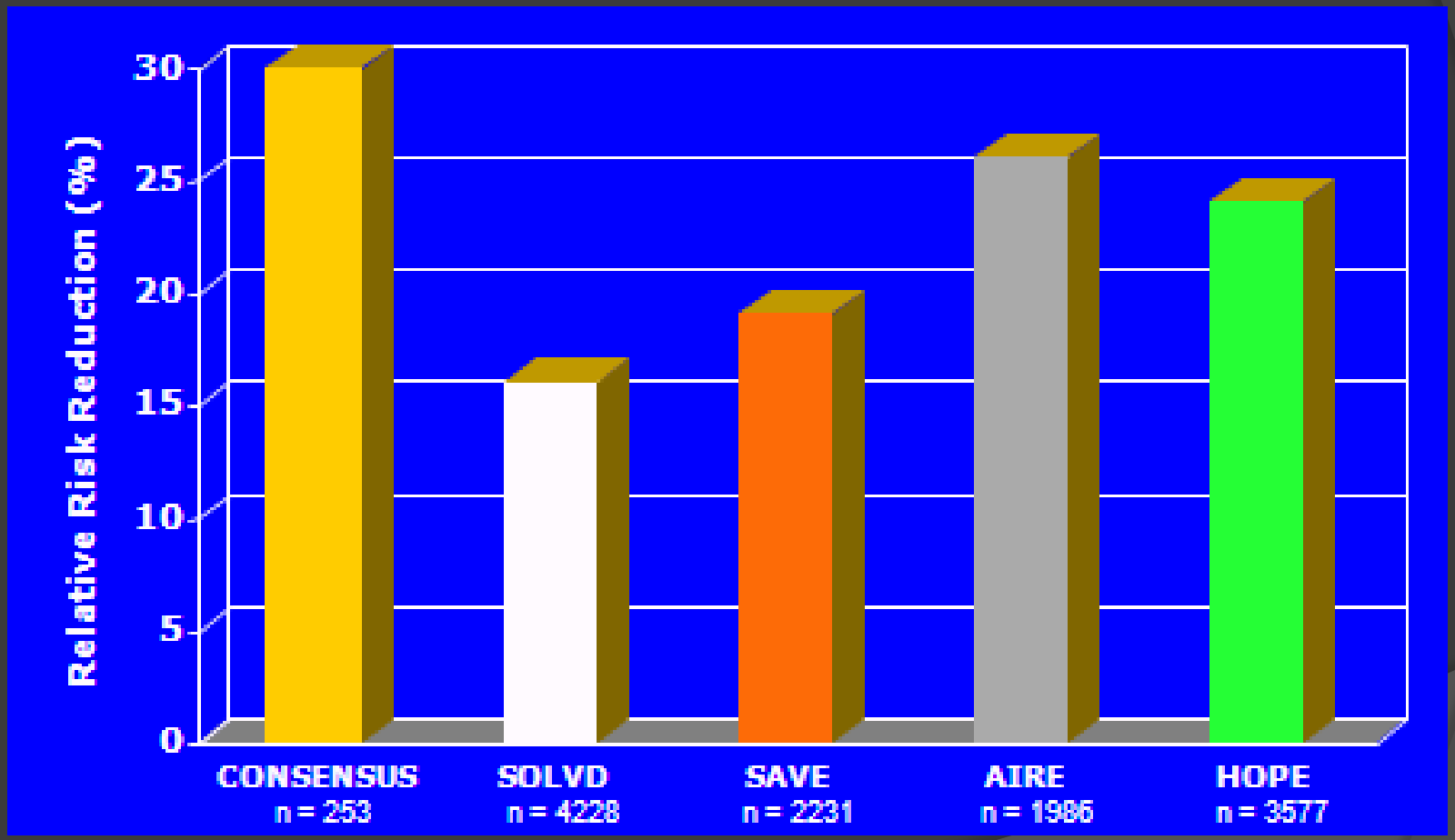
31% ↓ mortality at 1 year

27% ↓ mortality at end of study

- No difference in incidence of sudden cardiac death

SOLVD Investigators. N Engl J Med 1992;327:685-91.
SOLVD Investigators. N Engl J Med 1991;325:293-302.
CONSENSUS Study Trial Group. N Engl J Med 1987;316:1429-35.

Mortality reductions with ACEI



CONSENSUS: *NEJM* 1987;316:1429-435, SOLVD: *NEJM* 1991;325:293-302, SAVE: *NEJM* 1992;327:669-677

AIRE: *Lancet* 1993;342:821-828, HOPE: *Lancet* 2000;355:253-259

Angiotensin Converting Enzyme Inhibitors

- Fluid retention can attenuate its effects -So optimize dose of diuretic first.
- Initiate at low dose
- Dose doubling every 3-5 days
- Target doses – as shown effective in clinical trials and as tolerated
- Add b-blockers before reaching target dose
- Check B.P. , renal function, potassium levels every 1-2 weeks

How much ACE-I?

ACE Inhibitor	Clinical Trial	Clinical Practice
Enalapril	18.4 mg/day (CONSENSUS I) 15 mg/day (VHeFT II) 16.6 mg/day (SOLVD)	2.5 – 5 mg/day (42% of doses)
Captopril	150 mg/day	75 mg/day (75% of doses)
Lisinopril	20 mg/day	10 mg/day (65% of doses)

How much ACE-I?

AGENTS	INITIATING DOSAGE	MAXIMAL DOSAGE
Angiotensin-Converting Enzyme Inhibitors		
Captopril	6.25 mg tid	50 mg tid
Enalapril	2.5 mg bid	10 mg bid
Lisinopril	2.5-5.0 mg qd	20 mg qd
Ramipril	1.25-2.5 mg qd	10 mg qd
Fosinopril	5-10 mg qd	40 mg qd
Quinapril	5 bid	40 mg bid
Trandolapril	0.5 mg qd	4 mg qd

Angiotensin Receptor Blocker

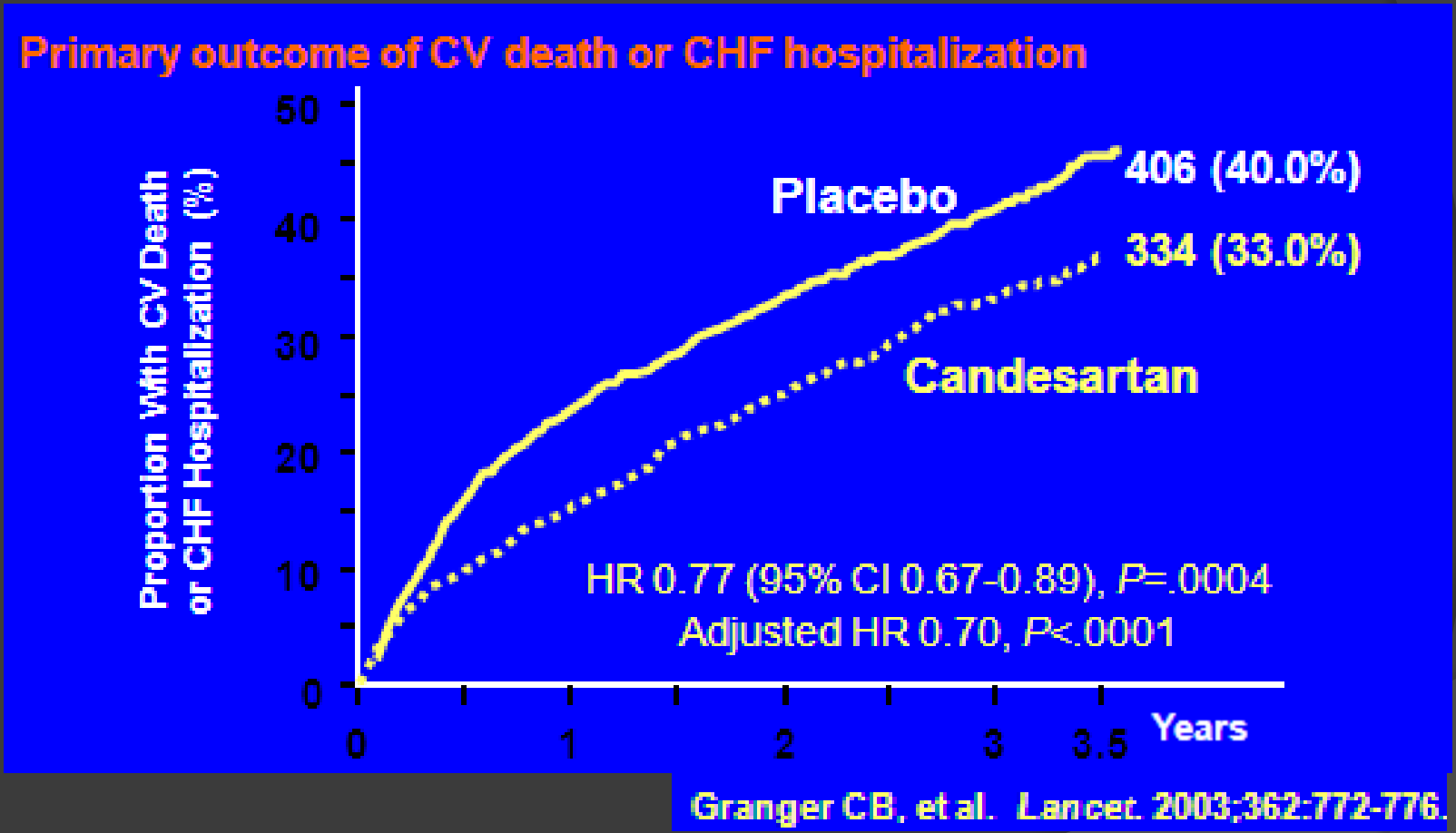
Act as antagonist at the AT1 receptors

Angiotensin Receptor Blocker

- Proven beneficial as alternative to ACE-I in HF treatment and prevention

  (e.g. CHARM, Val-HeFT, VALIANT, trial)
- Better tolerated than ACEI (in terms of cough, angioedema, skin rash)
- Some studies suggest concurrent use has additional benefit (e.g. CHARM-Added trial) while other studies negate (e.g. Val-HeFT, VALIANT trial)
- Reduces mortality, morbidity, hospitalisations.

CHARM-Alternative



ARBs are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF $\leq$ 40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency.

Strength of Evidence = A

How much ARB ?

AGENTS	INITIATING DOSAGE	MAXIMAL DOSAGE
Valsartan	40 mg bid	160 mg bid
Candesartan	4-8 mg qd	32 mg qd
Losartan	12.5-25 mg qd	50 mg qd

Beta-Adrenergic Receptor Blockers

- Beta blockers interfere with the harmful effects of sustained activation of the nervous system by competitively antagonizing one or more adrenergic receptors (alpha$_1$, beta$_1$, and beta$_2$)
- Reverse LV remodeling

Efficacy of beta blockers

- Three beta blockers have been shown to be effective in reducing the risk of death in patients with chronic HF; bisoprolol , sustained-release metoprolol succinate and carvedilol.

  (MERIT-HF, CIBIS, COPERNICUS trials)

- Reduces Mortality, Hospitalization, SCD

- Additional benefit when added to ACEI

Effect of beta-blockade on outcome

TRIAL NAME	AGENT	NYHA CLASS	NO. OF PATIENTS IN STUDY	12-MO PLACEBO MORTALITY (%)	12-MO EFFECT SIZE (%)	*P* VALUE AT 12 mo (Full follow-up)
CIBIS-I	Bisoprolol	III, IV	641	21	↓20 [†]	NS (0.22)
U.S. Carvedilol	Carvedilol	II, III	1094	8	↓66 [†]	NS (< 0.001)
ANZ-Carvedilol	Carvedilol	I-III	415	NS	NS	NS (>0.1)
CIBIS-II	Bisoprolol	III, IV	2647	12	↓34 [†]	NS (0.001)
MERIT-HF	Metoprolol CR	II-IV	3991	10	↓35 [†]	NS (0.006)
BEST	Bucindolol	III, IV	2708	23	↓10 [†]	NS (0.16)
COPERNICUS	Carvedilol	Severe	2289	28	↓38 [†]	NS (0.0001)

Modified from Bristow MR, Linas S, Port DJ: Drugs in the treatment of heart failure. In Zipes DP, Libby P, Bonow RO, Braunwald E (eds): Braunwald's Heart Disease. 7th ed. Philadelphia, Elsevier, 2004, p 573.

Beta- blockers...

General considerations	Initiate at low doses
	Up-titrate gradually, generally no sooner than at 2 week intervals
	Use target doses shown to be effective in clinical trials
	Aim to achieve target dose in 8-12 weeks
	Maintain at maximum tolerated dose
If symptoms worsen or other side effects appear	Adjust dose of diuretic or concomitant vasoactive med.
	Continue titration to target after symptoms return to baseline
If up-titration continues to be difficult	Prolong titration interval
	Reduce target dose
	Consider referral to a HF specialist

How much beta-blocker?

AGENTS	INITIATING DOSAGE	MAXIMAL DOSAGE
Carvedilol	3.125 mg bid	25 mg bid (50 mg bid if body weight > 85 kg)
Carvedilol-CR	10 mg qd	80 mg qd
Bisoprolol	1.25 mg bid	10 mg qd
Metoprolol succinate CR	12.5-25 mg qd	200 mg qd

Beta-blockers (using 1 of the 3 proven to reduce mortality, i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated. ***(Level of Evidence: A)***

Start with ACEI or BB?

- CIBIS III did not provide clear-cut evidence to justify starting with a beta blocker first
- The overall safety profile of the two strategies was similar.
- Current guidelines continue to recommend starting with an ACEI first, followed by the subsequent addition of a beta blocker.

Effects of Adding β-Blockers vs Increasing ACE Inhibitor Dose in HF

	Symptoms	Morbidity	Mortality
Increase dose of ACE inhibitor[1]	No effect	↓ 10-15%	NS
Add β-blockade[2]	↓	↓ 20-35%	↓ 35%

No evidence for the need to maximize ACE-I doses before starting β-blocker therapy (BB + ACE-I better than high dose ACE alone)

[1]Packer M et al. Circulation. 1999;100:2312–2318.
[2]Lechat P et al. Circulation. 1998;98:1184–1191.

- Few isolated trials for efficacy of Bucindolol(BEST trial) and Nevibolol (SENIORS trial) in various populations have shown enthusiastic results.

- However these drugs are not yet included in guidelines.

Aldosterone antagonists

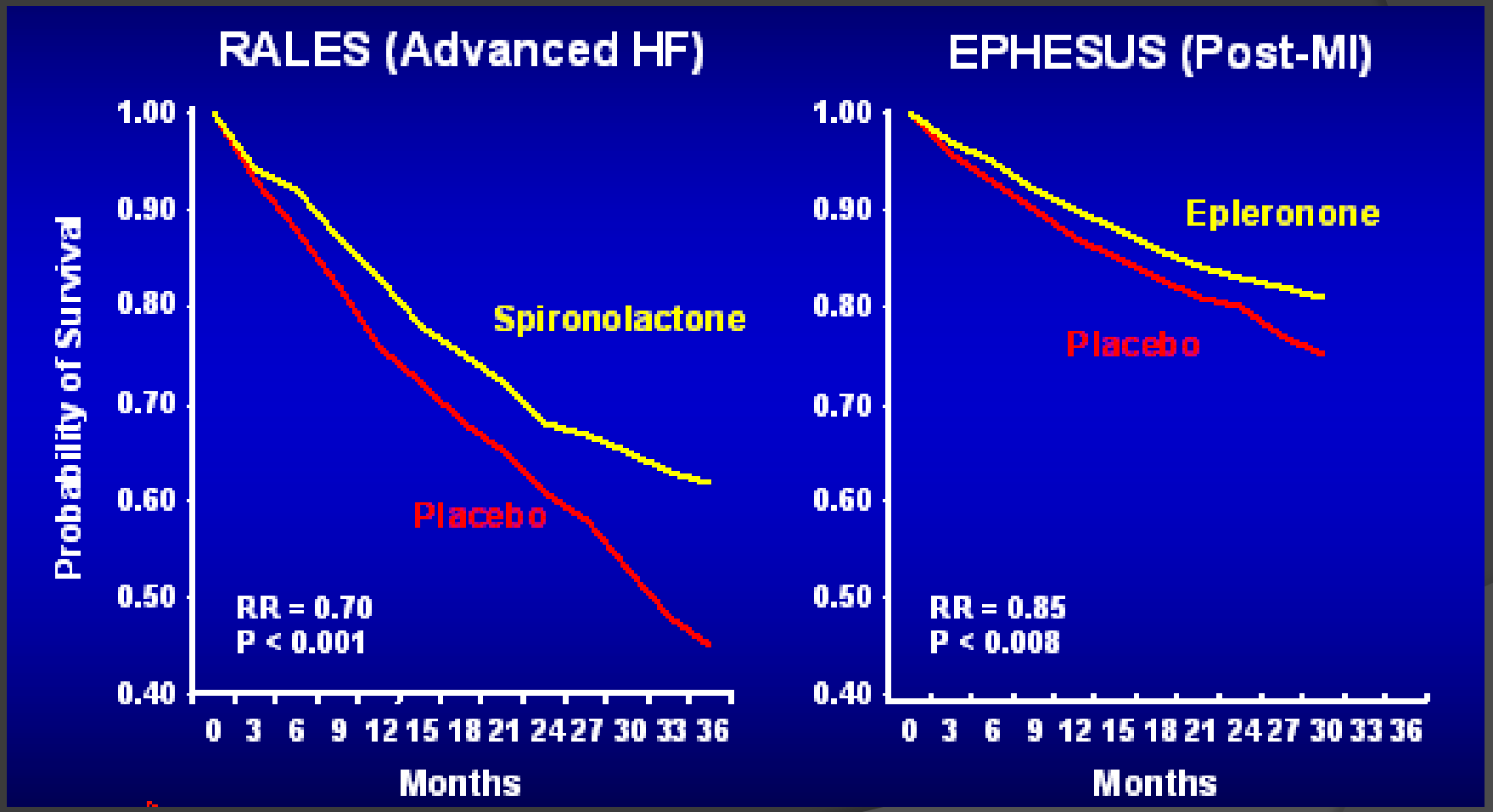
•Spironolactone and its active metabolite, canrenone, competitively inhibit the binding of aldosterone to mineralocorticoid or type I (thus preventing Na + and water retention and K+ wasting)

•These cytosolic receptors translocate to the nucleus, bind to promoter regions of some genes, including several involved in vascular and myocardial fibrosis, inflammation, and calcification; and supress their expression.

Aldosterone antagonists

- The first evidence was RALES trial showing a 30% reduction in total mortality.
- EPHESUS trial showed benefit with Eplerenone in Post-Acute Myocardial Infarction Heart Failure patients.
- Lower risk of death from progressive pump failure and sudden death.
- Significant improvement in NYHA functional class

Aldosterone Antagonists in HF



The administration of an aldosterone antagonist is recommended for patients with NHA Class III or IV HF who have a depressed EF (<35%), and are receiving standard therapy, including diuretics, ACEIs, and beta blockers.

Aldosterone antagonists…

- Before initiation Creatinine should be <2.5 mg/dl in men and <2 mg/dl in women & K+ should be <5 mmol/L
- K+ levels and renal function should be rechecked within 3 days and at 1 week after initiation.
- Subsequent monitoring at least monthly for the first 6 months.

How much Aldosterone antagonists?

AGENTS	INITIATING DOSAGE	MAXIMAL DOSAGE
Spironolactone	12.5-25 mg qd	25-50 mg qd
Eplerenone	25 mg qd	50 mg qd

Cardiac glycosides (Digoxin)

- Inhibits the Na^+,K^+-ATPase pump in cell membranes leading to an increase in intracellular calcium and hence increased cardiac contractility

- Sensitize Na^+,K^+-ATPase activity in vagal afferent nerves, leading to an increase in vagal tone

- Inhibits Na^+,K^+-ATPase activity in the kidney and therefore blunt renal tubular resorption of sodium.

Cardiac glycosides (Digoxin)...

- Initial trials e.g. RADIANCE, PROVED,etc. provided strong support for clinical benefit .
- DIG showed a neutral effect on the primary endpoint of mortality.
- Digoxin reduced hospitalizations caused by worsening HF.
- Strong trend toward a decrease in deaths secondary to progressive pump failure, which was offset by an increase in sudden and other non–pump failure cardiac deaths .

Class IIa indications for digitalis

- Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. *(Level of Evidence: B)*
- Dose should be of 0.125-0.25mg QD, without loading and lower if patient is over age 70, has renal impairment or low lean body mass
- Serum levels are followed for purpose of toxicity and not to guide therapy

Isosorbide dinitrate and Hydralazine

- Reasonable and can be effective in African-Americans with NYHA Class III or Class IV HF on standard medical therapy

- Class IIa indication for patients with reduced LVEF who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms. *(Level of Evidence: A)*

Management of other ailments

- Management of atherosclerotic disease (Coronary Artery Disease)
- Management of Arrythmias
- Management of Acute LVF
  (use of inotropes and inodilators)

Newer medical therapies

- Recombinant BNP analogues (Nesiritide- VMAC **Trial**)
- Vasopressin antagonist (Tolvaptan- EVEREST Trial)
- Neutral Endopeptidase inhibitor (Candoxatril)
- Calcium sensitizer (Levosimendan- CASINO Trial)
- Positive inotropic and lucitropic agent (Istaroxime- HORIZON HF Trial)

Future Perspectives

- Cell replacement therapy
- Gene therapy
- Pharmacogenetics

THANK YOU