

State of Art: Heart Failure 2008

Marc A. Pfeffer, MD, PhD

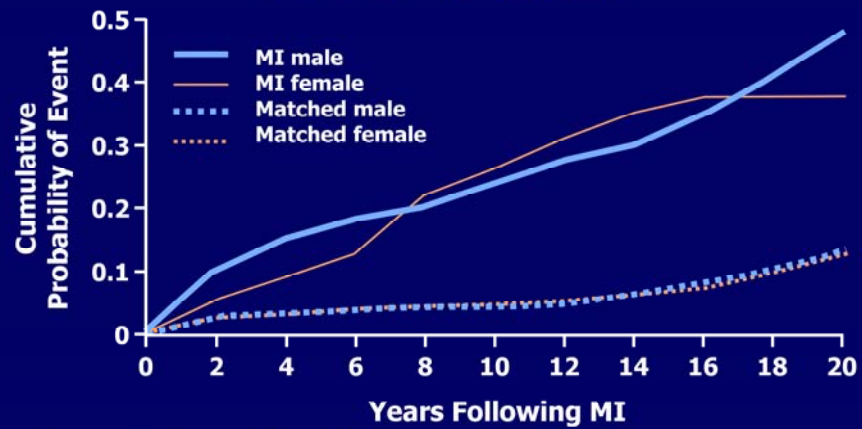
**Dzau Professor of Medicine, Harvard Medical School
Cardiovascular Division, Brigham & Women's Hospital
Boston, Massachusetts**

Disclosures:

Grants, honorarium, consultations with several manufacturers of ACE-I and ARB including Astra-Zeneca. Dr. Pfeffer is a co-inventor on patent for use of ACE-I and ARBs following myocardial infarction. BWH has licensing agreements with NOVARTIS and ABBOTT which are not related to sales.

The Framingham Heart Study: 1987

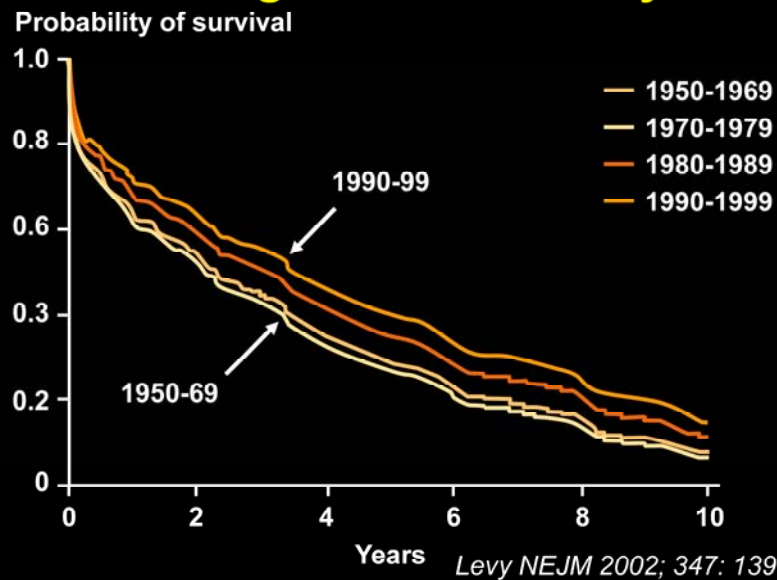
Risk of Heart Failure After MI (Age 35 to 94 at Diagnosis)



Cupples et al. The Framingham Study, NIH Publication No. 87-2703. 1987.

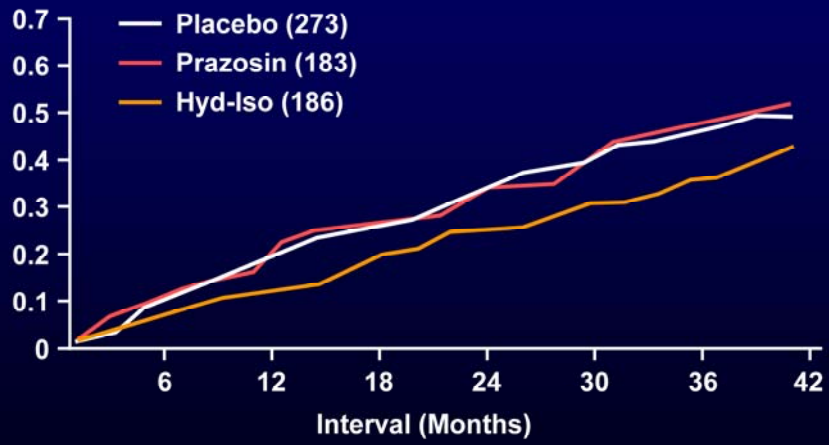
The probability of HF was approximately 15% at 5 yrs, and approached 40% at 20yrs

Falling case-fatality from CHF in the Framingham Heart Study



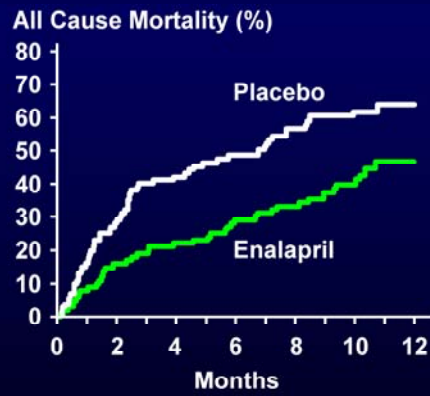
V-HEFT I

Cumulative Mortality Rate



Cohn et al. NEJM 1986.

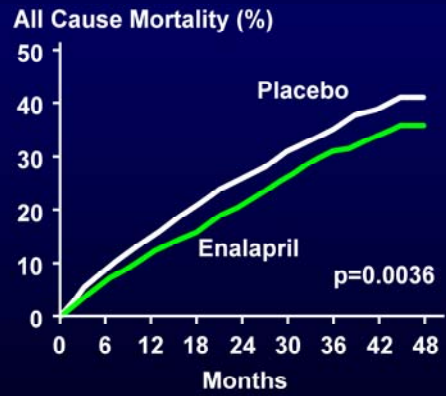
CONSENSUS



Placebo N: 128 102 78 63 59 53 47 42 34 30 24 18 17
 Enalapril N: 127 111 98 88 82 79 73 64 50 49 42 31 28

NEJM 1987

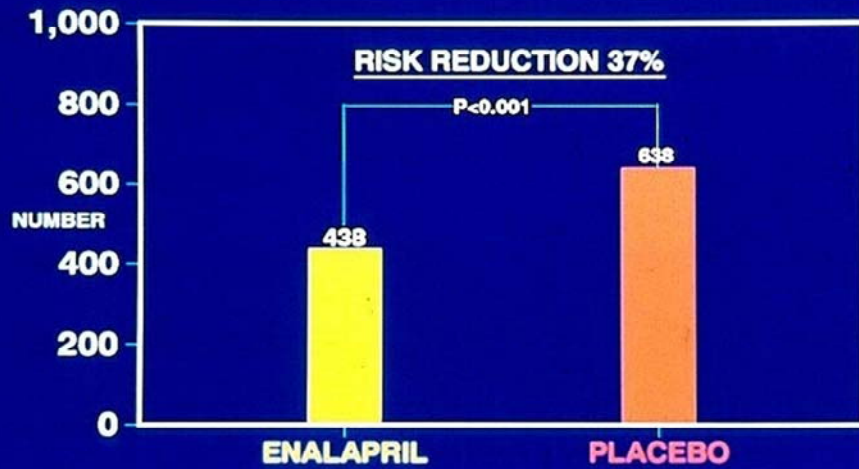
SOLVD



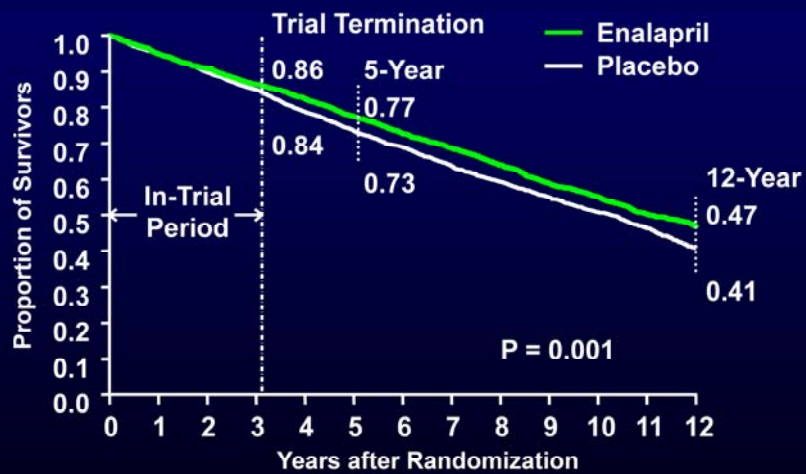
Placebo N: 1284 1159 1085 1005 939 819 669 487 299
 Enalapril N: 1285 1195 1127 1069 1010 891 697 526 333

NEJM 1992

SOLVD-PREVENTION TRIAL DEVELOPMENT OF HEART FAILURE



Cumulative 12-Year Survival in Prevention Trial



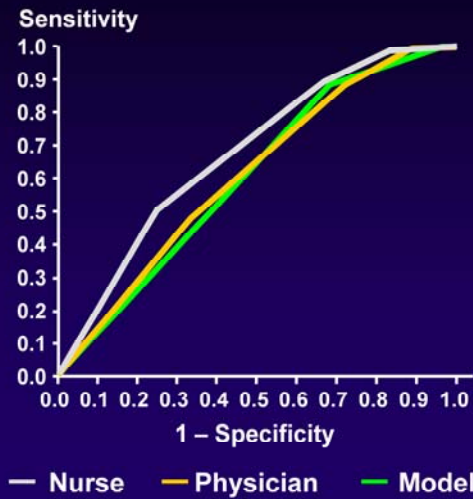
Jong et al. Lancet 2003

Seattle Heart Failure Score



Levy W C et al. Circulation 2006;113:1424-33

Prediction of Rehospitalization and Death in Severe Heart Failure by Physicians and Nurses of the ESCAPE Trial



	C-index
Nurse	0.68
Physician	0.61
Model	0.60
Nurse + model*	0.71

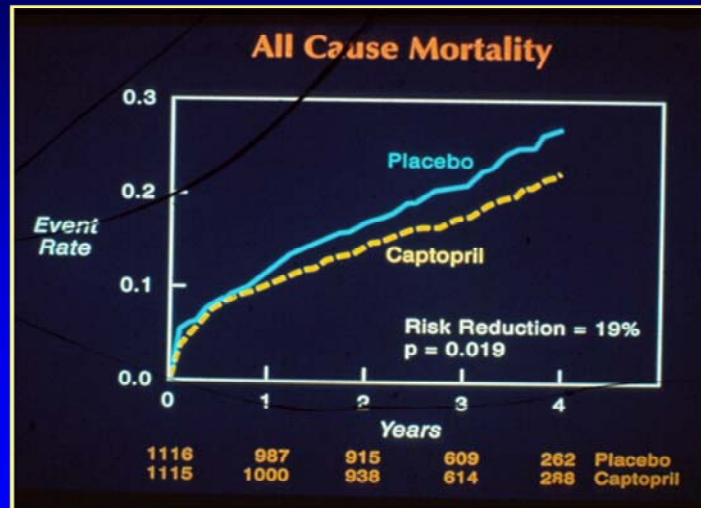
* BUN, 6-minute walk, systolic BP

Yamokoski. J Card Failure 2007;13:8-13

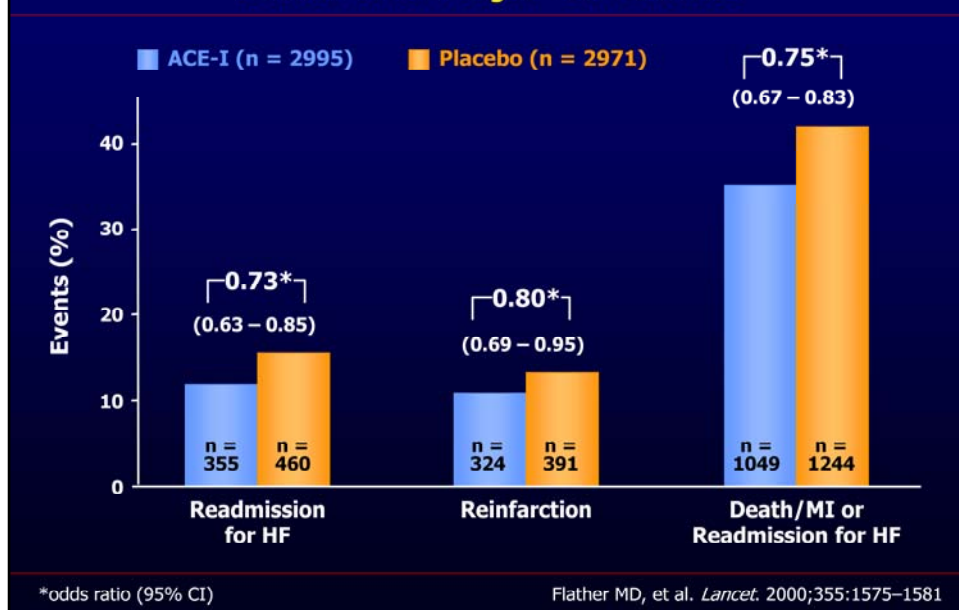




Survival And Ventricular Enlargement Trial



SAVE / AIRE / TRACE: Death and Major CV Events

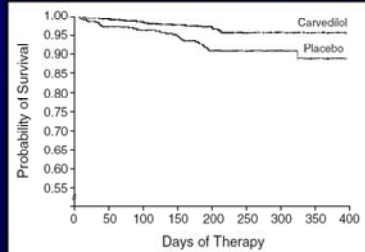


In addition to the survival benefit shown in the three post-infarction trials with ACEIs, rates of readmission for heart failure were lower than with placebo, as were rates of reinfarction or the composite of these events. The benefits were observed early after the start of therapy and persisted long term. The benefits of treatment on all outcomes were independent of age, sex, and baseline use of diuretics, aspirin, and beta-blockers.¹

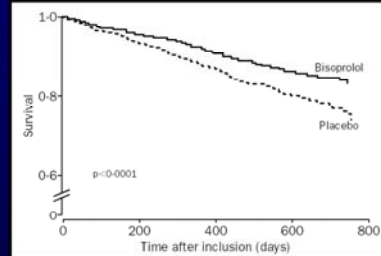
1. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet*. 2000;355:1575–1581.

Beta-blocker HF trials

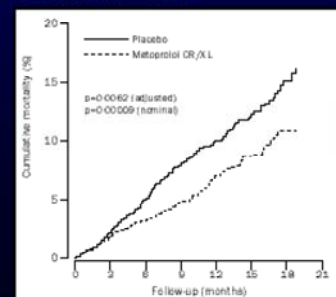
US carvedilol programme 1996



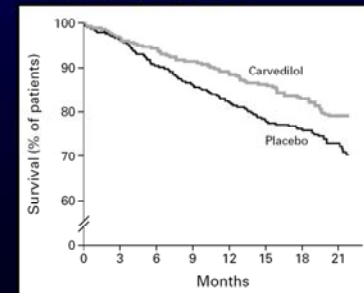
CIBIS-2 1998



MERIT-HF 1999

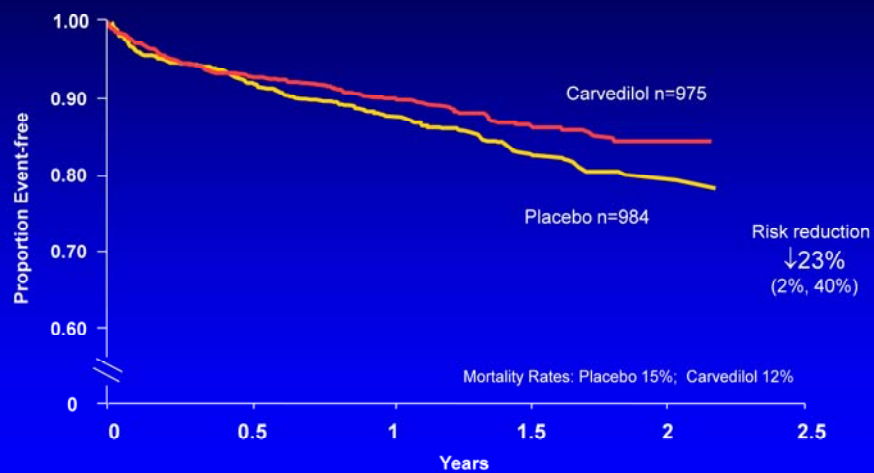


COPERNICUS 2001



CAPRICORN All-Cause Mortality

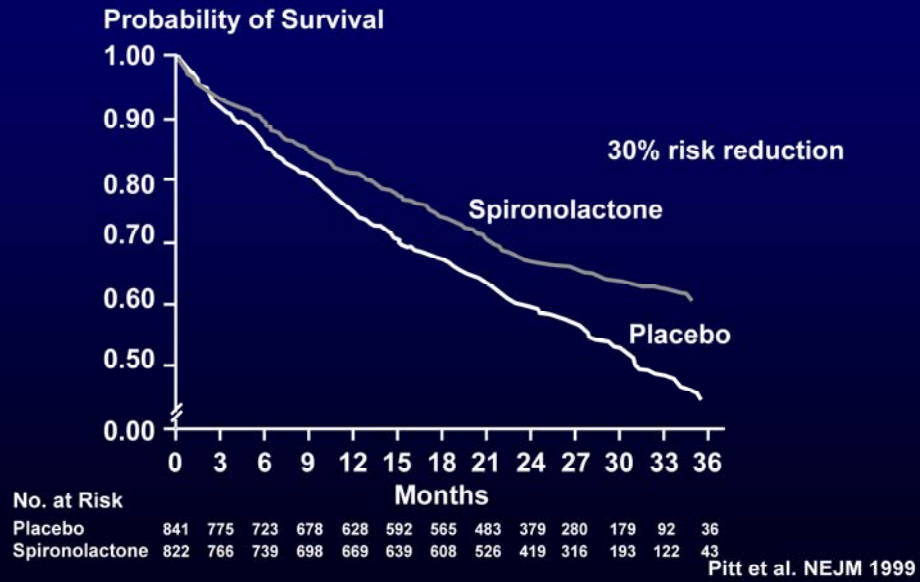
Carvedilol Post-Infarct Survival Control in LV Dysfunction



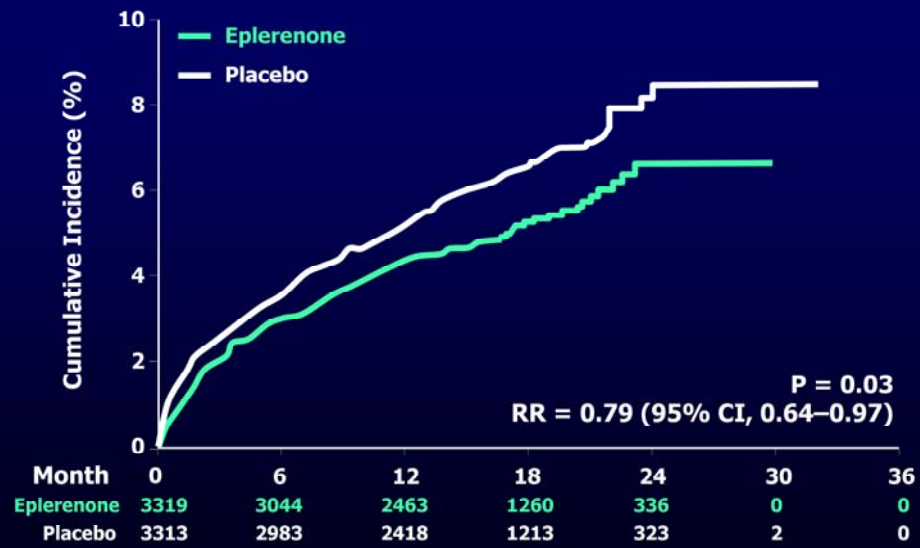
The CAPRICORN Investigators. *Lancet*. 2001;357:1385-90.

RALES

Randomized ALdactone Evaluation Study



EPHESUS: Sudden Cardiac Death



Pitt et al. *N Engl J Med* 2003;348:1309-1321

RCT Progress

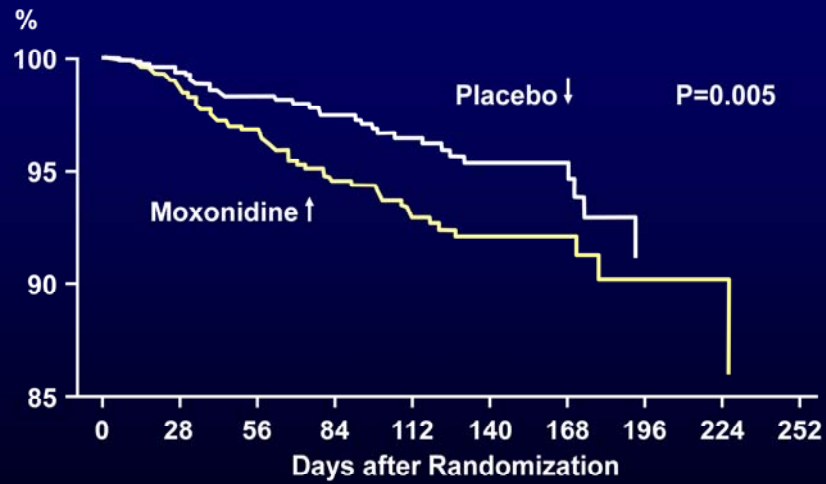
New “to do’s”

Not “to do’s” (undo’s)

Changes in Practice (Education)

“to do’s” (I)	IIa	IIb	“undo’s” (III) (false comfort zone)
<ul style="list-style-type: none">• ASA• Lytics, PCI• ACE I• BB• Statins• ICDs			<ul style="list-style-type: none">• anti-arrhythmics• Inotropic agents• CCB high risk MI• HRT

MOXCON moxonidine CHF trial



Number of Patients at Risk
1913 1482 1067 594

PRAISE 2
Prospective Randomized Amlodipine Survival Evaluation 2

	Placebo	Amlodipine	HR (95% CI)
All cause mortality	31.7%	33.7%	1.09 (0.92 – 1.29)

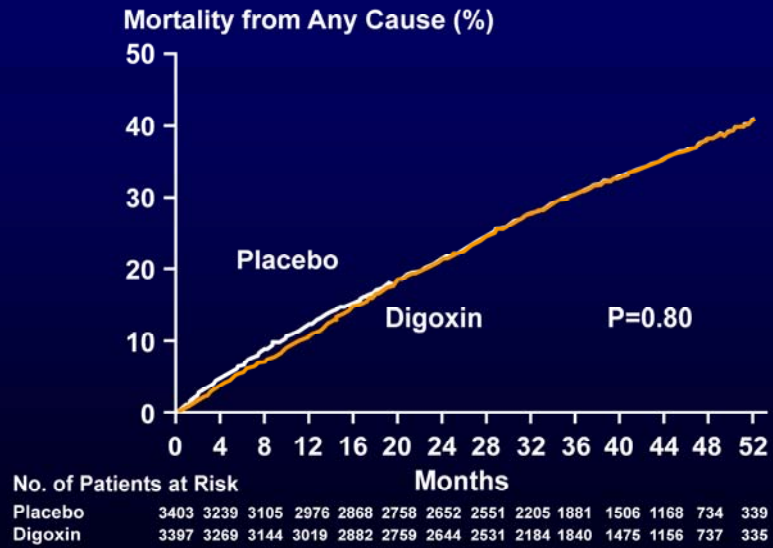
Combined PRAISE 1 AND 2

All cause mortality	34%	33.4%	0.98 (0.87 – 1.12)
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Hypertension ↔ Heart Failure

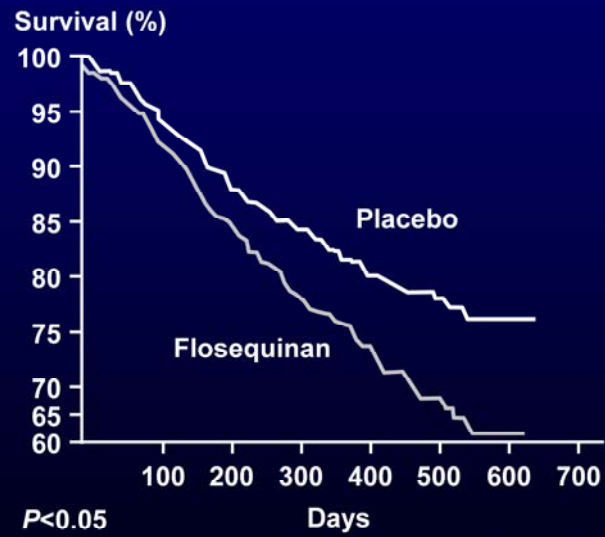


Digoxin and mortality in HF DIG trial



Digitalis Investigation Group. NEJM 1997

PROFILE: flosequinan in HF



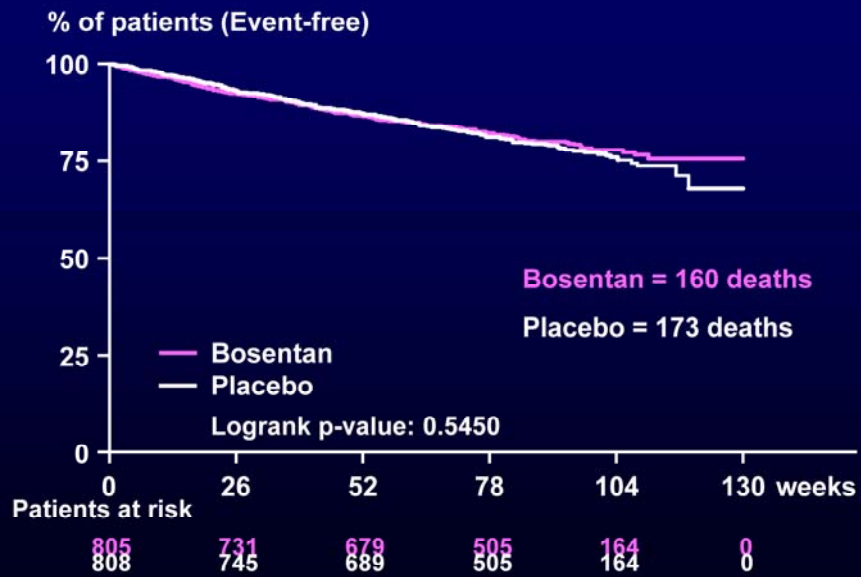
Van Veldhuisen and Poole-Wilson. Int J Cardiol 2001

Positive Inotropic Drugs and HF

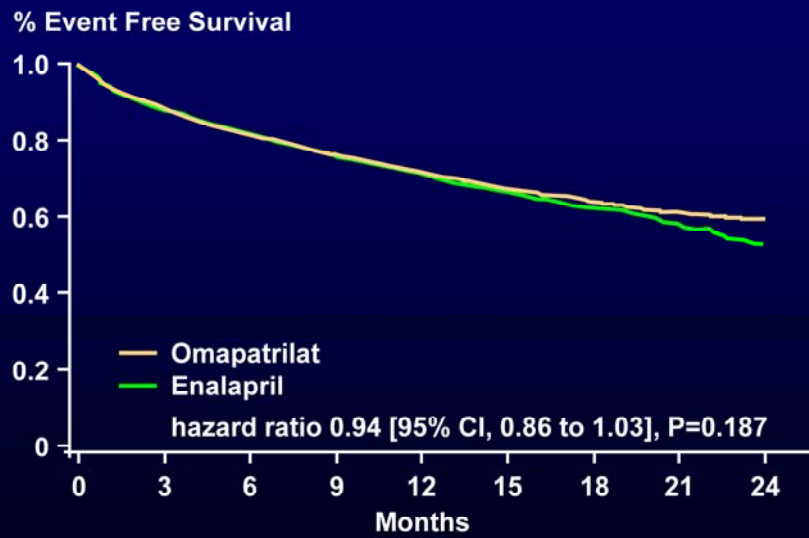
	Placebo	Therapy	RR (p-value)
PROMISE (milrinone) n = 1088	127 / 527	168 / 561	1.28 (p=0.38)
PROFILE (flosequinan) n=2345	138/937 43/238	201/964 40/206	75mg: 1.48 (p=0.0004) 40mg: 1.05 (p=0.83)
	181/1175	214/1170	1.39 (p=0.0009)
VEST (vesnarinone) n=3833	242/1283	268/1275 292/1275	30mg: 1.11 (p=0.21) 60mg: 1.21 (p=0.016)

DeMets Am Heart J 2000;139:S207

ENABLE - All-Cause Mortality



OVERTURE: Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events

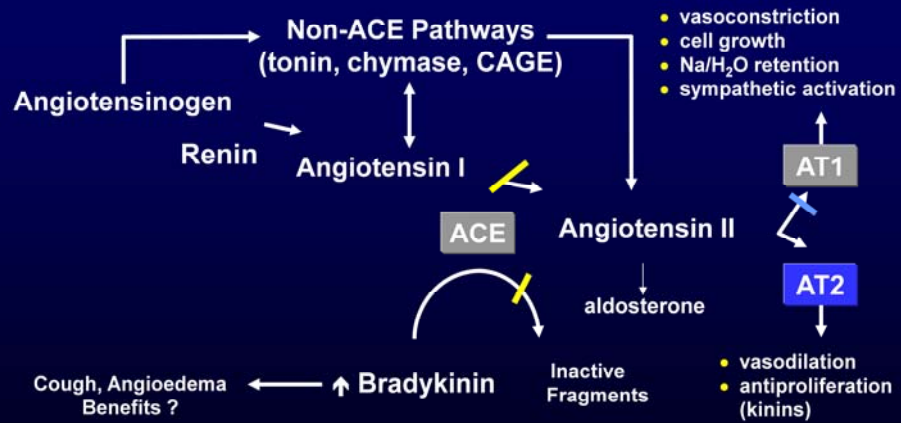


Packer et al. Circulation 2002

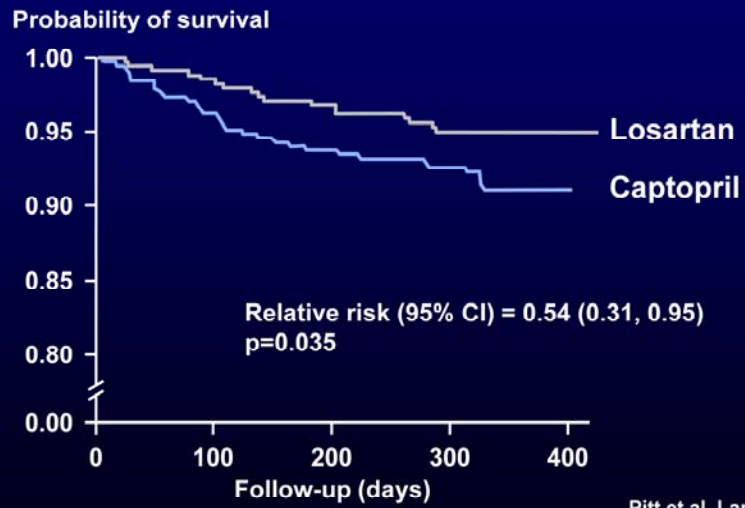
The unexpected



Angiotensin System

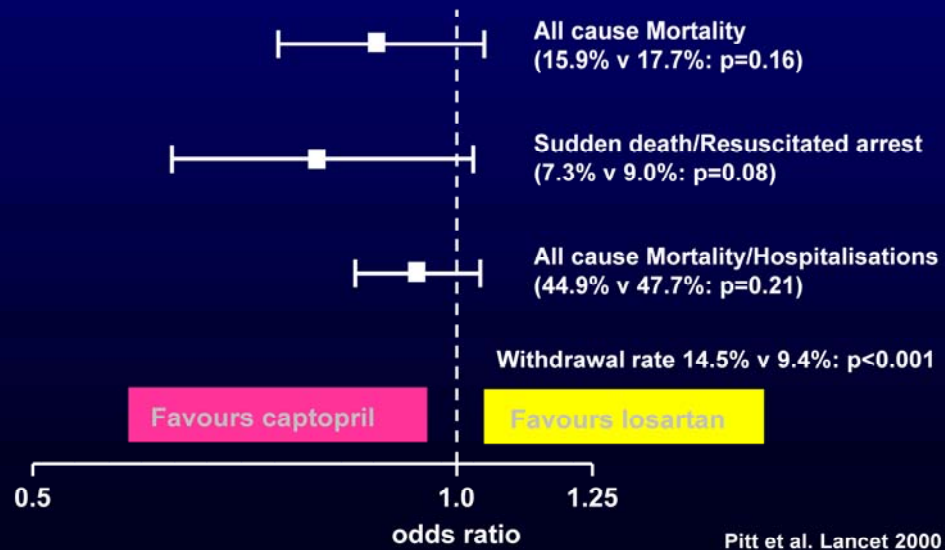


**Randomized trial of losartan versus captopril in patients over 65
with heart failure
(Evaluation of Losartan in the Elderly Study, ELITE)**



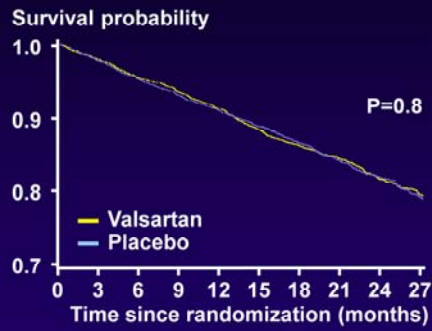
Pitt et al. Lancet 1997

**3152 elderly CHF patients randomised to losartan (50 mg od) or
captopril (50 mg tid)**

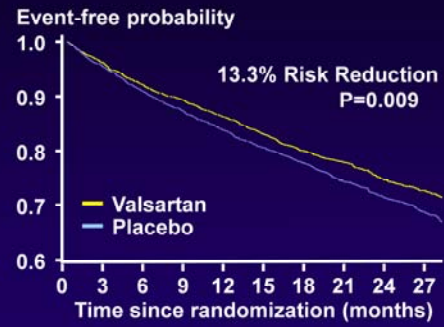


Val-HeFT: Co-primary Outcomes

All cause mortality

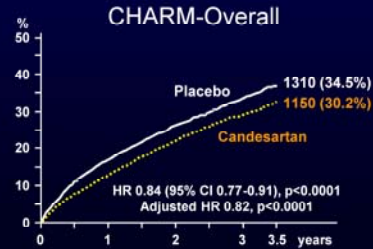
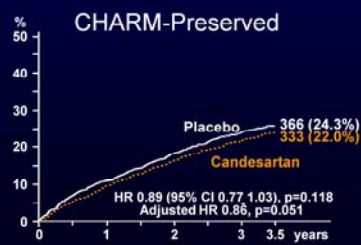
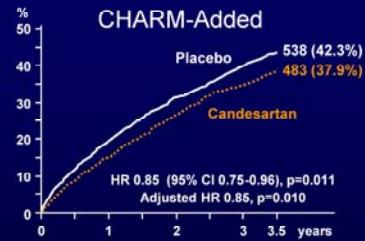
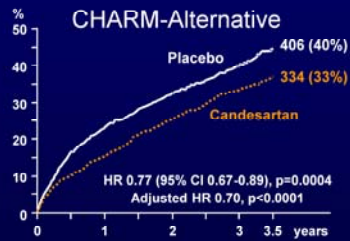


Mortality and morbidity



also 27.5% risk reduction in CHF hospitalization
P = 0.00001

CHARM: CV death or CHF hospitalisation



The FDA position



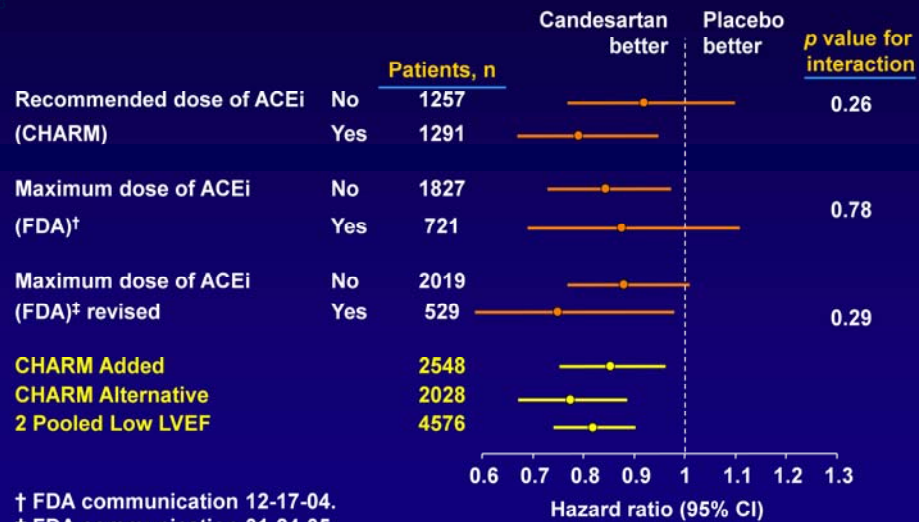
Questions

NDA 20-838/S-022, S-024, S-025
ATACAND® (candesartan cilexetil)
February 24, 2005

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory

- **The issue:**
 - Two drugs acting through the same pathway
- **The questions:**
 - Were the patients in CHARM-Added treated with an “optimal” dose of ACE inhibitor?
 - Could the same effect be obtained by giving a bigger dose of ACE inhibitor?

CV Death or CHF Hospitalization— Maximum Range of ACEi Doses



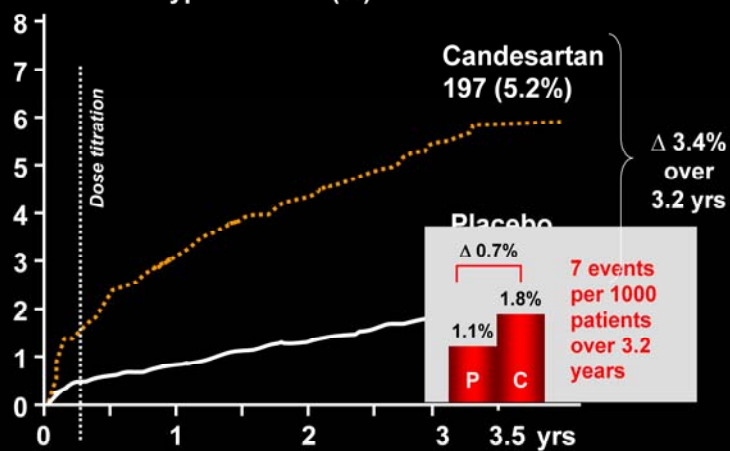
What Next – after an ACE inhibitor and Beta-blocker?

- Do nothing?
- Add an aldosterone antagonist?
- Add an ARB?
- Add hydralazine and ISDN?
- The combination of your choice!



Cumulative Incidence of Concerning Hyperkalemia (CHARM-Overall)

Cumulative Hyperkalemia (%)



Number at risk

Candesartan

Placebo

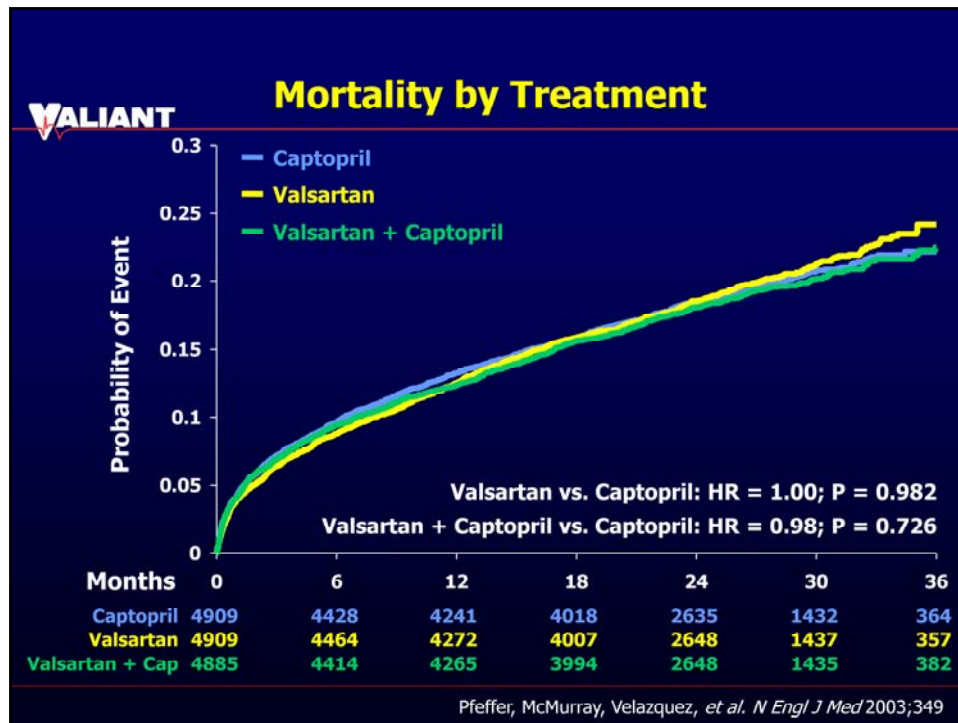
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1

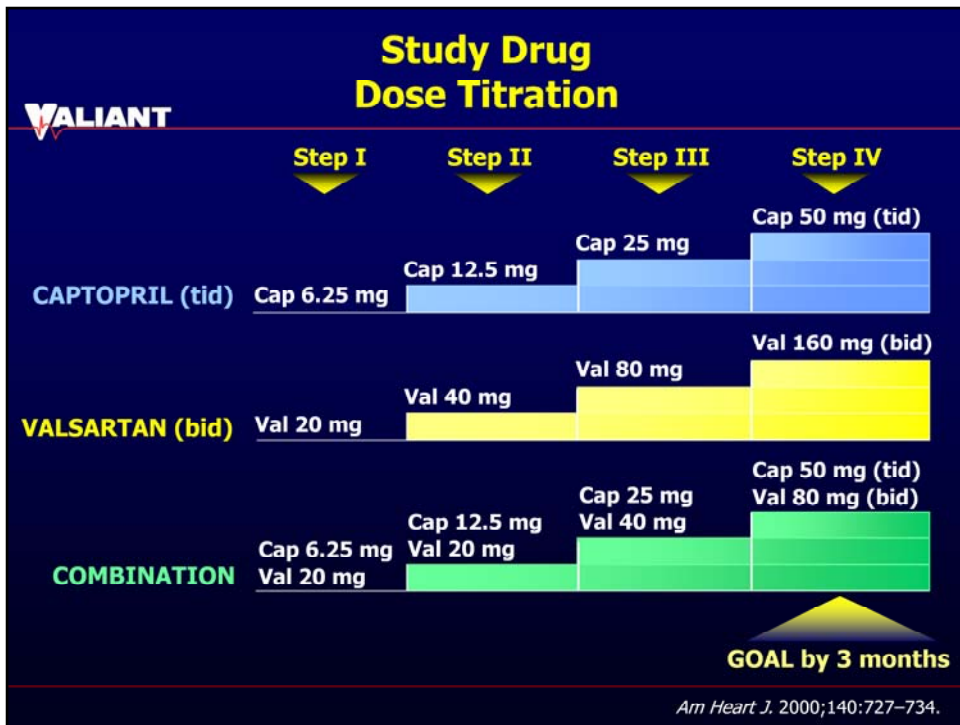
2

3

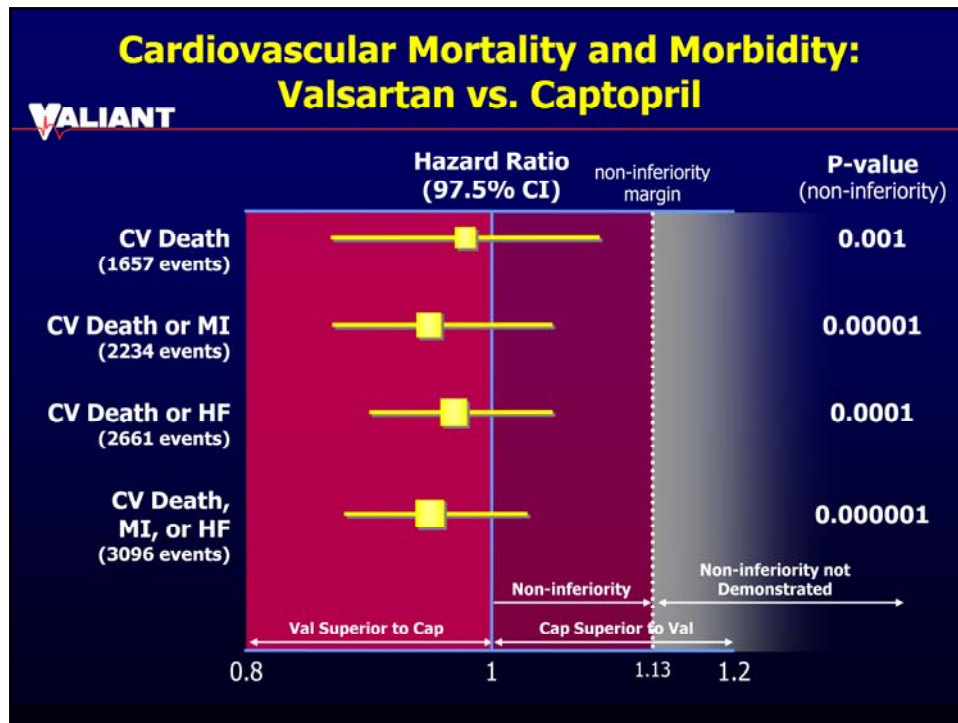
3.5 yrs



Mary Ann Sellers and Sue Edwards.



Rafael Diaz



Steve Zelenkofske

VALIANT Combination vs. Val-HeFT and CHARM-Added

- ◆ **Different clinical problem**
- ◆ **Simultaneous initiation of ACE inhibitor and ARB in VALIANT**
- ◆ **Valsartan added to a proven dose of captopril in VALIANT**
- ◆ **Target dose of valsartan in VALIANT combination arm half that in Val-HeFT**

OPTIMAAL: Captopril Versus Losartan After AMI



Study Design

≥ 50 years; AMI **and** clinical/radiological signs of HF;
EF ≤ 35%/LVEDD > 65 mm; new anterior Q waves/LBBB;
re-infarction and old anterior Q waves

Captopril
50 mg 3 times daily
(n = 2733)

Event-driven
(Target 937 Deaths)
2.7 years

Losartan
50 mg daily
(n = 2744)

Primary Endpoint: All-Cause Mortality
Secondary Endpoint: Sudden Cardiac Death or Resuscitated Arrest
Other Endpoints: Fatal and Non-fatal MI
Safety and Tolerability

VALIANT

OPTIMAAL: All-Cause Mortality

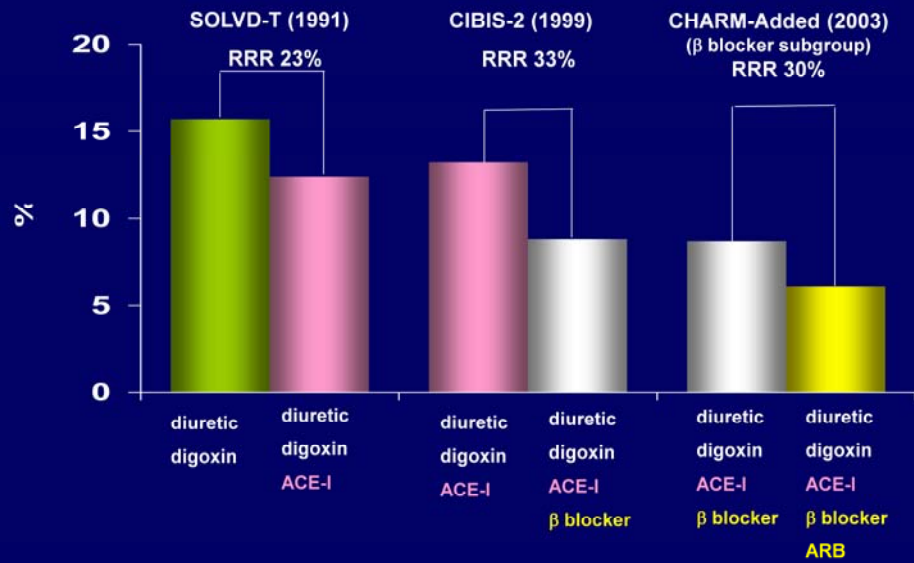
— Losartan (n = 499 events)
— Captopril (n = 447 events)

Event Rate (%)

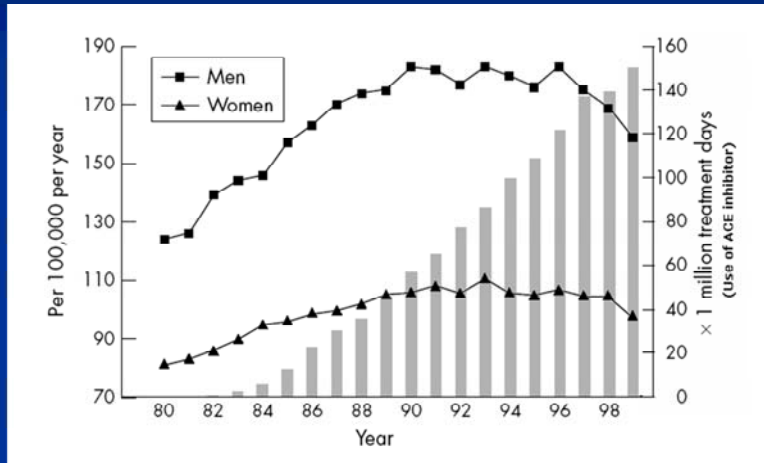
Relative Risk = 1.13 (0.99–1.28); P = 0.069

Month	0	6	12	18	24	30	36
Losartan	2744	2504	2432	2390	2344	2301	1285
Captopril	2733	2534	2463	2423	2374	2329	1309

Improving survival in CHF (1yr mortality)



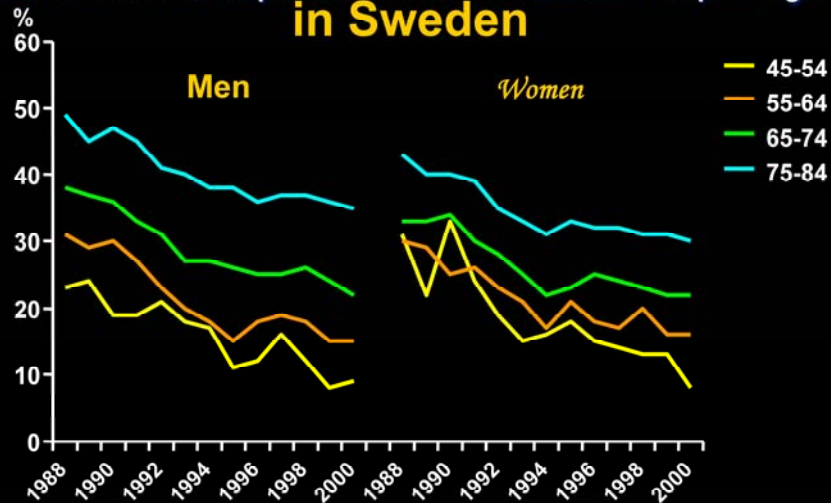
Angiotensin Converting Enzyme Inhibition and Hospitalisation Rates for Heart Failure in the Netherlands, 1980 to 1999: The End of an Epidemic?



A. Mosterd, J B Reitsma, D E Grobbee : Heart 2002; 87: 75-76

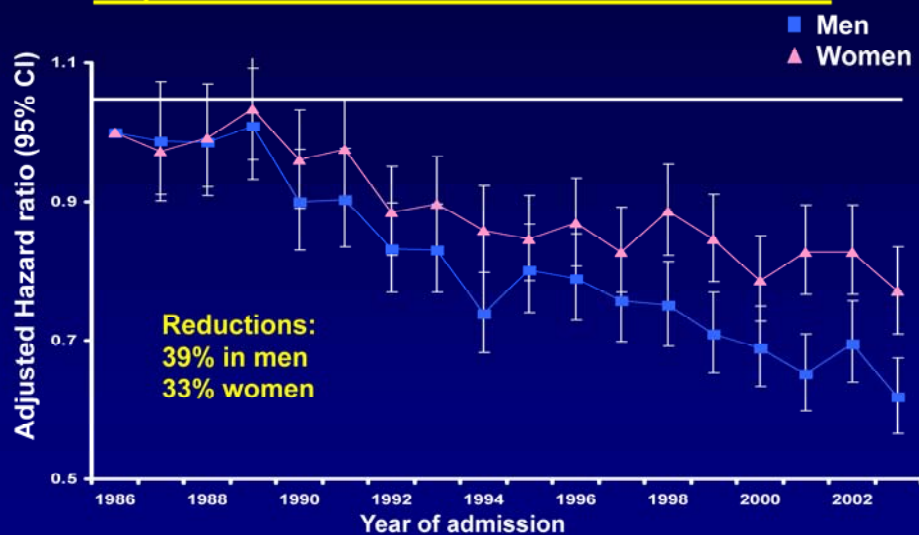
One-year mortality after admission for first hospitalisation for heart failure in 1988-2000 in Sweden

Data from 295 000 hospitalisations from the Swedish hospital registry



Schaufelberger et al, EHJ 2004

Adjusted 1 year mortality after first HF hospitalization in Scotland 1986-2003



MacIntyre *Circulation* 2000;102:1126-31.
Update via personal communication: J McMurray

Heart Failure Guidelines

ESC Guidelines

Guidelines for the diagnosis and treatment of Chronic Heart Failure: full text (update 2005)
The Task Force for the diagnosis and treatment of CHF of the European Society of Cardiology

Authors/Task Force Members, Karl Swedberg, Chairperson, *

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guideline for the Evaluation and Management of Heart Failure)

Developed in Collaboration With the American College of Chest Physicians and the International Society for Heart and Lung Transplantation
Endorsed by the Heart Rhythm Society

WRITING COMMITTEE MEMBERS
Sharon Ann Hunt, MD, FACC, FAHA, Chair

HFSA 2006 Guideline Executive Summary
Executive Summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline

HEART FAILURE SOCIETY OF AMERICA
St. Paul, Minnesota

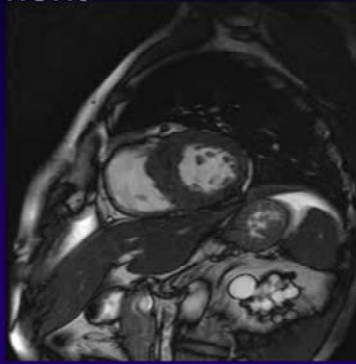
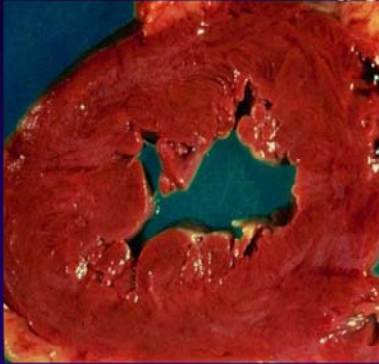
Committee Members
Kirkwood F. Adams, Jr, MD¹ (Co-Chair)
JoAnn Lindenfeld, MD² (Co-Chair)

Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management

J Malcolm O Arnold MD FRCP (Chair)¹, Peter Liu MD FRCP (Co-Chair)², Catherine Demers MD FRCP³, Paul Doran MD FRCP⁴, Nadia Gaspars MD FRCP⁵, Haissam Haddad MD FRCP⁶, George A Heckman MD FRCP⁷, Jonathan C Howlett MD FRCP⁸, Andrew Ignaszewski MD FRCP⁹, David E Johnstone MD FRCP¹⁰, Philip Long MD FRCP¹¹, Robert S McKelvie MD FRCP¹², Gordon W Moe MD FRCP¹³, John D Parker MD FRCP¹⁴, Vivek Rao MD FRCP¹⁵, Heather J Ross MD FRCP¹⁶, Errol J Sequeira MD FRCP¹⁷, Anna M Svendsen MD FRCP¹⁸, Koon Teo MBBCh FRCP¹⁹, Ross T Tsuyuki PharmD FCSHP²⁰, Michel White MD²¹

HF with preserved LVEF

We still do not have evidence-based treatment



I-PRESERVE

- Hypothesis: Irbesartan will reduce morbidity and mortality in HF and preserved LV systolic function
- Population: 4133 pts ≥ 60 yrs with clinical HF and EF $\geq 45\%$
- NYHA class II-IV and HF hospitalisation ≤ 6 months or NYHA class III-IV
- Intervention: Irbesartan (300 mg) vs placebo
- Primary endpoint: Death or CV hospitalisation
- Status: Due to report 2008
- Sponsor: Sanofi-Aventis

TOPCAT

- Hypothesis: Spironolactone will reduce morbidity and mortality in mild HF and preserved LV function
- Population: 4500 patients >50 yrs with NYHA II HF (and admission or elevated BNP), EF \geq 45%
- Intervention: Spironolactone (15-45 mg) vs placebo
- Primary endpoint: CV death, resuscitated cardiac arrest, HF hospitalisation
- Status: Expected to complete 2010
- Sponsor: NHLBI

Clinical (Outcomes) Trials, Why do them?

To provide the foundation for evidence-based medicine (safety as well as efficacy)

To continue to improve the practice of medicine

What are the alternatives?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

BMJ 2003

Certainly, there are rare occasions when rigorous hypothesis testing is not needed. Some types of clinical outcomes with clinical trials.