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Trials of Significance

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Standard of Care

Important past clinical trials

- **ACE Inhibitors**
*CONSENSUS, SOLVED, others
now standard of care
LV dysfunction and/or symptoms*
- **β-blockers**
*MERIT-HF, CIBIS II, COPERNICUS
Improve survival, remodeling and EF*

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These trials have resulted in significant “Standard of Care” changes in the way we care for patients.

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Moving to Standard of Care

Important current clinical trials

- **Spironolactone**
*RALES
III-IV with LV dysfx improved survival*
- **Valsartan added to ACEI & β-blocker**
VAL-HEFT
- **Biventricular pacing**
widened QRS, improved EF
- **Assist devices**
REMATCH, extreme failure

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Other trials are in progress and getting us there.

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Future Significance

Important future clinical trials

- **Surgical**
*revascularization
restoration*
- **Cell therapeutics**
skeletal myoblasts
- **Genetic modification**
diagnosis and therapeutics

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And there a future significant directions.

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A Compendium of Trials in Heart Failure
 Harry Rakowski, MD
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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 15mo
TRACE	trandolapril	MI, WMI >=1.2	3-7 d	24-60 mo	62.3	34.7	24-?
SMILE	zofenopril	Anterior MI, no/ytic	6-24 h	6 wk	6.5	4.9	12 mo
ISIS-4	captopril	MI	≤1 d	1 mo	7.7	7.2	1 mo
GISSI-3	lisinopril	MI	≤1 d	6 wk	7.1	6.3	42 d
Consensus II	enalapril	MI	≤1 d	41-180 d	9.4	10.2	41-180 d, mean 6 mo

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These are the ACE Inhibitor trials.

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ACEI in CHF

Study	Drug	Inclusion	Duration of Treatment	Follow-up	Outcomes (Mortality)		N Rx to save one life
					Control	Treated	
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	22-56 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%	

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These are more ACE Inhibitor trials.

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ARB in CHF

Study	Drug	Inclusion	Duration of treatment	Outcome (mortality)
ELITE II (N=3162)	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			

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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 III) EF < 35%	25 bid	Stopped early	65% reduction
CIBIS (N=641)	bisoprolol (β1 selective)	FC II-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	

These are the Beta Blocker trials.

Echo in Context 2002: Heart Failure

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Studies pending

- EPHEBUS
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