Cardiology Update® 2013

An ESC Update Programme
Davos, Switzerland, 10–15 February 2013

20th International Postgraduate Course on Cardiovascular Disease

EUROPEAN SOCIETY OF CARDIOLOGY®

Therapeutic Value of Renin Inhibitors

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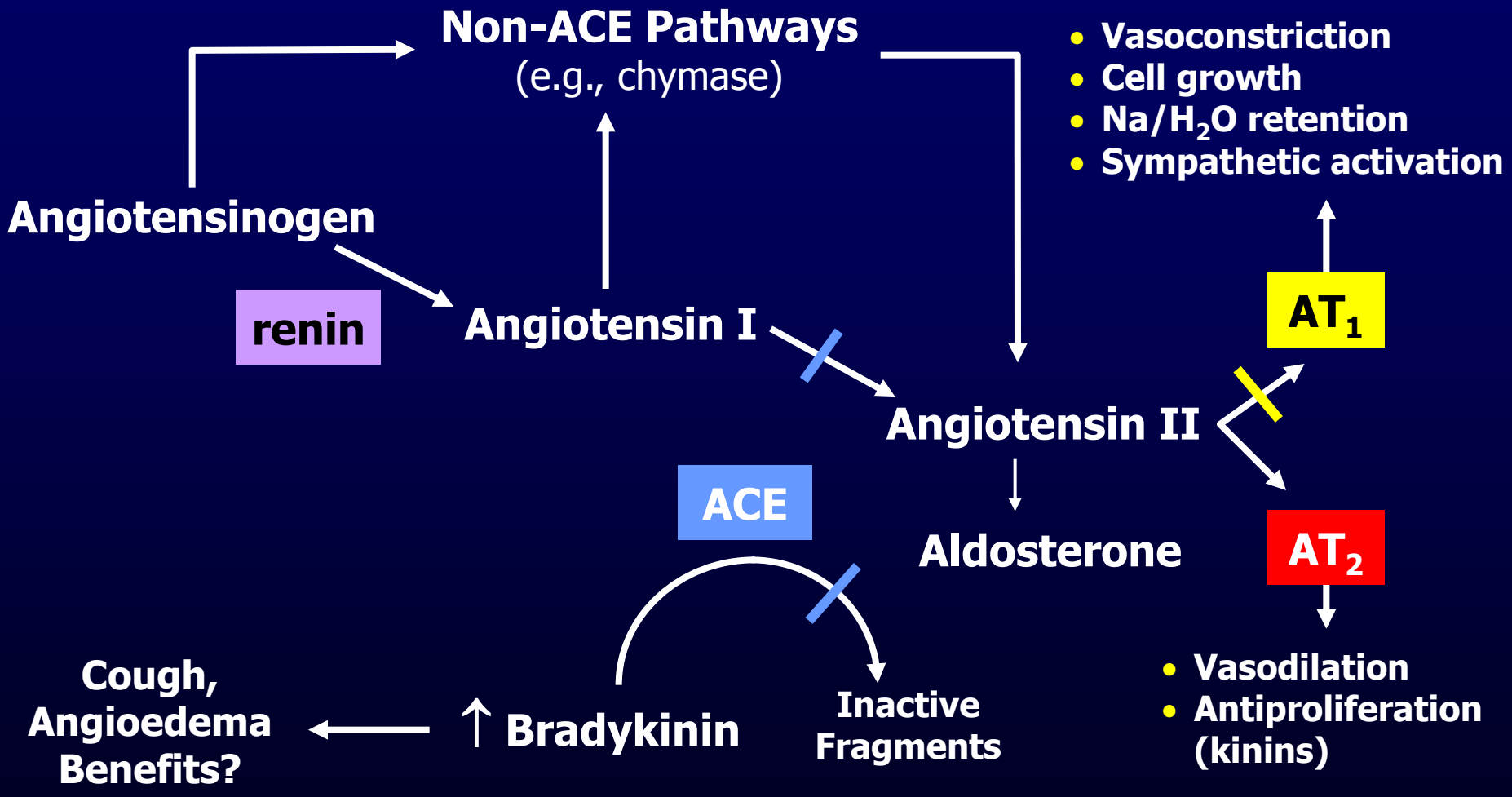
Disclosures:
Research Grant Support: Amgen, Celladon, Novartis, Sanofi Aventis
Consultant: Aastrom, Amgen, Anthera, Bayer, Boehringer, Bristol-Myers Squibb, Cerenis, Concert, Genzyme, Hamilton Health Sciences, Keryx, Medtronic, Novartis, Roche, Servier, Teva, the University of Oxford and XOMA.
Other: The Brigham and Women's Hospital has patents for the use of inhibitors of the renin-angiotensin system in selected survivors of MI with Novartis and Boehringer Ingelheim. Dr. Pfeffer is a co-inventor. His shares of the licensing agreements are irrevocably transferred to charity.

Renin-Angiotensin Aldosterone System



ACE-I Across CV Disease Spectrum

1987 – 2007

HBP
CAPPP
ALLHAT
ANZ2

CAD
EUROPA
PEACE
IMAGINE

VASCULAR
HOPE

MI
CONSENSUS II
ISIS-4
GISSI-3
SMILE
SAVE
AIRE
TRACE

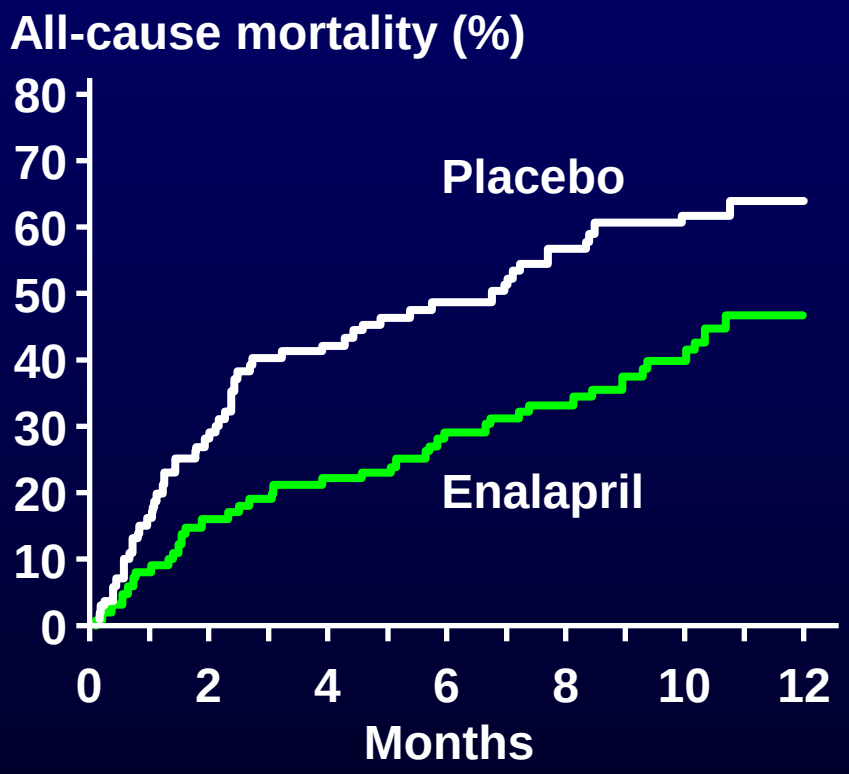
HF
CONSENSUS I
SOLVD
V-HeFT II
PEP-CHF

DM Prevention
DREAM

DM Renal
Collab Study
ABCD
REIN
AASK

CVA
PROGRESS

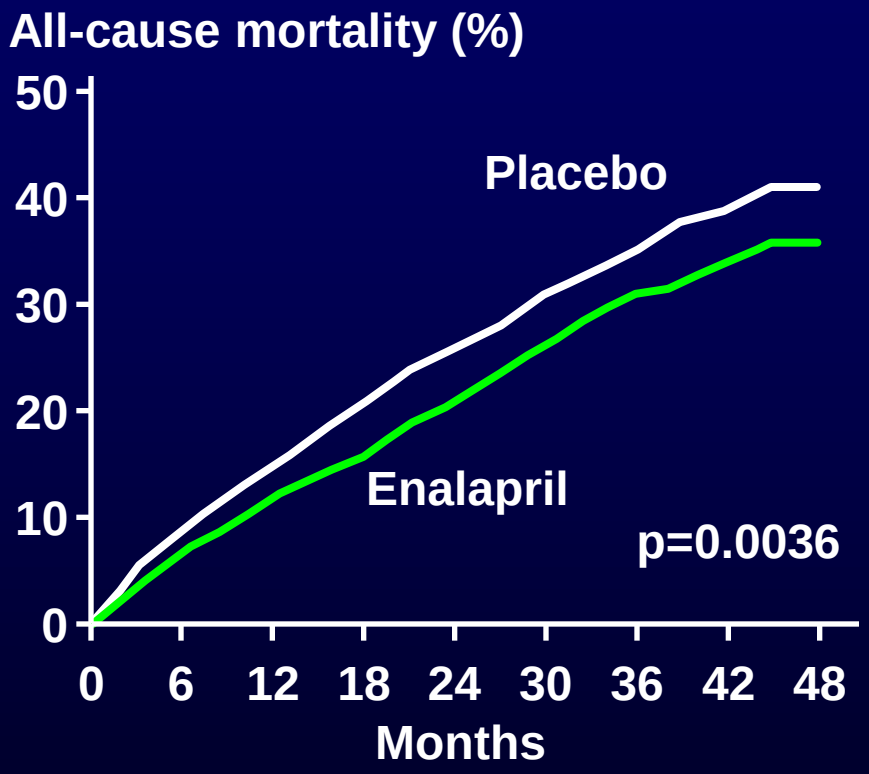
CONSENSUS



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

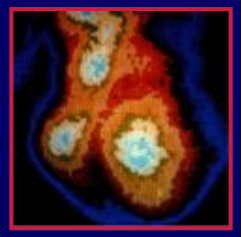
NEJM 1987

SOLVD

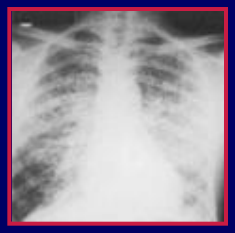


Placebo N:	1284	1159	1085	1005	939	819	669	487	299
Enalapril N:	1285	1195	1127	1069	1010	891	697	526	333

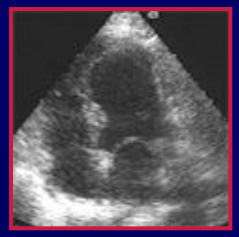
NEJM 1992



SAVE
Radionuclide
EF ≤ 40%

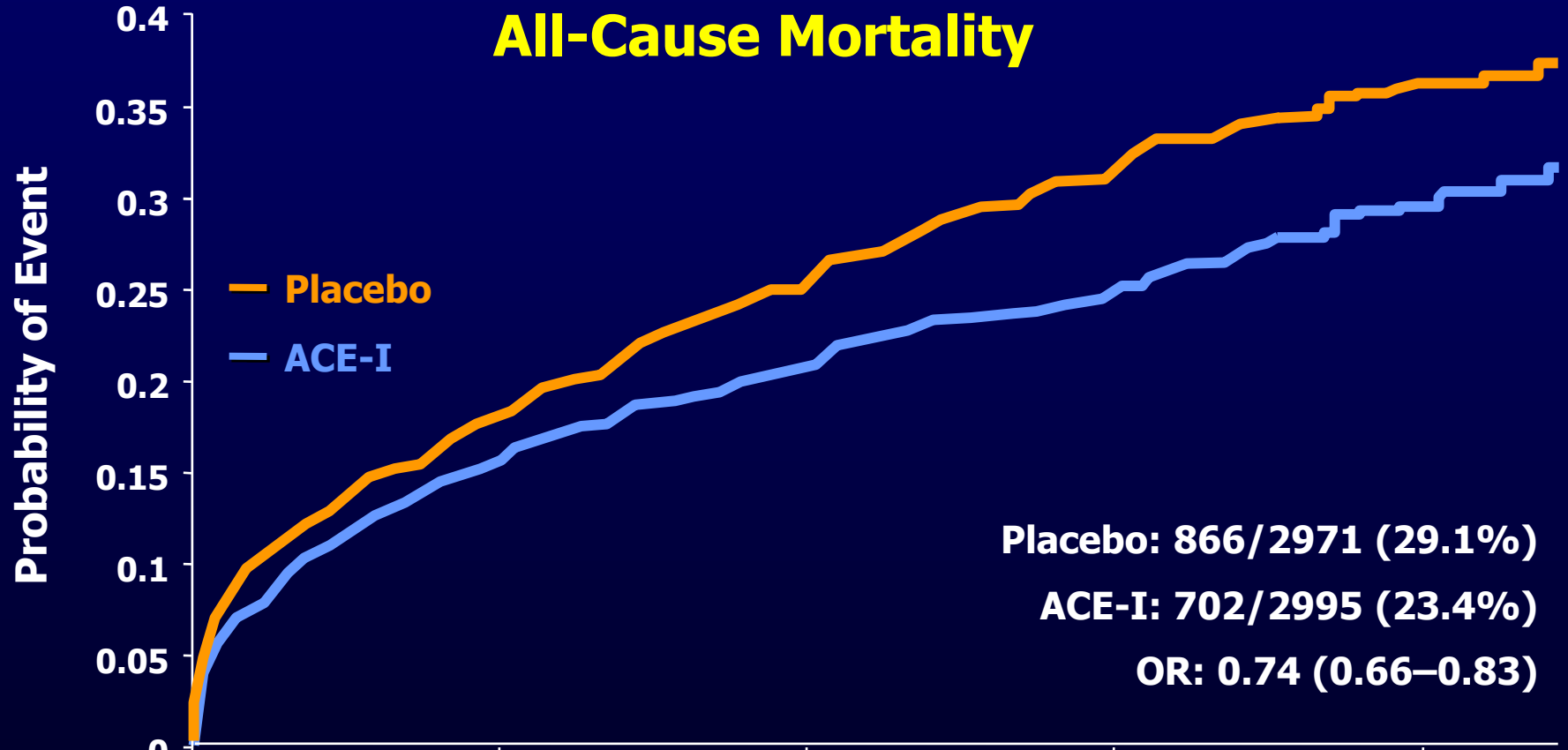


AIRE
Clinical and/or
radiographic
signs of HF



TRACE
Echocardiographic
EF ≤ 35%

All-Cause Mortality

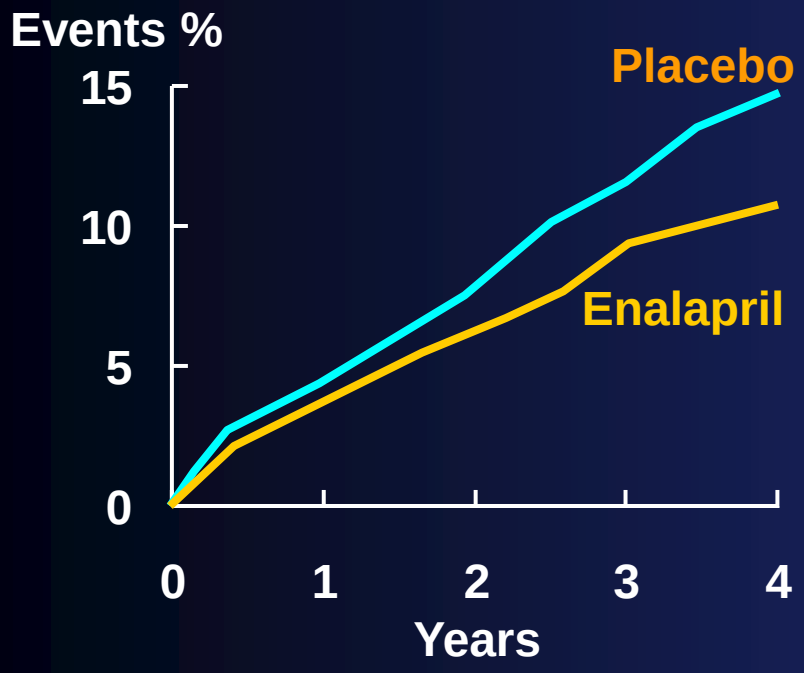


Years	0	1	2	3	4
ACE-I	2995	2250	1617	892	223
Placebo	2971	2184	1521	853	138

Flather MD, et al. *Lancet*. 2000;355:1575–1581

Reinfarction

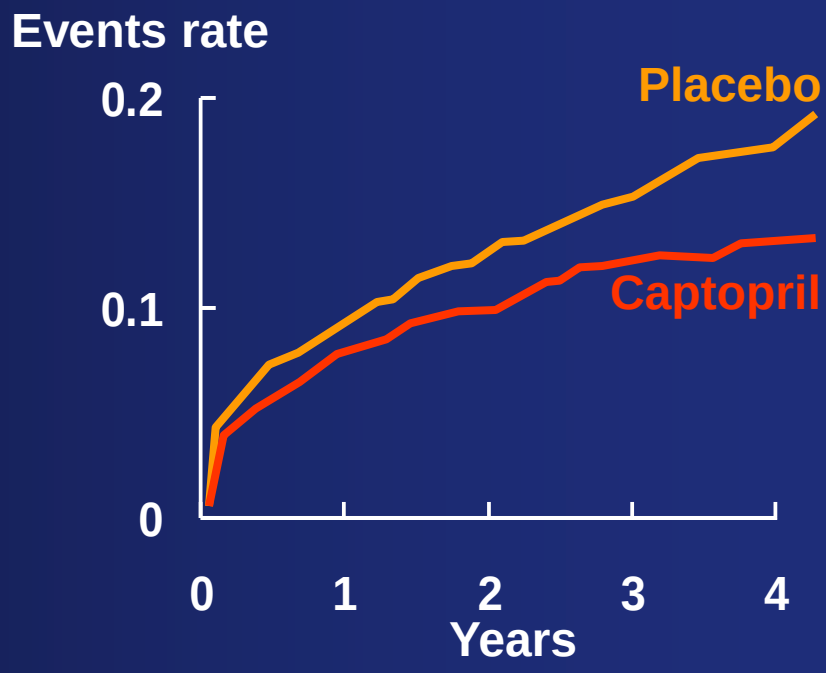
SOLVD



Risk reduction (95% CI) = 22% (6-35%)
P < 0.001

NEJM 1991

SAVE

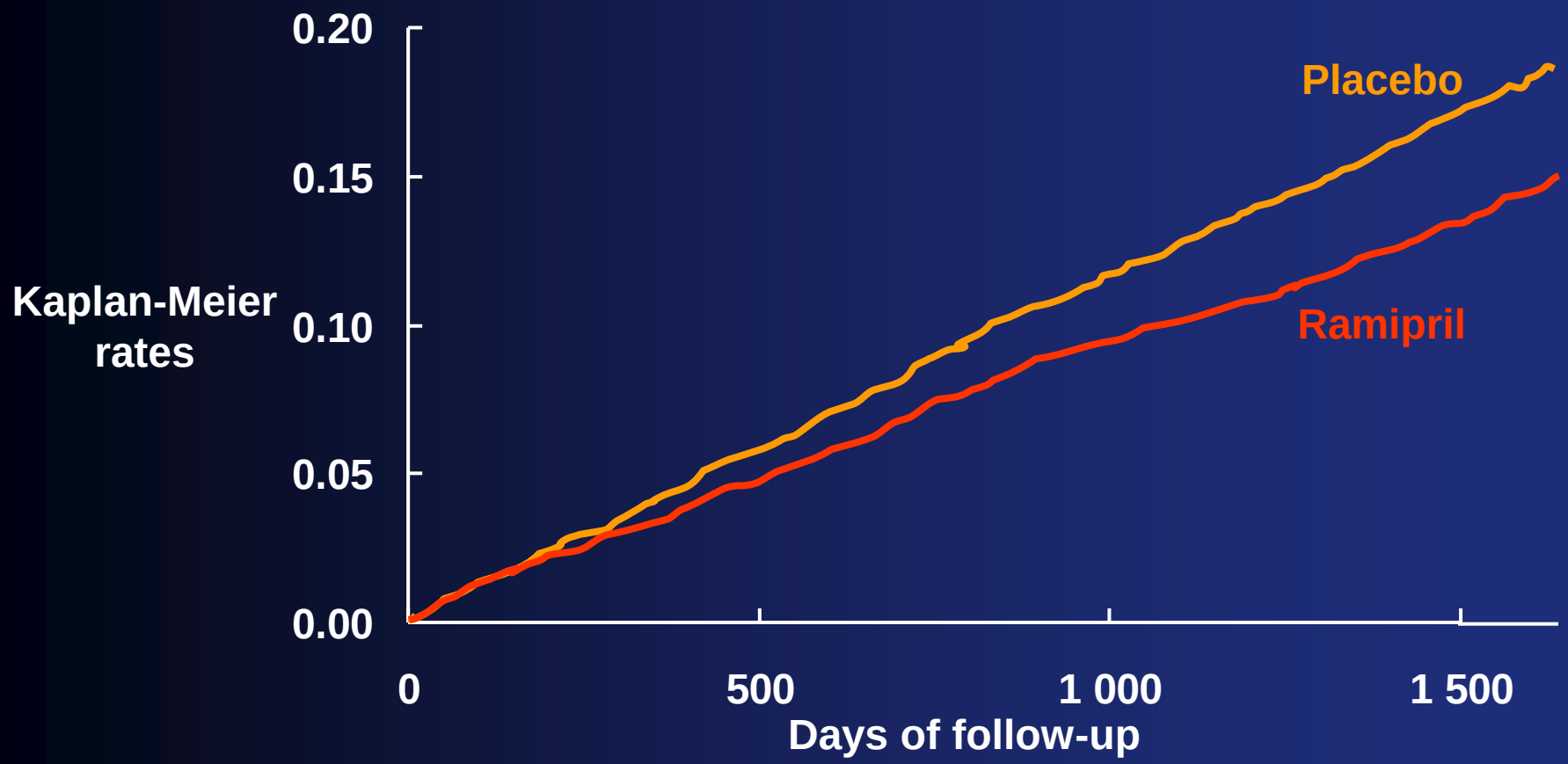


Risk reduction (95% CI) = 25% (5-40%)
P = 0.015

NEJM 1992

Hope Final

Primary Outcome – Ramipril vs Placebo

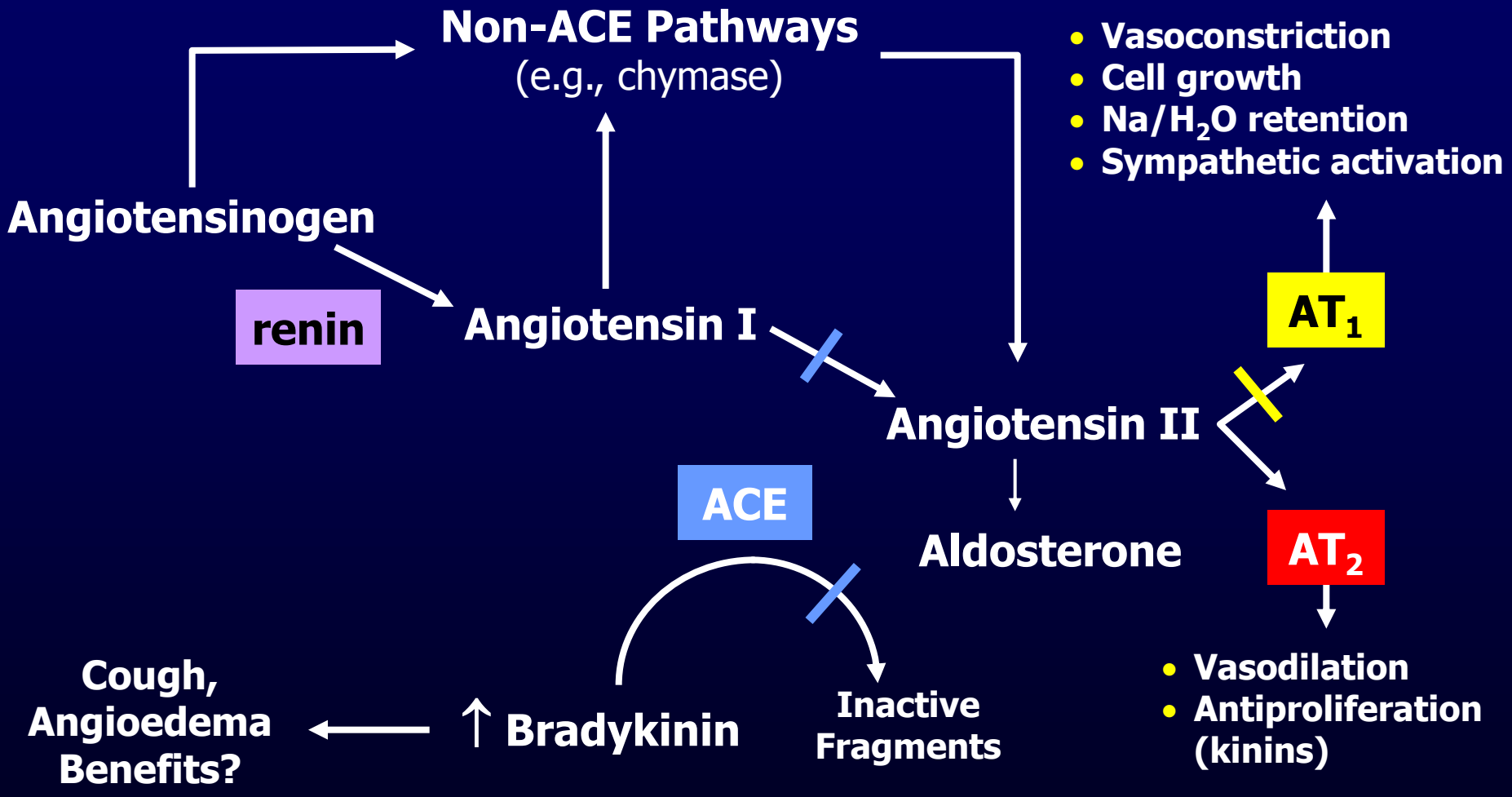


RR = 0.78 (0.70–0.86) P = 0.000002

NEJM 2000


HOPE
FILTER CIGARETTES
Europa Style
Europa
Milds
20 CIGARETTES
20 CIGARETTES
FILTER KINGS
Peace
LIGHTS
Low tar with "Peace" flavor

Renin-Angiotensin Aldosterone System



AT_1-Receptor Blocker (ARB) Clinical Outcome Studies

2002 – ongoing

HBP

LIFE

SCOPE

VALUE

Vascular

ONTARGET

TRANSCEND

JIKEI

HIJ-CREATE

MI

OPTIMAAL

VALIANT

HF

ELITE II

Val-Heft

CHARM

I-PRESERVE

Pre Diabetes

NAVIGATOR

Diabetes Opht

DIRECT

Diabetes Renal

RENAAL

IDNT

ROADMAP

(VA NEPHRON-D)

Atrial Fib

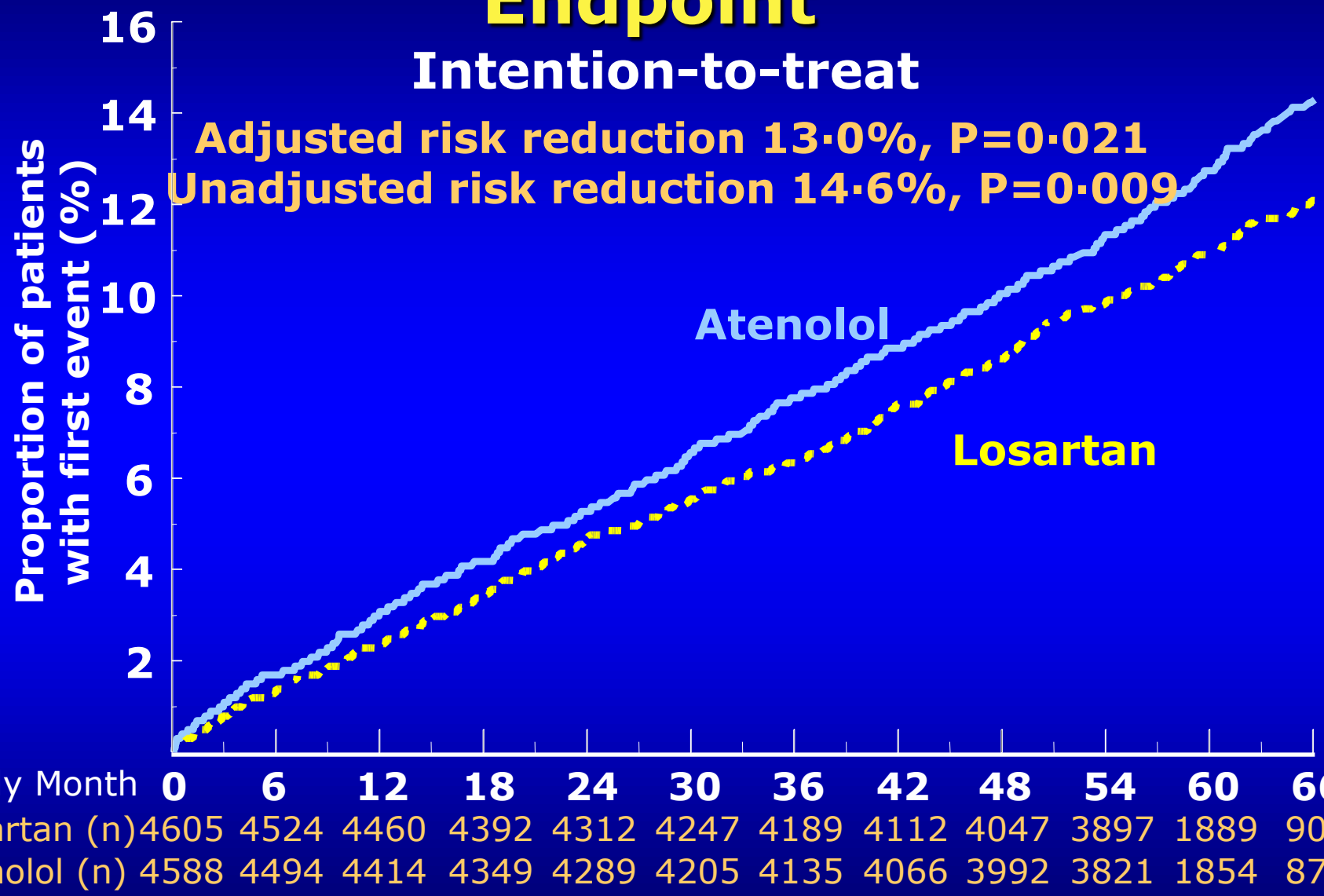
ACTIVE

GISSI-AF

CVA

PRoFESS

LIFE Study Primary Composite Endpoint

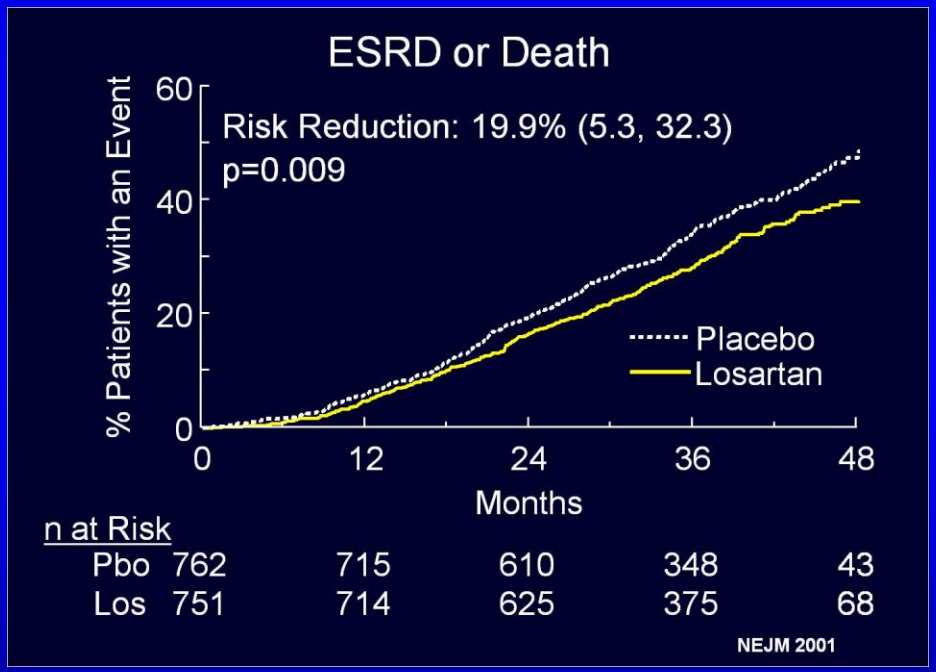


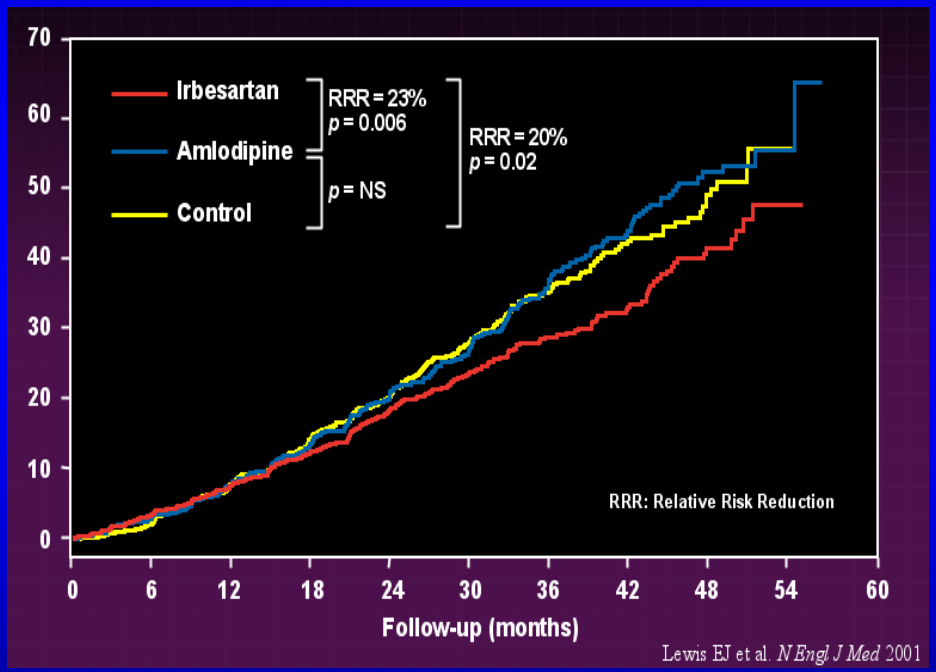
Dahlof B, et al. Lancet. 2002;359:995-1003.

RENAAL and IDNT

RENAAL: Primary End Point
ESRD or Death

IDNT: Primary endpoint
Time to doubling of serum Creatinine, ESRD, or Death

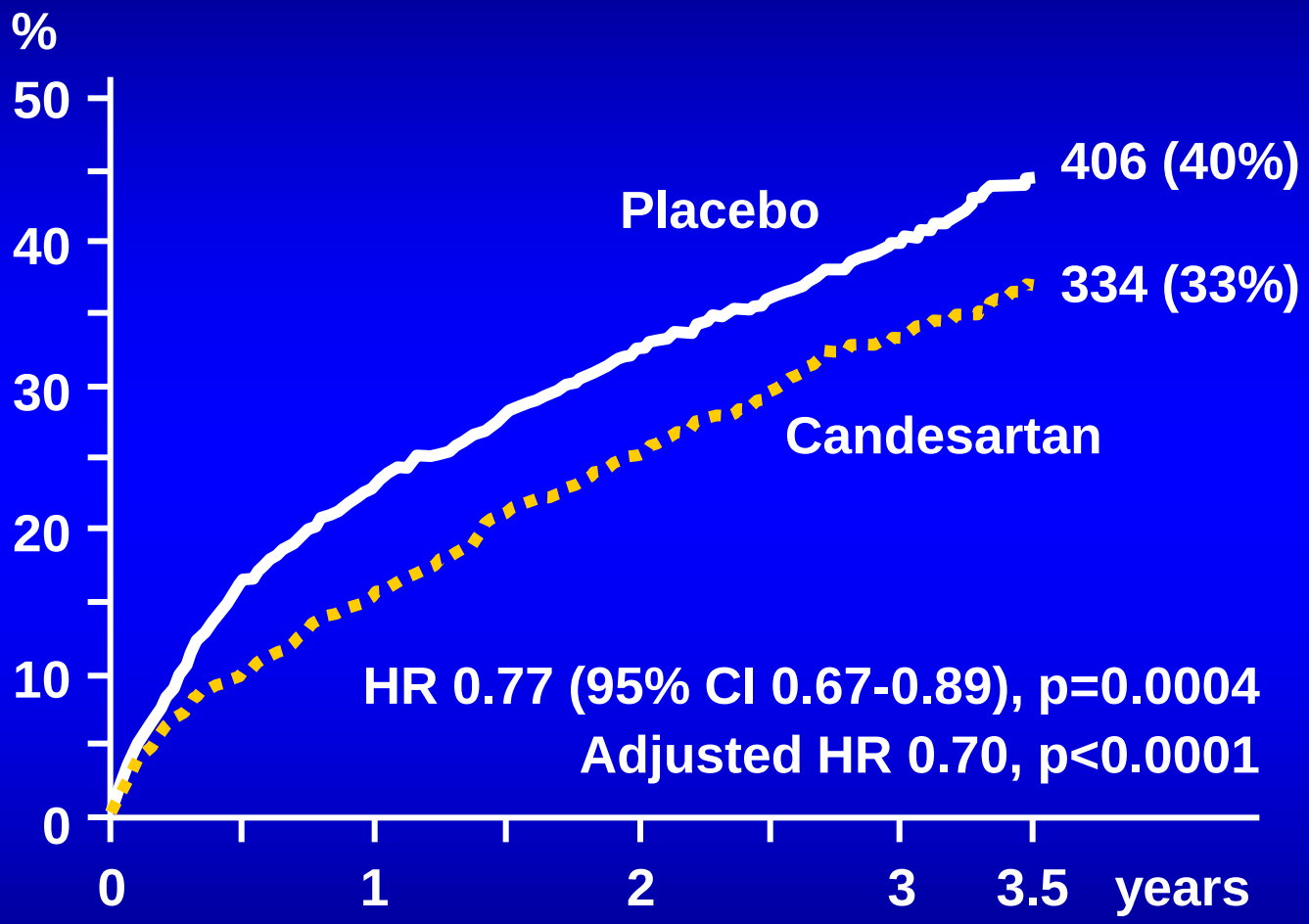




CHARM

CHARM-Alternative:

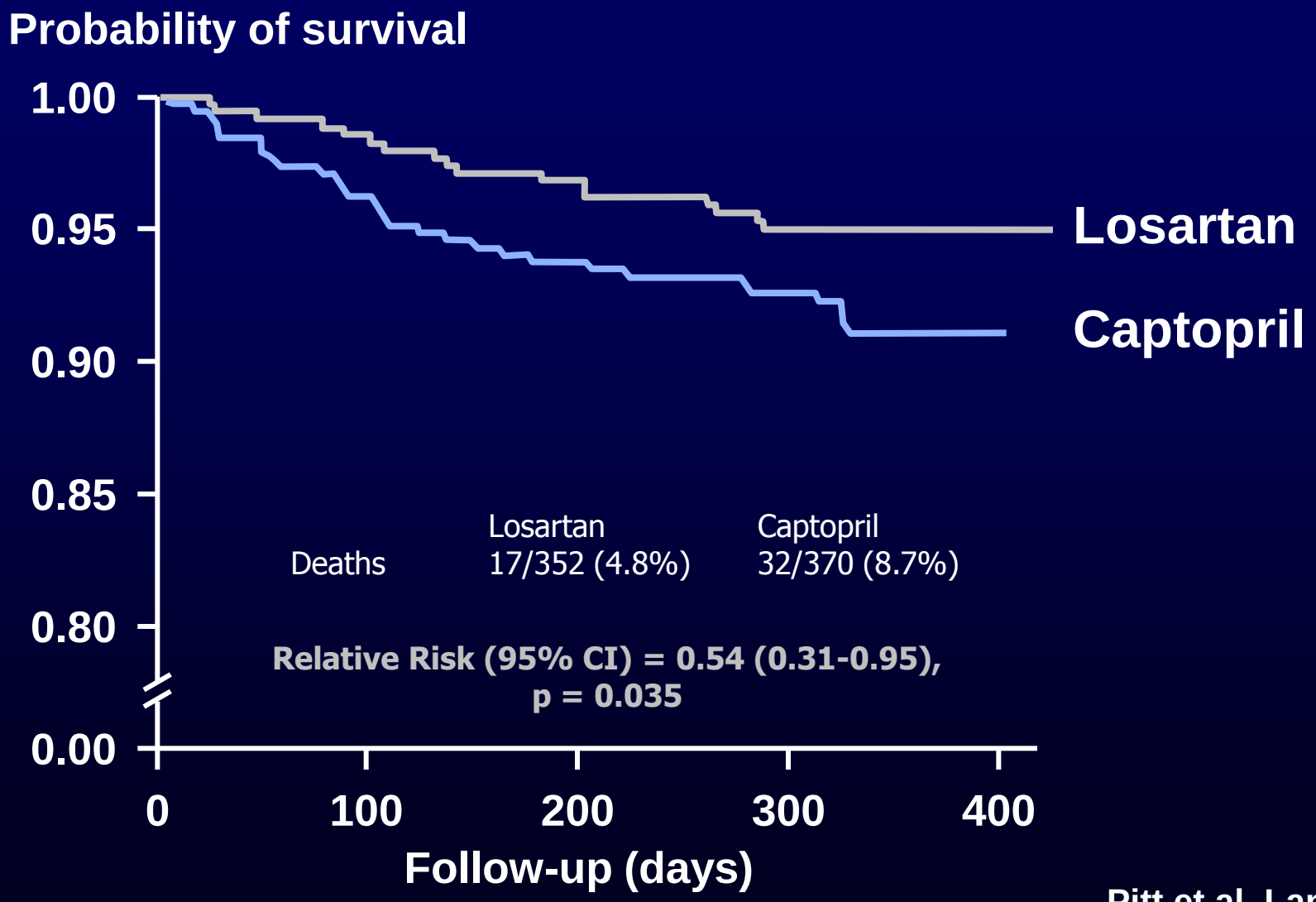
CV death or CHF hospitalization



Number at risk					
Candesartan	1013	929	831	434	122
Placebo	1015	887	798	427	126

Granger et al. Lancet 2003

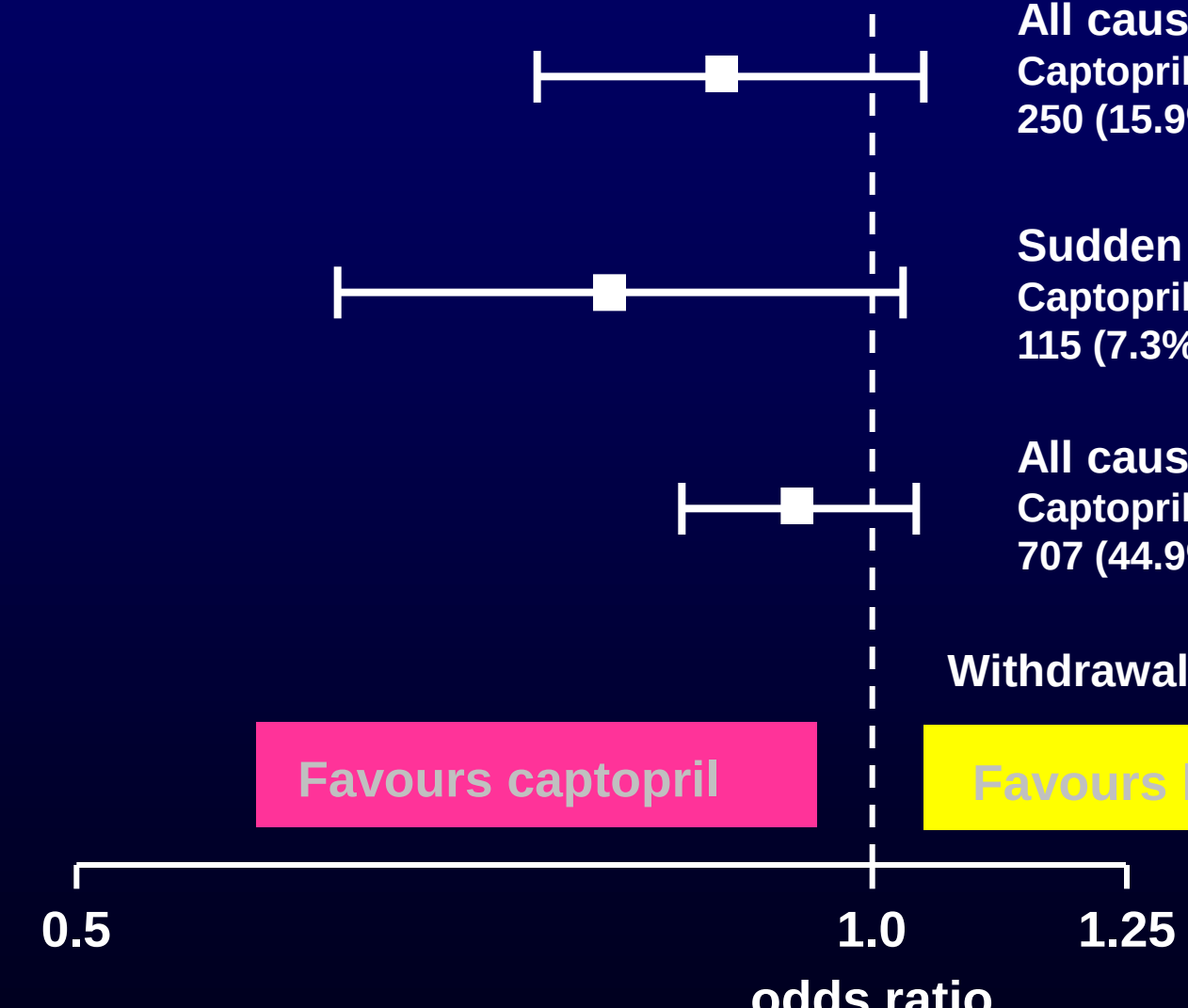
Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Eldely Study, ELITE)



Pitt et al. Lancet 1997

ELITE II: Summary of Major Findings

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



All cause Mortality

Captopril	Losartan	
250 (15.9%)	280 (17.7%)	p=0.16

Sudden death/Resuscitated arrest

Captopril	Losartan	
115 (7.3%)	142 (9.0%)	p=0.08

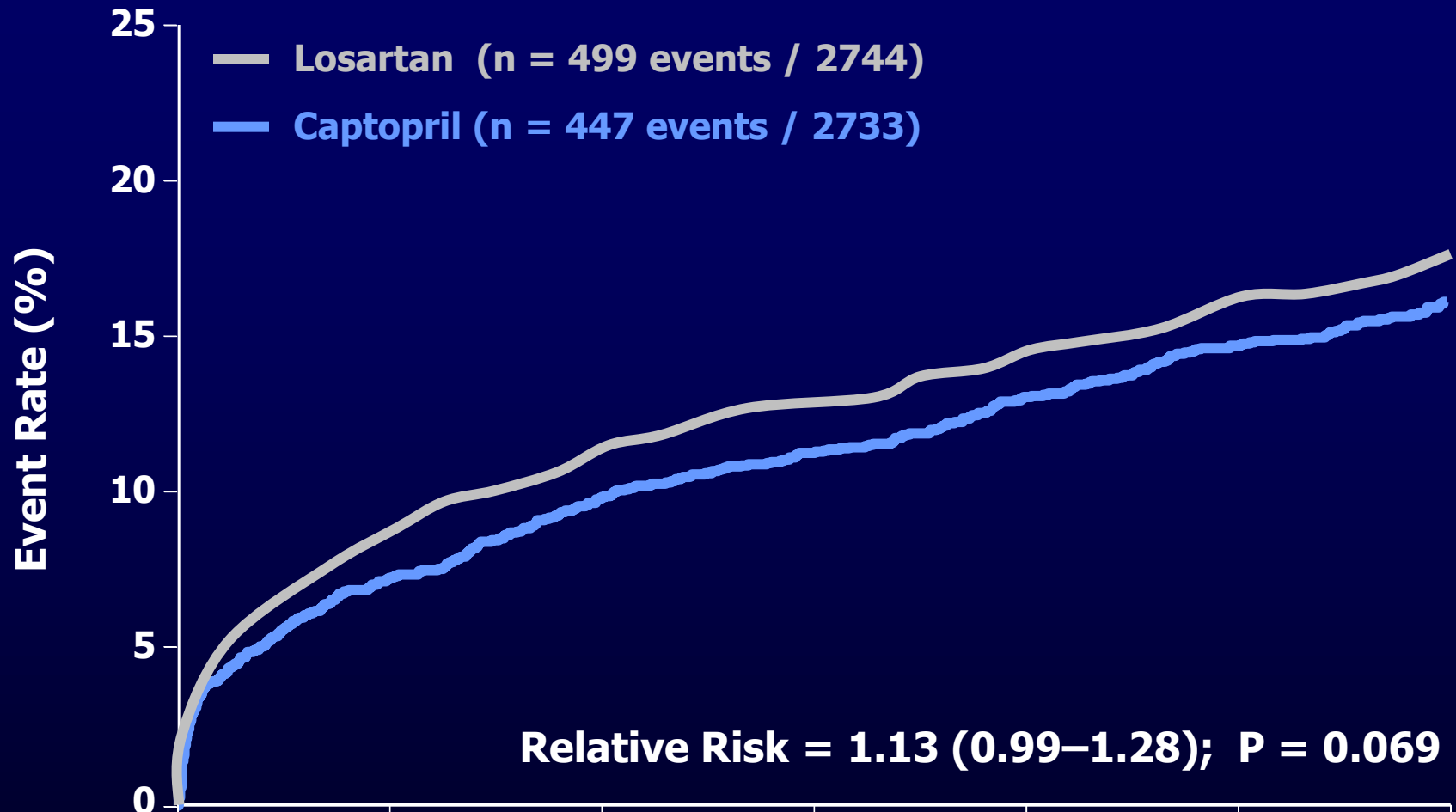
All cause Mortality/Hospitalisations

Captopril	Losartan	
707 (44.9%)	752 (47.7%)	p=0.21

Withdrawal rate 14.5% v 9.4%: p<0.001

Pitt et al. Lancet 2000

OPTIMAAL: All-Cause Mortality



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

Lancet 2002

VALIANT

Acute MI (0.5–10 days)—SAVE, AIRE or TRACE eligible
(either clinical/radiologic signs of HF or LV systolic dysfunction)

Major Exclusion Criteria:
— BP < 100 mm Hg
— Serum creatinine > 2.5 mg/dL
— Prior intolerance of an ARB or ACE-I
— Nonconsent

double-blind active-controlled

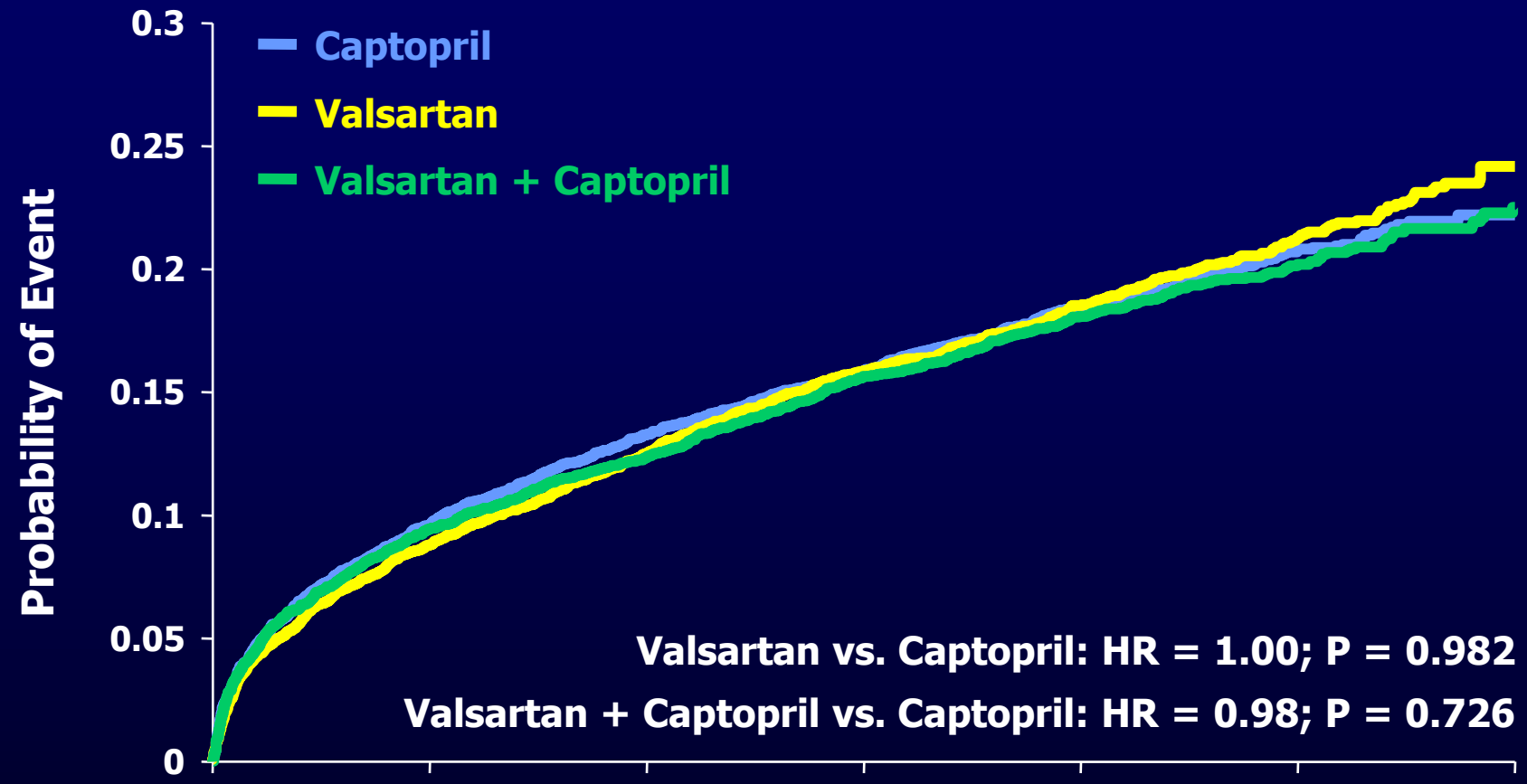
Captopril 50 mg tid (n = 4909)	Valsartan 160 mg bid (n = 4909)	Captopril 50 mg tid + Valsartan 80 mg bid (n = 4885)

median duration: 24.7 months
event-driven

Primary Endpoint:	**All-Cause Mortality**
Secondary Endpoints:	**CV Death, MI, or HF**
Other Endpoints:	**Safety and Tolerability**

N Engl J Med 2003

Mortality by Treatment



Months	0	6	12	18	24	30	36
Captopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan + Cap	4885	4414	4265	3994	2648	1435	382

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

Conclusion

Presented at AHA 2003; *N Engl J Med* 2003

In patients with MI complicated by heart failure, left ventricular dysfunction or both:

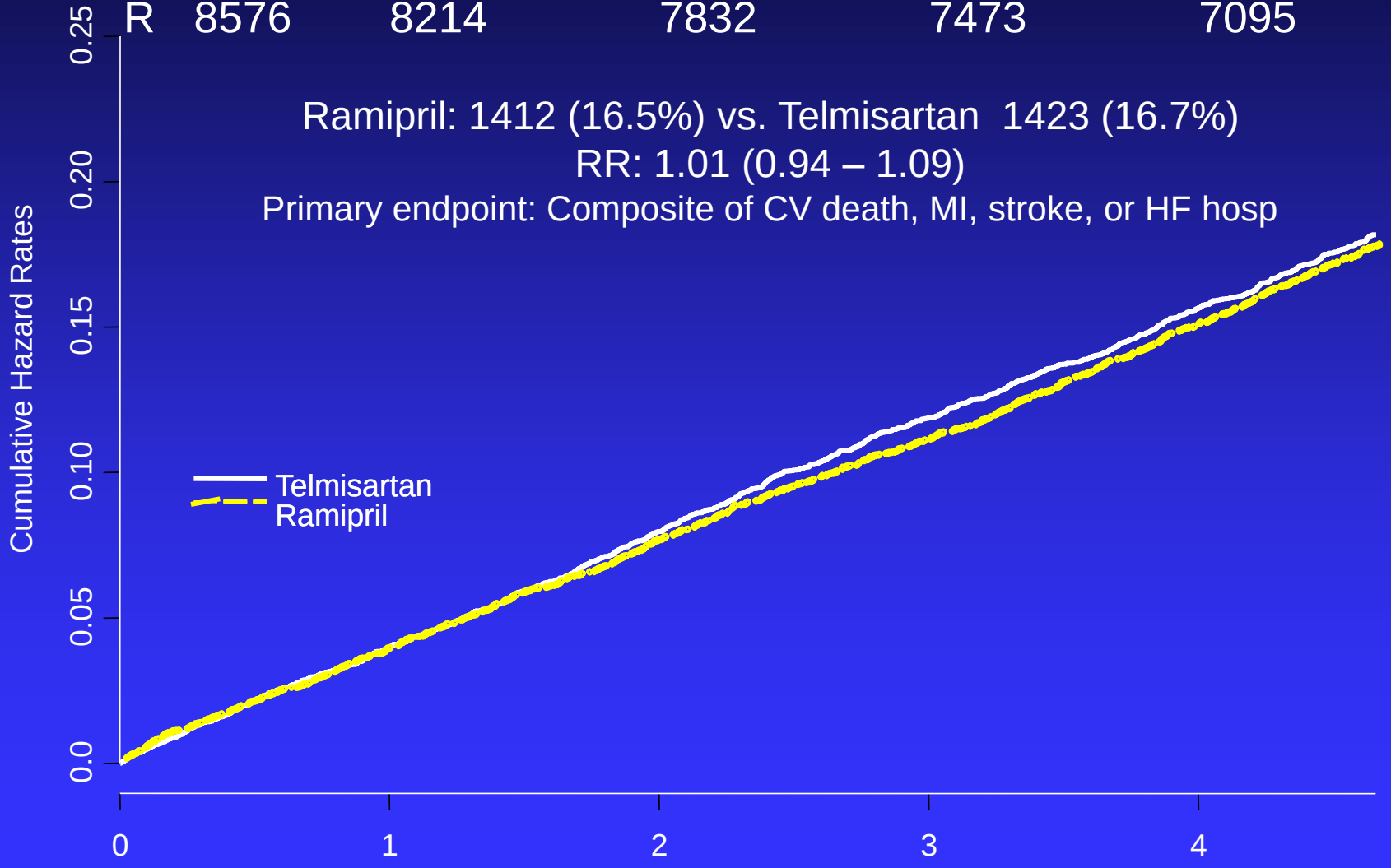
- **Valsartan is as effective as a proven dose of captopril in reducing the risk of:**
  - —Death
  - —CV death or nonfatal MI or heart failure admission
- **Combining valsartan with a proven dose of captopril produced no further reduction in mortality—and more adverse drug events.**

ONTARGET

Time to Primary Outcome

	# at Risk	Yr 1	Yr 2	Yr 3	Yr 4
T	8542	8176	7778	7420	7051
R	8576	8214	7832	7473	7095

Ramipril: 1412 (16.5%) vs. Telmisartan 1423 (16.7%)
RR: 1.01 (0.94 – 1.09)
Primary endpoint: Composite of CV death, MI, stroke, or HF hosp



N Engl J Med 2008;358:1547-59.

ONTARGET Conclusions: Telmisartan plus Ramipril vs. Ramipril

1. Combination therapy does not reduce the primary outcome to a greater extent compared to ramipril alone

2. Higher rates of adverse events:
   - -hypotension related, including syncope
   - -renal dysfunction

N Engl J Med 2008;358:1547-59.

Inhibiting RAS - 3 decades…..

ACE I – Work Horse

- HF (low EF)
- MI
- Vascular Disease
- Diabetes
- Renal Disease

ACE I or ARB (dose)

- VALIANT
- ONTARGET
- CHARM Alt.
- TRANSCEND

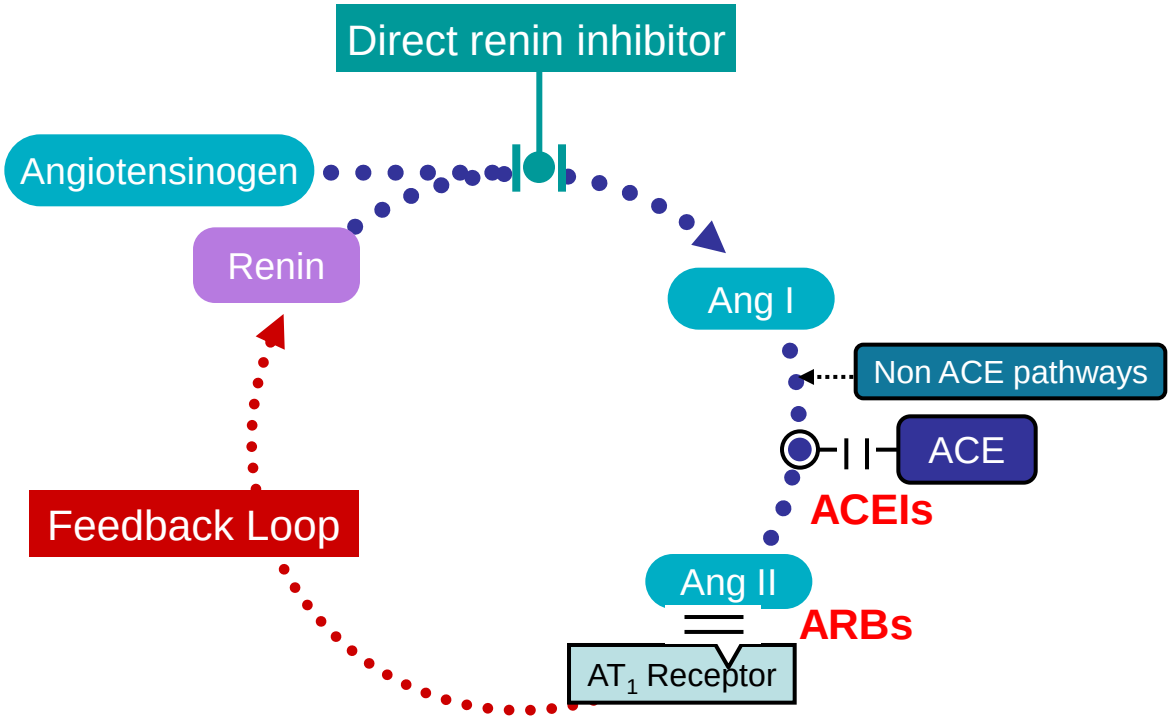
→ Population Not Improved:
DREAM
PRoFESS
I-PRESERVE
GISSI-AF

Combination ACE I and ARB

- VALIANT
- ONTARGET
- ? CHARM Added

→ No Incremental Benefit with Increase in Adverse Events

Aliskiren reduces Ang I, Ang II and PRA



	Ang I	Ang II	PRA
ACEI	↑	↓	↑
ARB	↑	↑	↑
Aliskiren	↓	↓	↓

Azizi M et al. 2006; Adapted from: Müller DN & Luft FC. 2006

ASPIRE HIGHER Program

Surrogate endpoint trials

AVOID
Albuminuria reduction in patients with hypertension, diabetes, and nephropathy
Parving et al. N Engl J Med 2008;358:2433-6

ALOFT
BNP reduction in chronic heart failure
McMurray et al. Circ Heart Fail 2008;1:17-24

ALLAY
LV mass regression in hypertensive patients with LVH
Solomon et al. Circulation 2009;119:530-7

ASPIRE
Reduction in LV remodeling following MI complicated by LV dysfunction
Solomon et al. Eur Heart J 2011;32:1227-34

Morbidity and mortality trials

ALTITUDE n=8606
In diabetic nephropathy at high risk for CV disease

ATMOSPHERE n≈7000
(head to head not add on)
In chronic heart failure

ASTRONAUT n≈1700
In acute heart failure

APOLLO n≈11000
BP in elderly (some add on)

A Post-MI trial n=zero

European Heart Journal
doi:10.1093/eurheartj/ehq522

CLINICAL RESEARCH
2011

Effect of the direct renin inhibitor aliskiren on left ventricular remodelling following myocardial infarction with systolic dysfunction

Scott D. Solomon[1]*, Sung Hee Shin[1], Amil Shah[1], Hicham Skali[1], Akshay Desai[1], Lars Kober[2], Aldo P. Maggioni[3], Jean L. Rouleau[4], Roxzana Y. Kelly[5], Allen Hester[5], John J. V. McMurray[6,7], and Marc A. Pfeffer[1], for the Aliskiren Study in Post-MI Patients to Reduce Remodeling (ASPIRE) investigators

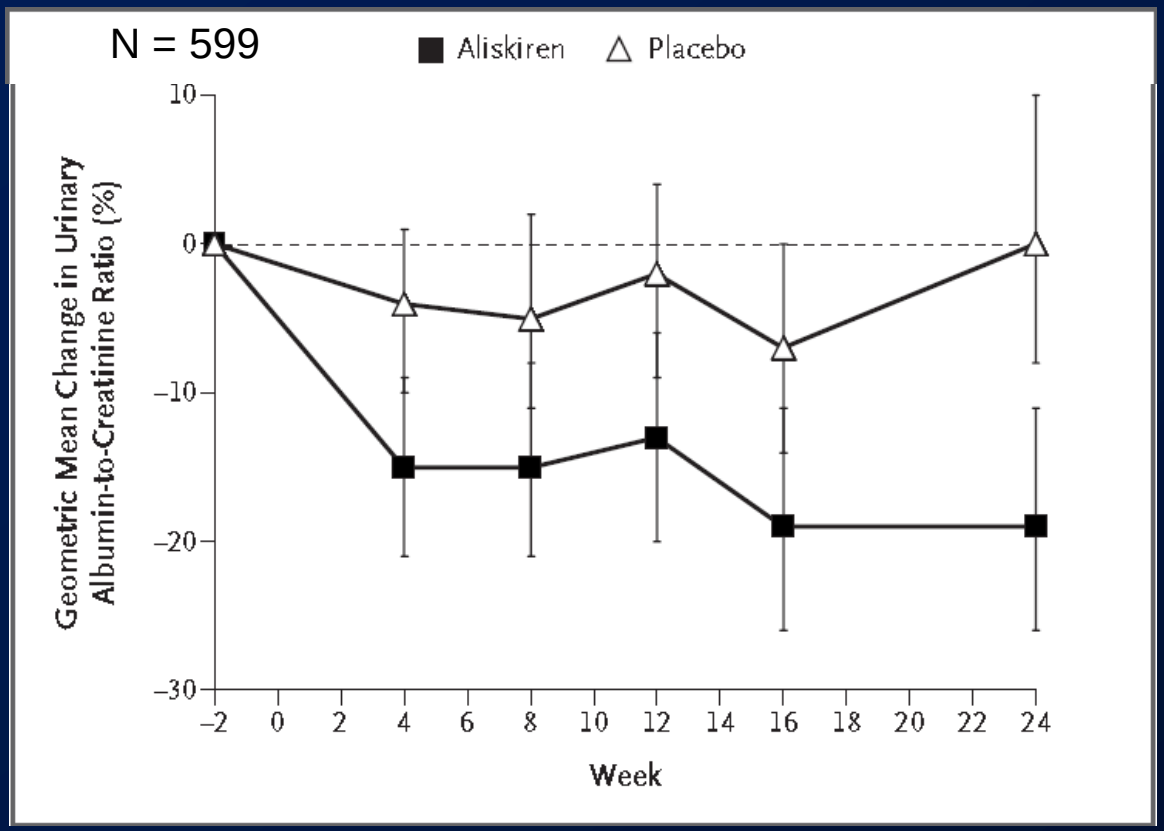
Conclusion: Adding the direct renin inhibitor aliskiren to the standard therapy, including an inhibitor of the RAAS, in high-risk post-MI patients did *not* result in further attenuation of left ventricular remodelling, and was associated with more adverse effects. These findings do not suggest that dual RAAS blockade with aliskiren would provide additional benefit in these high-risk post-MI patients.

Solomon et al Eur Heart J 2011

June 2008

Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

Hans-Henrik Parving, M.D., D.M.Sc., Frederik Persson, M.D., Julia B. Lewis, M.D., Edmund J. Lewis, M.D., and Norman K. Hollenberg, M.D., Ph.D., for the AVOID Study Investigators*



Conclusions: Aliskiren may have reno-protective effects that are independent of its blood pressure–lowering effect in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended reno-protective treatment.

ALTITUDE

Type II Diabetes

Population

8561 Patients with type II diabetes with eGFR ≥ 30 mL/min/1.73 m² :

- **UACR ≥ 200 mg/g , *or***
- **eGFR <60 mL/min/1.73 m² *and***
  - **Either UACR ≥ 20 and <200 mg/g *or***
  - **CVD history**

Endpoints

Primary: Composite of CV and renal components

(CV or renal death, RSD, non-fatal MI, non-fatal stroke, HF hospitalization, ESRD, doubling SCr)

Treatment arms

Aliskiren vs. Placebo – All on RAS inhibitor

End Date

Early termination December 2011

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

Nov. 2012

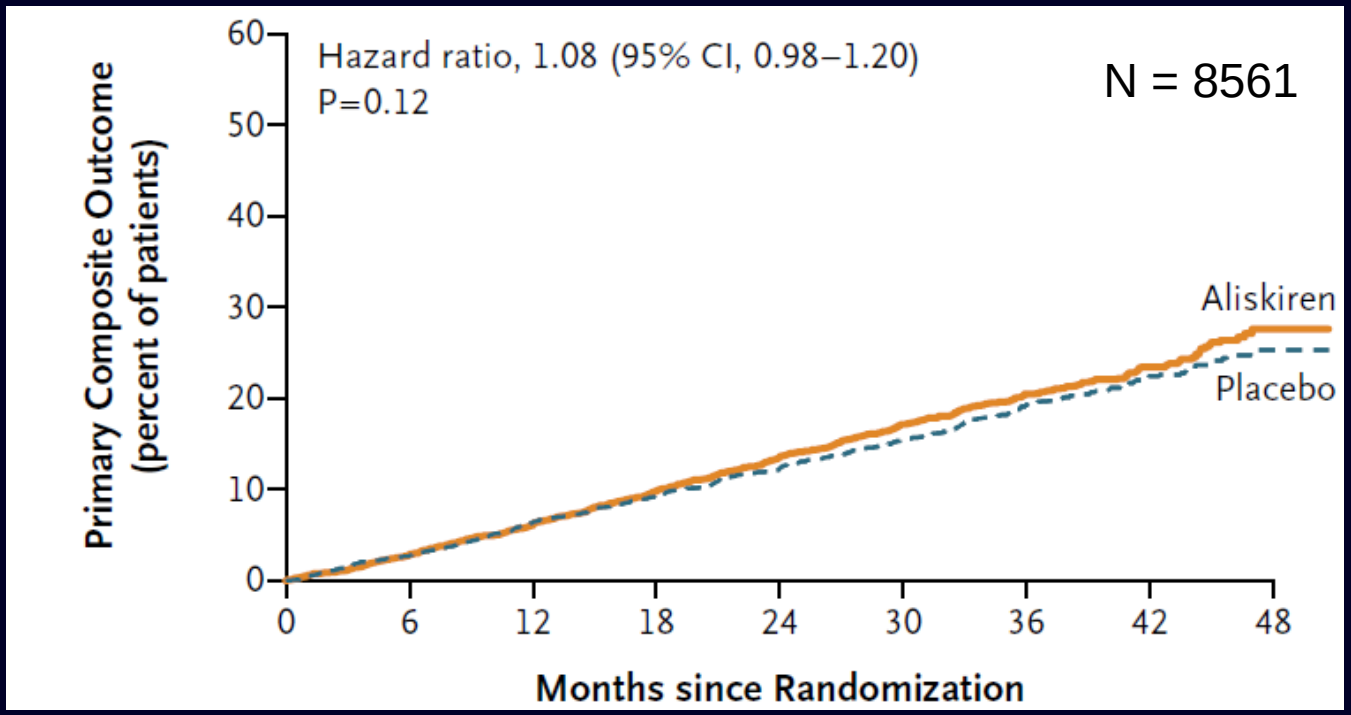
Hans Henrik Parving MD DM Sc, Barry M. Brenner MD PhD, John JV McMurray MD, Dick de Zeeuw MD PhD, Steven M Haffner MD, Scott D. Solomon MD, Nish Chaturvedi MD, Frederik Persson MD, Akshay S. Desai MD MPH, Maria Nicolaides MD, Alexia Richard MSc, Zhihua Xiang PhD, Patrick Brunel MD, and Marc A Pfeffer MD PhD for the ALTITUDE Investigators

Primary composite end point:
CV Death, Resuscitated Cardiac Arrest, Non-fatal MI, Nonfatal stroke, HF hospitalization, ESRD, Renal Death, Need for RRT, Doubling of Creatinine

Compared to placebo
Aliskiren reduced

SBP/DBP = 1.3/0.6 mmHg

albuminuria = 14%
(95%CI 11-17%)



CONCLUSIONS:

The addition of aliskiren to standard therapy with renin-angiotensin system blockade in patients with type 2 diabetes who are at high risk for cardiovascular and renal events is not supported by these data and may even be harmful.

2012

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

Hans Henrik Parving MD DM Sc, Barry M. Brenner MD PhD, John JV McMurray MD, Dick de Zeeuw MD PhD, Steven M Haffner MD, Scott D. Solomon MD, Nish Chaturvedi MD, Frederik Persson MD, Akshay S. Desai MD MPH, Maria Nicolaides MD, Alexia Richard MSc, Zhihua Xiang PhD, Patrick Brunel MD, and Marc A Pfeffer MD PhD for the ALTITUDE Investigators

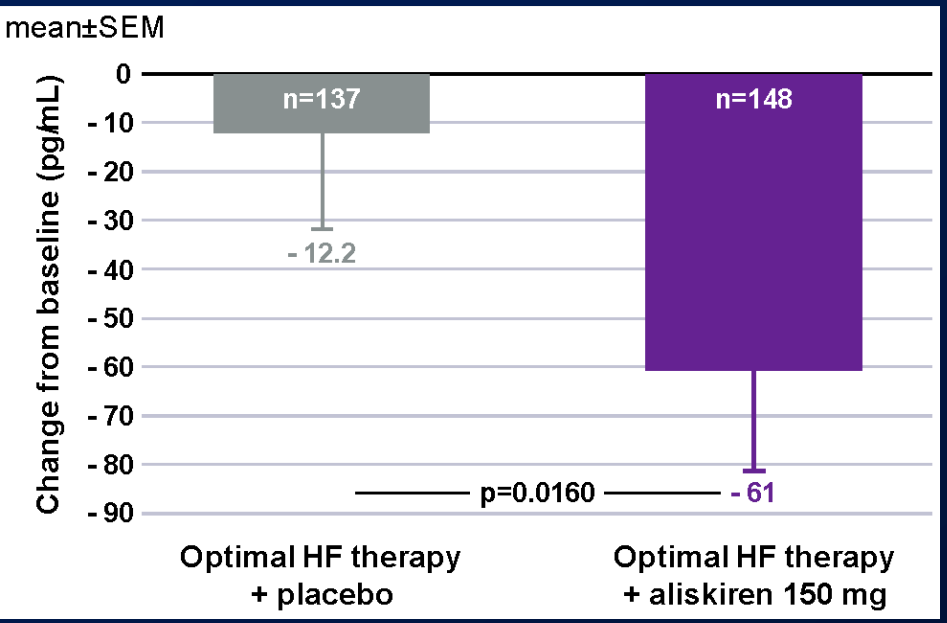
Adverse events and Study – Drug Discontinuation

Event	Any Event Reported		P Value	Event Leading to Permanent Study-Drug Discontinuation		P Value
	Aliskiren (N=4272)	Placebo (N=4285)		Aliskiren (N=4272)	Placebo (N=4285)	
	no. of patients (%)			*no. of patients (%)*		
Hyperkalemia	1670 (39.1)	1244 (29.0)	<0.001	205 (4.8)	111 (2.6)	<0.001
Peripheral edema	686 (16.1)	706 (16.5)	0.60	11 (0.3)	7 (0.2)	0.34
Hypotension	519 (12.1)	357 (8.3)	<0.001	28 (0.7)	13 (0.3)	0.02
Diarrhea	417 (9.8)	312 (7.3)	<0.001	11 (0.3)	7 (0.2)	0.34
Hypertension	429 (10.0)	469 (10.9)	0.17	3 (0.1)	9 (0.2)	0.15
Renal impairment	418 (9.8)	371 (8.7)	0.07	65 (1.5)	54 (1.3)	0.30

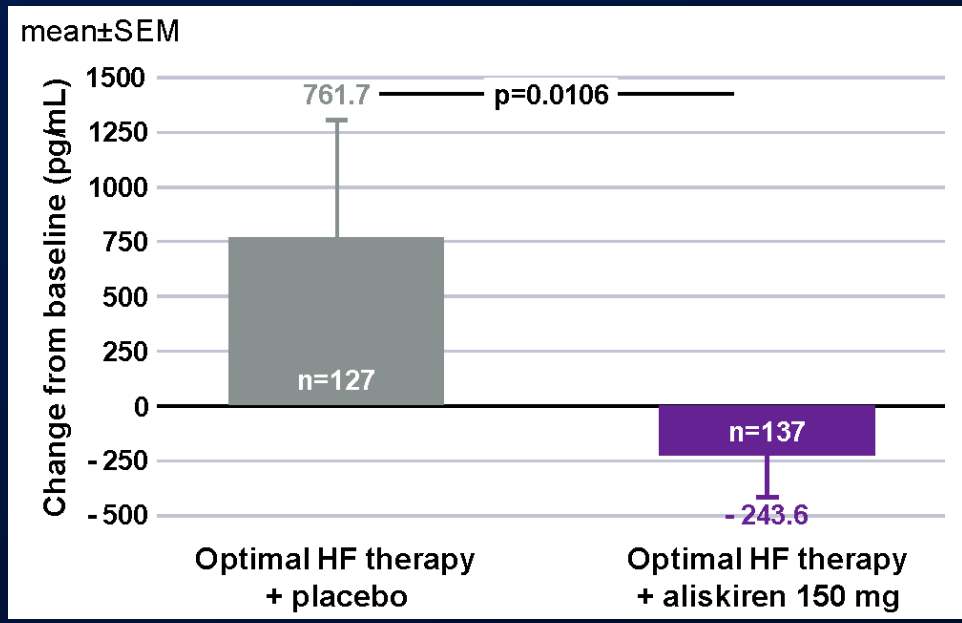
Effects of the Oral Direct Renin Inhibitor Aliskiren in Patients With Symptomatic Heart Failure

John J.V. McMurray, MD; Bertram Pitt, MD; Roberto Latini, MD; Aldo P. Maggioni, MD; Scott D. Solomon, MD; Deborah L. Keefe, MD; Jessica Ford, MSc; Anil Verma, MD; Jim Lewsey, PhD; for the Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators

BNP



NTpro-BNP



Circ Heart Fail 2008;1:17-24

ASTRONAUT

Acute Heart Failure

Population

1639 Patients randomized within 2 days of admission for an acute heart failure hospitalization (SBP > 110 mm Hg)

- **BNP $\geq$ 400 pg/ml**
- **LVEF $\leq$ 40%**

Endpoints

Primary: CV death, rehospitalization for HF in 6 months

Treatment arms

Aliskiren vs. placebo (on top of standard therapy)

Presentation at

ATMOSPHERE

Chronic Heart Failure

Population

6573 Patients with low ejection fraction heart failure

- **NYHA class II – IV, LVEF ≤ 35%**
- **BNP ≥ 150 pg/ml or ≥ 100 pg/ml with HF hospitalization**

Endpoints

Primary: CV death or heart failure hospitalization

Secondary: QoL / BNP / other CV / renal endpoints

Treatment arms

Enalapril vs aliskiren vs enalapril/aliskiren combo (on top of usual care – excluding ACEI)

APOLLO High Risk Elderly

Population

~ 12500 Patients; SBP 130-159 mmHg

≥ 65 yrs with CVD or addl. risk factor(s)

or ≥ 70 y/o with or without other CV risks

Endpoints

Primary: CV death, non-fatal MI, non-fatal stroke, CHF hospitalization

Secondary: cognitive function ("successful aging"), renal dysfunction

Treatment arms

2x2 factorial (baseline HCTZ or amlo therapy): Plus Aliskiren or Placebo

Discontinued by sponsor Jan 2013

Combination of renin angiotensin inhibitors: VALIANT

Presented at AHA 2003; NEJM 2003

In patients with MI complicated by heart failure, left ventricular dysfunction or both:

- **Valsartan is as effective as a proven dose of captopril in reducing the risk of:**
  - —Death
  - —CV death or nonfatal MI or heart failure admission
- **Combining valsartan with a proven dose of captopril produced no further reduction in mortality—and more adverse drug events.**

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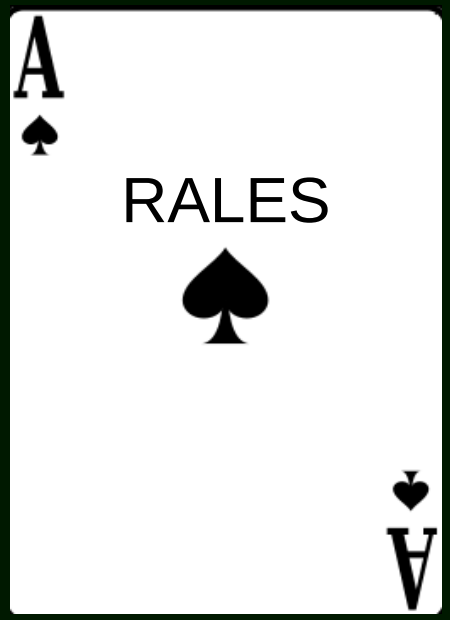
- **Combining valsartan with a proven dose of captopril produced no further reduction in mortality—and more adverse drug events.**

Historical perspective: what if ARBs and/or direct renin inhibitors came before ACEI?

Biomarkers & Surrogates ≠ CV Outcomes

- Ventricular arrhythmias post MI
- LV ejection fraction in HF
- Plasma NE in HF
- Hemoglobin in CKD
- Endothelial function with HRT
- HbA1C in diabetes
- HDL
- Blood pressure
- Proteinuria

The 4th Ace?



TOPCAT ? American Heart Association® 2013