Advances in Cardiac Arrhythmias and Great Innovations in Cardiology

Direct renin inhibition in patients with heart failure: is it the missing piece of the puzzle?

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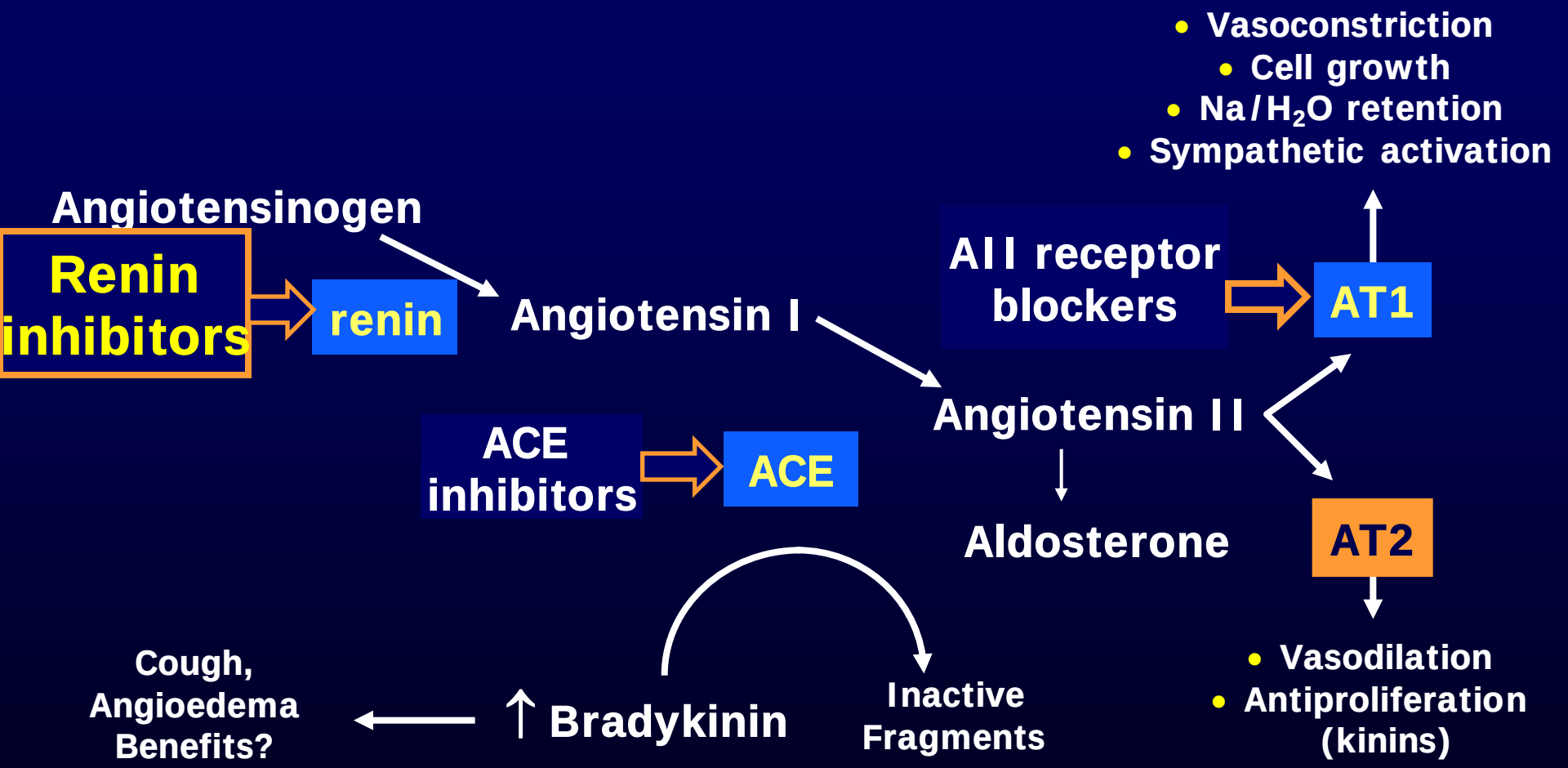
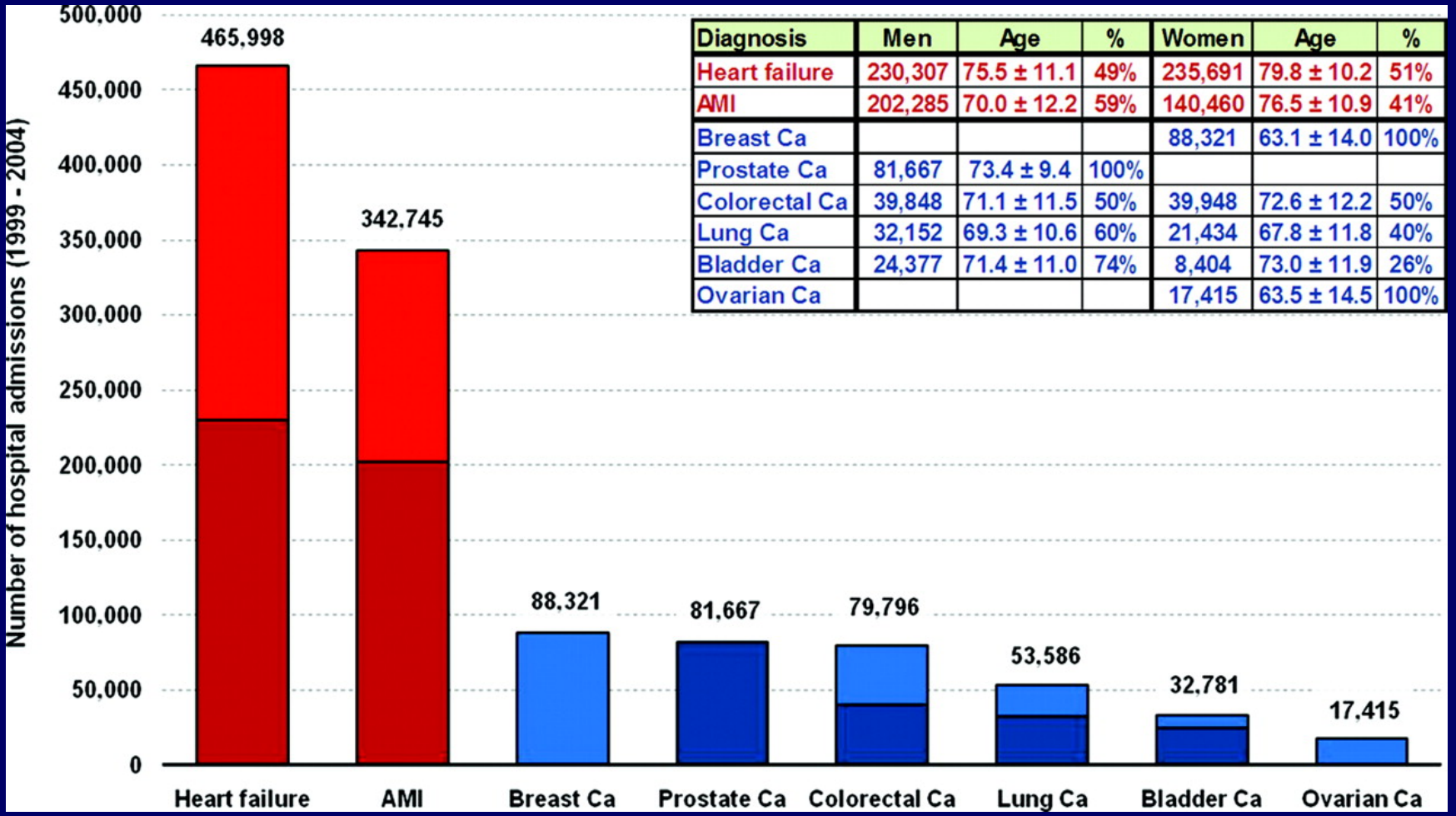
Pharmacologic modulation of the Renin-Angiotensin System



Advantages of direct renin inhibition

- Rate limiting step for angiotensin biosynthesis
- Suppression of the synthesis of both angiotensin II and its other active fragments
- Unmet needs
  - Hypertension: better BP control
  - Heart failure: better prognosis

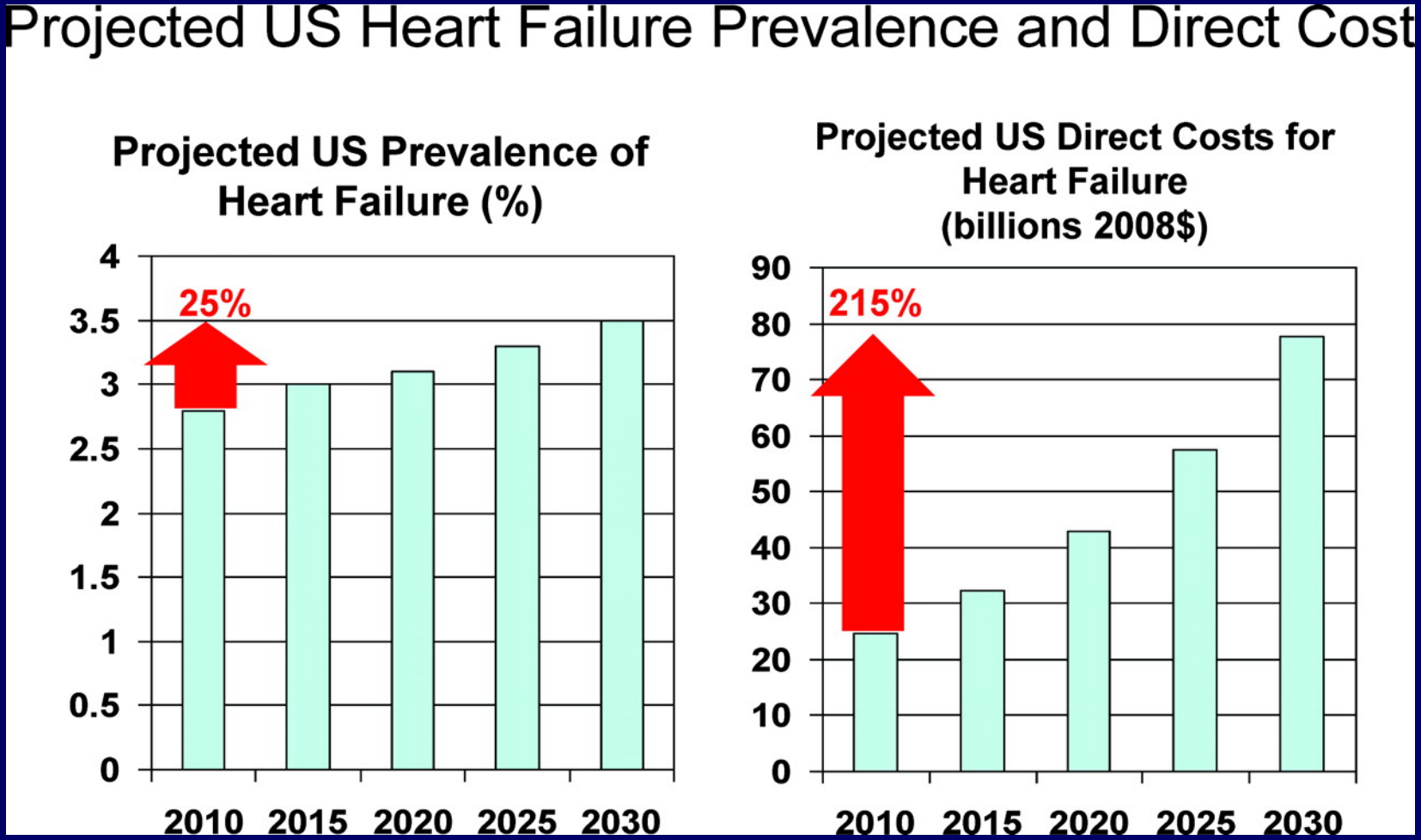
Distribution of 1,162,309 hospital admissions associated with a first-time diagnosis of HF, AMI, and common forms of cancer in Sweden during 1988 to 2004.



Diagnosis	Men	Age	%	Women	Age	%
Heart failure	230,307	75.5 ± 11.1	49%	235,691	79.8 ± 10.2	51%
AMI	202,285	70.0 ± 12.2	59%	140,460	76.5 ± 10.9	41%
Breast Ca				88,321	63.1 ± 14.0	100%
Prostate Ca	81,667	73.4 ± 9.4	100%			
Colorectal Ca	39,848	71.1 ± 11.5	50%	39,948	72.6 ± 12.2	50%
Lung Ca	32,152	69.3 ± 10.6	60%	21,434	67.8 ± 11.8	40%
Bladder Ca	24,377	71.4 ± 11.0	74%	8,404	73.0 ± 11.9	26%
Ovarian Ca				17,415	63.5 ± 14.5	100%

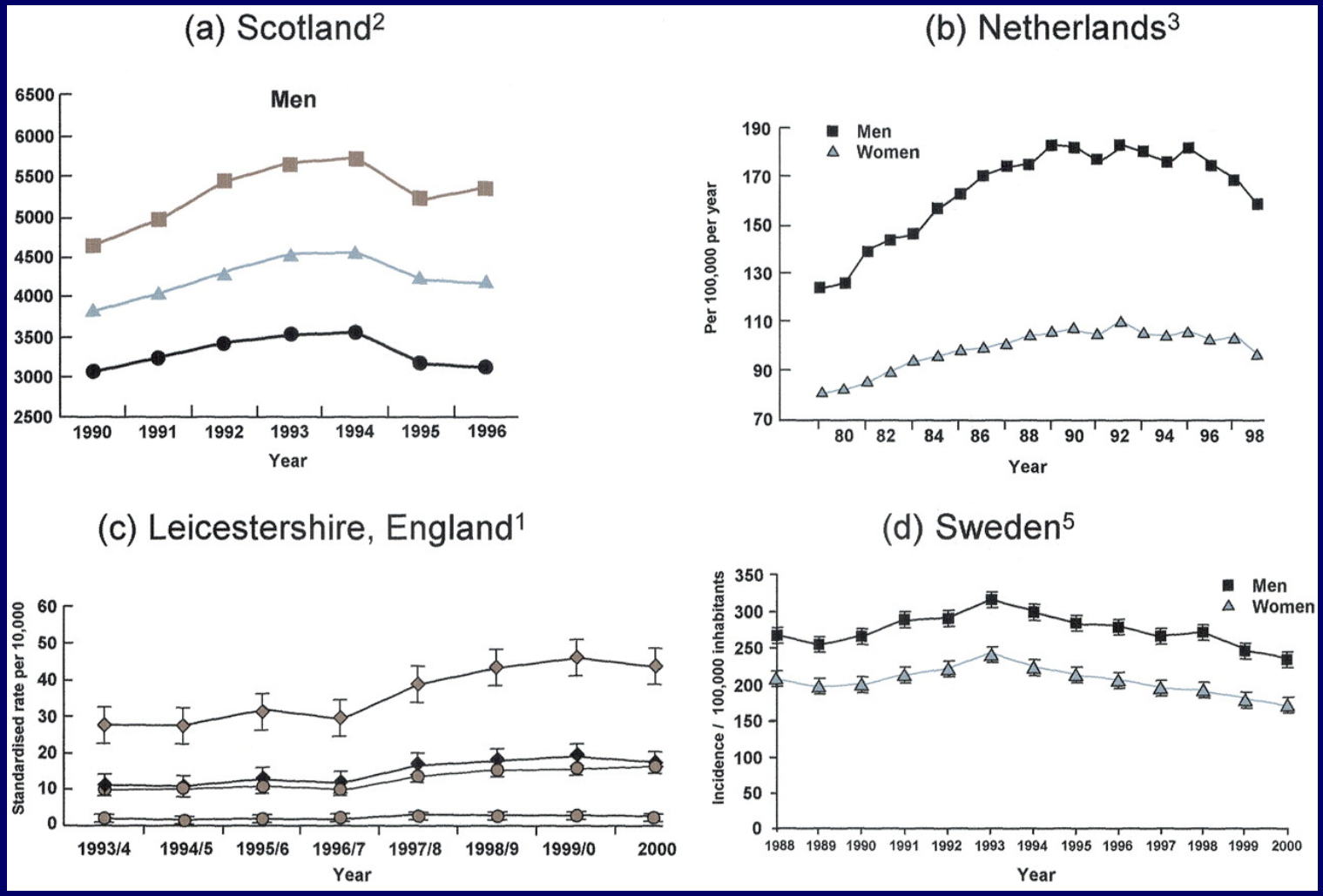
Stewart S et al. Circ Cardiovasc Qual Outcomes 2010;3:573-580

Twenty-year projections for U.S. heart failure prevalence and associated direct medical costs based on current trends.



Konstam M A Circulation 2012;125:820-827

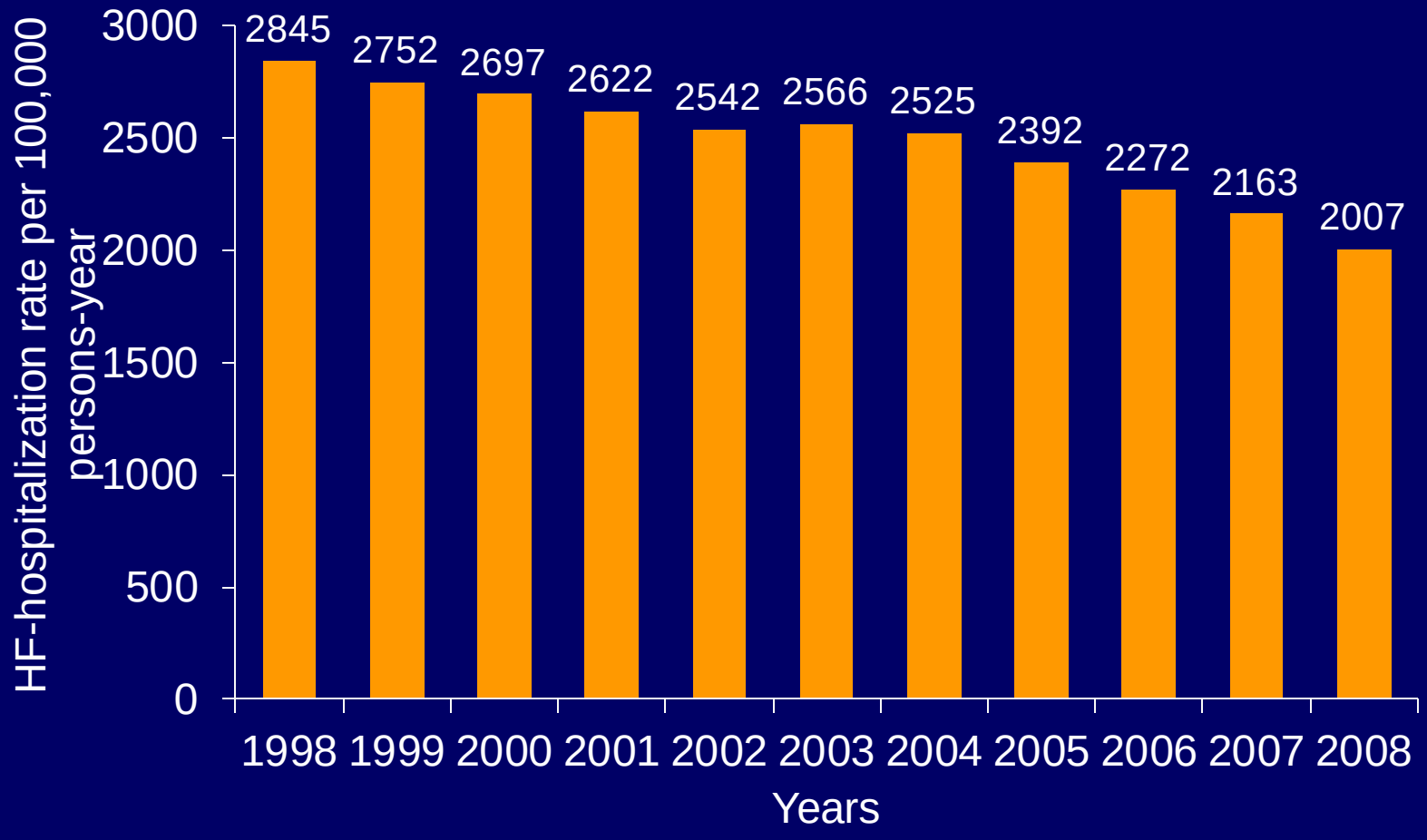
Recent trends in hospital admissions for heart failure demonstrating recent plateau or decline



1Blackledge et al., Heart 2003; 89:615; 2MacIntyre et al., Circulation 2000;102:1126; 3Levy et al., NEJM 2002; 347:1397; 4Scahufelberger et al., EHJ 2004; 25:300; McMurray, J. J.V. et al. J Am Coll Cardiol 2004;44:2398-2405

One-Year Mortality Rates After Heart Failure Hospitalization for Medicare beneficiaries

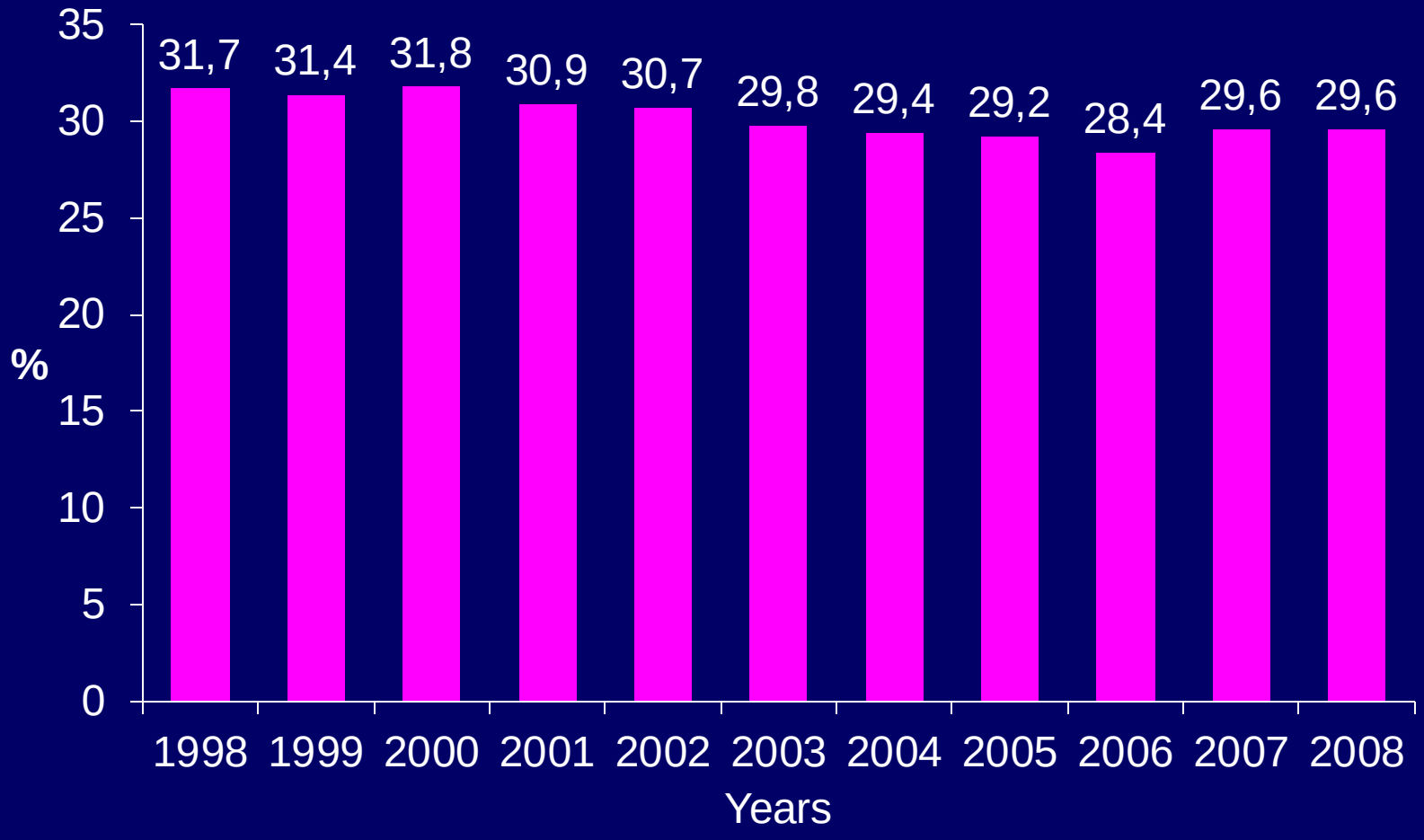
Risk-adjusted hospitalization rates



Chen, J. et al. JAMA 2011;306:1669-1678

One-Year Mortality Rates After Heart Failure Hospitalization for Medicare beneficiaries

Risk-adjusted one-year mortality rates



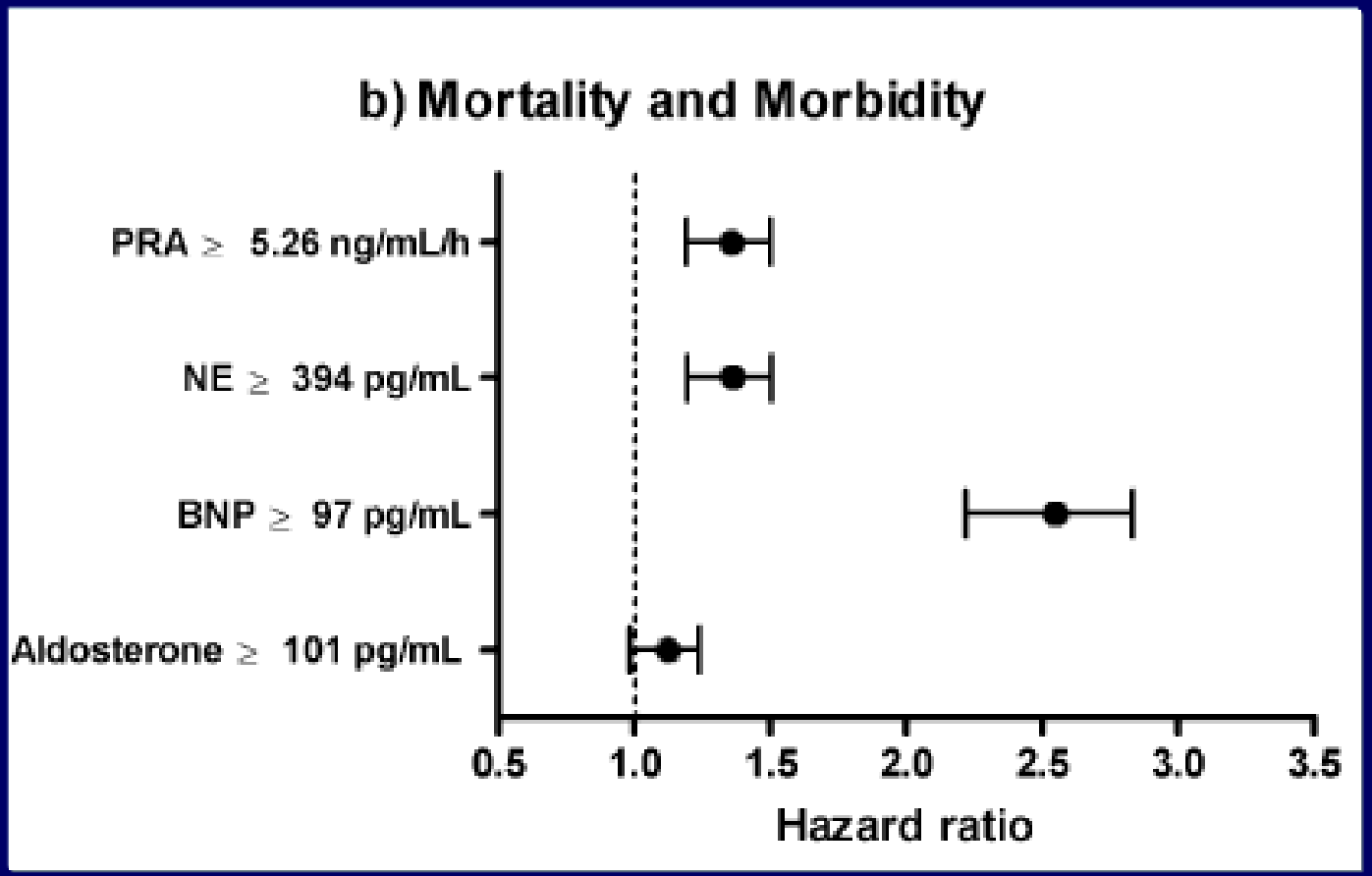
Chen, J. et al. JAMA 2011;306:1669-1678

Current medical treatment of chronic HF: Key evidence (ESC guidelines)

Trial	Drug	Mortality relative risk reduction	Absolute risk reduction	Number needed to treat
2008 Guidelines				
CONSENSUS, 1987	Enalapril	27%	14.6%	7
SOLVD Treatment, 1991	Enalapril	16%	4.5%	22
CIBIS, MERIT-HF, 2001	Bisoprolol metoprolol	34%	4.3%	23
COPERNICUS, 2003	carvedilol	35%	7.1%	14
RALES, 1999	Spironol.	30%	11.4%	9
ValHeFT, 2001	Valsartan	24% HF hosp	3.3%*	30*
CHARM-Added, 2003	Candesartan	16%†	4.4%‡	23‡
CHARM-Alt., 2003	Candesartan	23%‡	7%‡	14‡
Added in 2012 Guidelines				
EMPHASIS	Eplerenone	24%	3%	33
SHIFT	Ivabradine	18%‡	4.2%‡	24‡

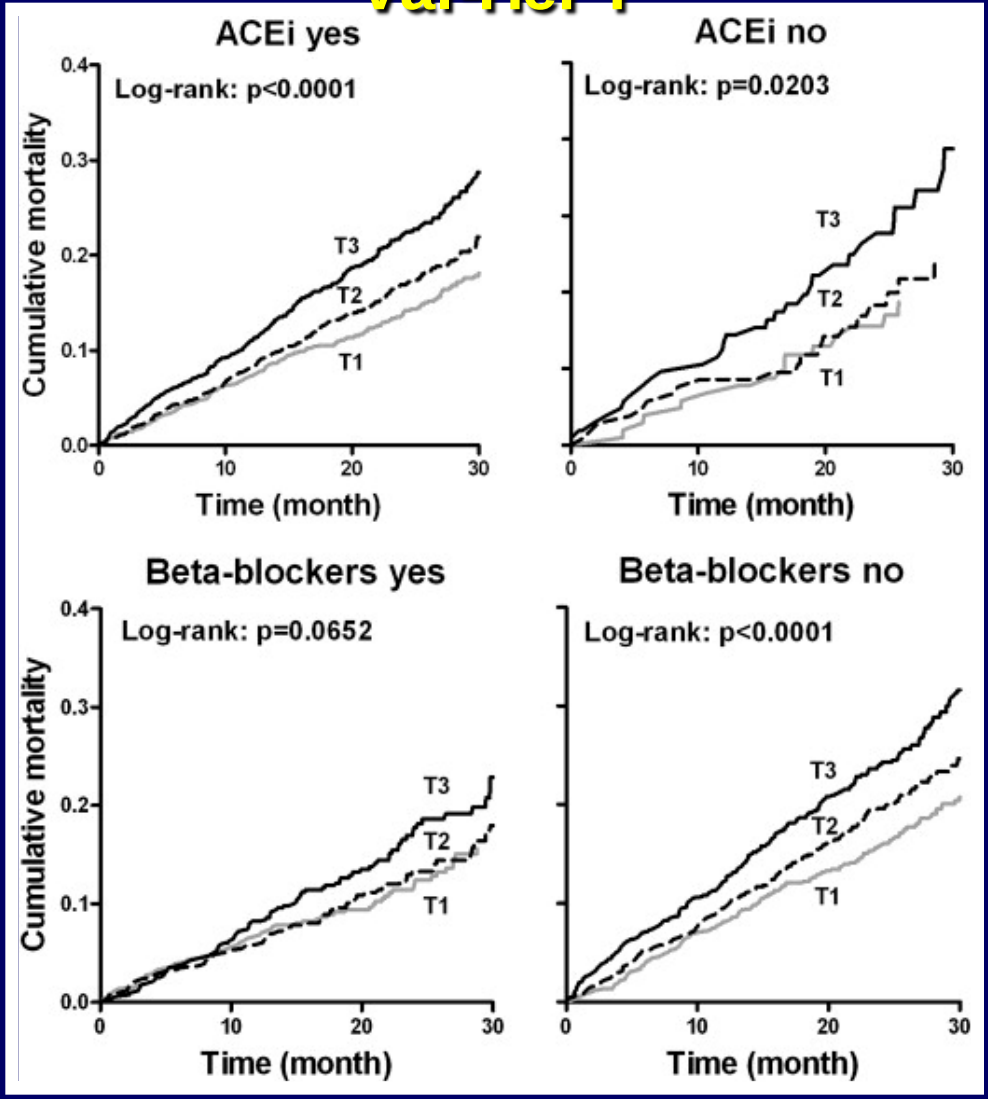
*Death or HF hospitalization; †CV death; ‡CV death or HF hospitalization

Risk of mortality and morbidity according to baseline neurohormones (above versus below the median): VAL-HeFT



Latini et al. Eur J Heart Fail 2004; 25: 292

Elevated plasma renin activity predicts adverse outcome in HF, independently of pharmacologic therapy: data from Val-HeFT



Masson et al.
J Card Fail
2010;16:964-70

European Journal of Heart Failure (2011) **13**, 107–114
doi:10.1093/eurjhf/hfq212

Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) study

Henry Krum[1]*, Barry Massie[2], William T. Abraham[3], Kenneth Dickstein[4,5], Lars Kober[6], John J.V. McMurray[7], Ashkay Desai[8], Claudio Gimpelewicz[9], Albert Kandra[9], Bernard Reimund[9], Henning Rattunde[9], and Juergen Armbrecht[9], on behalf of the ATMOSPHERE Investigators

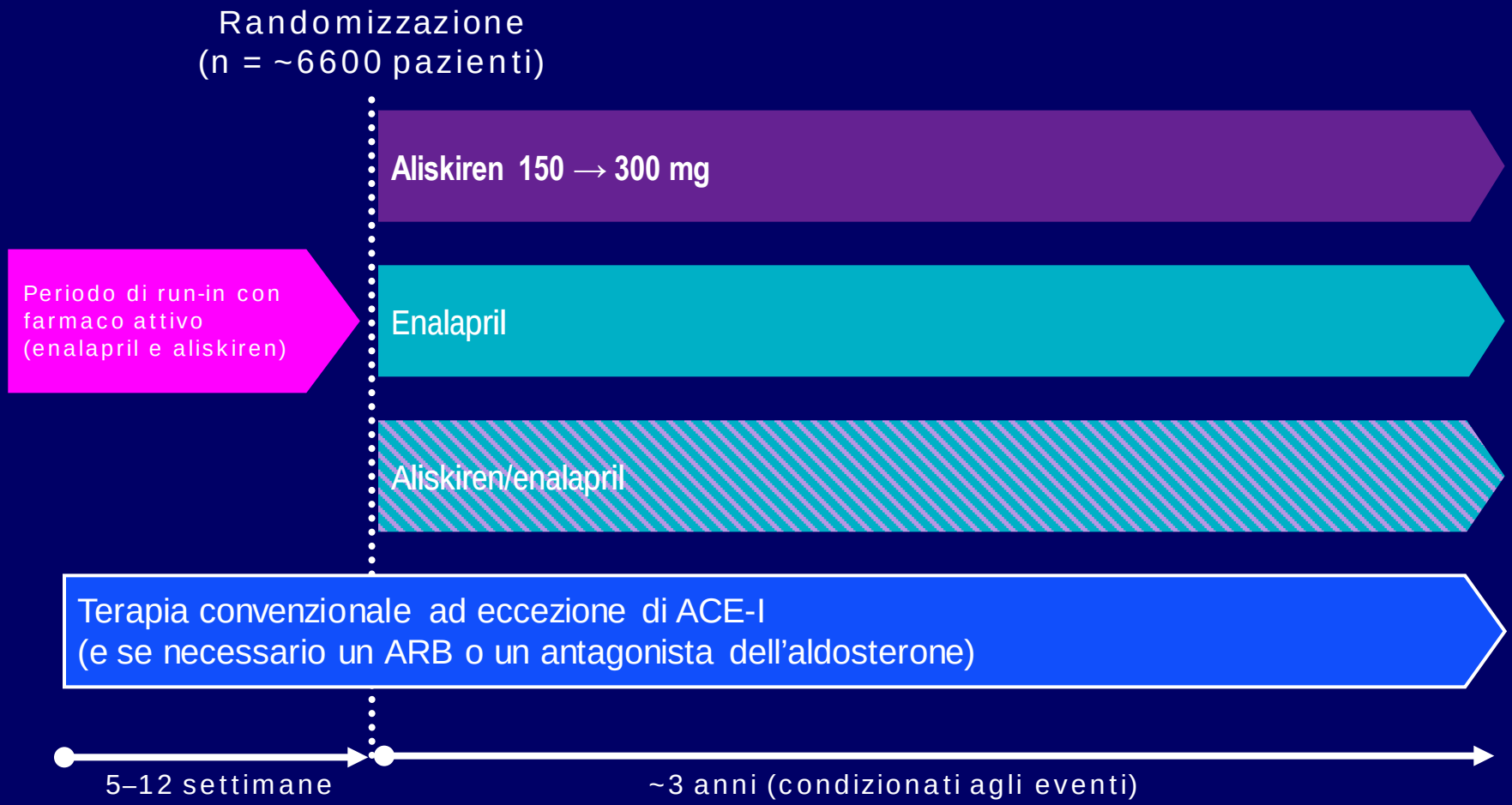
European Journal of Heart Failure (2011) **13**, 100–106
doi:10.1093/eurjhf/hfq209

Rationale and design of the multicentre, randomized, double-blind, placebo-controlled Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT)

Mihai Gheorghiade[1]*, Mazen Albaghdadi[1], Faiez Zannad[2], Gregg C. Fonarow[3], Michael Böhm[4], Claudio Gimpelewicz[5], Jaco Botha[5], Shelley Moores[5], Eldrin F. Lewis[6], Henning Rattunde[5], and Aldo Maggioni[7] on behalf of the ASTRONAUT investigators and study coordinators

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

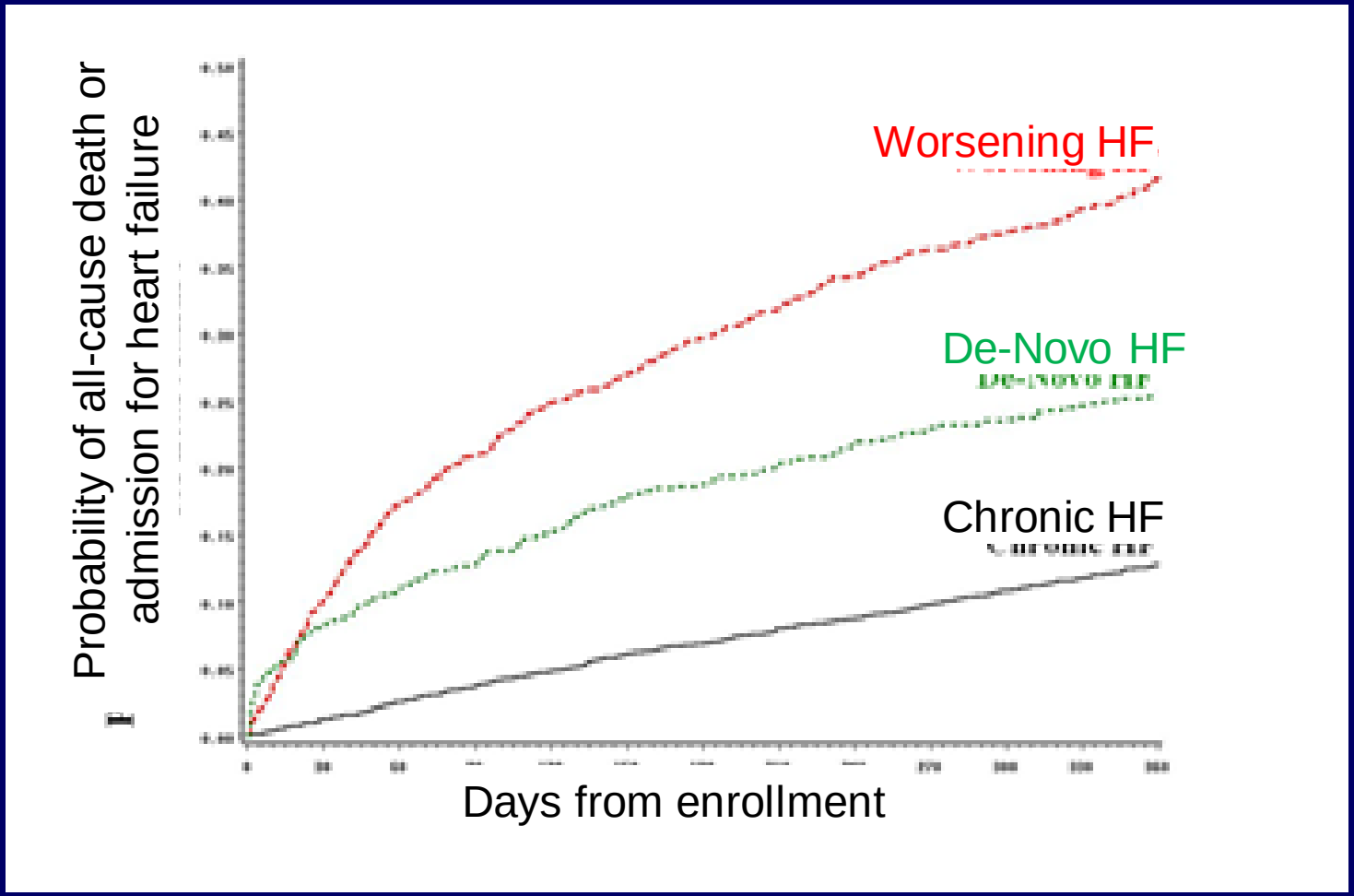
Disegno dello studio



ATMOSPHERE inizierà nel 1° trimestre del 2009

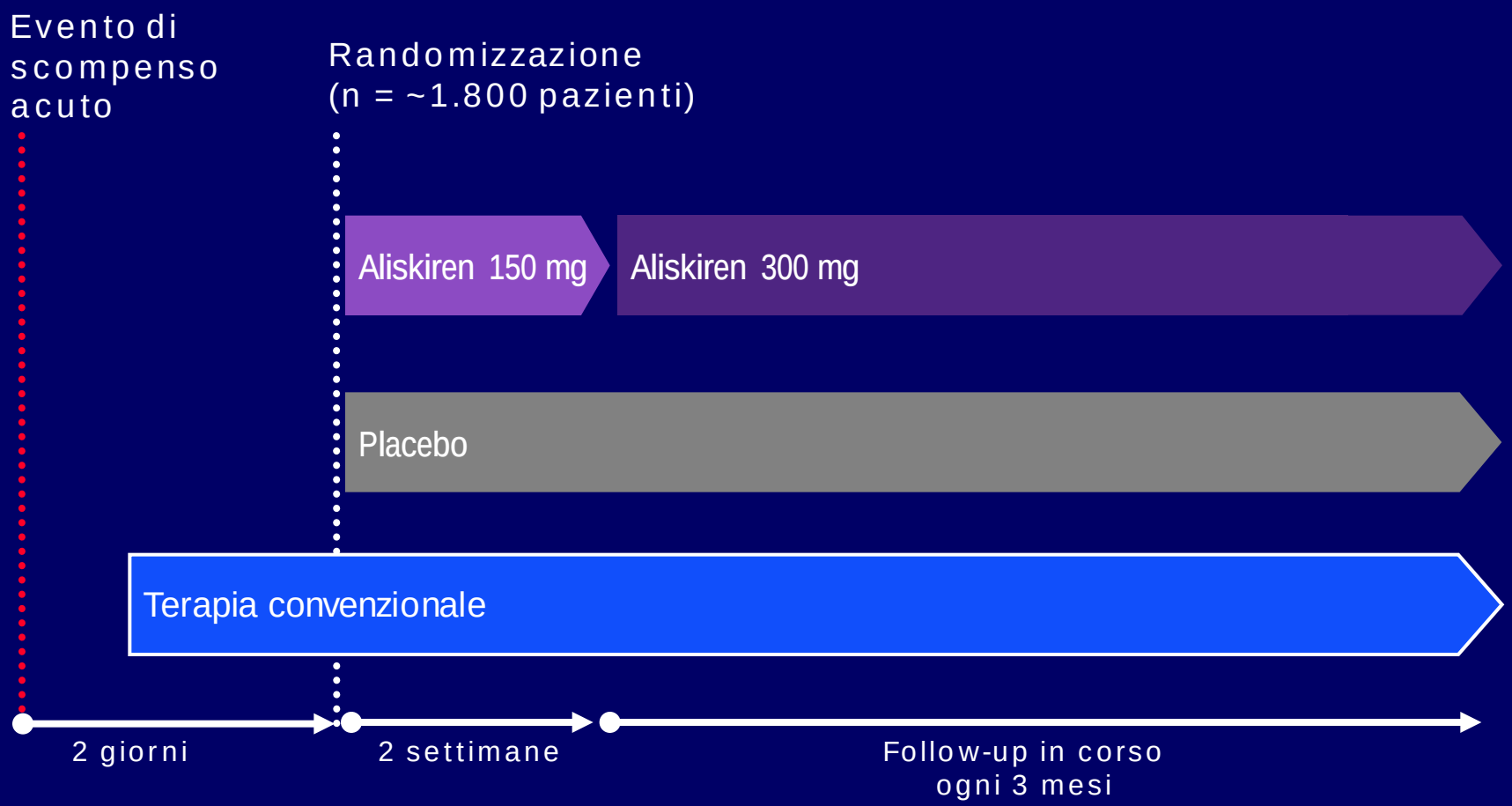
Dati disponibili in archivio, Novartis 2008

Mortality and HF hospitalizations in worsening HF, new onset HF and chronic HF: IN-HF Outcome registry (n=5610 patients)



Courtesy of L. Tavazzi and A. Maggioni

Disegno dello studio



ASTRONAUT inizierà nel 1° trimestre del 2009

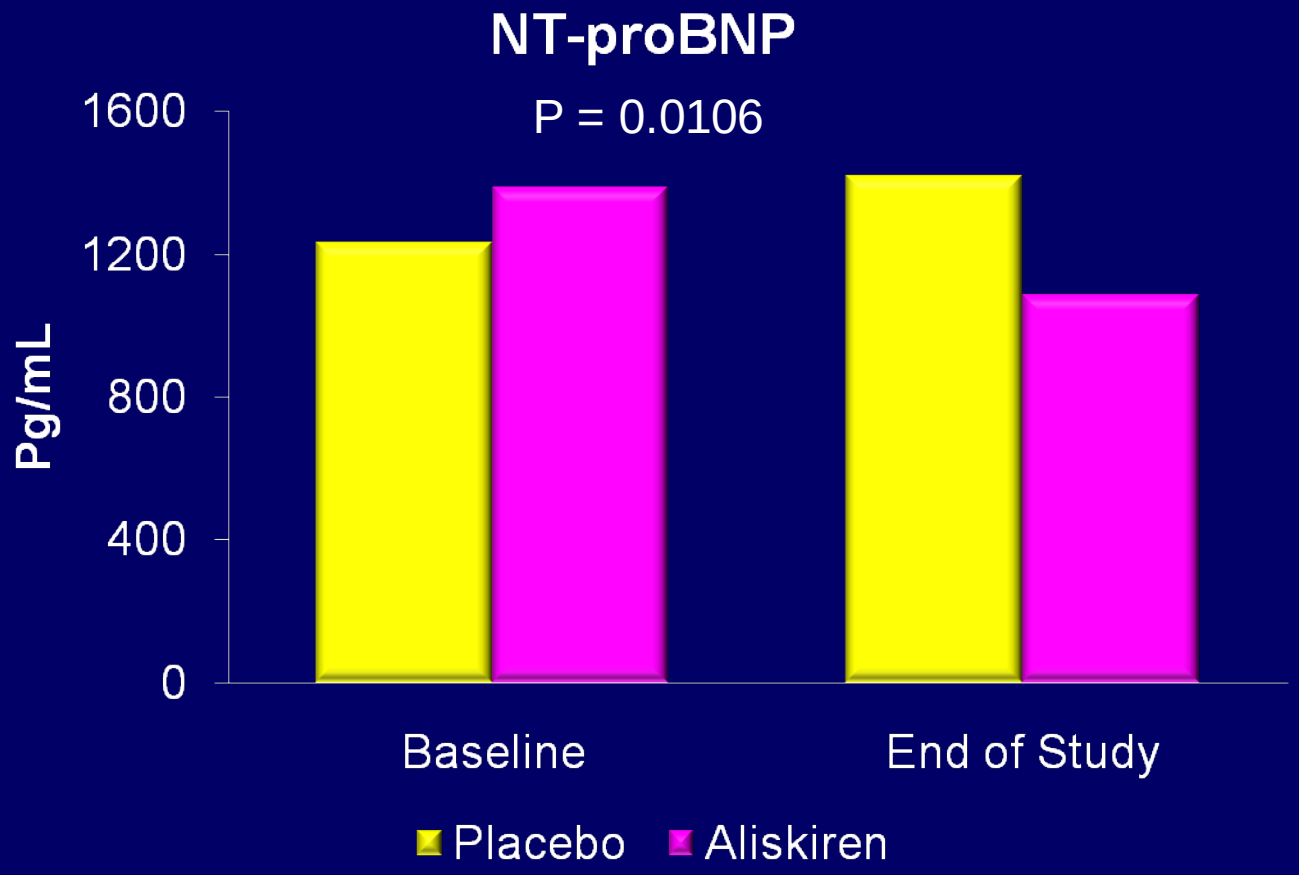
Dati disponibili in archivio, Novartis 2008

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

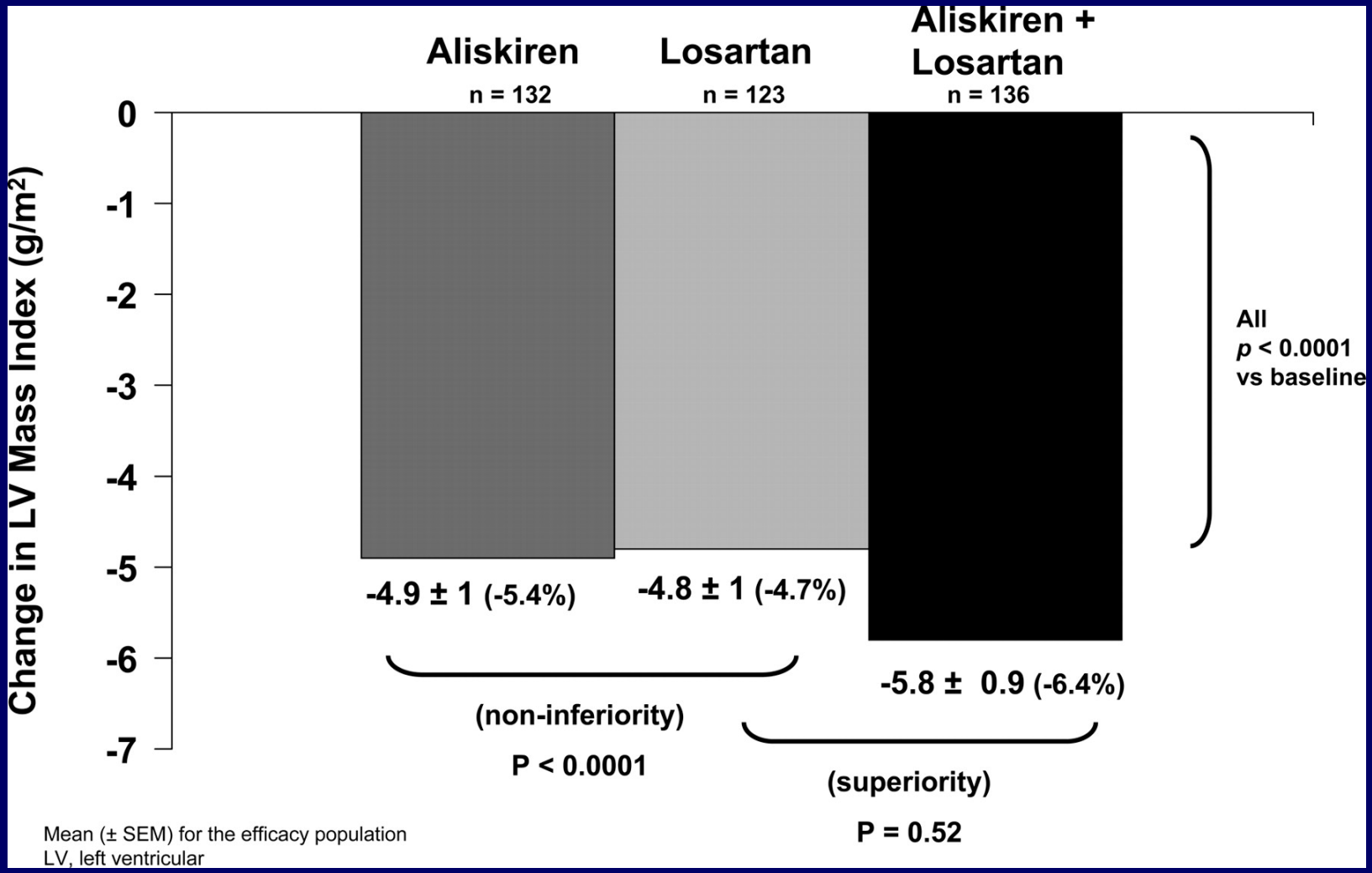
(*Circ Heart Fail.* 2008;1:17-24.)

Effects of the Oral Direct Renin Inhibitor Aliskiren in 202 Patients With Symptomatic Heart Failure (ALOFT)



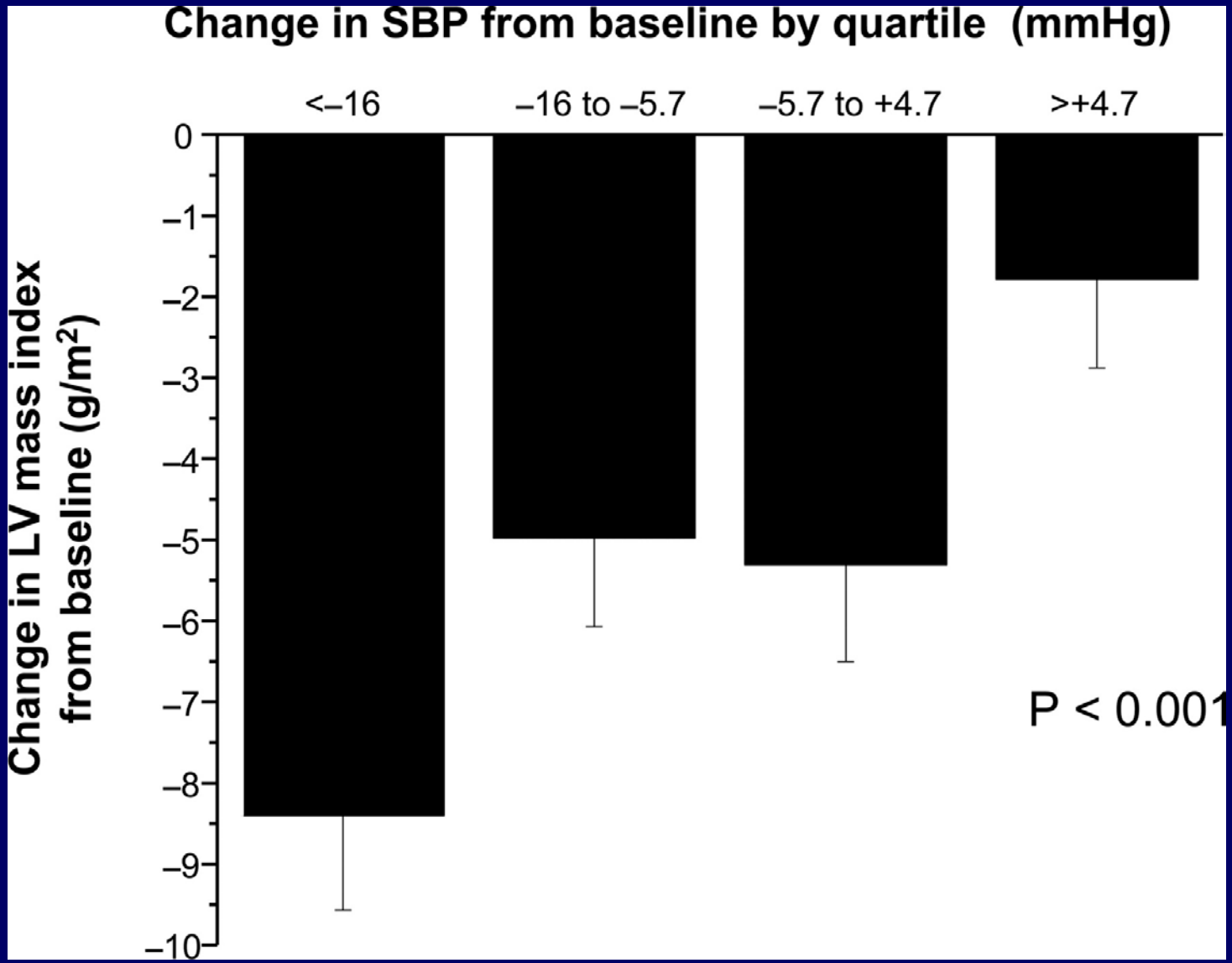
McMurray et al. Circ Heart Fail 2008; 1:74

Effect of the Direct Renin Inhibitor Aliskiren, the ARB Losartan, or Both on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy



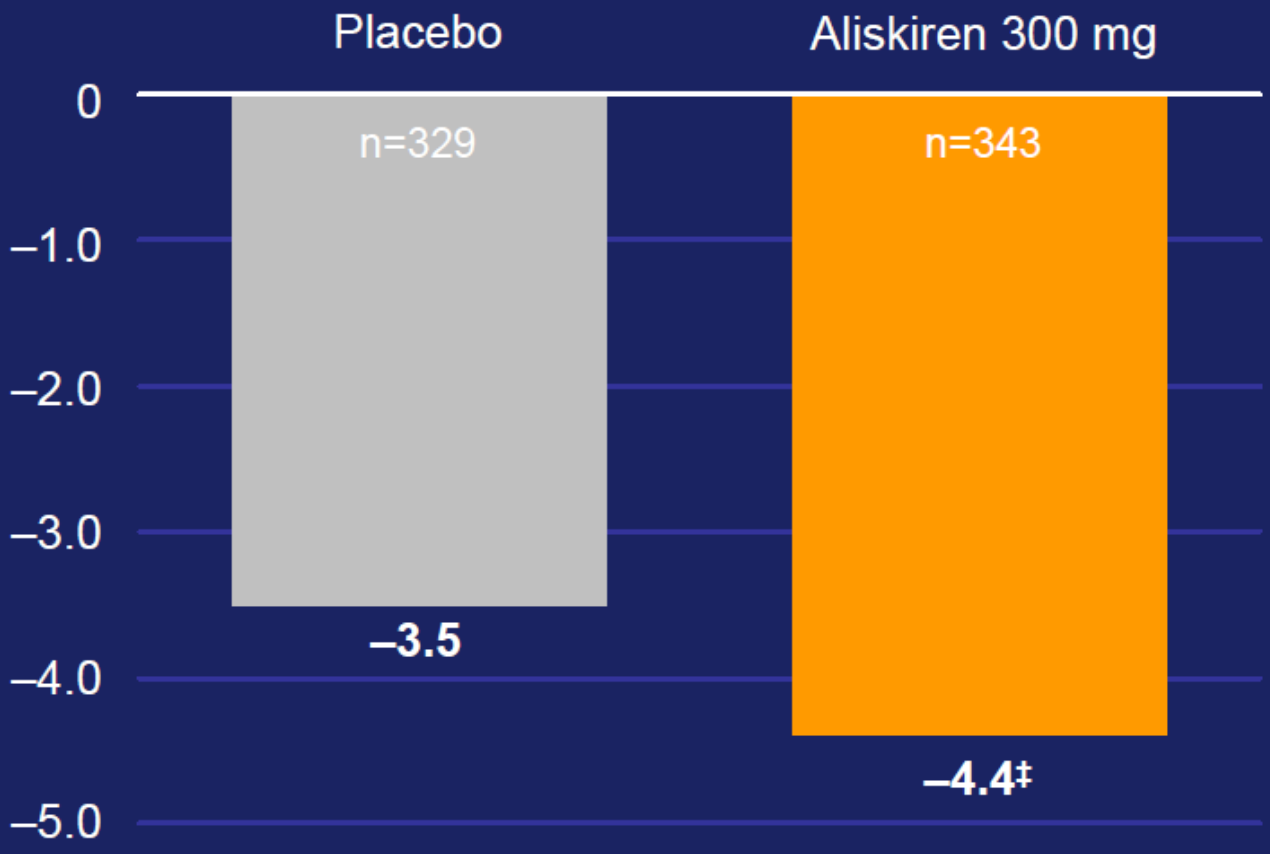
Solomon, S. D. et al. Circulation 2009;119:530-537

SBP reduction is the main determinant of changes in LV mass. Relationship between change in systolic BP (SBP) and change in LVM



Solomon, S. D. et al. Circulation 2009;119:530-537

Aliskiren provided numerically, but not significantly, greater reductions in LVESV from baseline compared with placebo



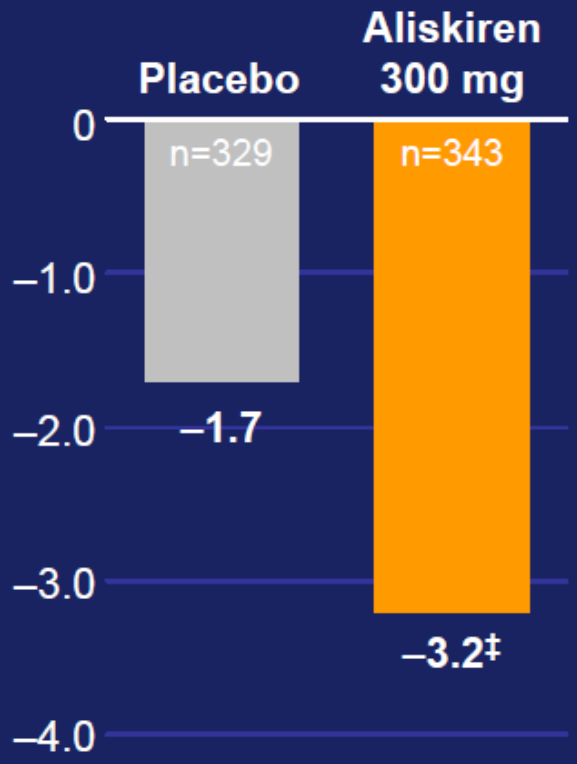
‡p = non-significant vs placebo

Baseline LVESV values: placebo = 84.2 mL, aliskiren = 82.5 mL.

Data on file, Novartis Pharma AG 2010

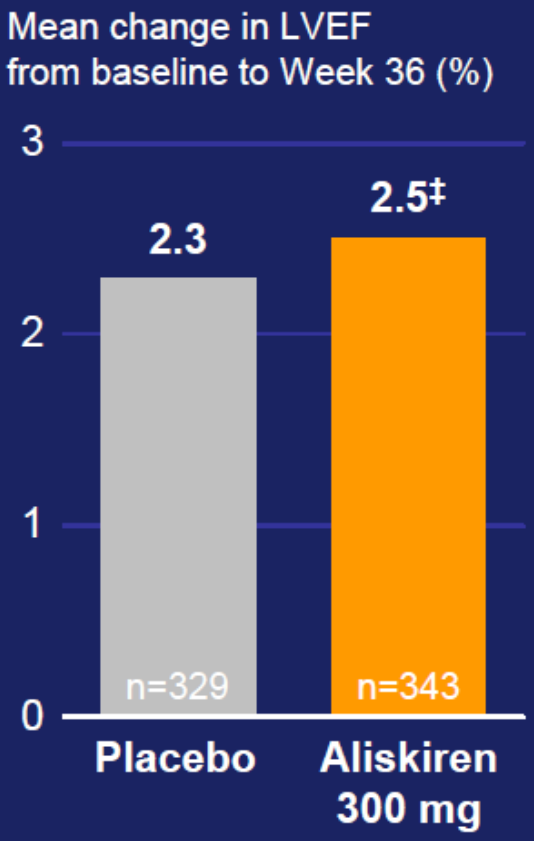
Aliskiren provided numerically, but not significantly, greater improvements in echocardiographic measures of LV dysfunction compared with placebo

LVEDV

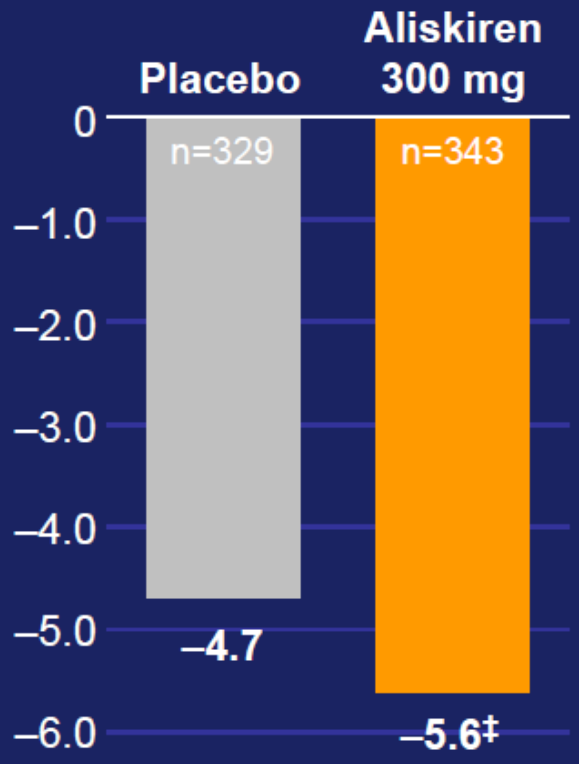


Mean change in LVEDV from baseline to Week 36 (mL)

LVEF



Infarct length



Mean change in infarct length from baseline to Week 36 (% of total perimeter)

‡p = non-significant vs placebo

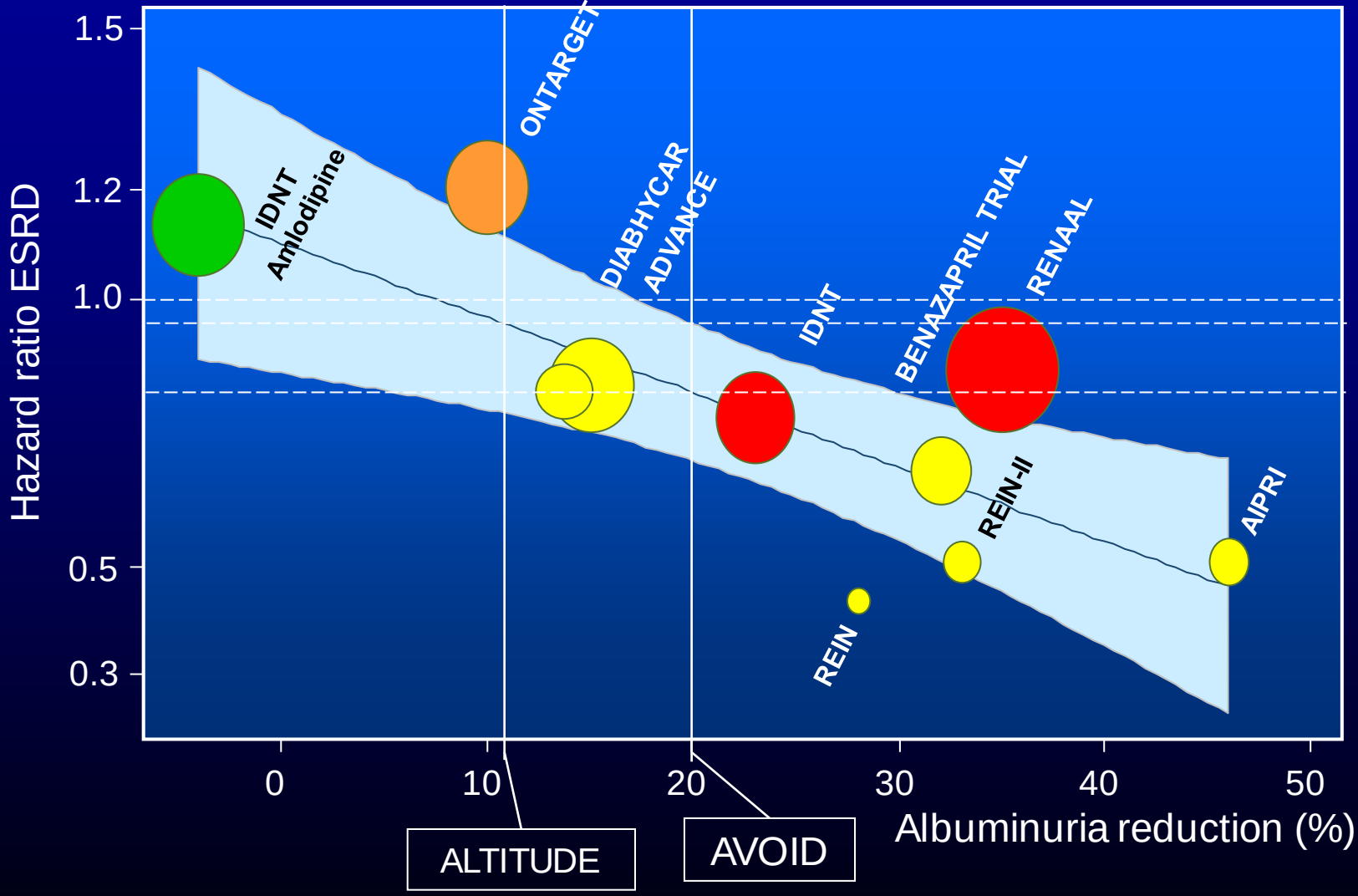
LVEDV: study population baseline = ~132.4 mL; LVEF: study population baseline = ~37.8%

Infarct length: study population baseline values = ~24.8%

Data on file, Novartis Pharma AG 2010

Relationship between short-term decrease in albuminuria and long term **renal** risk reduction

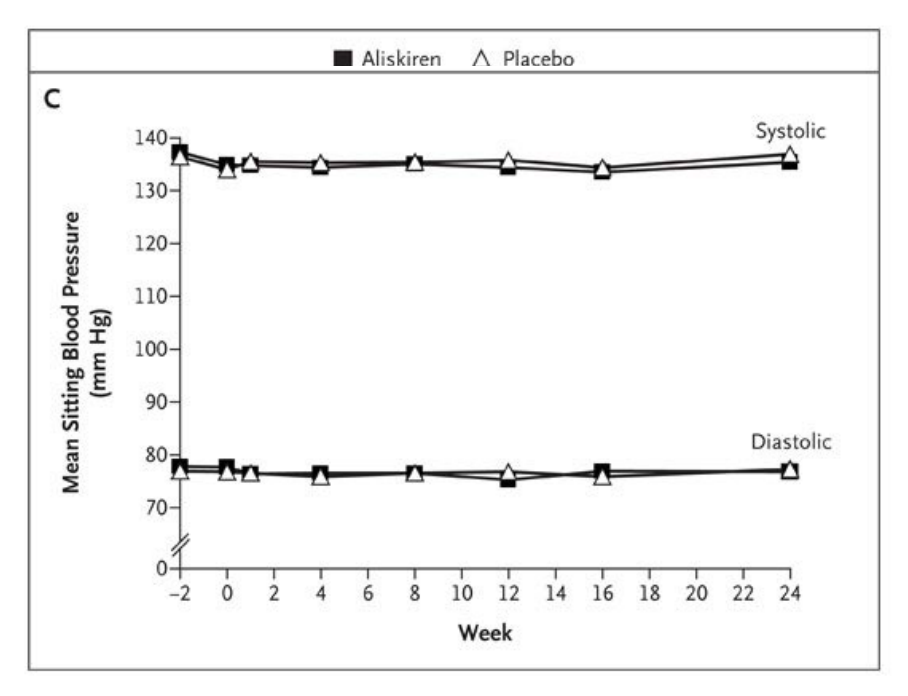
different randomized clinical trials in different populations



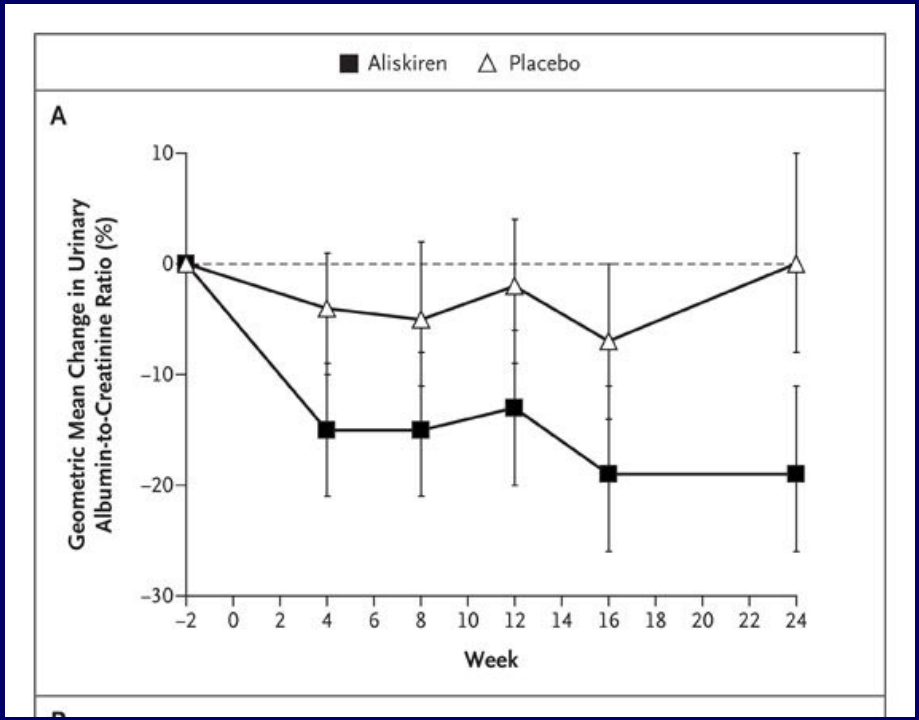
Lambers Heerspink / De Zeeuw Nephron. Clin Prac 2010

Renoprotective effects of Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy: Changes in BP and the Urinary Albumin-to-Creatinine Ratio

Blood pressure

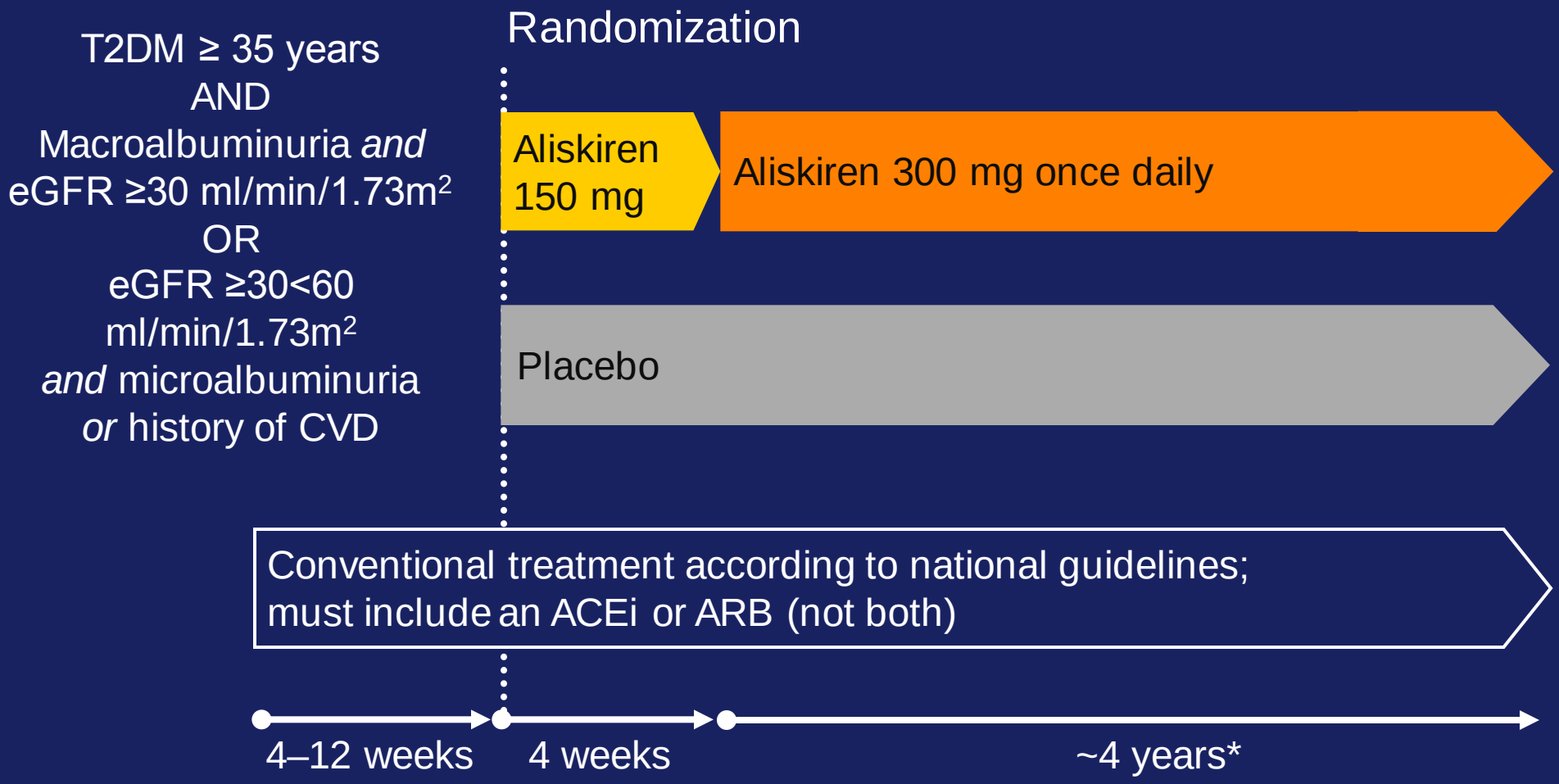


Urinary albumin/ creatinine ratio



Parving HH et al. N Engl J Med 2008;358:2433-2446

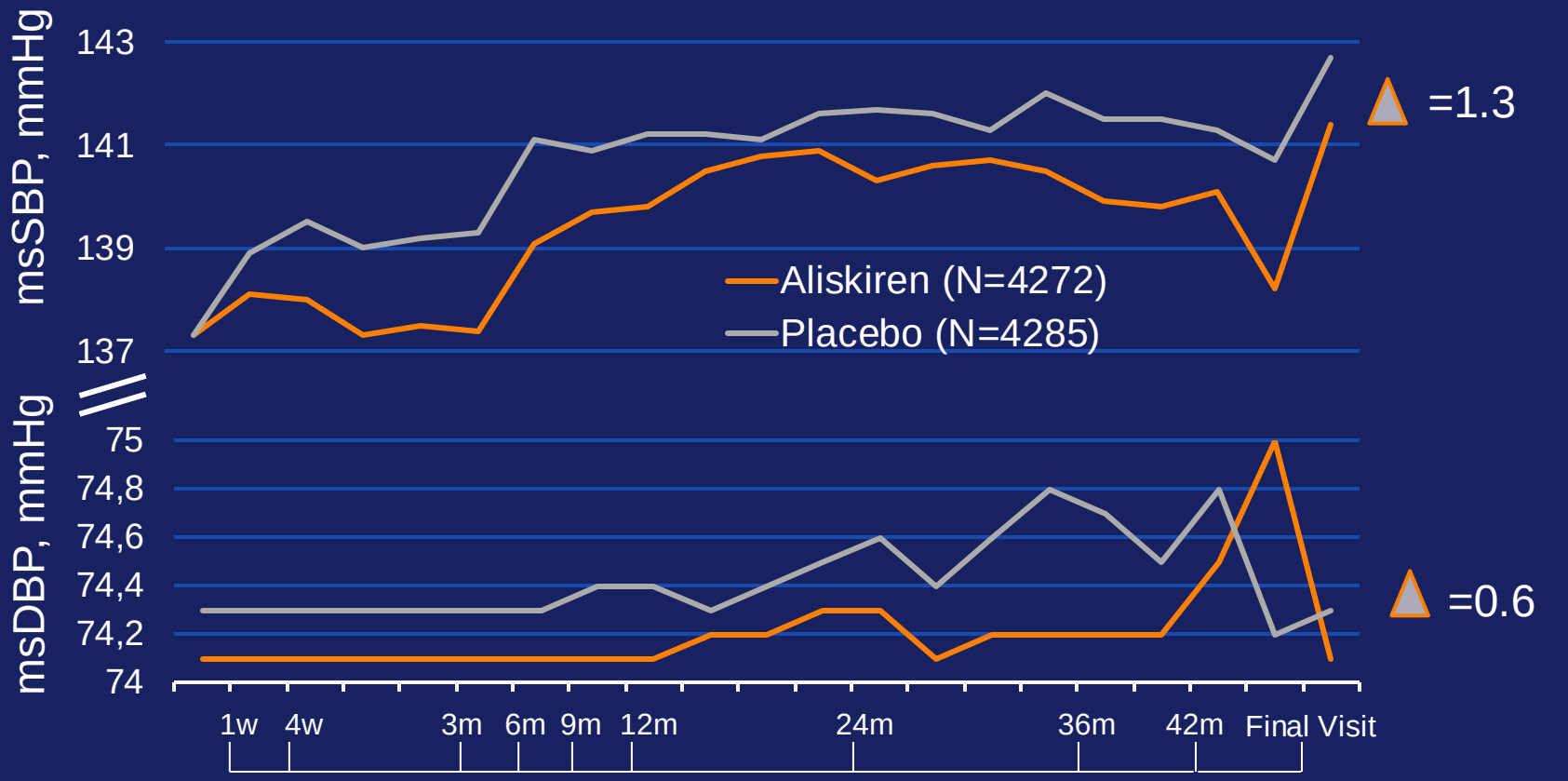
ALTITUDE design overview



*ALTITUDE was an event driven study and was planned to conclude when ~1620 patients met the primary endpoint
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

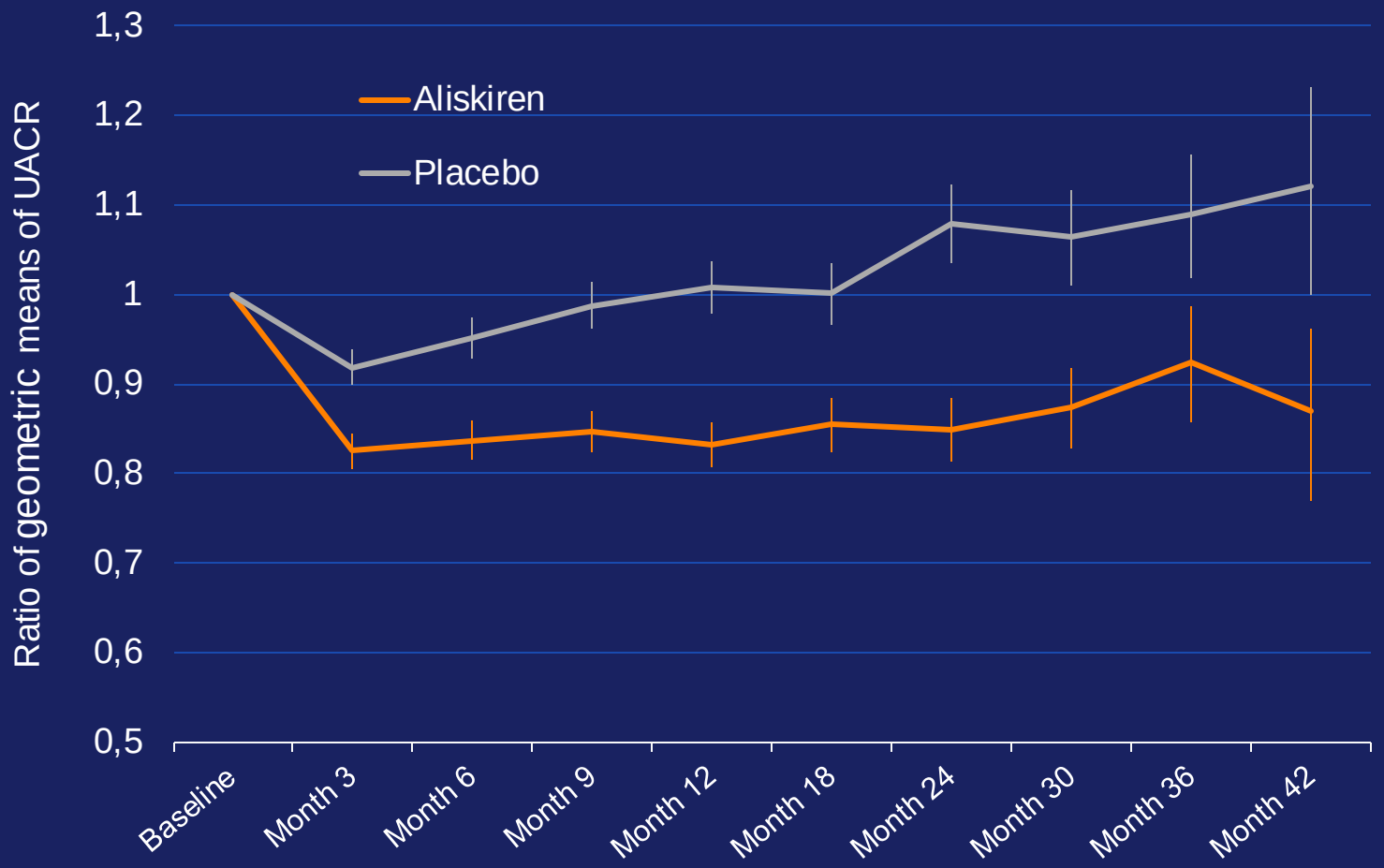
Parving H-H, et al
Nephrol Dial Transplant 2009;24:1663–1671

ALTITUDE blood pressure course during the trial



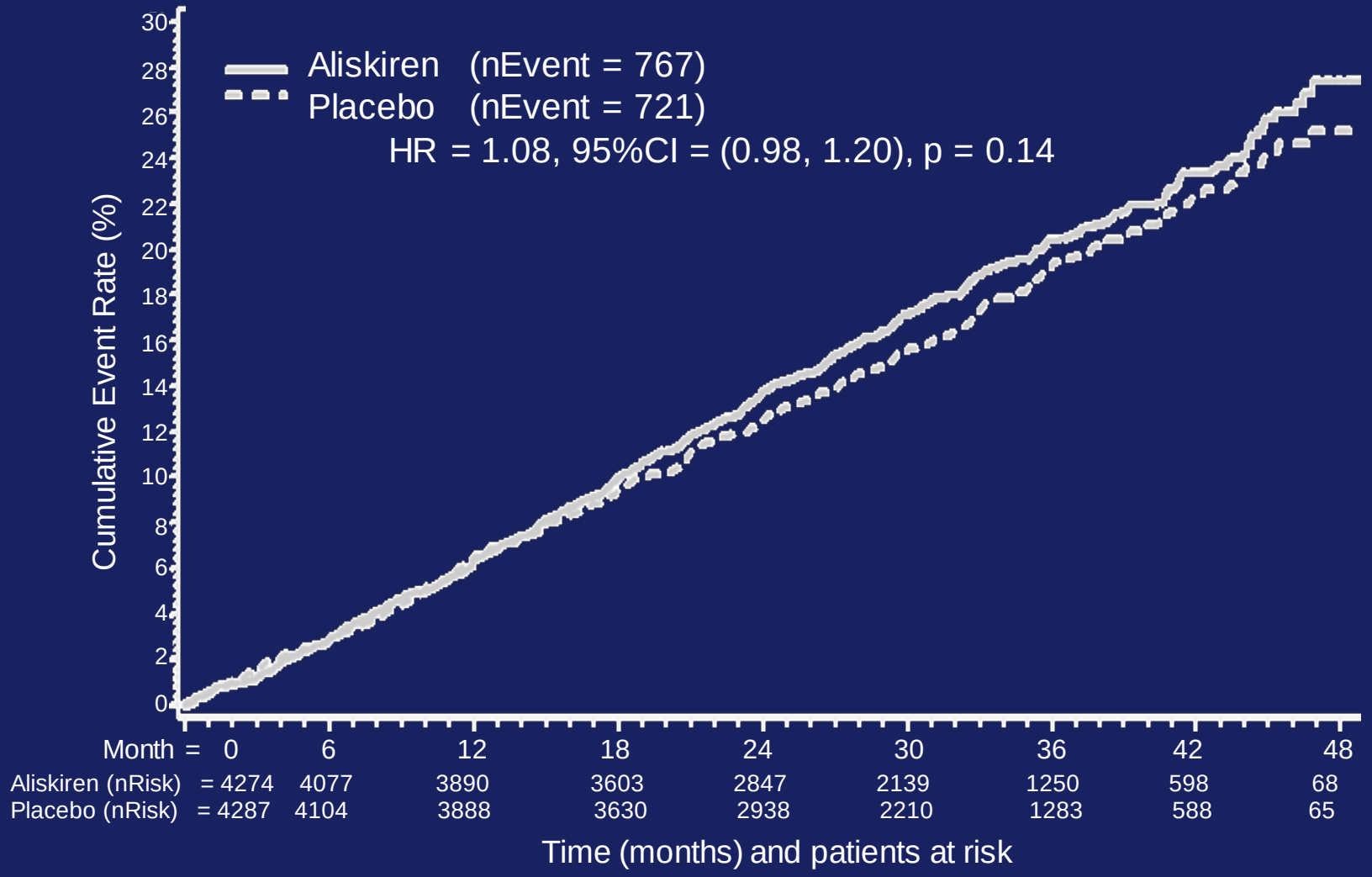
msSBP, mean sitting systolic blood pressure; msDBP, mean sitting diastolic blood pressure

ALTITUDE Ratio of geometric mean of UACR relative to baseline over time by treatment



Data are shown as change from baseline in geometric mean (95% CI)
UACR, urinary albumin:creatinine ratio

Kaplan-Meier estimate for time to the primary composite end-point



ALTITUDE Hazard ratios for the individual components of the primary endpoint

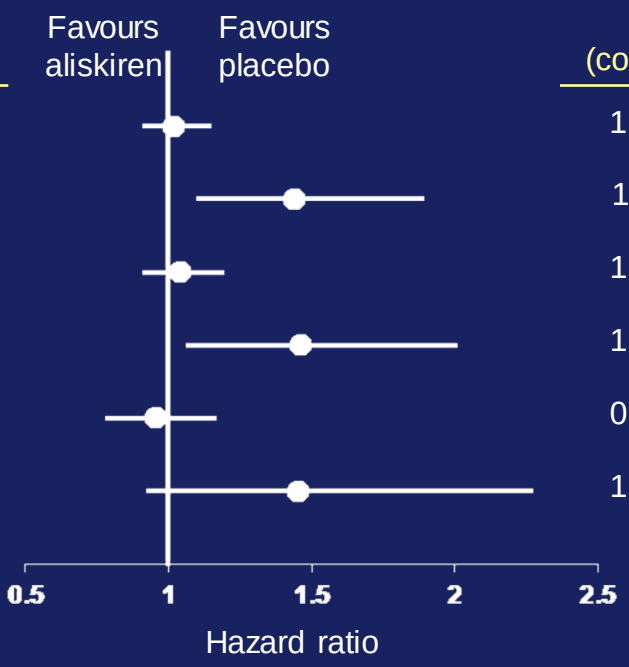
	Patients with events, n (%)			
	Aliskiren N = 4274	Placebo N = 4287	Hazard ratio (95 % CI)	P-value
Composite Endpoint	767 (17.9)	721 (16.8)	1.08 (0.98, 1.20)	0.142
CV death	239 (5.6)	213 (5.0)	1.13 (0.94, 1.36)	0.184
Resuscitated sudden death	18 (0.4)	8 (0.2)	2.28 (0.99, 5.23)	0.053
Myocardial infarction	142 (3.3)	140 (3.3)	1.02 (0.81, 1.29)	0.858
Stroke	146 (3.4)	118 (2.8)	1.25 (0.98, 1.60)	0.070
Unplanned hospitalization for heart failure	202 (4.7)	219 (5.1)	0.93 (0.77, 1.13)	0.462
Doubling of baseline serum creatinine	205 (4.8)	215 (5.0)	0.96 (0.79, 1.16)	0.650
Onset of ESRD or renal death	118 (2.8)	108 (2.5)	1.10 (0.85, 1.43)	0.465
Death	375 (8.8)	355 (8.3)	1.07 (0.92, 1.23)	0.388

Endpoints shown represent 92% of projected value of 1620 events for the primary composite endpoint
Adjusted for UACR and CVD history
Events adjudicated with cut-off date 31 Jan 2012

Heterogeneity between baseline serum potassium and primary, CV and renal secondary composite endpoints

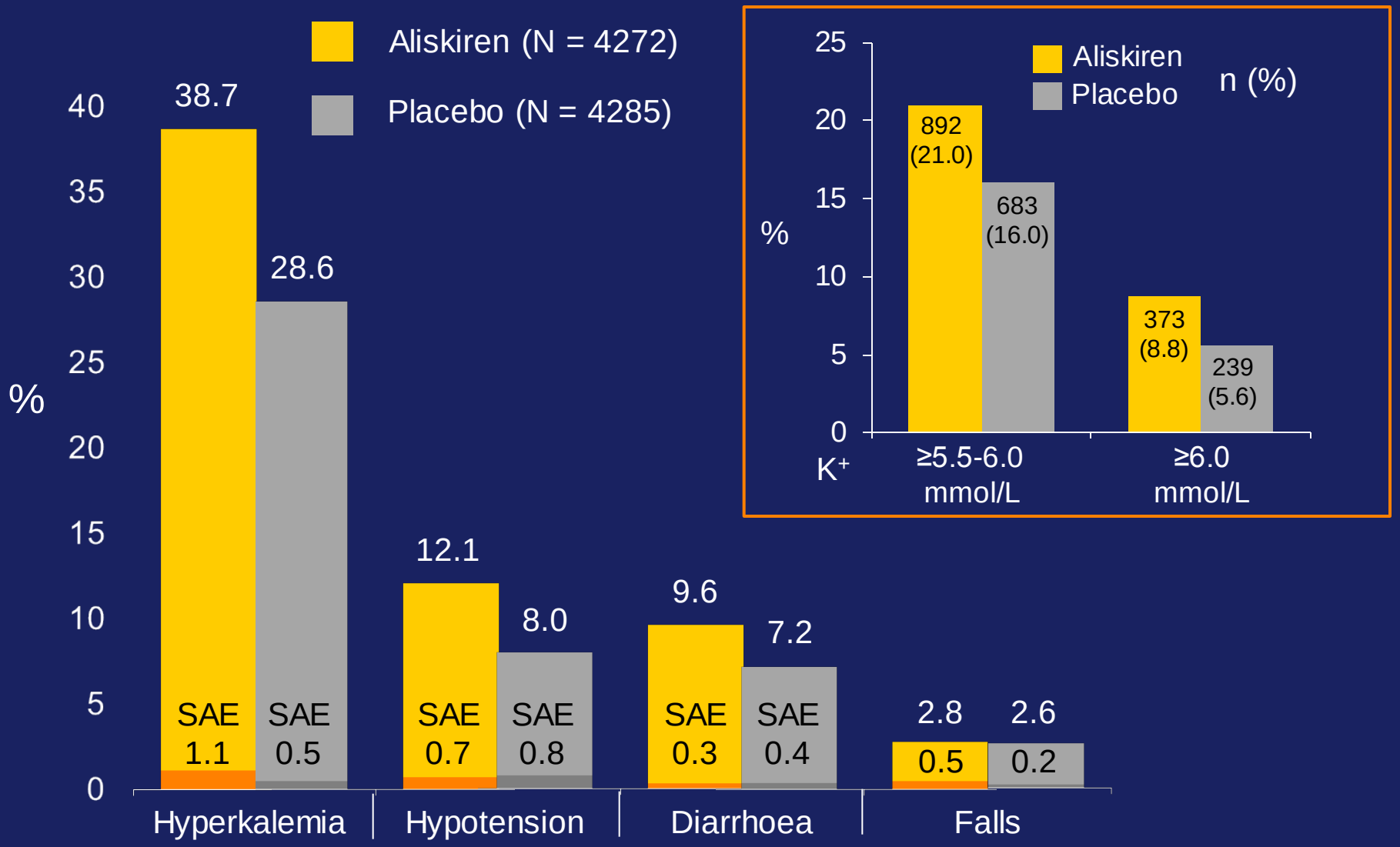
Full analysis set

	Baseline Potassium	Patients with events (% by category) Aliskiren (N=4274)	Placebo (N=4287)	Hazard ratio (confidence interval)	P-value for heterogeneity
Primary composite endpoint	<5.0	630 (17.5)	631 (17.2)	1.02 (0.92, 1.14)	0.0174*
	≥5.0	137 (20.1)	90 (14.6)	1.44 (1.11, 1.89)	
CV composite endpoint	<5.0	477 (13.3)	468 (12.7)	1.04 (0.92, 1.19)	0.0454*
	≥5.0	100 (14.7)	64 (10.4)	1.46 (1.07, 2.00)	
Renal composite endpoint	<5.0	202 (5.6)	215 (5.9)	0.96 (0.79, 1.16)	0.0895*
	≥5.0	49 (7.2)	32 (5.2)	1.45 (0.93, 2.27)	



* indicates significant p-value at ≤0.10 level

ALTITUDE AEs/SAEs – Potassium Lab analysis



Conclusions

- Any drug has multiple mechanisms of action
  - A favorable effect on a surrogate end-point may be attended by unfavourable effects on other meachnisms (i.e. albuminuria and hyperkaliemia)
- Trial design and inclusion / exclusion criteria must take into account drug's characteristics
  - Study patients must be carefully selected
- Many data still need large patients' groups and may be difficult to predict

ATMOSPHERE and ASTRONAUT: trials with aliskiren in systolic HF (2)

- **Both trials are already substantially recruited (ATMOSPHERE n=5441/ASTRONAUT n=1593). As expected, the pattern of clinical events* is very different than in ALTITUDE – most events are CV deaths (n~435 between the 2 trials) or HF hospitalizations (n~900 between the 2 trials), with relatively few strokes (n~100 between the 2 trials), MIs (n~100 between the 2 trials) or cases of ESRD (n~13 in ATMOSPHERE).**
- **Both trials overseen by the same very experienced DMC *(Chair Karl Swedberg, Co-chair Stuart Pocock; Jeffrey Borer, Bertram Pitt, John Rouleau)*. They have been alerted to the safety issues and have reviewed a very large number of events recently (20 December 2011) without raising any concern.**

**approximate number of investigator reported events*