Element 73.00

Rakowski

Andy: Note booklet slides at end. Keep in this file

Goals of HF Therapy

- **Improve hemodynamics/symptoms**
- **Reduce remodeling/prevent cell death**
- **Increase survival**

    risk factor modification (BP, statins, exercise)

    ACE inhibitors, β-blockers

    arrhythmias (Amiodarone, AICD)

    transplantation, heart replacement

Evidence Based Management

Strategy	Mortality Reduction
ACE Inhibitors	17-36%
β-blockers	20-35%
Aldactone	25-30%
Inotropic Drugs	36-50% *increase*

Treatment Strategies

Asymptomatic	Mild/Mod	Severe	Refractory

Angiotensin Converting Enzyme Inhibitors

β-Blockers *(Carvedilol)*

Diuretics *(Spironolactone)*

Digoxin

Tailored Rx

Inotropes, resynch, surgery, transplant

Correct cause:
- ***arrhythmias***
- ***ischemia***
- ***toxins/infection***
- ***non-compliance***

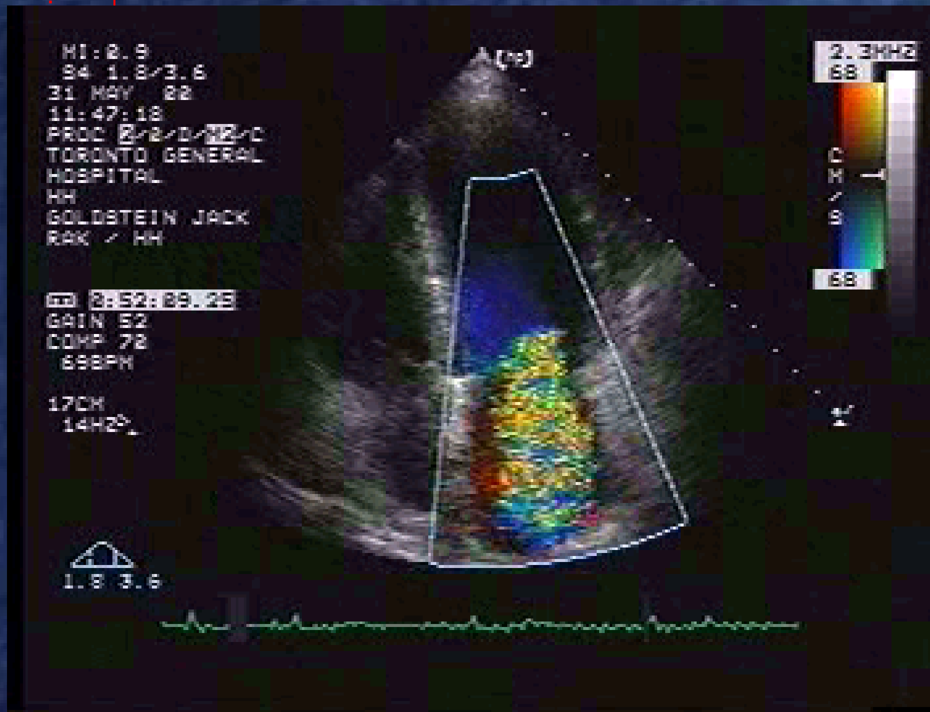
No added salt — **2 gm Na**

Activity as tolerated — **customized ex training**

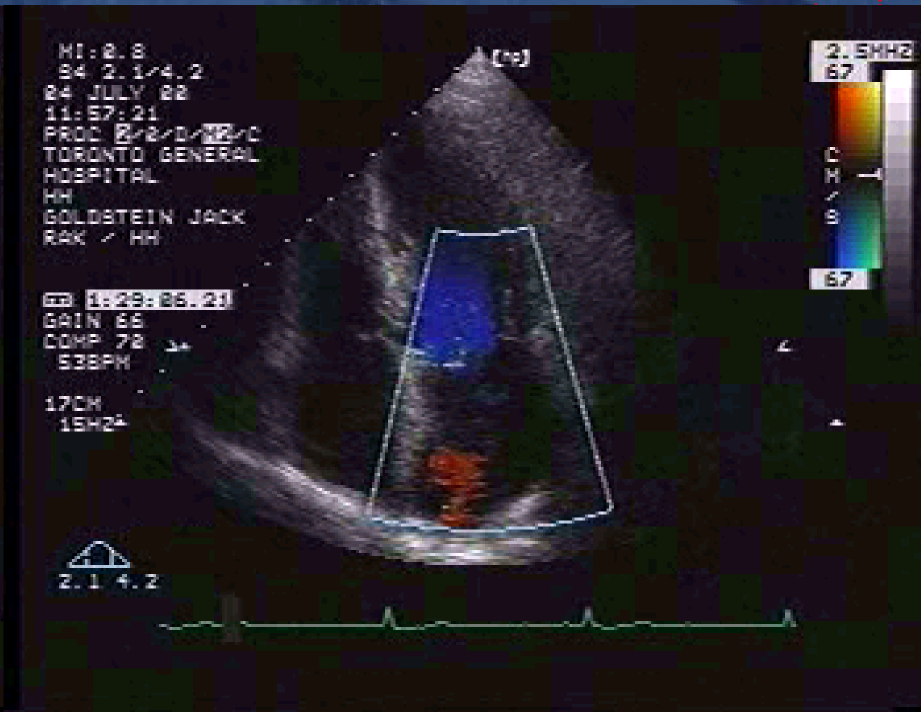
Modified from Warner-Stevenson, ACC HF Summit

80 y.o. male with CAD

Previous CABG - 2 MI



Pre

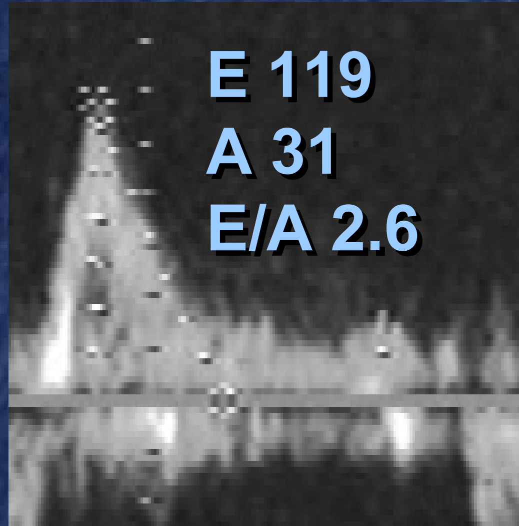


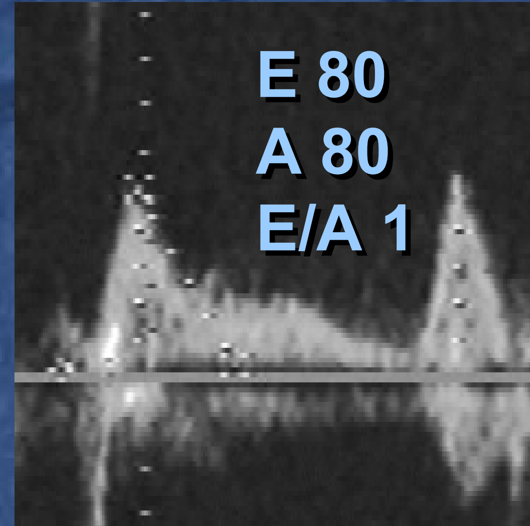
Post

PRE

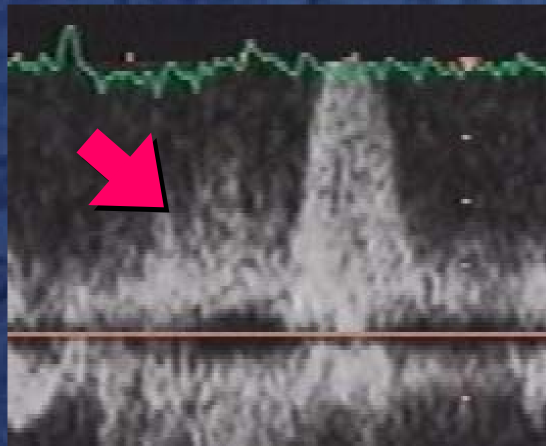
POST

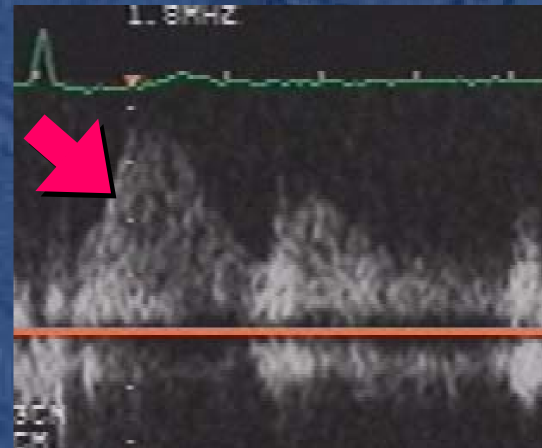
MV



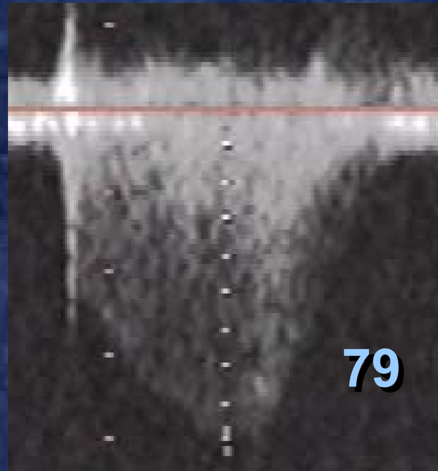


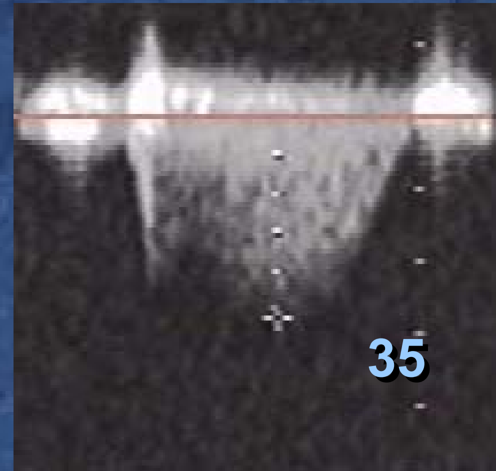
PV





RVSP PRE POST

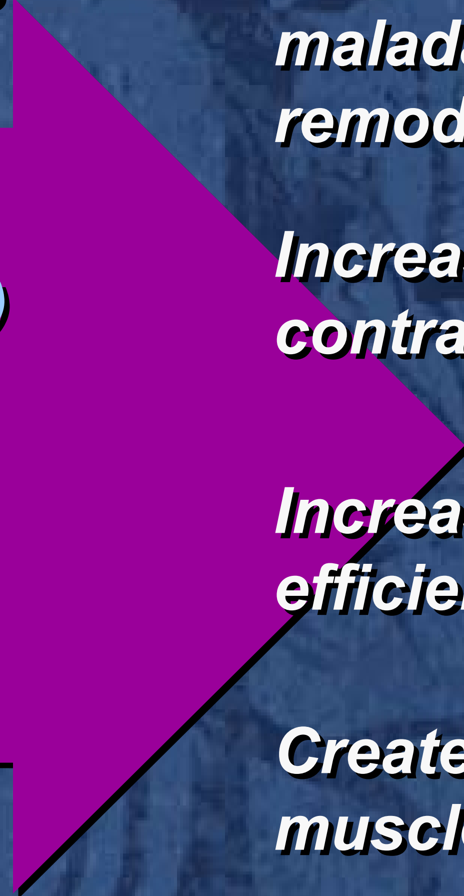




- Reduce LV size
- Increase systolic function (EF)
- Decrease LV filling pressures
  - *LVEDP, LAP, RVSP*
- Decrease MR

Novel CHF Strategies

- **Neurohumoral blockers**
  endothelin, cytokine, vasopressin antagonists
- **Novel inotropic agents**
  Ca^{++} sensitizers (levosimendan) growth hormone
- **Mechanical therapies**
  resynchornization / ICDs LVAD, mechanical heart, CPAP
- **Gene therapies**
  gene/cell replacement



Decrease maladaptive remodeling

Increase contractility

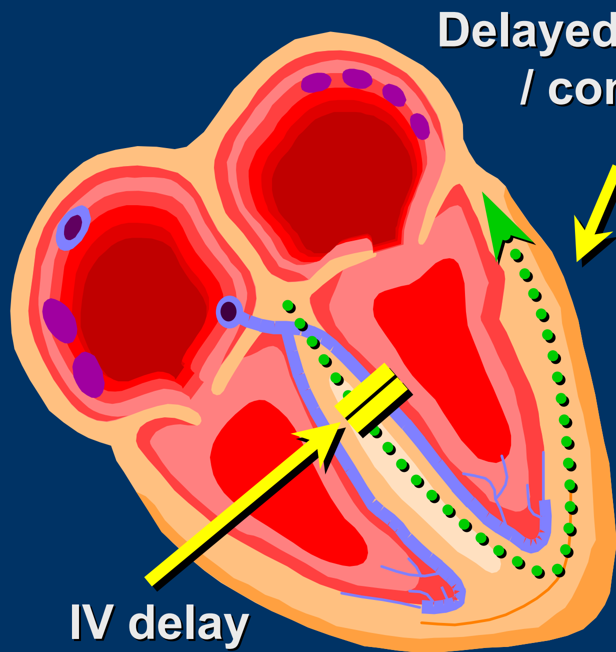
Increase efficiency

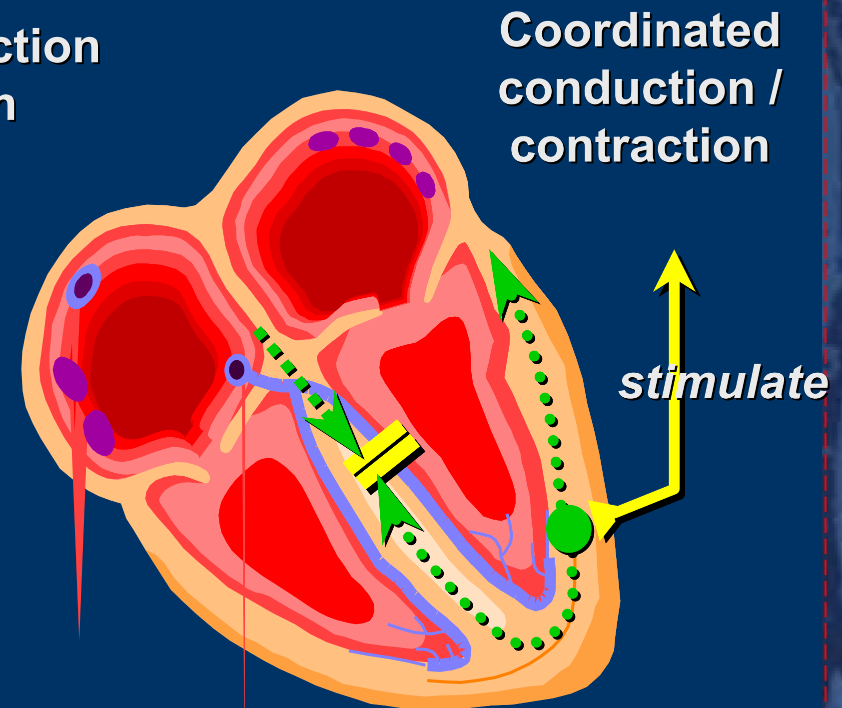
Create new muscle cells

Coordinate Ventricular Contractions

Biventricular pacing

Intrinsic conduction **Coordinating stimulation**





Inefficient ejection **More efficient ejection**

Biventricular Pacing
Severe CHF & LBBB

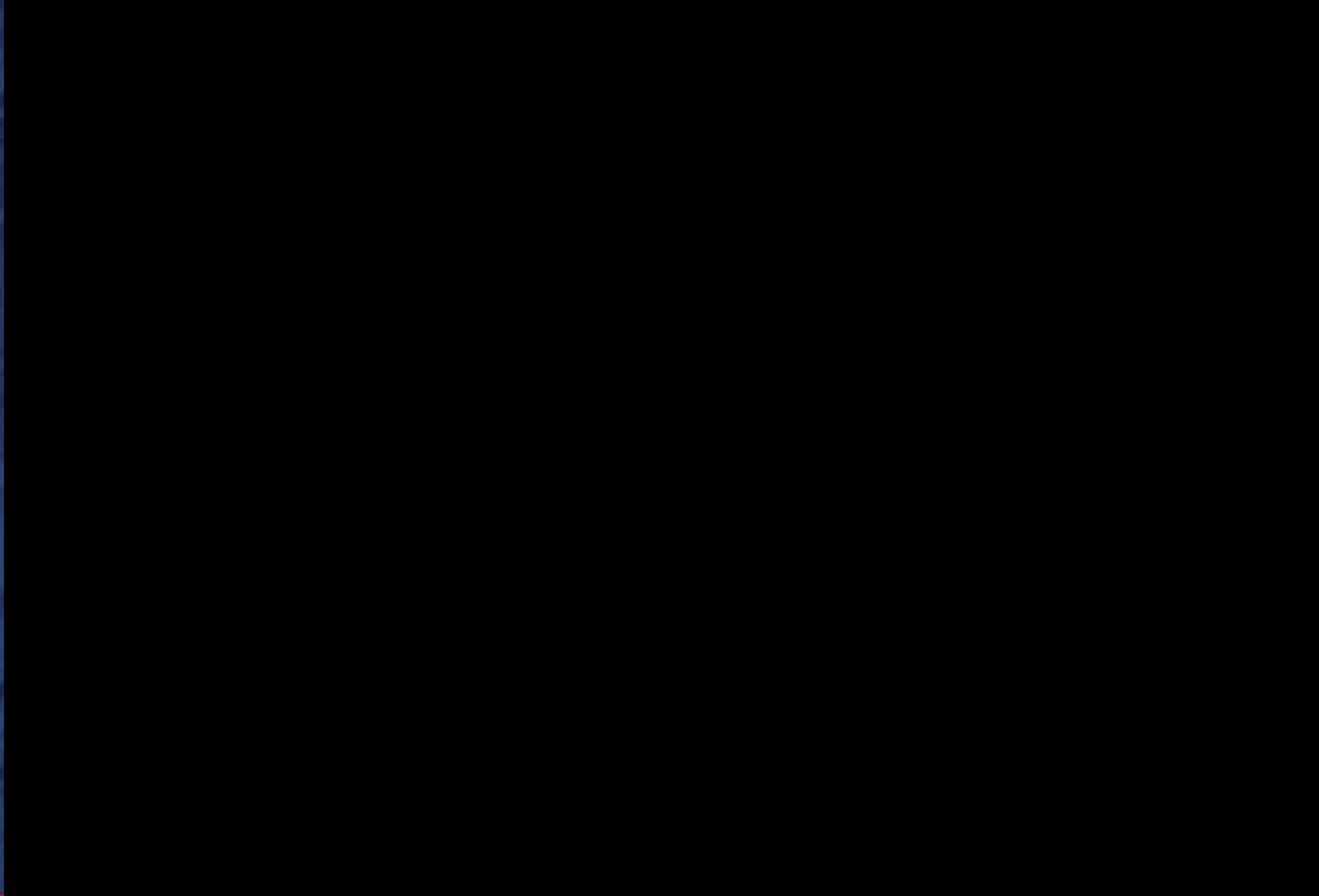
- Resynch LV filling/EF in pts with IVCD
- Pace LV via coronary sinus tributary
- 3D echo demonstrated

LV volume decreased	*5%*
MR decreased	*12%*
forward SV increased	*19%*
exercise capacity increased	*43%*

- Mortality/arrhythmias awaiting randomized trial results

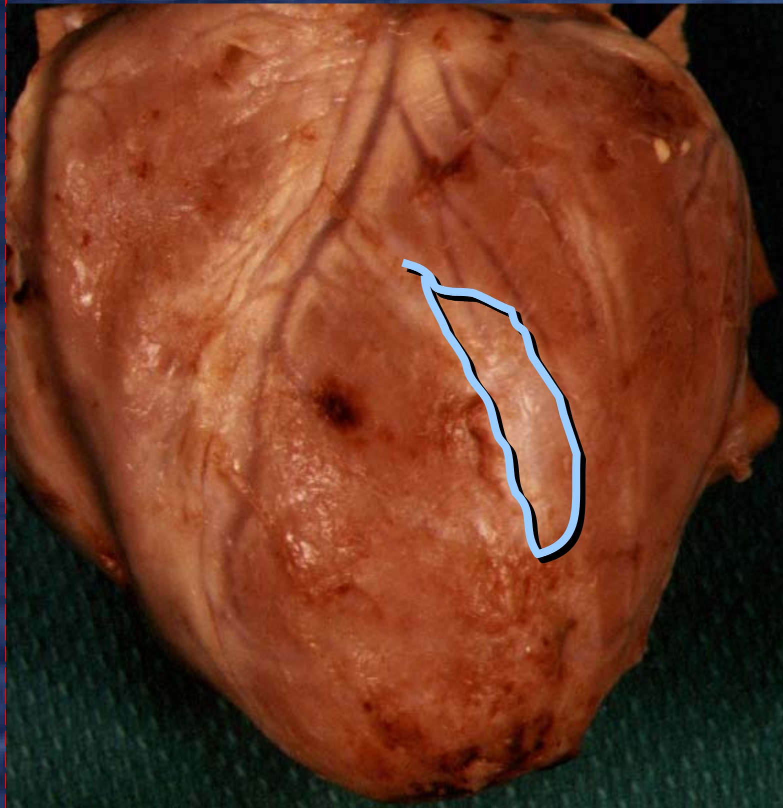
Kim et al Heart 85:2001

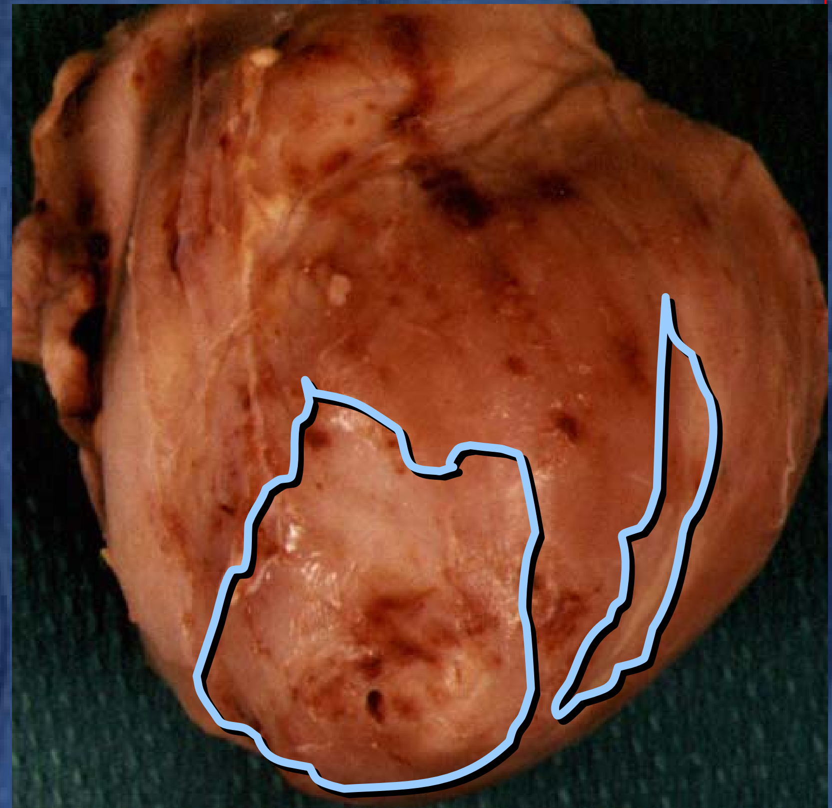
LV Assist Device



Pig Cell Transplant Post MI

Transplanted | **Control**



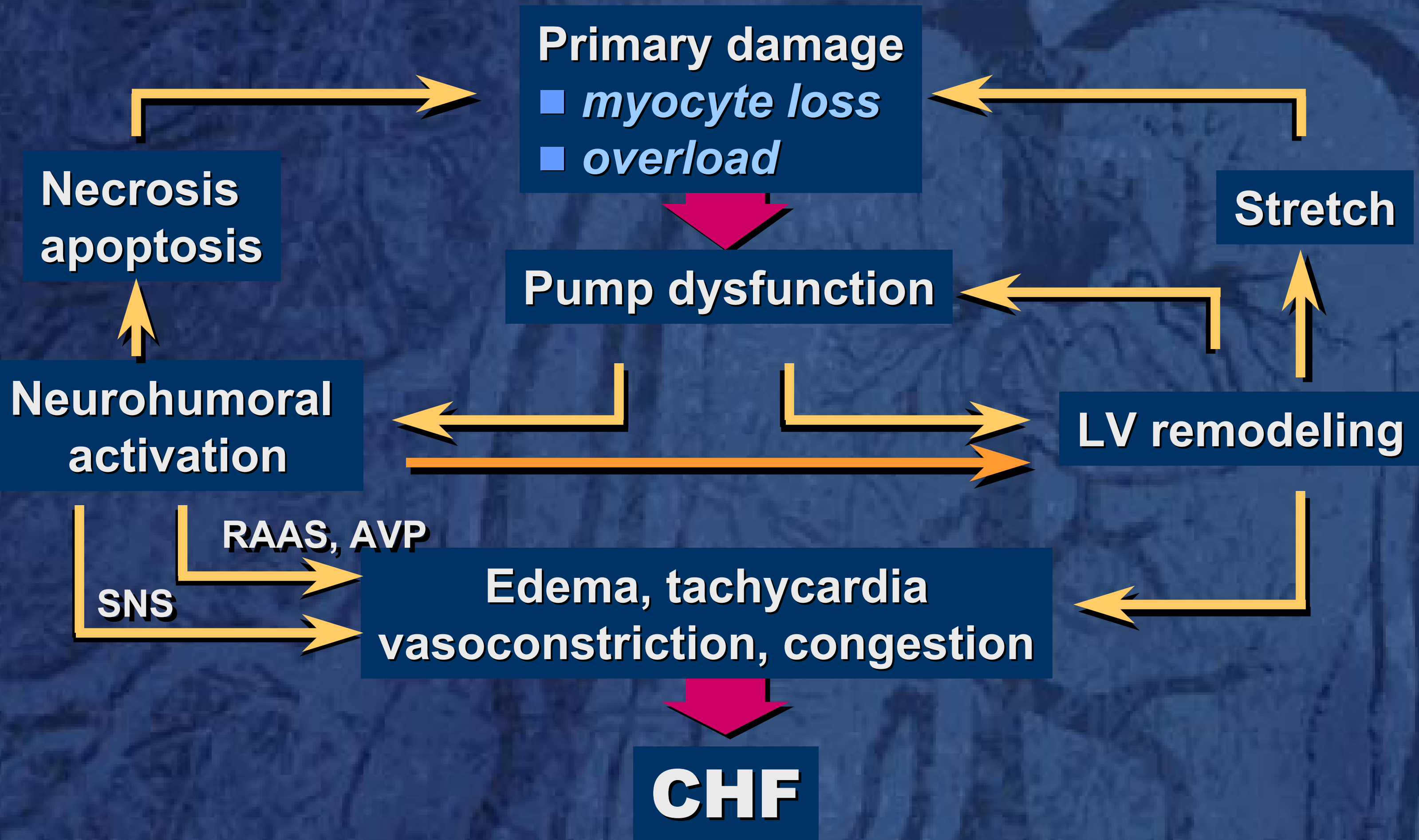


Treatment of CHF

- Target to disease stage/patient status
- Treat underlying disease/risk factors
- Treat congestive symptoms
- Reduce mortality: *Evidence based trials*
- Novel therapy for end stage/transplant
- Morbidity/mortality high despite treatment

Rakowski Element 73
Extra Slides

Pathogenesis



Pathogenesis

Treat underlying disease

Prevention

Primary damage
- *myocyte loss*
- *overload*

Necrosis apoptosis

Stretch

Pump dysfunction

Neurohumoral activation

LV remodeling

RAAS, AVP

SNS

Edema, tachycardia vasoconstriction, conges

ACE

CHF

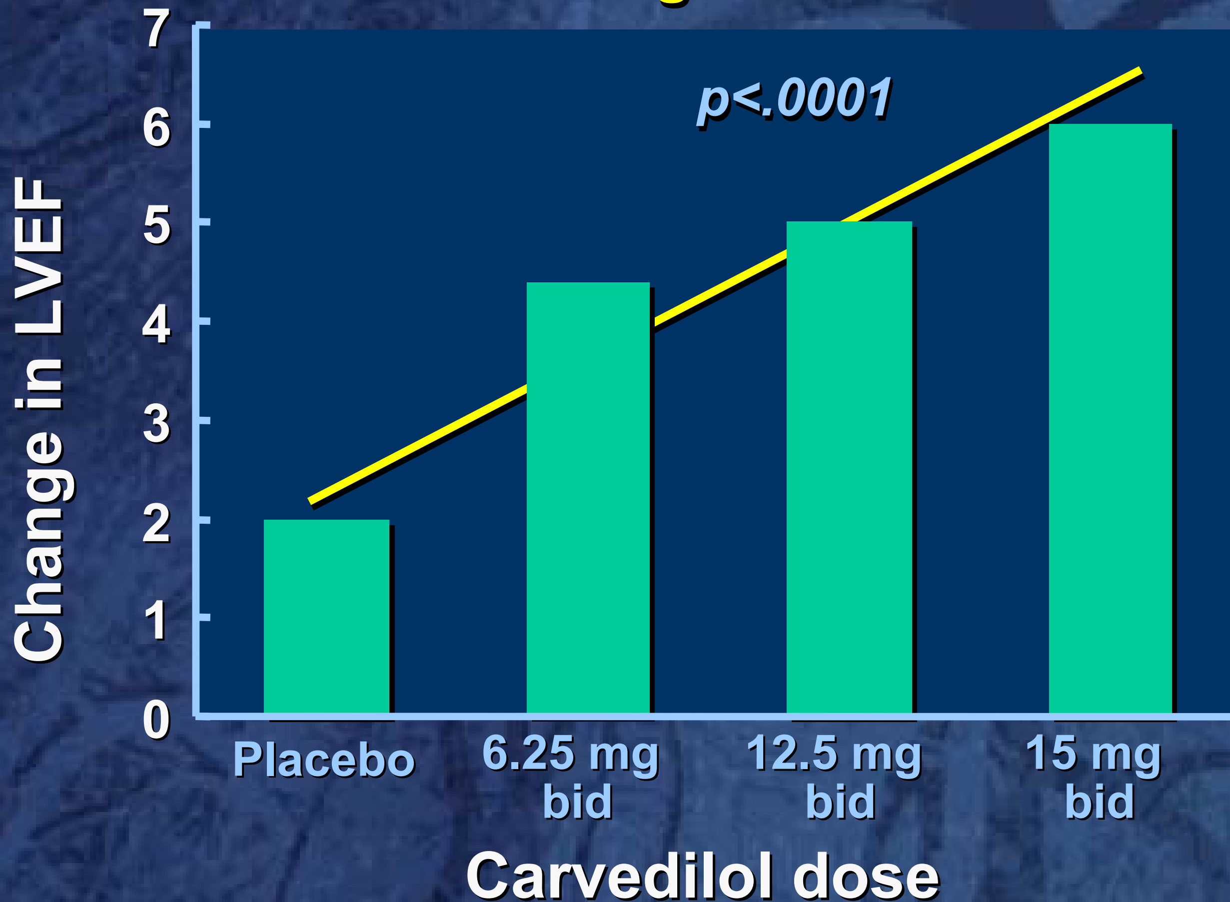
β-blockers diuretics LVAD, CPAP

ACE Inhibitors Reduce Mortality

Trial	Pts	Rx	mortality
CONSENSUS	IV	enalapril	↓ 36%
SOLVD *(treatment)*	II & III	enalapril	↓ 17%
SOLVD *(prevention)*	I & II *EF<35%*	enalapril	↓ 8%
SAVE	post MI *EF<40%*	captopril	↓ 18%
AIRE	post MI	ramipril	↓ 25%

MOCHA Trial

LVEF change at 6 months



Bristow et al Circulation 1996

Therapy for Heart Failure

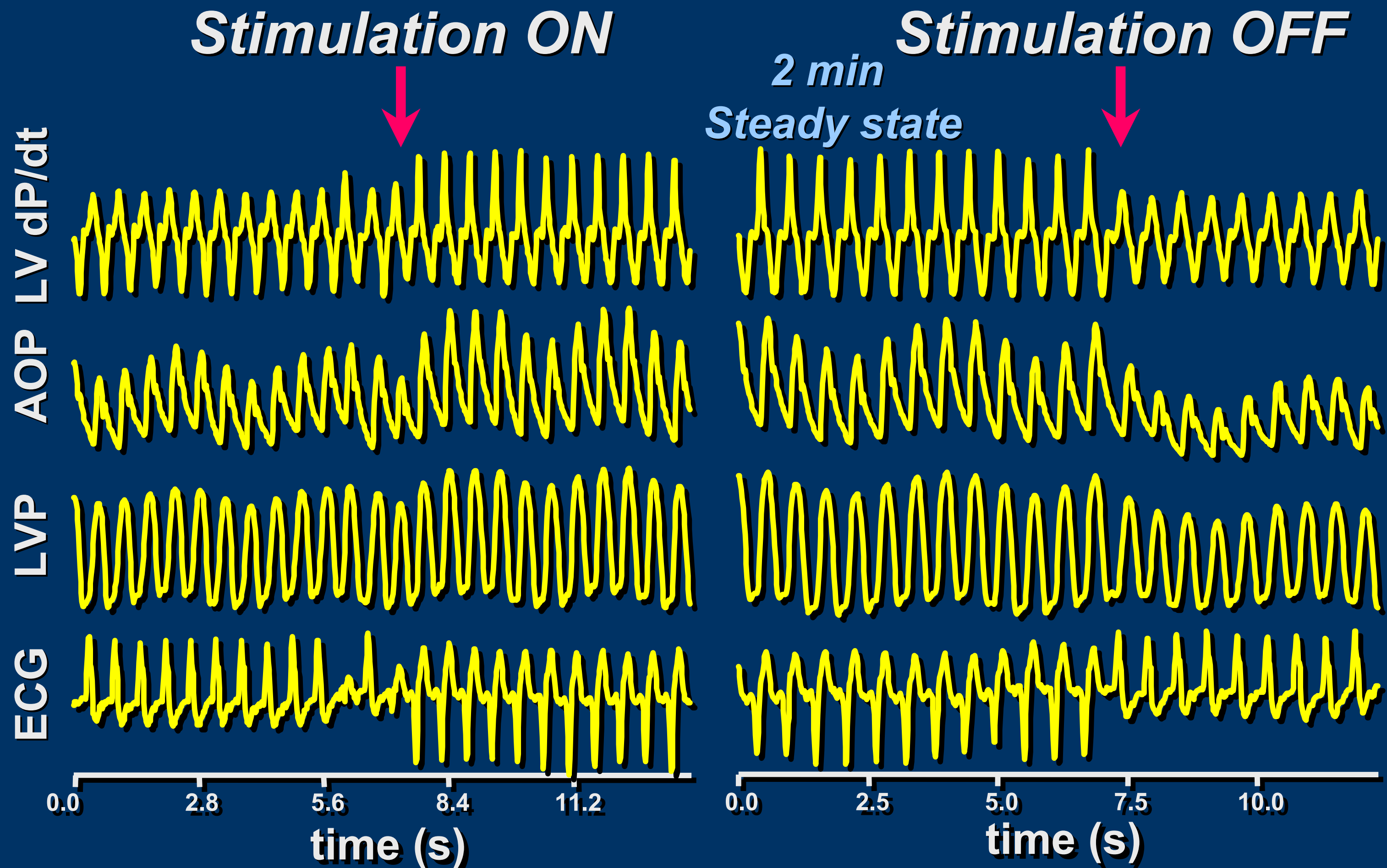
- **Decrease preload**
  - *salt restriction*
  - *diuretics*
  - *venous vasodilators*
- **Decrease afterload**
  - *arterial vasodilators*
  - *ACE inhibitors*
  - *Angiotensin II receptor blockers*
- **Increase contractility**
  - *inotropic agents*
  - *β-blockers*

Diastolic Failure

Health Care Crisis

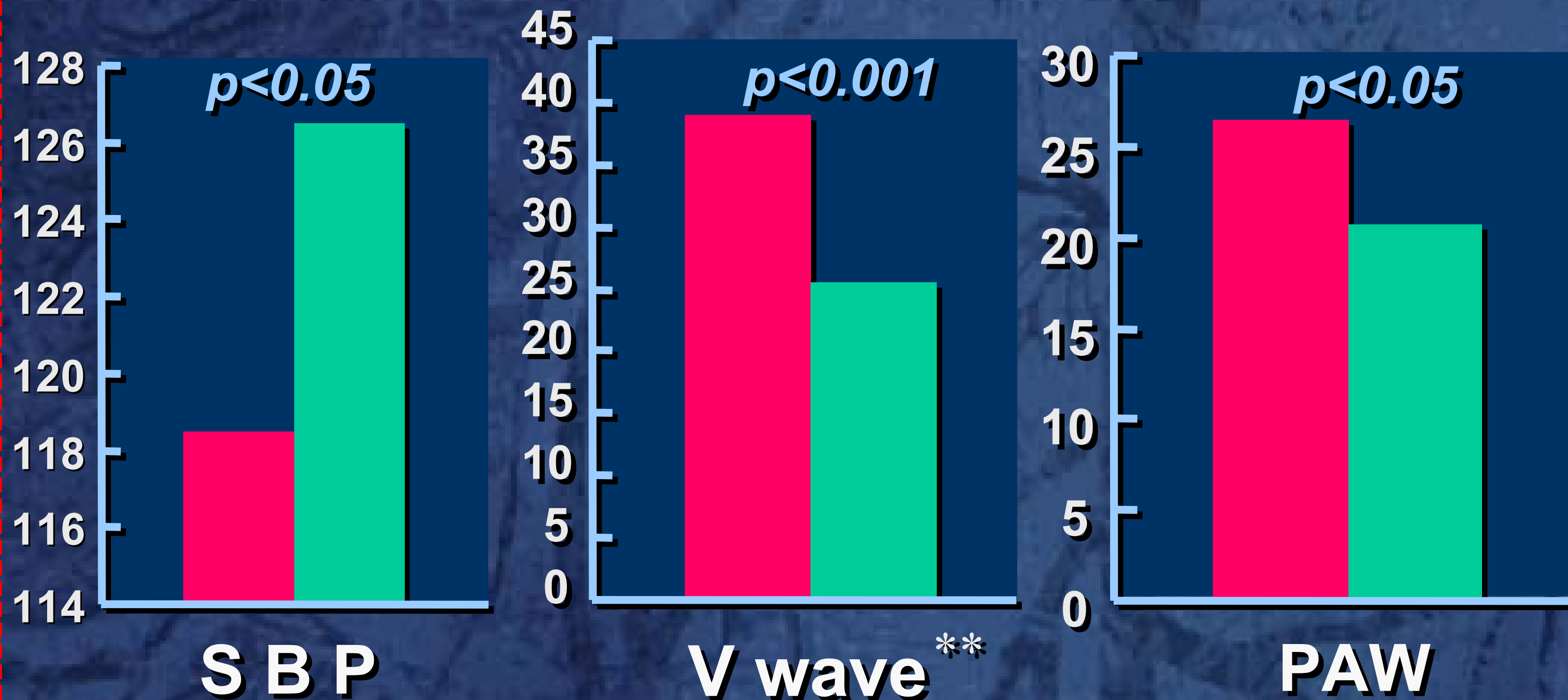
Study	Pts	% DHF /age	DHF %mort	SHF %mort
Cohen *1999*	623	13 / 60	8	19
Permenkil *1997*	501	34 / 81	28	38
McAllister *1999*	566	21 / 65	12	17
Ansari *2001*	376	27 / 72	20	20

CT Direct Hemodynamic Improvement



Kass et al Circulation (1999) 99:1567

Multi-site Pacing



Blanc et al, Circ 1997

LVAD for CHF

Reverse Remodeling

- Pathologic analysis
- 87 transplanted human hearts
- 34 LVAD support *(press/vol unloading)*
- LVAD hearts reverse remodeled LV and not RV

  more normal LV myocyte size
  reduced chamber size
  improved muscle strip function (force frequency)

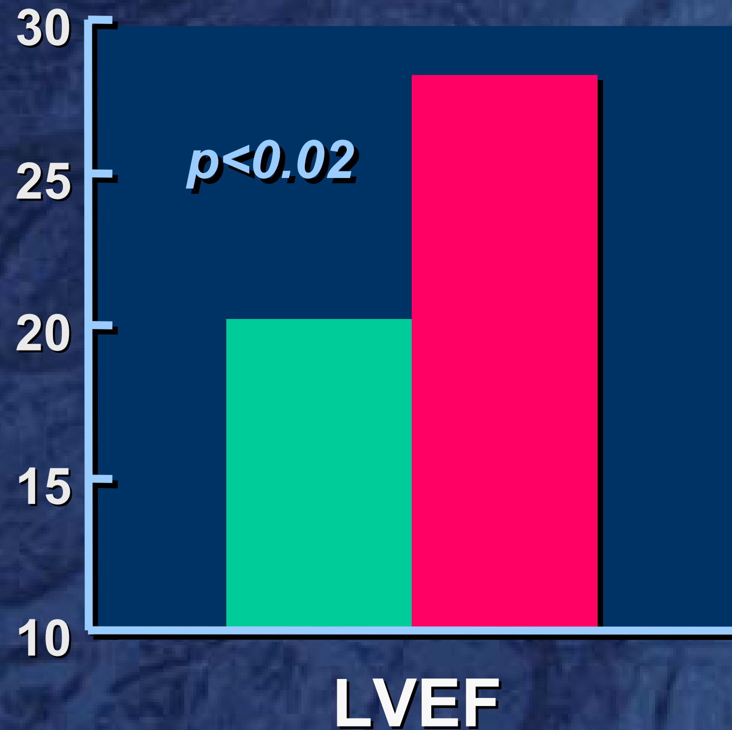
Barbone et al Circulation 2001

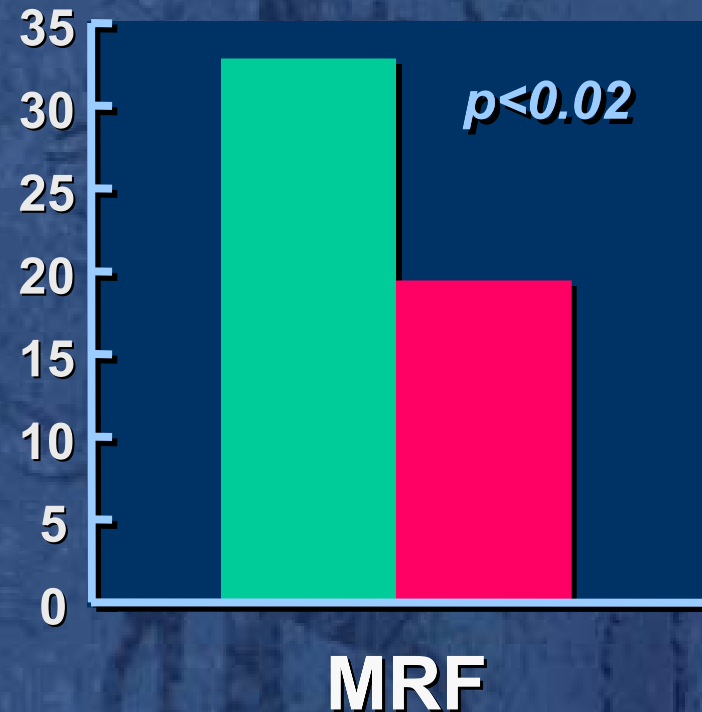
CPAP in CHF

N=17

- randomized to CPAP vs medical Rx
- no sig change in medical group

Baseline
CPAP *(3 months)*





Tkacova et al JACC 1997

AHA/ACC Guidelines

Echo and Heart Failure

- Assess LV function
- Define likelihood of CAD *with LV dysfx*
- Detect ischemia/viability *in pts with known CAD & no angina, being considered for revasc*
- Screen asymptomatic *1^0 relatives of IDC pts*
- Repeat measurement of EF

  change in clinical status or
  experienced or recovered from clinical event or
  Rx that might have significant effect on function

Inotropic Drugs & Excess Mortality

Trial	Pts	Rx	mortality
Vesnarinone	III & IV *EF<30%*	Inotrope *Vesnarinone*	↑ hi ↓ lo
PROFILE	III & IV *EF<35%*	vasodilator *Flosequinan*	↑ 50%
PROMISE	III & IV *EF<35%*	enalapril *Milrinone*	↑ 36%
Euro Xamoterol	II & III	*β*-agonist *Xamoteral*	excess

Stages of Heart Failure

- **STAGE A:** *High risk LV dysfunction*
- **STAGE B:** *Structural heart disease without HF*
- **STAGE C:** *Current or prior HF with underlying structural heart disease*
- **STAGE D:** *Advanced structural heart disease and signs/symptoms of HF at rest despite maximal medical therapy*

2001 ACC/AHA Guidelines for the Evaluation and Management Of Chronic Heart Failure in the Adult

These formatted for booklet

Do not be concerned about title safe

ACEI - Post Infarction

Study	Drug	Inclusion criteria	Time after MI	Treatment duration	Outcome (Mortality %)		Study follow-up
					Control	*Treated*	
SAVE	captopril	MI, EF <40%	3-16 d	24-60 mo	24.6	20.4	24-60 mo
AIRE	ramipril	MI, clinical CHF	3-10 d	Minimum 6 mo	23	17	6-30, mean 15 mo
TRACE	trandolapril	MI, WMI >/=1.2	3-7 d	24-50 mo	62.3	34.7	24-?
SMILE	zofenopril	Anterior MI, nolytic	6-24 h	6 wk	6.5	4.9	12 mo
ISIS-4	captopril	MI	$\leq$1 d	1 mo	7.7	7.2	1 mo
GISSI-3	lisinopril	MI	$\leq$1 d	6 wk	7.1	6.3	42 d
Consensus II	enalapril	MI	$\leq$ 1d	41-180 d	9.4	10.2	41-180 d, mean 6 mo

ACEI in CHF

Study	Drug	Inclusion	Duration of Treatment	Follow-up	Outcome (Mortality) Control	Outcome (Mortality) Treated	N Rx to save one life
Consensus-I	enalapril	NYHA IV · 73% CAD · 47% prior MI	1d –20 mo.	1d-20 mo mean 188 d	54	39	7
SOLVD-T	enalapril	NYHA II-III EF </=35% · 71% CAD · 66% prior MI	22-55 mo.	Mean 41.4 mo	39.7	35.2	22
SOLVD-P	enalapril	NYHA I-II EF </=35% · 83% CAD · 80% prior MI	14.6-62 mo.	37.4 mo	15.8	14.8	
V-Heft II	enalapril	NYHA II-III EF < 45% · 54% CAD · 47% prior MI	0.5-5.7 y	Mean 30 mo	38.2	32.8	19
ATLAS (N=3164)	lisinopril	NYHA II-IV EF < 30%		5 yr study	Low 44.9%	High 42.5%	

ARB in CHF

Study ARB	Drug	Inclusion	Duration of treatment	Outcome (mortality)
ELITE II (N=3152)	losartan (50) vs. captopril (50 tid)	NYHA II-IV EF < 40%	555 d	L- 11.7% C- 10.4%
CHARM	candesartan ARB vs. placebo in ACEI intolerant			2002
Combination ACEI/ARB				
RESOLVD (Pilot)	candesartan			Improved LV remodeling Improved neurohormonal activation
VAL-HEFT (5010)	On ACEI valsartan vs. placebo	Mild to mod CHF	1.8 yr follow - up	19.7% val 19.4% placebo 13.3% reduction in composite endpoint
CHARM (2500)	candesartan			

β-Blockers in CHF

Study	Drug	Inclusion	dose	Duration of treatment	Outcome (mortality)
MDC (N=383)	metoprolol	FC II-III (90%)	50-75 bid		P-21 T-23
Carvedilol US (N=1094)	carvedilol	FC II-IV (3 % FC IV) EF < 35%	25 bid	Stopped early	65% reduction
CIBIS (N=641)	bisoprolol (b1 selective)	FC III-IV	10 od		20% reduction (p=ns)
CIBIS II (N=2647)	bisoprolol	FC II-III (17% FC IV) EF < 35%	10 od	1.3 yrs (stopped early)	32% reduction
BEST (N=2,708)	bucindolol	FC III-IV			P-16.8% T-15.1%
MERIT-HF (N=3991)	Metoprolol CR	FC II-III (3% FC IV) mean EF 28%	200 od	1 yr (stopped early)	38% reduction
COPERNICUS (N=2,289)	carvedilol	FC III-IV	25 bid	(stopped early)	35% reduction
COMET	carvedilol vs metoprolol	FC II-IV		ongoing	

Studies pending

- EPHESUS
  - *Eplierenone*
- ENABLE
  - *low dose Bosentan*
- SCUD-HeFT
  - *ICD vs Amiodarone vs best medical therapy*
- OPERA
- OVERTURE
  - *Omapatrilat*
- RENAISSANCE RECOVER
  - *TNF blockade*
- OPTIMAAL
  - *Losartan post MI*
- VITAL, AQUAVIT
  - *Block VP1 +/- VP2 receptors*
- PEP-CHF
  - *Perindopril vs. placebo*
  - *Diastolic heart failure*
  - *N=1000*
- CHARM
  - *Diastolic heart failure*
  - *Candesartan vs. placebo*