Therapeutics of Chronic heart failure

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Causes of heart failure

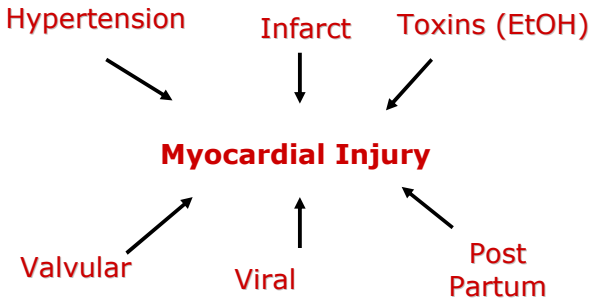
Myocardial disease
- **Coronary artery disease**
- **Dilated cardiomyopathy**
  (specific or **idiopathic**)
- Hypertension

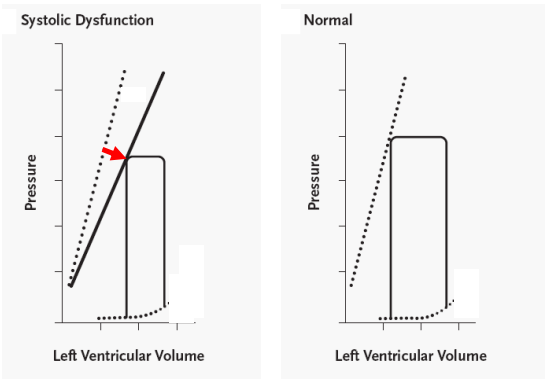
Valve disease
Arrhythmias

Pericardial disease
Congential heart disease

Pathophysiology

Haemodynamics
- **Preload**
- **Afterload**
- **Contractility**





Pathophysiology

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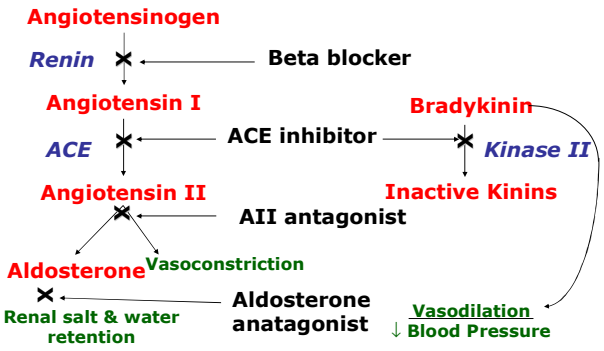
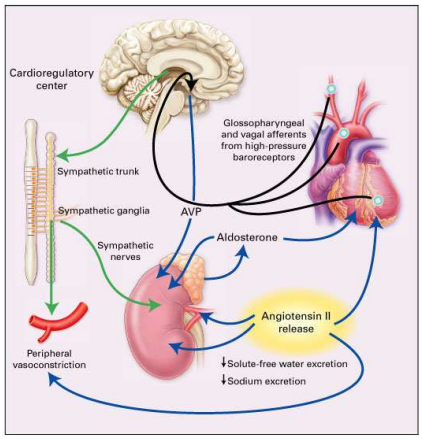
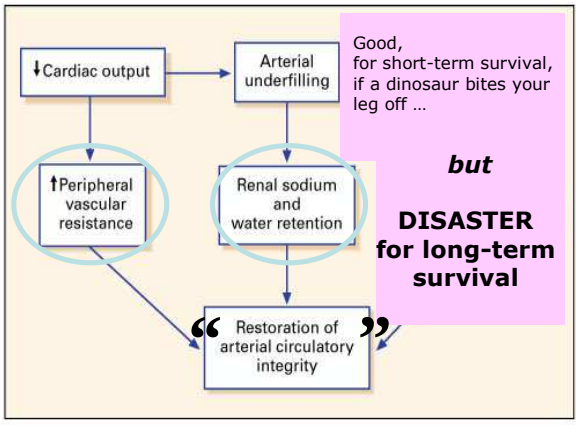
Neurohormonal

Neurohormonal disruption







Pathophysiology

Haemodynamics
- **Preload**
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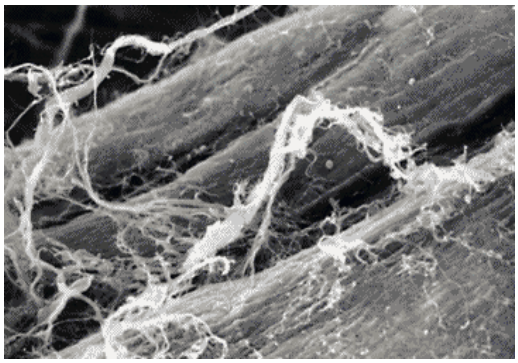
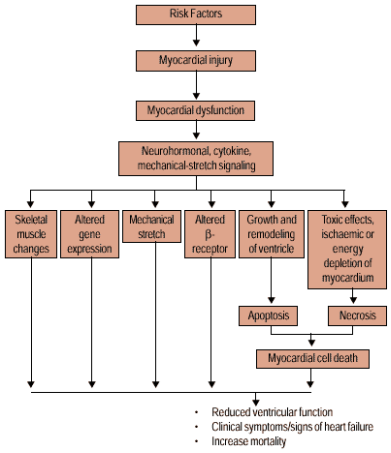
Neurohormonal

Remodelling

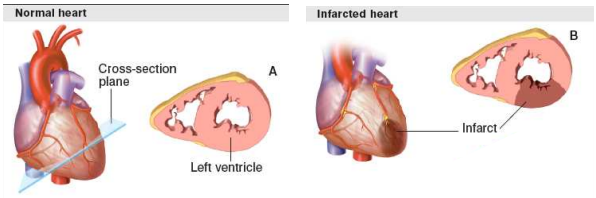


Collagen decomposition and deposition in heart failure



www.medpharm.co.za/safp/2002/jan/heart2.html

Pathophysiology
of heart failure

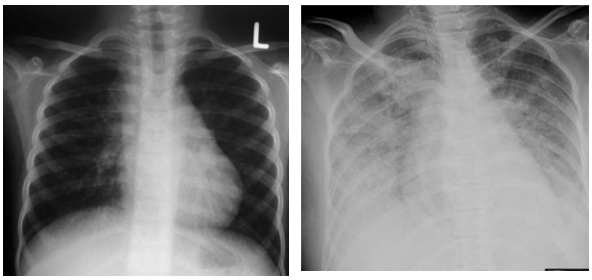


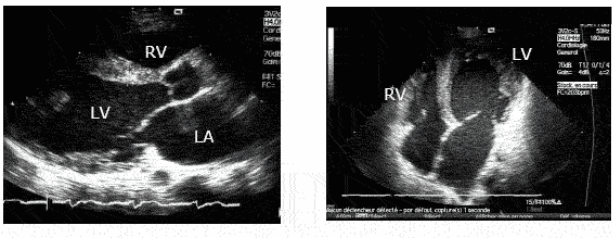
Initial injury

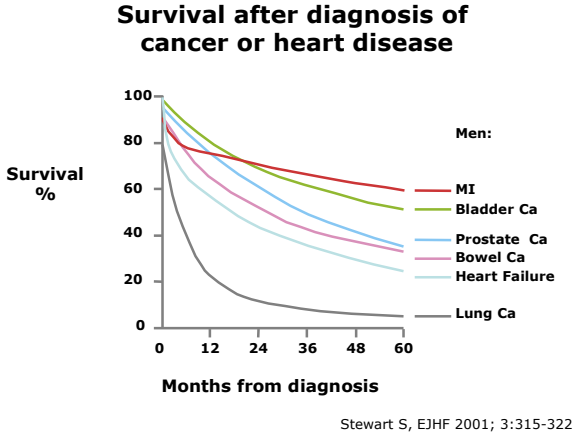
then

multiple pathways of deterioration

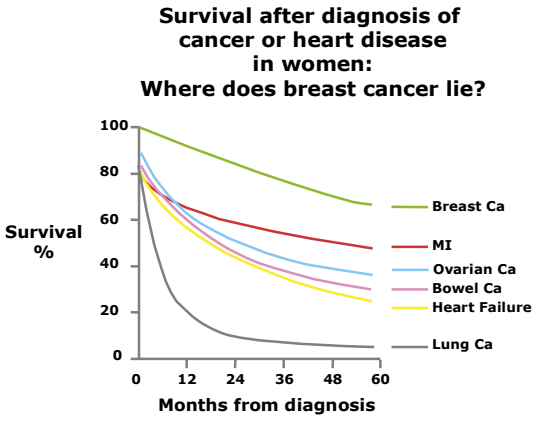
- **Haemodynamics**
  - Preload
  - Afterload
  - Contractility
- **Neurohormonal** disruption
- **Remodelling**







Stewart S, EJHF 2001; 3:315-322



Stewart S, EJHF 2001; 3:315-322

Prognostically proven therapies:

Enhancing survival and independence in systolic heart failure

ACE inhibitors

Beta blockers

AII receptor antagonists

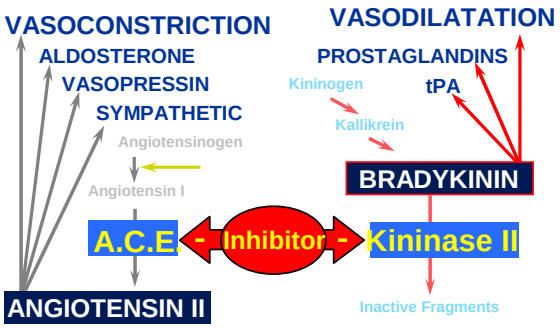
} Combine the first 2 usable agents

Spironolactone

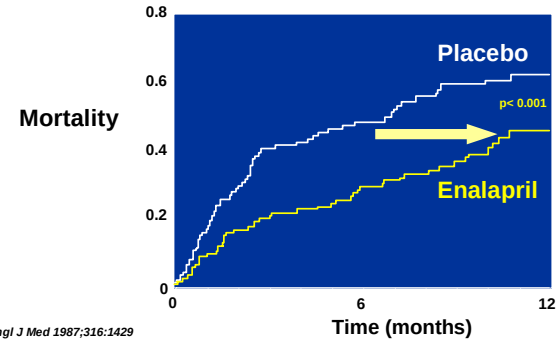
Referral for assessment for:
- Revascularisation
- Resynchronisation
- (Defibrillator implantation)

Exercise training

ACEi: mechanisms

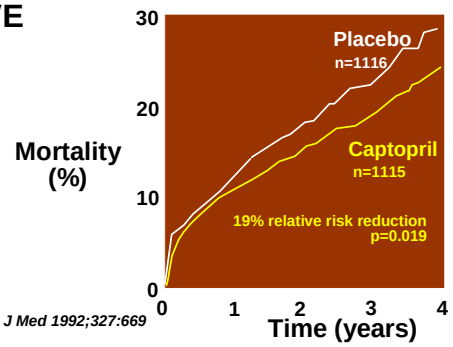


The landmark trial of ACE in *advanced* CHF
CoNSEnSuS



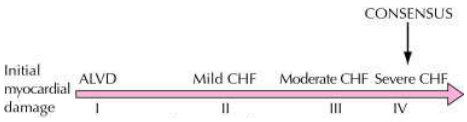
N Engl J Med 1987;316:1429

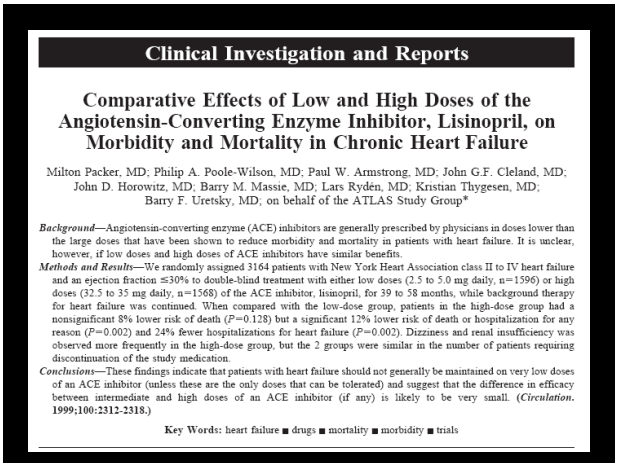
The landmark trial of ACE in *asymptomatic* LV dysfunction post MI
SAVE



N Engl J Med 1992;327:669

ACEi save lives
proven over and over **...**





Clinical Investigation and Reports

Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

Milton Packer, MD; Philip A. Poole-Wilson, MD; Paul W. Armstrong, MD; John G.F. Cleland, MD; John D. Horowitz, MD; Barry M. Massie, MD; Lars Rydén, MD; Kristian Thygesen, MD; Barry F. Uretsky, MD; on behalf of the ATLAS Study Group*

Background—Angiotensin-converting enzyme (ACE) inhibitors are generally prescribed by physicians in doses lower than the large doses that have been shown to reduce morbidity and mortality in patients with heart failure. It is unclear, however, if low doses and high doses of ACE inhibitors have similar benefits.

Methods and Results—We randomly assigned 3164 patients with New York Heart Association class II to IV heart failure and an ejection fraction ≤30% to double-blind treatment with either low doses (2.5 to 5.0 mg daily, n=1596) or high doses (32.5 to 35 mg daily, n=1568) of the ACE inhibitor, lisinopril, for 39 to 58 months, while background therapy for heart failure was continued. When compared with the low-dose group, patients in the high-dose group had a nonsignificant 8% lower risk of death ($P=0.128$) but a significant 12% lower risk of death or hospitalization for any reason ($P=0.002$) and 24% fewer hospitalizations for heart failure ($P=0.002$). Dizziness and renal insufficiency was observed more frequently in the high-dose group, but the 2 groups were similar in the number of patients requiring discontinuation of the study medication.

Conclusions—These findings indicate that patients with heart failure should not generally be maintained on very low doses of an ACE inhibitor (unless these are the only doses that can be tolerated) and suggest that the difference in efficacy between intermediate and high doses of an ACE inhibitor (if any) is likely to be very small. (*Circulation.* 1999;100:2312-2318.)

Key Words: heart failure ■ drugs ■ mortality ■ morbidity ■ trials

TABLE 2. Effect of Treatment on Major Clinical Events

	Low-Dose	High-Dose	Hazard Ratio	*P*
All-cause mortality	717 (44.9)	666 (42.5)	0.92 (0.82–1.03)	0.128
Cardiovascular mortality	641 (40.2)	583 (37.2)	0.90 (0.81–1.01)	0.073
All-cause mortality+hospitalization for any reason	1338 (83.8)	1250 (79.7)	0.88 (0.82–0.96)	0.002
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All-cause mortality+hospitalization for heart failure*	964 (60.4)	864 (55.1)	0.85 (0.78–0.93)	<0.001
Cardiovascular mortality+hospitalization for cardiovascular reason	1161 (72.7)	1088 (69.4)	0.91 (0.84–0.99)	0.027
Fatal and nonfatal myocardial infarction+hospitalization for unstable angina	224 (14.0)	207 (13.2)	0.92 (0.76–1.11)	0.374

Higher dose lisinopril (32.5-35 mg vs ~2.5-5mg / day) gives ~10% lower event rate

This is statistically significant for frequent events (i.e. when hospitalisation is included)

ACE inhibitors

Licensed ACEI	*Starting dose (mg)*	*Target dose (mg)*
Captopril	6.25 three times daily	50–100 three times daily
Cilazapril*	0.5 once daily	1–2.5 once daily
Enalapril	2.5 twice daily	10–20 twice daily
Fosinopril*	10 once daily	40 once daily
Lisinopril	2.5–5.0 once daily	30–35 once daily
Perindopril*	2.0 once daily	4 once daily
Quinapril*	2.5–5.0 once daily	10–20 once daily
Ramipril	2.5 once daily	5 twice daily or 10 once daily

ORIGINAL INVESTIGATION

Angiotensin-Converting Enzyme Inhibitor–Associated Elevations in Serum Creatinine

Is This a Cause for Concern?

George L. Bakris, MD; Matthew R. Weir, MD

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Background: Reducing the actions of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors (ACEIs) slows nephropathy progression in patients with or without diabetes. Post hoc analyses of many ACEI-based clinical trials demonstrate the greatest slowing of renal disease progression in patients with the greatest degree of renal insufficiency at study initiation. However, many physicians fail to use ACEIs or angiotensin receptor blockers in patients with renal insufficiency for fear that either serum creatinine or potassium levels will rise.

Objective: To determine if limited initial reduction in either glomerular filtration rate (GFR) or elevation in serum creatinine levels, associated with ACEI or angiotensin receptor blocker use, results in long-term protection against decline in renal function in patients with renal insufficiency.

Methods: We reviewed 12 randomized clinical trials that evaluated renal disease progression among patients with preexisting renal insufficiency. Six of these studies were multicenter, double-blinded, and placebo controlled, with the remainder being smaller randomized studies with a minimum 2-year follow-up on renal function. These investigations evaluated patients with and without diabetes or systolic heart failure. Average duration of follow-up for all studies was 3 years. Trials were examined in the context of changes in either serum creatinine levels or GFR in the group randomized to an ACEI (N = 1102). Sixty-four percent of these individuals (705/1102) had renal function data at both less than 6 months and at the end of the study.

Results: Most trials demonstrated that patients with preexisting renal insufficiency manifested an acute fall in GFR, a rise in serum creatinine, or both. Those randomized to an ACEI with a serum creatinine level of 124 μmol/L or greater (≥1.4 mg/dL) demonstrated a 55% to 75% risk reduction in renal disease progression compared with those with normal renal function randomized to an ACEI. An inverse correlation was observed between the amount of renal function loss at baseline and the subsequent rate of annual decline in renal function following randomization to an antihypertensive regimen that contained an ACEI.

Conclusions: A strong association exists between acute increases in serum creatinine of up to 30% that stabilize within the first 2 months of ACEI therapy and long-term preservation of renal function. This relationship holds for persons with creatinine values of greater than 124 μmol/L (>1.4 mg/dL). Thus, withdrawal of an ACEI in such patients should occur only when the rise in creatinine exceeds 30% above baseline within the first 2 months of ACEI initiation, or hyperkalemia develops, ie, serum potassium level of 5.6 mmol/L or greater.

Arch Intern Med. 2000;160:685-693

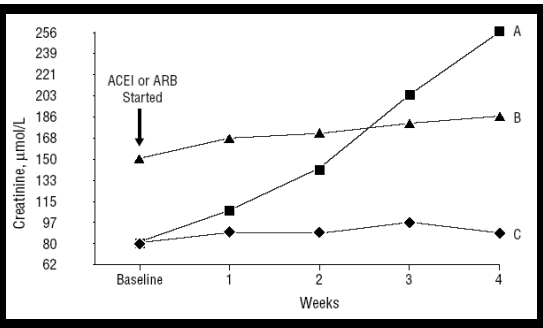
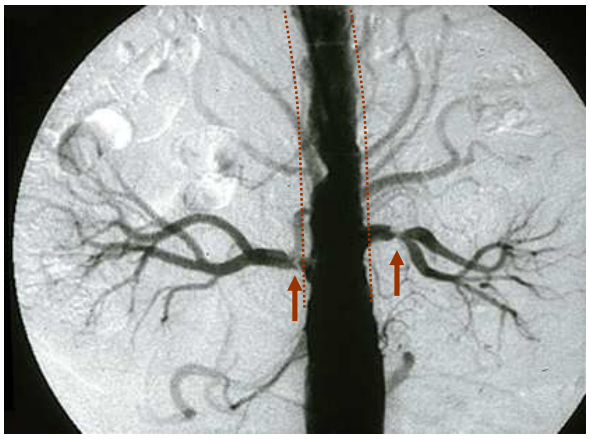


Figure 1. *Possible changes in serum creatinine levels in individuals with normal renal function with volume depletion, heart failure, or bilateral renal artery stenosis started on therapy with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) (A); individuals with abnormal renal function started on therapy with an ACEI or ARB, without conditions noted in case A (B); and individuals with normal renal function started on therapy with an ACEI or ARB (C).*

Long-term Outcome of Renal Function in Clinical Trials in Persons With Renal Disease: Impact of ACEI Therapy*

Study	N†	Duration of Follow-up, y	Achieved MAP, mm Hg	Δ Renal Function‡ <6 mo	Δ Renal Function‡ Trial End
Diabetic subjects					
Captopril Trial[27]	207	3	105	?	−0.15 (Cr clear)
Bakris et al[8]	18	5	98	−9.47 (GFR)§	−0.02 (Cr clear)
Lebovitz et al[13]	28	3	104	?	−6.3 (GFR)
Nielsen et al[28]	21	3	112	−3.97 (GFR)§	−7.1 (GFR)
Bjorck et al[14]	40	2.2	102	−3.8 (GFR)	−2.0 (GFR)
Nondiabetic subjects					
AIPRI Trial[29]	300	3	100	+26 (Cr)	+31 (Cr)
REIN Trial[19]	78	2.5	106	?	−6.3 (GFR)
Zucchelli et al[17]	32	3	100	?	−0.04 (Cr Clear)
Hannedouche et al[14]	52	3	105	?	−4.8 (GFR)
MDRD Trial[25]	255	3	105	−5.7 (GFR)	−3.8 (GFR)
			94	−14.4 (GFR)	−2.9 (GFR)
Ihle et al[18]	36	2	101	−0.42 (GFR)	−0.7 (GFR)
Kamper et al[16]	35	2.2	99	−3 (GFR)	−2.4 (GFR)

Conclusions: A strong association exists between acute increases in serum creatinine of up to 30% that stabilize within the first 2 months of ACEI therapy and long-term preservation of renal function. This relationship holds for persons with creatinine values of greater than 124 µmol/L (>1.4 mg/dL). Thus, withdrawal of an ACEI in such patients should occur only when the rise in creatinine exceeds 30% above baseline within the first 2 months of ACEI initiation, or hyperkalemia develops, ie, serum potassium level of 5.6 mmol/L or greater.



ACEi problems

Renal artery stenosis

Renal failure

Hyperkalemia

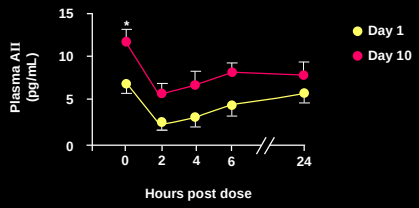
Hypotension

Cough

ACE inhibitors

- Key trials demonstrating survival benefit
  - CONSENSUS – late HF
  - V-HeFT II – mild/moderate
  - ISIS-4 – early HF after MI
- Main difference between class members is half-life
- Dose-limiting side effects are
  - Hypotension (if symptomatic)
  - Rising creatinine (N.B. renal artery stenosis)
    - <30% rise is acceptable, don't stop
- Other side effect, in some: Cough
- Start early, titrate up

AII initially supressed by ACEi but soon "escapes"

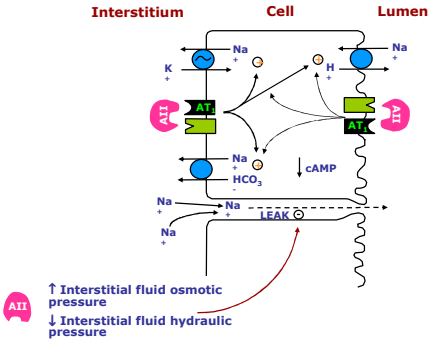


- Trandolapril 8 mg QD in 7 healthy subjects for 10 days
- AII levels higher on day 10 than on day 1
  - Non-ACE proteases, especially chymase
  - Mass effect (constant AII/AI ratio)

*P < 0.05 vs Day 1

Mooser V, et al. *J Cardiovasc Pharmacol*. 1990;15:276-282

AII promotes renal tubule sodium reabsorption



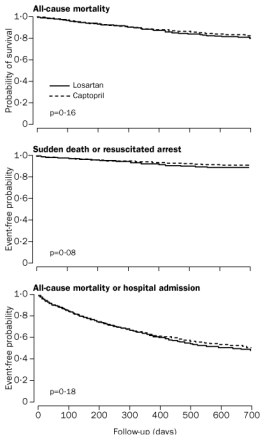
Hall. *J Am Soc Nephrol* 1999;10:S258

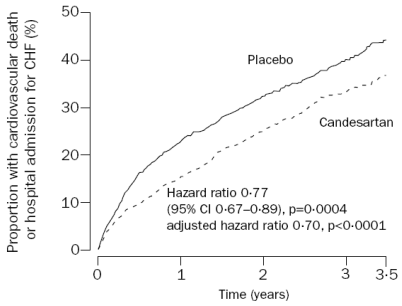
AII antagonists

Drug	% bio-available	Effect of food	$T_{1/2}$ (h)	Protein bound (%)
Losartan	33	None	2	99
(Metabolite: E-3174)	—	—	9	99
Valsartan	25	50% ↓	6	95
Irbesartan	60	None	15	90
Candesartan	40	None	—	—
(Metabolite: CV-11974)	—	—	9	99
Telmisartan	50	20% ↓	13	99
Eprosartan	13	25% ↓	9	98

AIIRA (losartan): about as good as ACEi (captopril)

ELITE II study





AIIRA:
Beneficial in patients who "can't take an ACE inhibitor"

CHARM-Added study

AIIRA (valsartan) may confer *additional benefit* in patients already on ACEi

ValHeFT study

Significant improvements in

- heart failure hospitalisations (by 27%)
- NYHA functional class,
- ejection fraction,
- signs and symptoms, and
- quality of life.

Mortality showed no significant difference (19.7% vs 19.4%).

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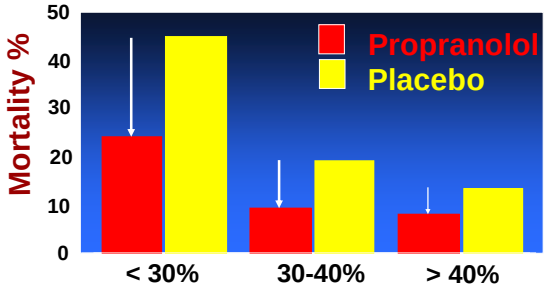
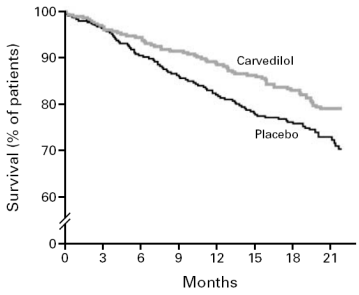
Early beta blocker work: BHAT, beta blocker heart attack trial



Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA*. 1982;247:1707-1714.

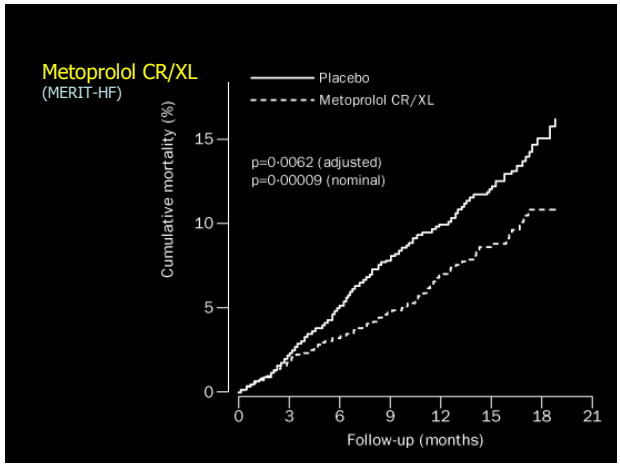


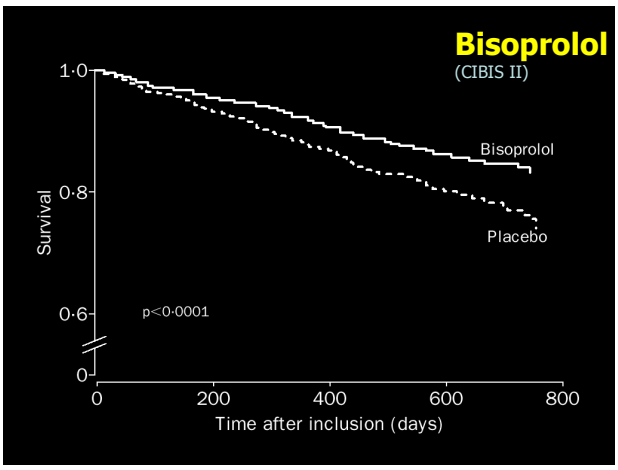
Carvedilol

Table 4. Most Frequent Adverse Reactions.*

Reaction	Placebo (N = 398)	Carvedilol (N = 696)
	no. (%)	
Dizziness	80 (20)	233 (33)
Fatigue	93 (23)	177 (25)
Dyspnea	101 (25)	150 (22)
Upper respiratory tract infection	74 (19)	133 (19)
Heart failure	84 (21)	111 (16)
Chest pain	61 (15)	104 (15)
Hyperglycemia	34 (9)	88 (13)
Diarrhea	24 (6)	83 (12)
Increase in weight	30 (8)	71 (10)
Cough	40 (10)	58 (8)
Pain	33 (8)	62 (9)
Headache	30 (8)	57 (8)
Nausea	18 (5)	60 (9)
Hypotension	15 (4)	60 (9)
Asthenia	27 (7)	49 (7)
Bradycardia	4 (1)	65 (9)
Worsening renal function	20 (5)	46 (7)
Vomiting	18 (5)	46 (7)

*Patients may have had more than one adverse reaction.





Clinical Challenge
Beta blockers and low blood pressure

When is blood pressure too low to start beta blockade?

120?

110?

100?

Heart Failure

Influence of Pretreatment Systolic Blood Pressure on the Effect of Carvedilol in Patients With Severe Chronic Heart Failure

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study

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Montreal, Canada; Madison, Wisconsin; Katowice, Poland; Bern and Basel, Switzerland; Prahran, Victoria, and Sydney, Australia; Heidelberg, Germany; Stanford, California; Paris, France; Philadelphia, Pennsylvania; New York, New York

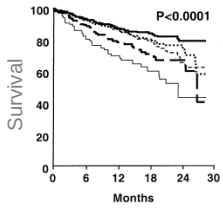
OBJECTIVES We sought to evaluate the influence of pretreatment systolic blood pressure (SBP) on the efficacy and safety of carvedilol in patients with chronic heart failure (CHF).

BACKGROUND Although beta-blockers reduce the risk of death in CHF, there is little reported experience with these drugs in patients with a low pretreatment SBP, who may respond poorly to beta-blockade.

METHODS We studied 2,289 patients with severe CHF who participated in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial.

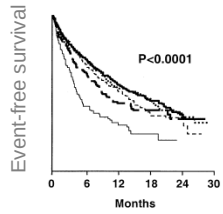
RESULTS Compared with placebo, carvedilol improved the clinical status and reduced the risk of death and the combined risk of death or hospitalization for any reason, for a cardiovascular reason, or for worsening heart failure ($p < 0.001$ for all). The relative magnitude of these benefits did not vary as a function of the pretreatment SBP (all interaction $p > 0.10$). However, because patients with the lowest SBP were at highest risk of an event, they experienced the greatest absolute benefit from treatment with carvedilol. The lower the pretreatment SBP, the more likely that patients would report an adverse event, be intolerant of high doses of the study drug, or require permanent withdrawal of treatment ($p < 0.001$ for all). However, these risks were primarily related to the severity of the underlying illness and not to treatment with carvedilol.

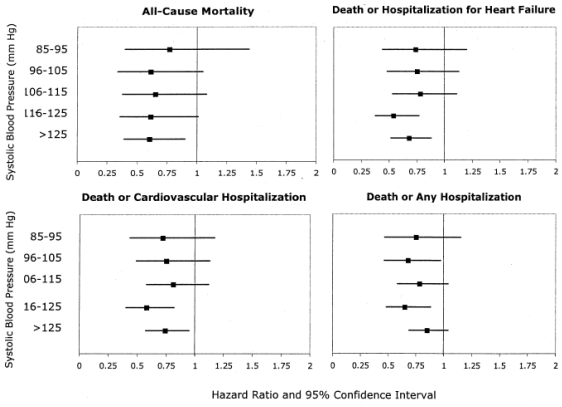
CONCLUSIONS The current study provides little support for concerns about using beta-blockers (particularly those with vasodilatory actions) in patients with severe CHF who have a low SBP. Pretreatment blood pressure can identify patients who have the greatest need for risk reduction with carvedilol. (J Am Coll Cardiol 2004;43:1423–9) © 2004 by the American College of Cardiology Foundation

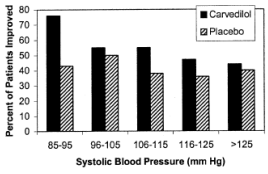


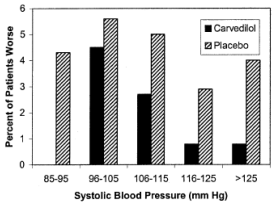
Baseline systolic BP

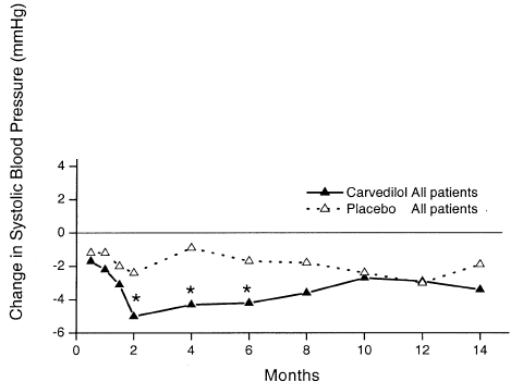
85- 95
96-105
106-115
116-125
> 125

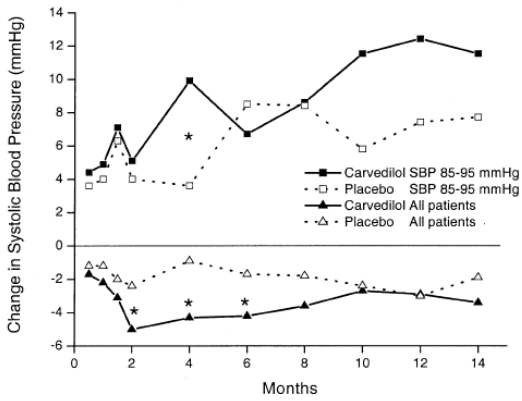


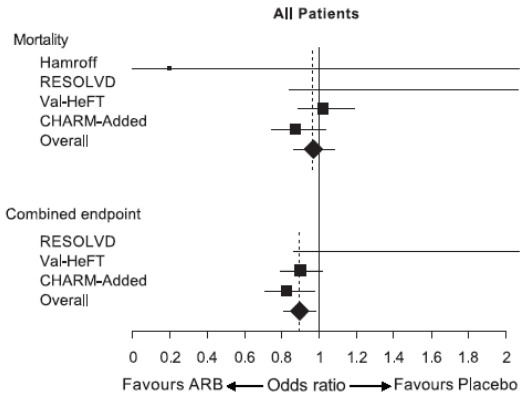


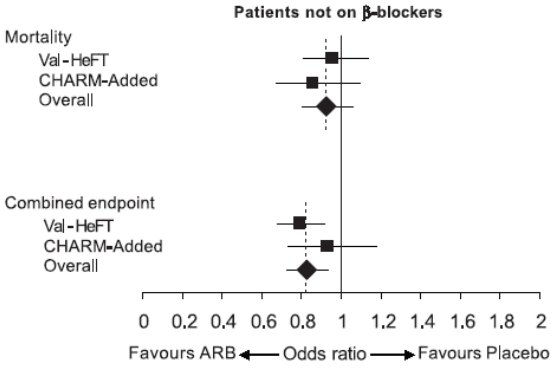


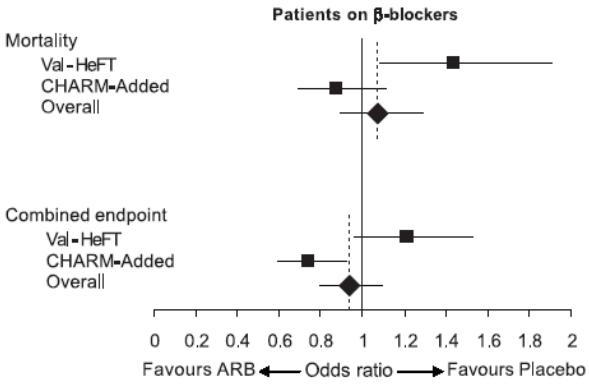












Are AIIRA an equal-status replacement for ACEi?

Yes

Losartan	**ELITE II**
Candesartan	**CHARM**
Valsartan	**ValHeFT**

ACE inhibition

Give full therapeutic doses

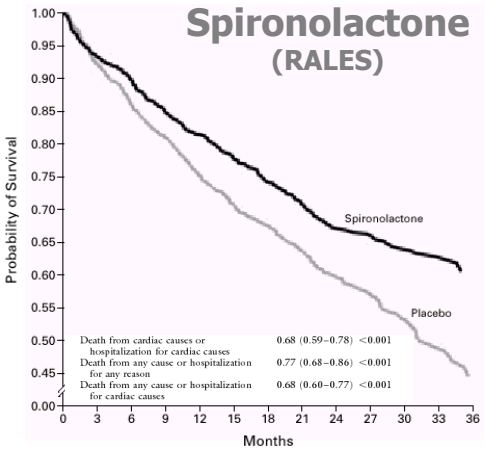
Small creatinine rises (<30%)
are not grounds for discontinuation

If cough, there is strong research grounding to switch to AIIRA

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	PLACEBO GROUP (N=841)	SPIRONOLACTONE GROUP (N=822)
Age — yr	65±12	65±12
White race — %	86	87
Sex — no. (%)		
Male	614 (73)	603 (73)
Female	227 (27)	219 (27)
Blood pressure — mm Hg		
Systolic	122±20	123±21
Diastolic	75±11	75±12
Heart rate — beats/min	81±15	81±14
New York Heart Association class — no. (%)		
II	3 (0.4)	4 (0.5)
III	581 (69)	592 (72)
IV	257 (31)	226 (27)
Left ventricular ejection fraction — %†	25.2±6.8	25.6±6.7
Cause of heart failure — no. (%)‡		
Ischemic	453 (54)	454 (55)
Nonischemic	386 (46)	368 (45)
Medications — %		
Loop diuretics	100	100
ACE inhibitors	94	95
Digitalis	72	75
Aspirin	37	36
Potassium supplements	27	29
Beta-blockers	10	11
Mean dose of ACE inhibitors — mg/day		
Captopril	62.1	63.4
Enalapril	16.5	15.5
Lisinopril	15.1	15.5

Spironolactone
(RALES)



Clinical challenges with spironolactone

Renal dysfunction
* use only 25 mg od
* beware long half-life
* first agent to drop if Cr^

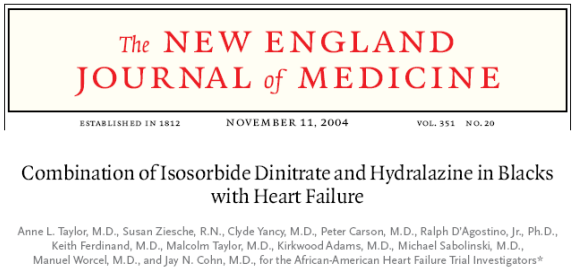
Hyperkalaemia
* average rise only 0.1 mM
* but wide spread

Gynaecomastia?
* Eplerenone (off-licence)

Enhancing survival in heart failure

ACE inhibitors
Beta blockers
AII receptor antagonists
} First 2

Spironolactone -- evidence for NYHA III/IV


The NEW ENGLAND JOURNAL of MEDICINE

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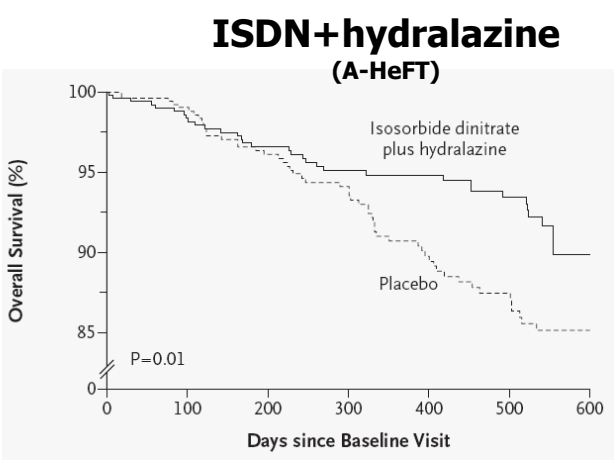
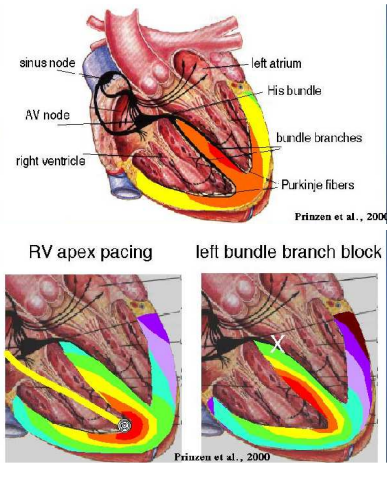
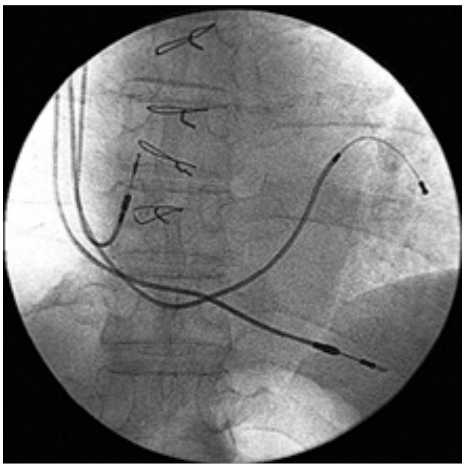
Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

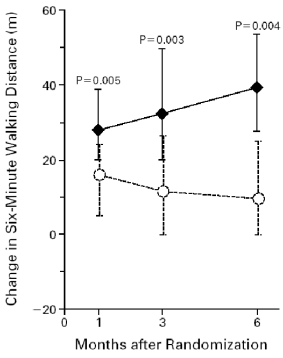
Anne L. Taylor, M.D., Susan Ziesche, R.N., Clyde Yancy, M.D., Peter Carson, M.D., Ralph D'Agostino, Jr., Ph.D., Keith Ferdinand, M.D., Malcolm Taylor, M.D., Kirkwood Adams, M.D., Michael Sabolinski, M.D., Manuel Worcel, M.D., and Jay N. Cohn, M.D., for the African-American Heart Failure Trial Investigators*



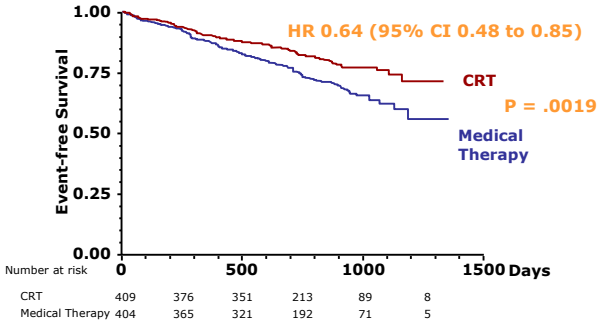




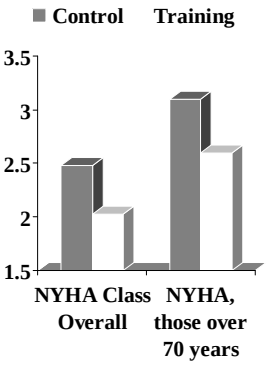
Cardiac resynchronisation: Effect on walking distance



Impact of cardiac resynchronisation on transplant-free survival



N Engl J Med. 2005;352:1539-49.



Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH)

ExTraMATCH Collaborative

Abstract

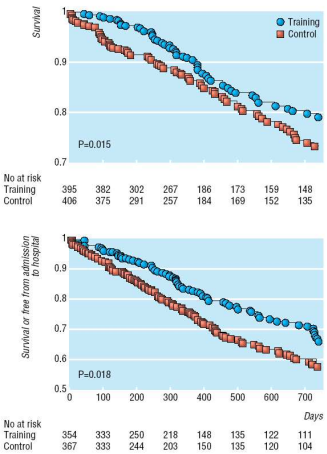
Objective To determine the effect of exercise training on survival in patients with heart failure due to left ventricular systolic dysfunction.
Design Collaborative meta-analysis.
Inclusion criteria Randomised parallel group controlled trials of exercise training for at least eight weeks with individual patient data on survival for at least three months.
Studies reviewed Nine datasets, totalling 801 patients: 395 received exercise training and 406 were controls.
Main outcome measure Death from all causes.
Results During a mean (SD) follow up of 705 (720) days there were 88 (22%) deaths in the exercise arm and 105 (26%) in the control arm. Exercise training significantly reduced mortality (hazard ratio 0.65, 95% confidence interval, 0.46 to 0.92; log rank $\chi^2 = 5.9$; $P = 0.015$). The secondary end point of death or admission to hospital was also reduced (0.72, 0.56 to 0.93; log rank $\chi^2 = 6.4$; $P = 0.011$). No statistically significant subgroup specific treatment effect was observed.
Conclusion Meta-analysis of randomised trials to date gives no evidence that properly supervised medical training programmes for patients with heart failure might be dangerous, and indeed there is clear evidence of an overall reduction in mortality. Further research should focus on optimising exercise programmes and identifying appropriate patient groups to target.

Methods

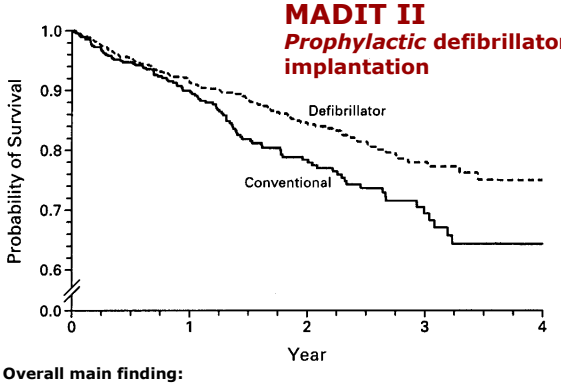
A collaborative group was established, coordinated from the Heart Failure Unit of the Imperial College School of Medicine, London. A prospective protocol was written and agreed by the collaborative group before data collection, specifying the methods to be used, the main prespecified analyses, and a common dataset of collected variables.

We searched Medline for randomised controlled trials since 1990 of exercise training in patients with chronic congestive heart failure or left ventricular dysfunction. We cross checked our findings to identify any other published or unpublished trials by consulting researchers and colleagues in exercise physiology and heart failure and by scrutinising reference lists from review articles, and abstracts presented at scientific sessions and published in *Circulation*, the *Journal of the American College of Cardiology*, and the *European Heart Journal*. A subsequent search of the Cochrane Reviews database yielded no additional studies.

Selection and validity assessment
The characteristics of trials to be included were that they should be randomised parallel group controlled trials and should evaluate exercise training without any other simultaneous intervention that could confound the results, should study patients with death and on the secondary end point of death or admission to hospital.



MADIT II
Prophylactic defibrillator implantation



Overall main finding:

Previous MI and LVEF ≤ 0.30 – *without additional risk stratification* –

identifies a high-risk patient cohort, which benefits from ICDs

How you can make a difference between life and death for your heart failure patient

Life-saving
- ACE inhibitor
- Beta blocker
- AII antagonist (if not on ACEi and BB)
- Spironolactone/Epleronone (if NYHA III/IV)
- Biventricular pacing (if electrcial dyssynchrony)
- Implanted defibrillator (if infarct, or poor LV)
- Supervised exercise training (not just advice)

Possibly life-saving
- Revascularisation (if viability - disputed)

Palliative (reducing symptoms, reducing admissions)
- Digoxin
- Diuretic