AUTUMN MEETING

Hotel Russell, London

28th November 2008


God Jul
önskar
vännerna på
ZENECA

AUTUMN MEETING

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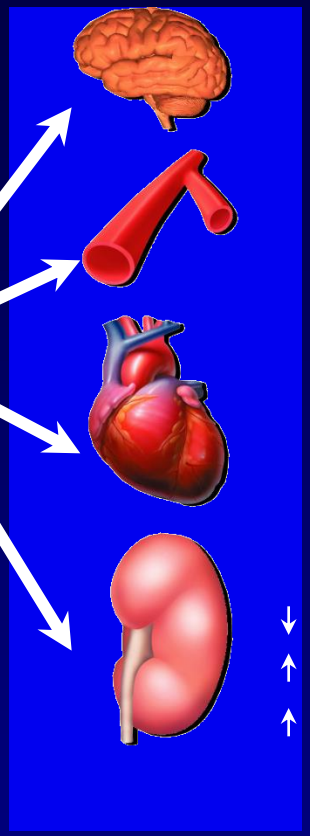
Angiotensin II Plays a Central Role in Organ Damage



A II → AT_1 receptor

Atherosclerosis* → Stroke
Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction → Hypertension

LV hypertrophy
Fibrosis
Remodeling
Apoptosis → Heart failure
MI → DEATH

↓ GFR
↑ Proteinuria
↑ Aldosterone release
Glomerular sclerosis → Renal failure

*preclinical data
LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

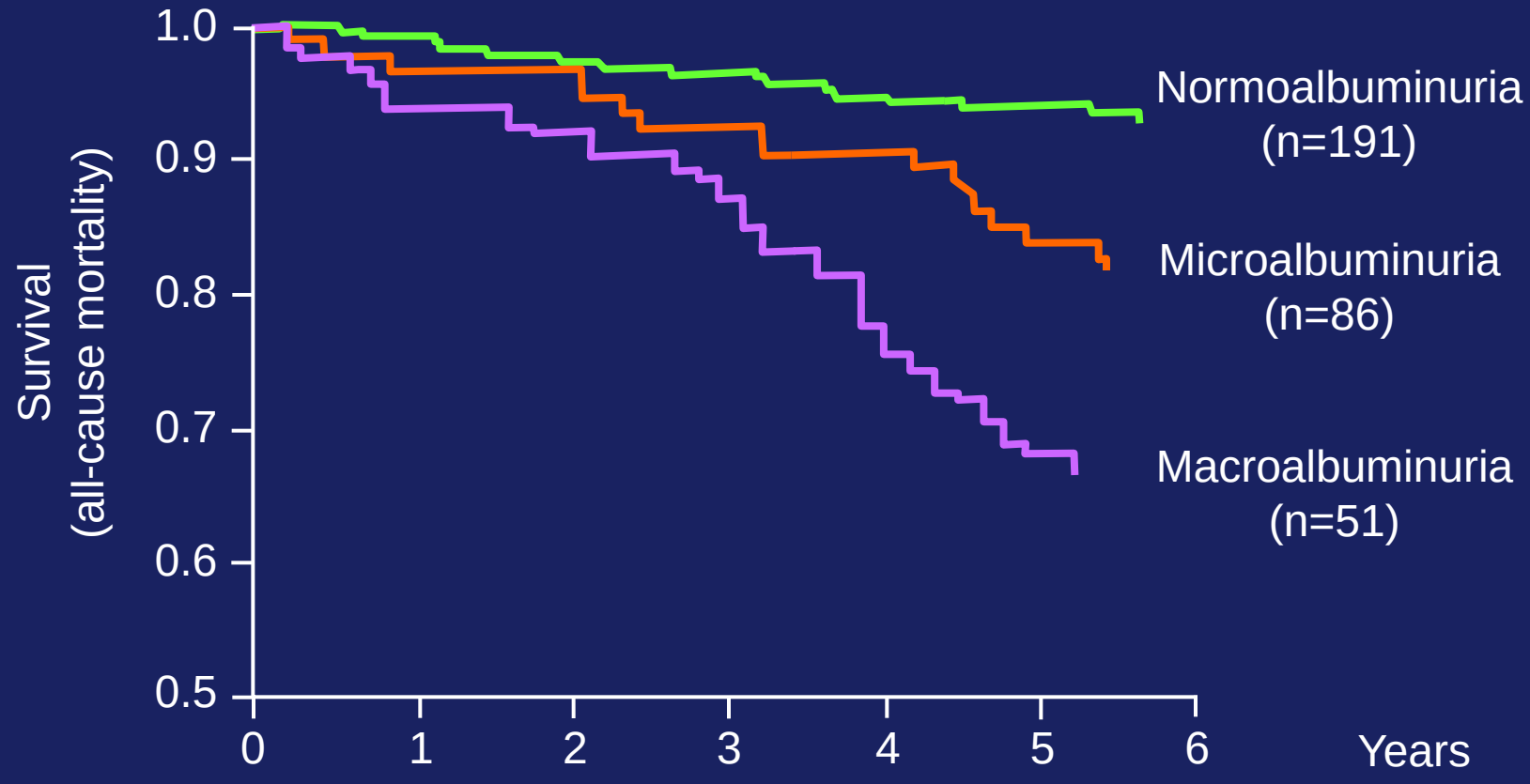
Adapted from Willenheimer R et al *Eur Heart J* 1999; 20(14): 997–1008, Dahlöf B *J Hum Hypertens* 1995; 9(suppl 5): S37–S44, Daugherty A et al *J Clin Invest* 2000; 105(11): 1605–1612, Fyhrquist F et al *J Hum Hypertens* 1995; 9(suppl 5): S19–S24, Booz GW, Baker KM *Heart Fail Rev* 1998; 3: 125–130, Beers MH, Berkow R, eds. *The Merck Manual of Diagnosis and Therapy*. 17th ed. Whitehouse Station, NJ: Merck Research Laboratories 1999: 1682–1704, Anderson S *Exp Nephrol* 1996; 4(suppl 1): 34–40, Fogo AB *Am J Kidney Dis* 2000; 35(2):179–188

Diabetic Nephropathy

40%

CKD & CVD screening ?

Proteinuria Is an Independent Risk Factor for Mortality in Type 2 Diabetes

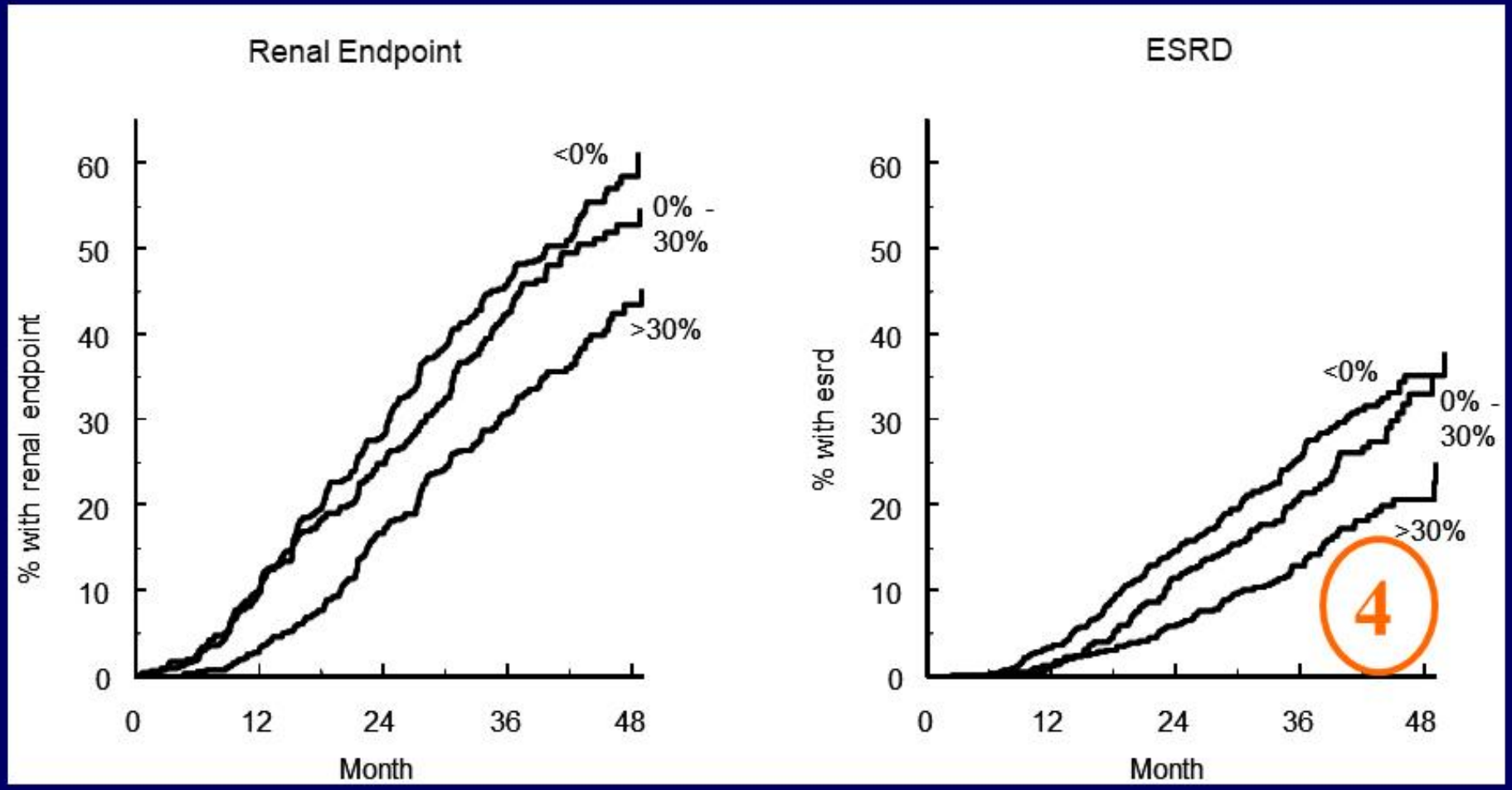


P<0.01 normo vs. micro- and macroalbuminuria
P<0.05 micro vs. macroalbuminuria

Gall, MA et al. Diabetes 1995;44:1303

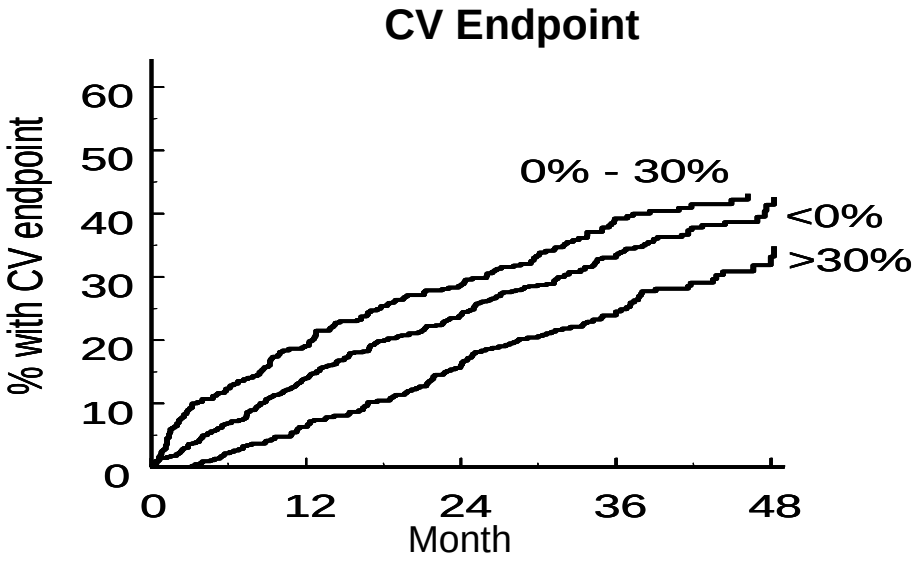
Event Rate of Renal Endpoints Stratified by Albuminuria Change

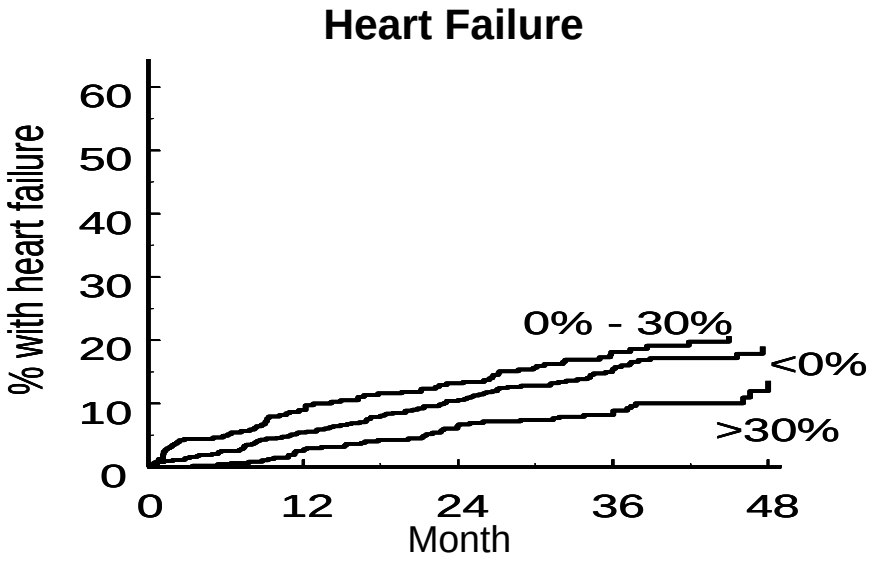
Baseline to 6 Months

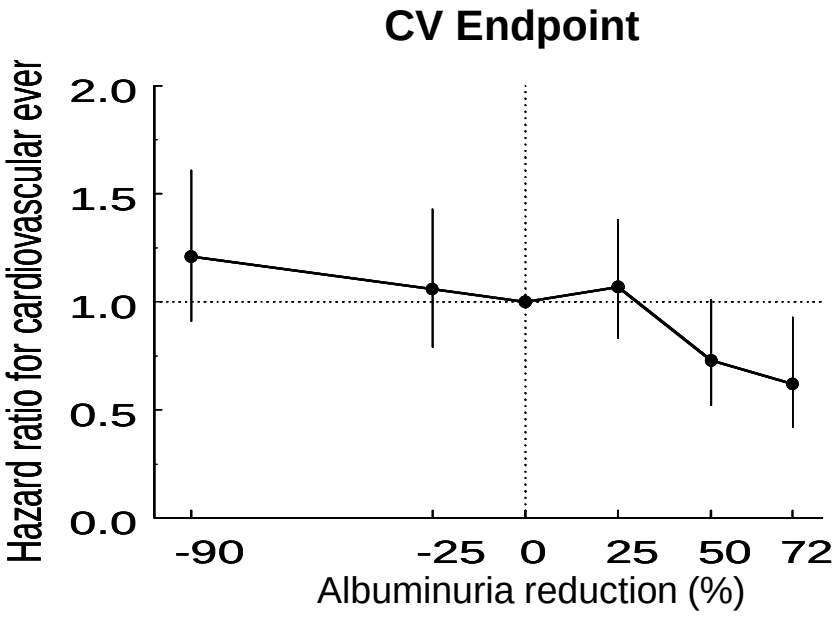


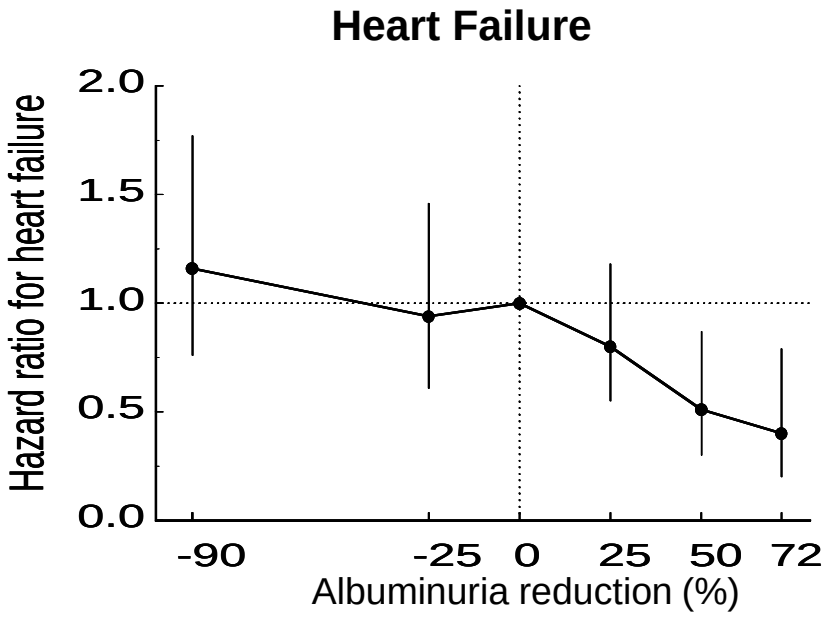
De Zeeuw et al, 2004

RENAAL: CV End-Points By Change in Proteinuria





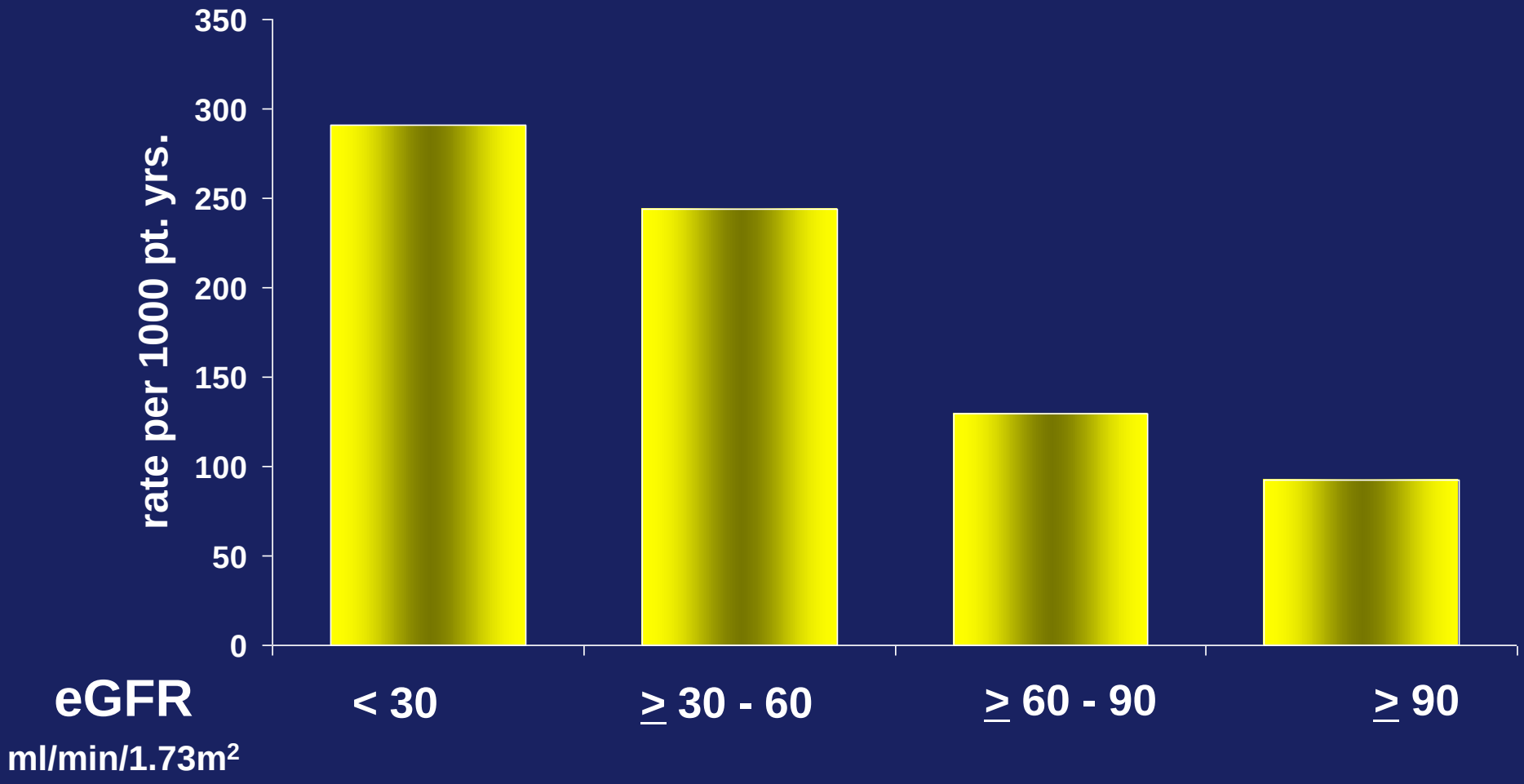




De Zeeuw et al, 2004

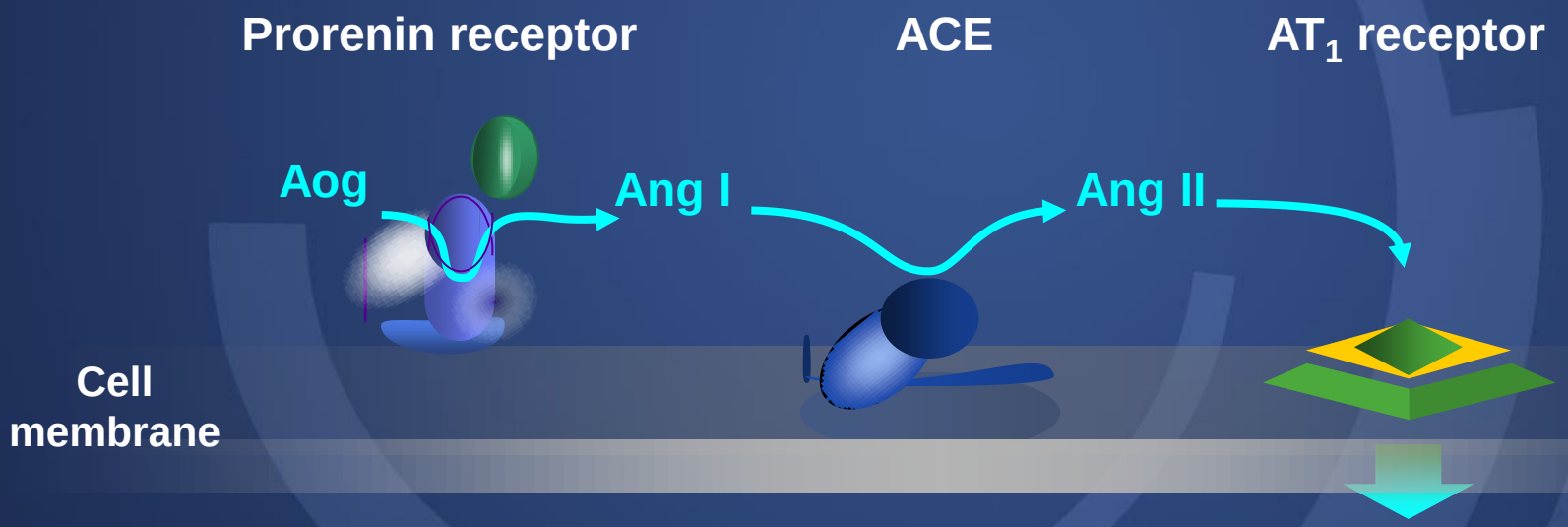
Renal dysfunction is a risk factor for adverse CV Outcomes

CV death or HF hospitalisation in CHARM



Receptor-bound Prorenin Generates Ang II in the Tissues

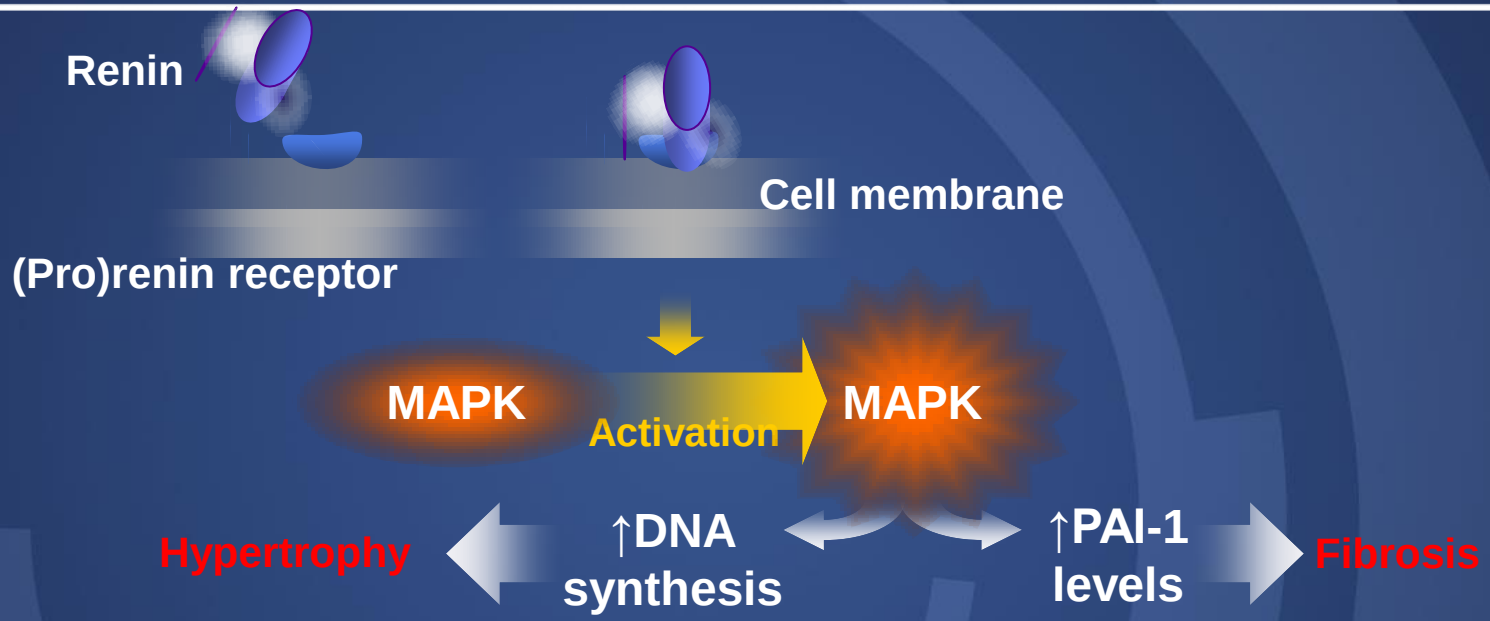
- How are these effects mediated?
  - Studies suggest that receptor-mediated prorenin activation leads to tissue synthesis of Ang II[1–4]



[1]Ichihara et al. J Clin Invest 2004;114:1128–35
[2]Ichihara et al. J Am Soc Nephrol 2006;17:1950–61
[3]Ichihara et al. Hypertension 2006;47:894–900
[4]Saris et al. Hypertension 2002;39:573–7

NOVARTIS

Activation of MAPK Cell Signalling Pathways in Cell Culture by Renin



- Binding of renin to the prorenin receptor activates cell signalling pathways and may lead to increased tissue fibrosis and cellular hypertrophy[1-3]
  - Activation of cell signalling is independent of Ang II generation[4]

MAPK=mitogen-activated protein kinase
PAI-1=plasminogen activator inhibitor-1

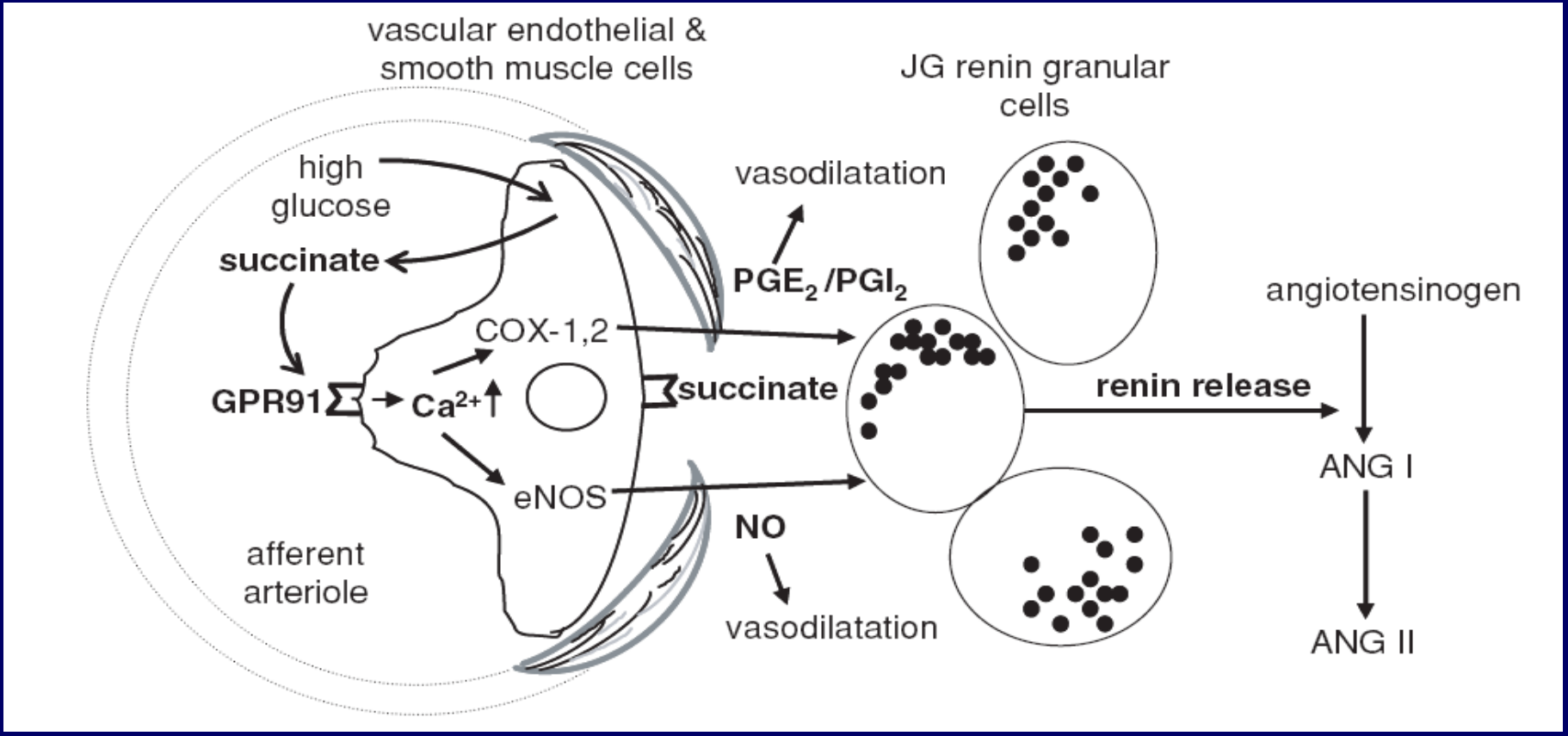
[1]Nguyen et al. 2002; [2]Nguyen et al. 1996
[3]Ichihara et al. 2006; [4]Saris et al. Hypertension 2006;48:564–71

NOVARTIS

Renin / Prorenin

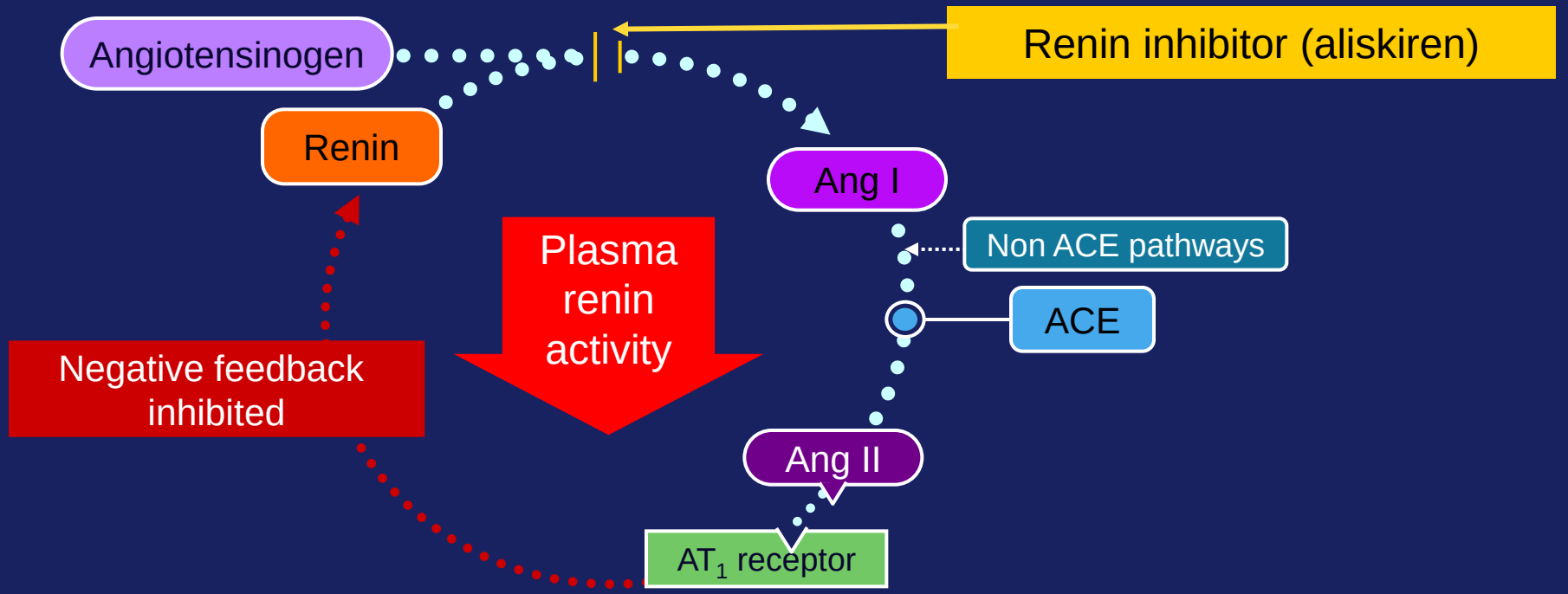
- Renin receptor, localized in brain, heart, kidney, liver (vasculature)
- Renin and prorenin bind to the renin receptor
- Renin receptor activation induces 4 to 5 increase in AGT to Ang1.
  Intracellular signaling: e.g. MAP kinases

Elevated Glucose leading to Renin release
GPR91 is the link



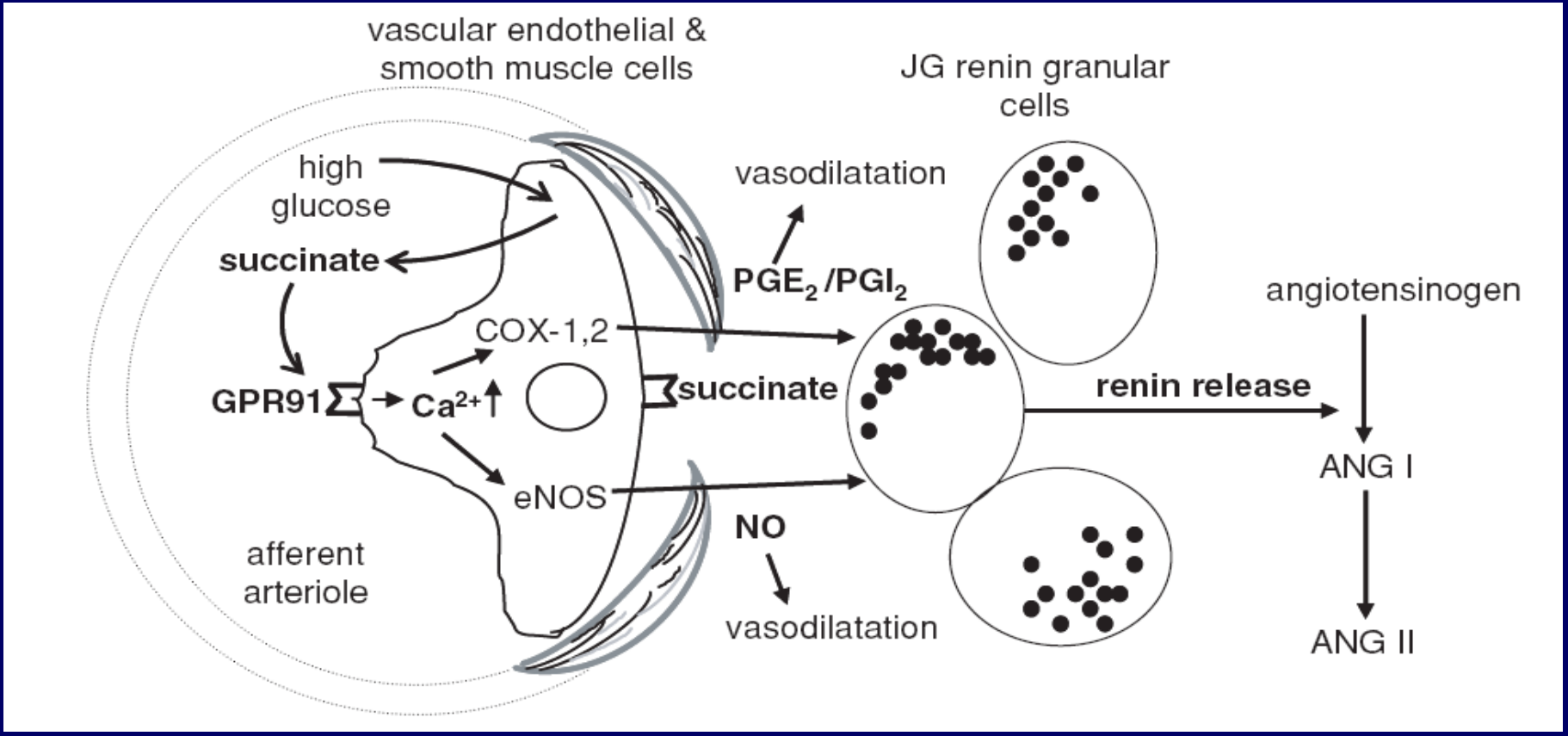
J Peti-Peterdi et al NDT 2008

Renin inhibition acts at the Renin System's point of activation and neutralizes the PRA rise



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

Elevated Glucose leading to Renin release
GPR91 is the link



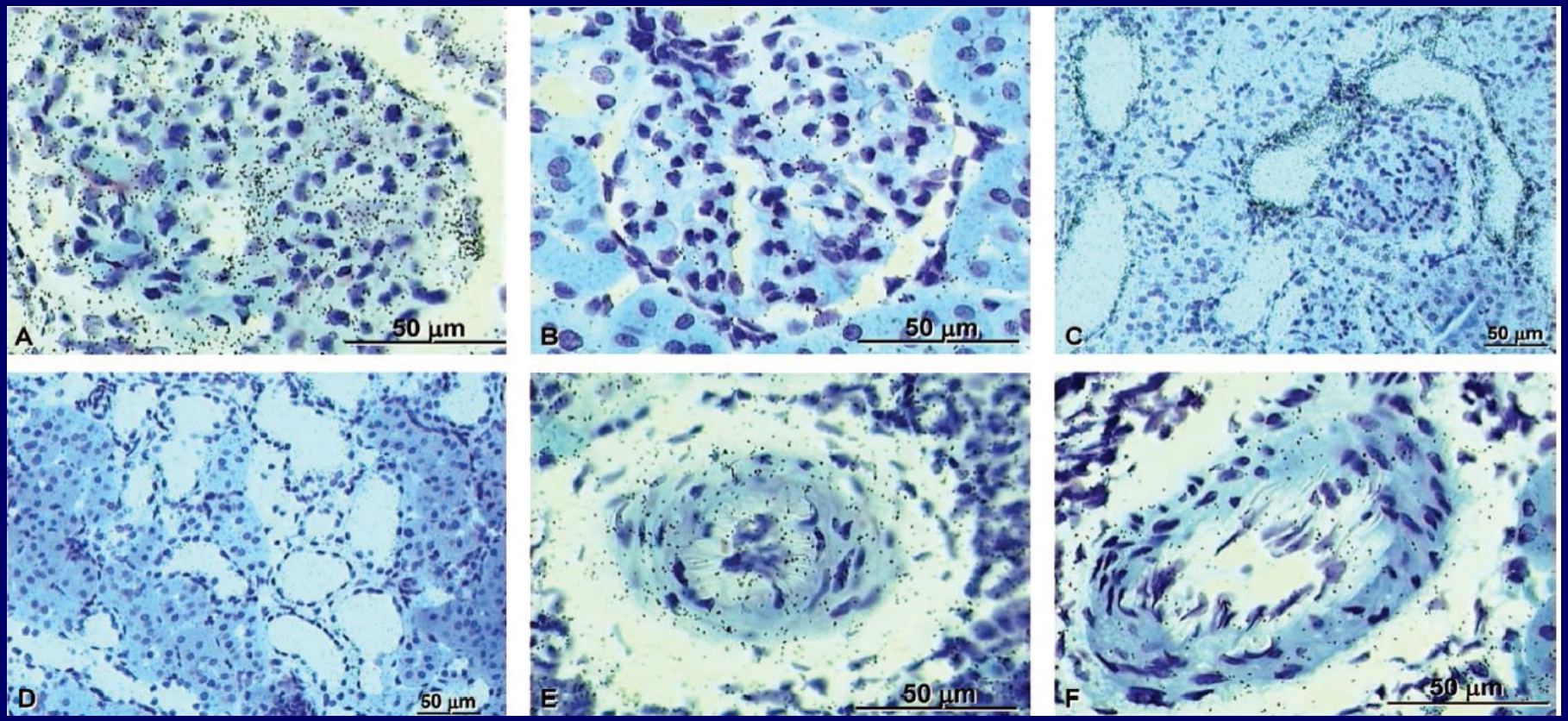
J Peti-Peterdi et al NDT 2008

Gene expression of (pro)renin receptor in TG(mRen-2)27 diabetic rats, with or without Aliskiren

Glomeruli -

Glomeruli +

Tubules -



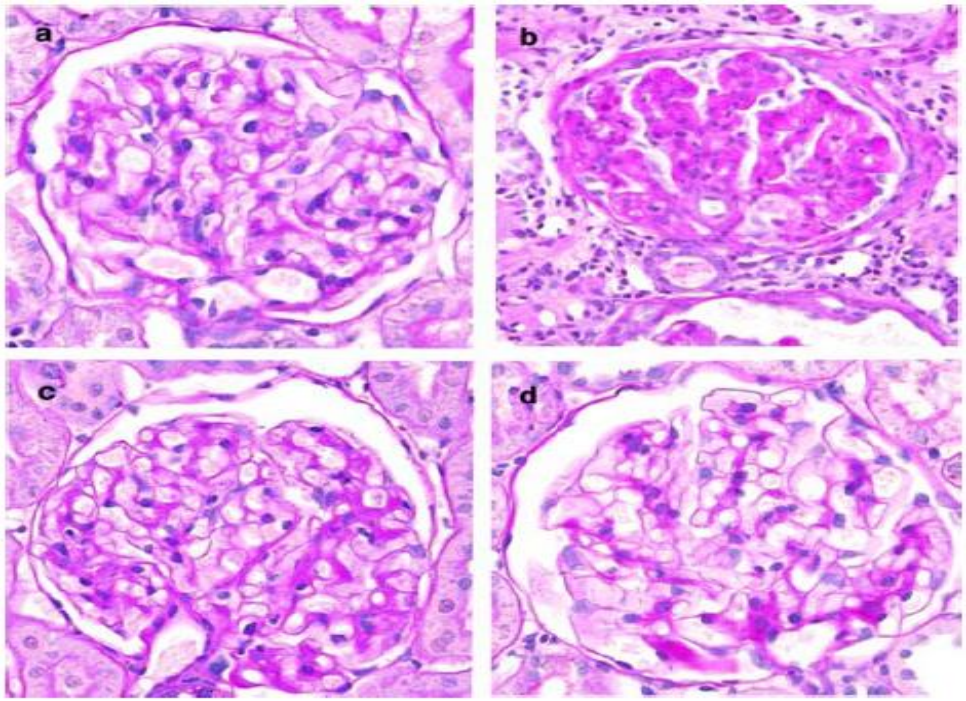
Tubules +

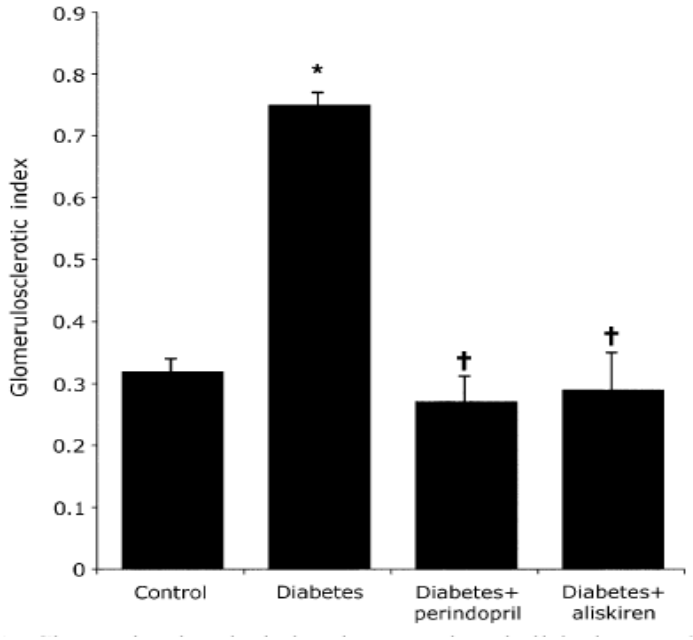
cortical vessels -

cortical vessels +

DL Feldman et al Hypertension 2008

Glomerulosclerosis in control and diabetic Ren-2 rats, treated or not with aliskiren and perindopril.

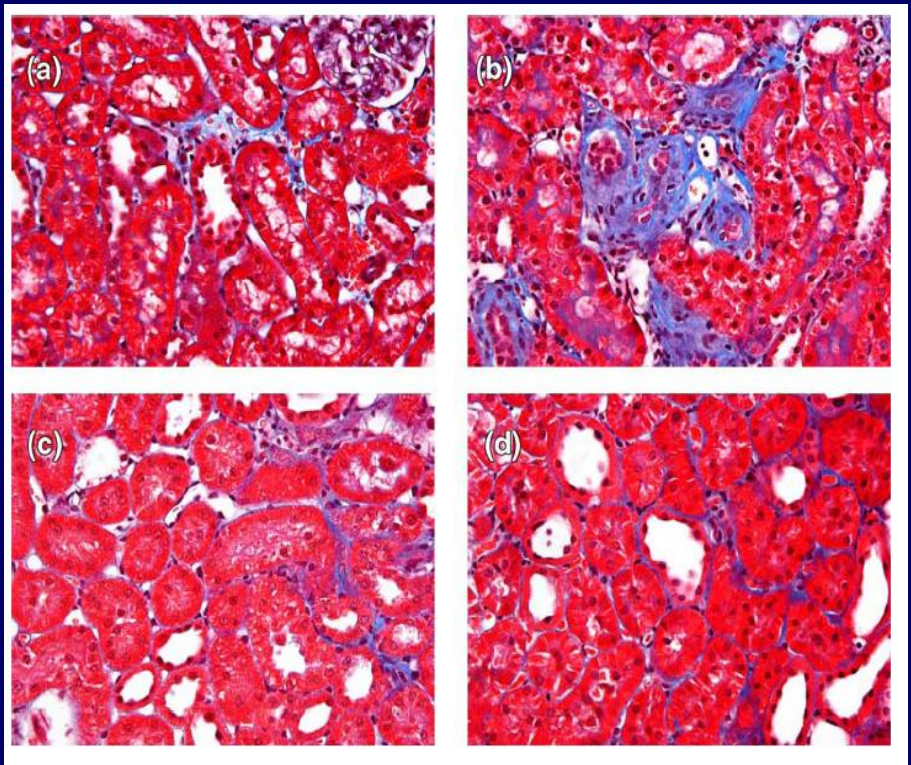




diabetic Ren-2 rats, treated or not with aliskiren and perindopril.

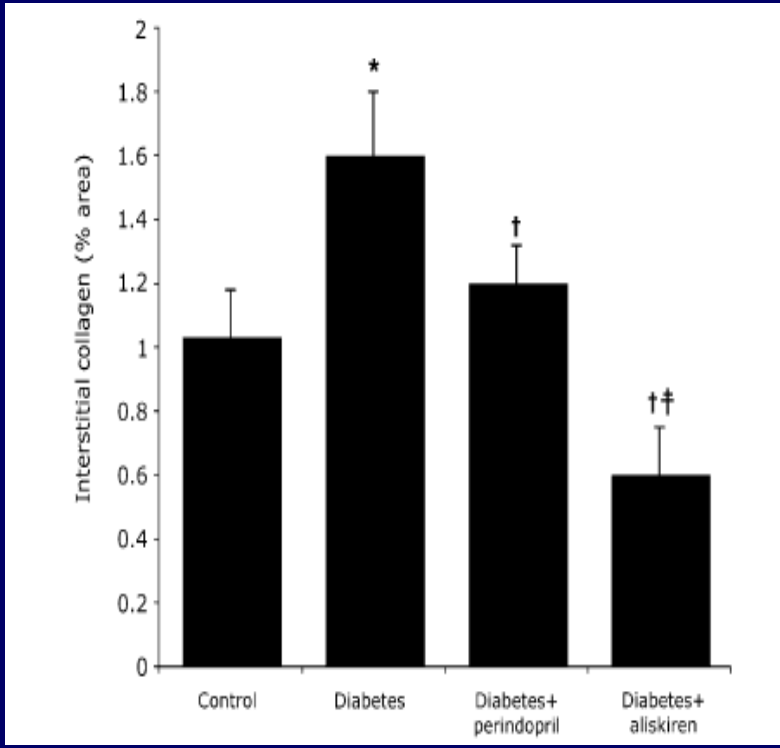
Control

Diabetes



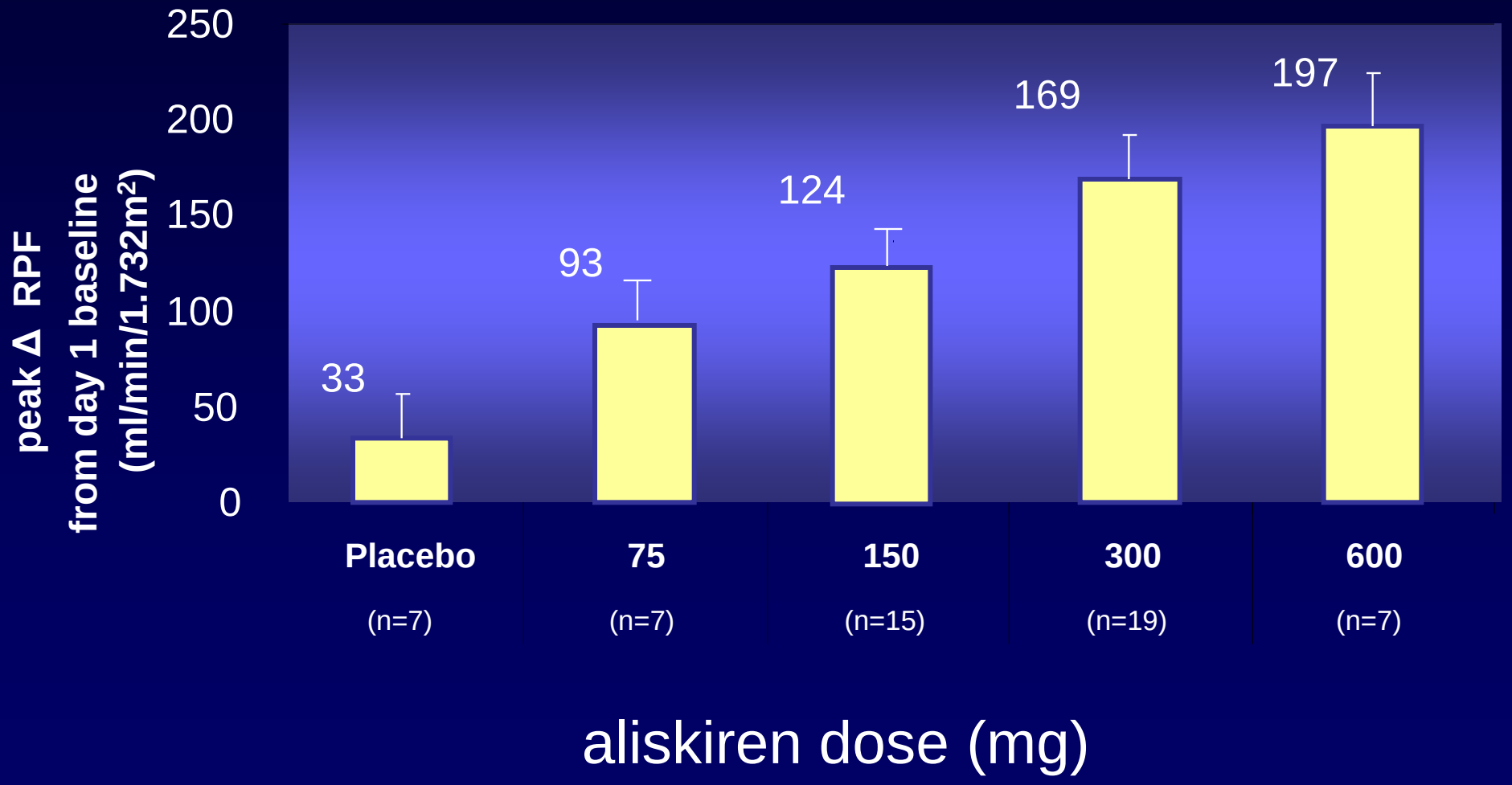
DM+Perindopril

DM+Aliskiren

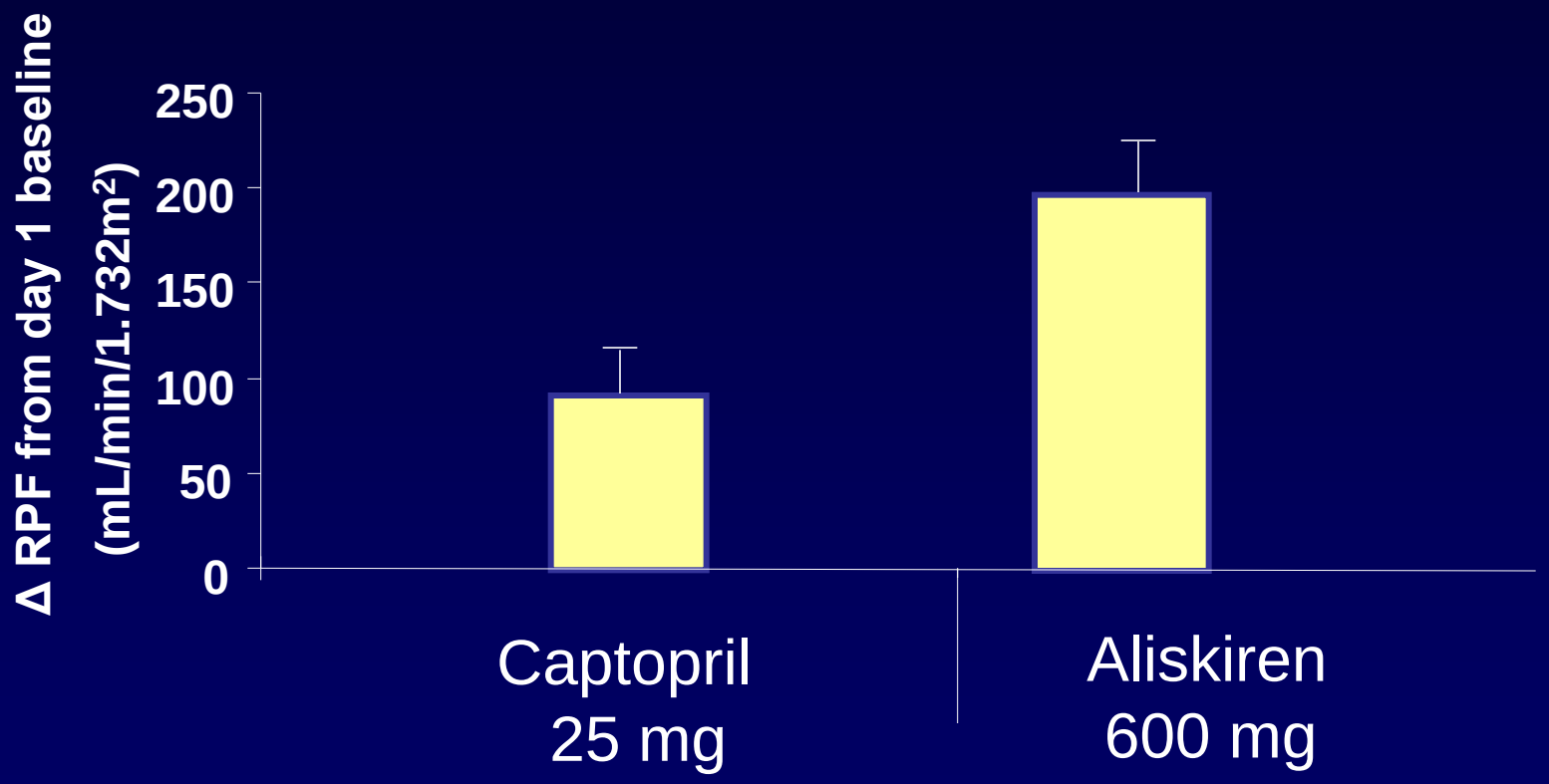


D Kelly et al Diabetologia 2007

Peak RPF Responses to Aliskiren



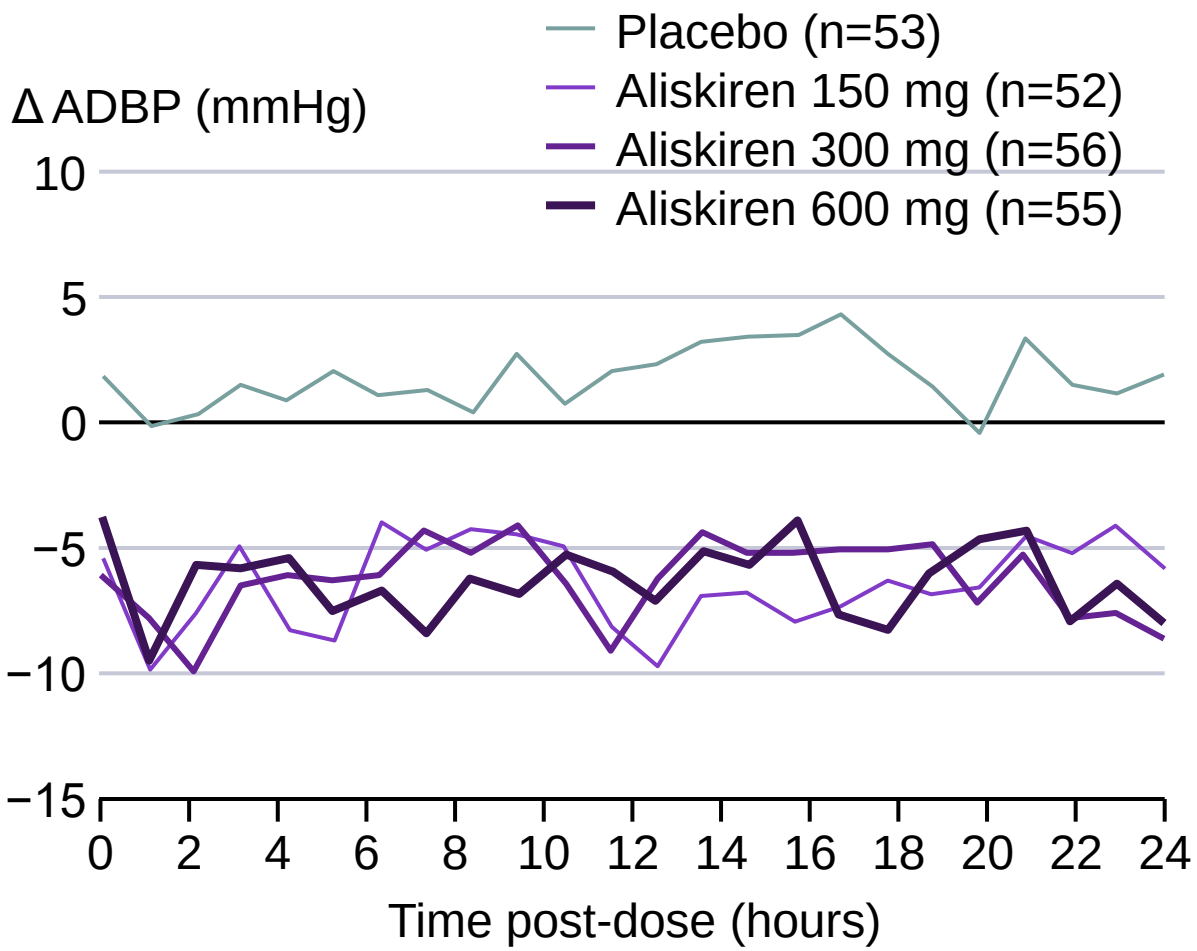
Rise in Renal Plasma Flow: captopril vs. aliskiren



92 ± 20 vs 197 ± 27 ml/min/1.73m^2

With a half life of 40 hours – BP reductions are sustained over 24 hours

Trough to peak ratio:	
150 mg	0.64
300 mg	0.98
600 mg	0.86



Mitchell J, *et al.* 2006 (Study 2308)

ALISKIREN- diabetic animals/in vitro conditions

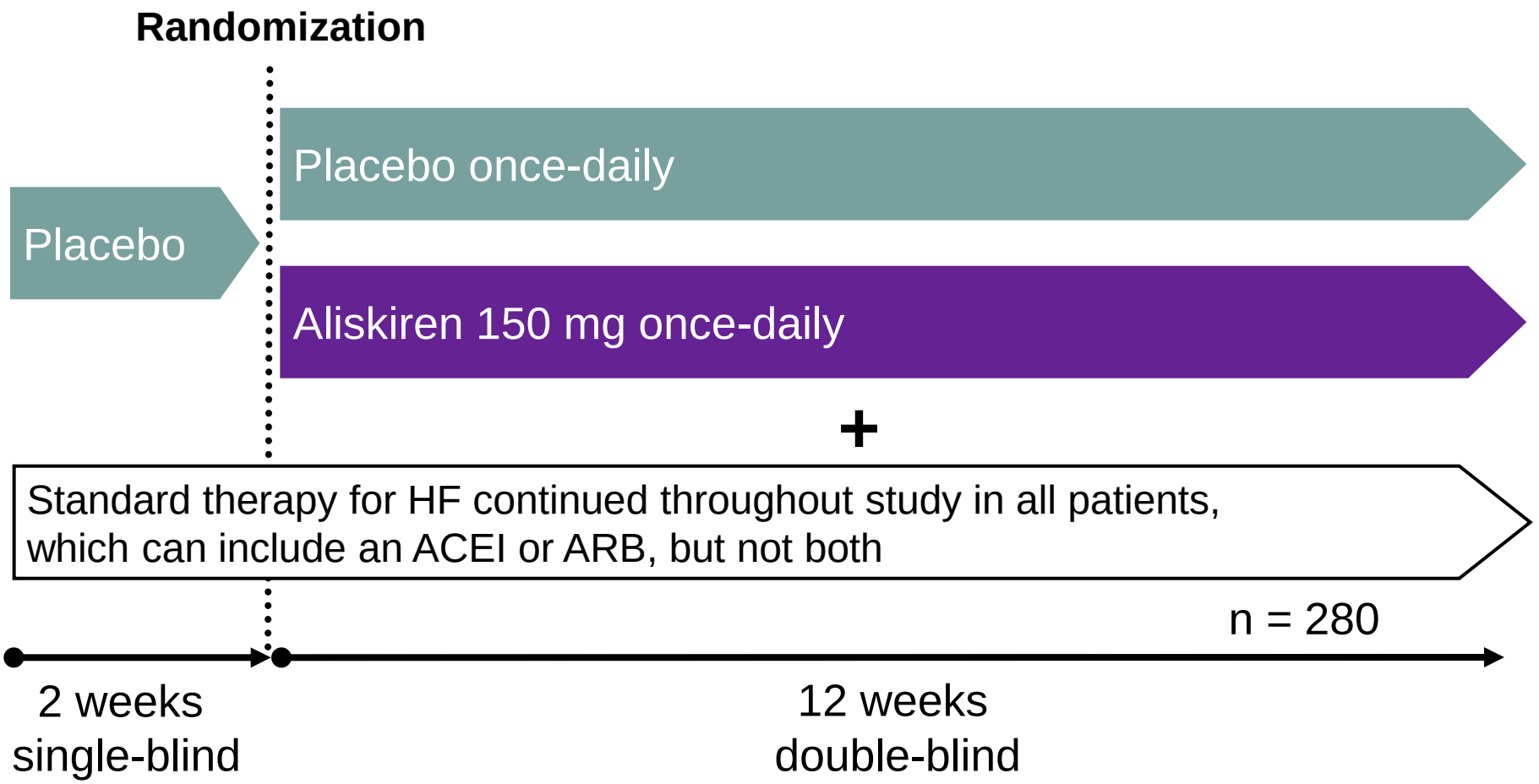
- Reduces numbers of (pro)renin receptors in the kidney
- Mitigates profibrotic activity in the kidney
- Nearly abolish glucose apoptotic effects on podocytes
- JASN 2007,18:61a;168a;169a

Impact of Aliskiren(DRI) on angiotensin II-induced cardiovascular damage

- DRI profoundly reduces atherosclerosis in mice (fat-fed LDL-receptor-deficient)
- DRI reduces TNF-α,CRP and complement activation in double transgenic rats (renin, angiotensinogen genes)
- DRI reduces arrhythmia in double transgenic rats.

ALOFT
ALiskiren Observation of Heart Failure Treatment

Patients with hypertension, stable HF, BNP levels >100 pg/mL

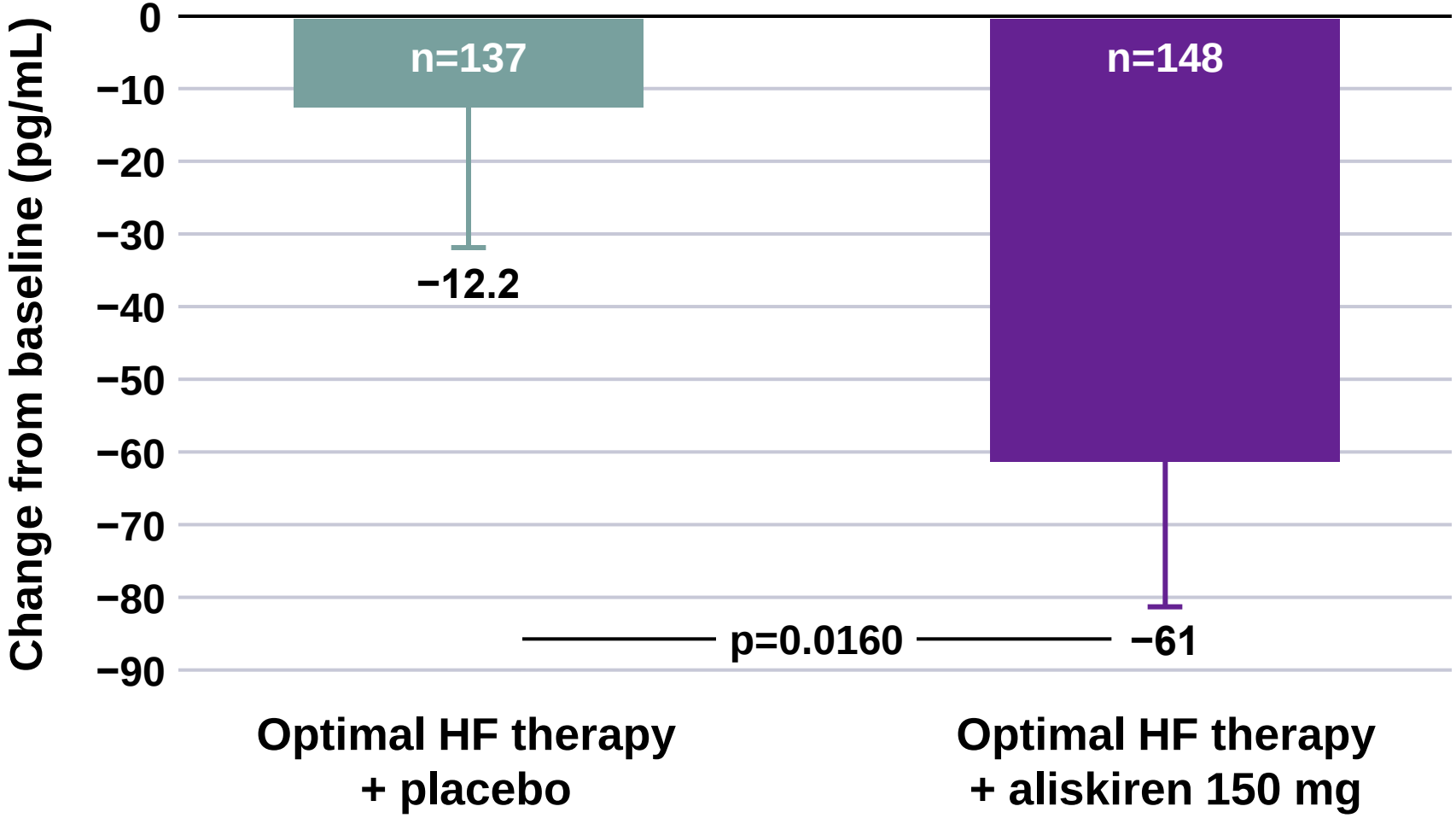


Clinicaltrials.gov; 2006; Data on File, Novartis 2007

ALOFT
ALiskiren Observation of Heart Failure Treatment

Significant reduction in BNP levels

mean±SEM

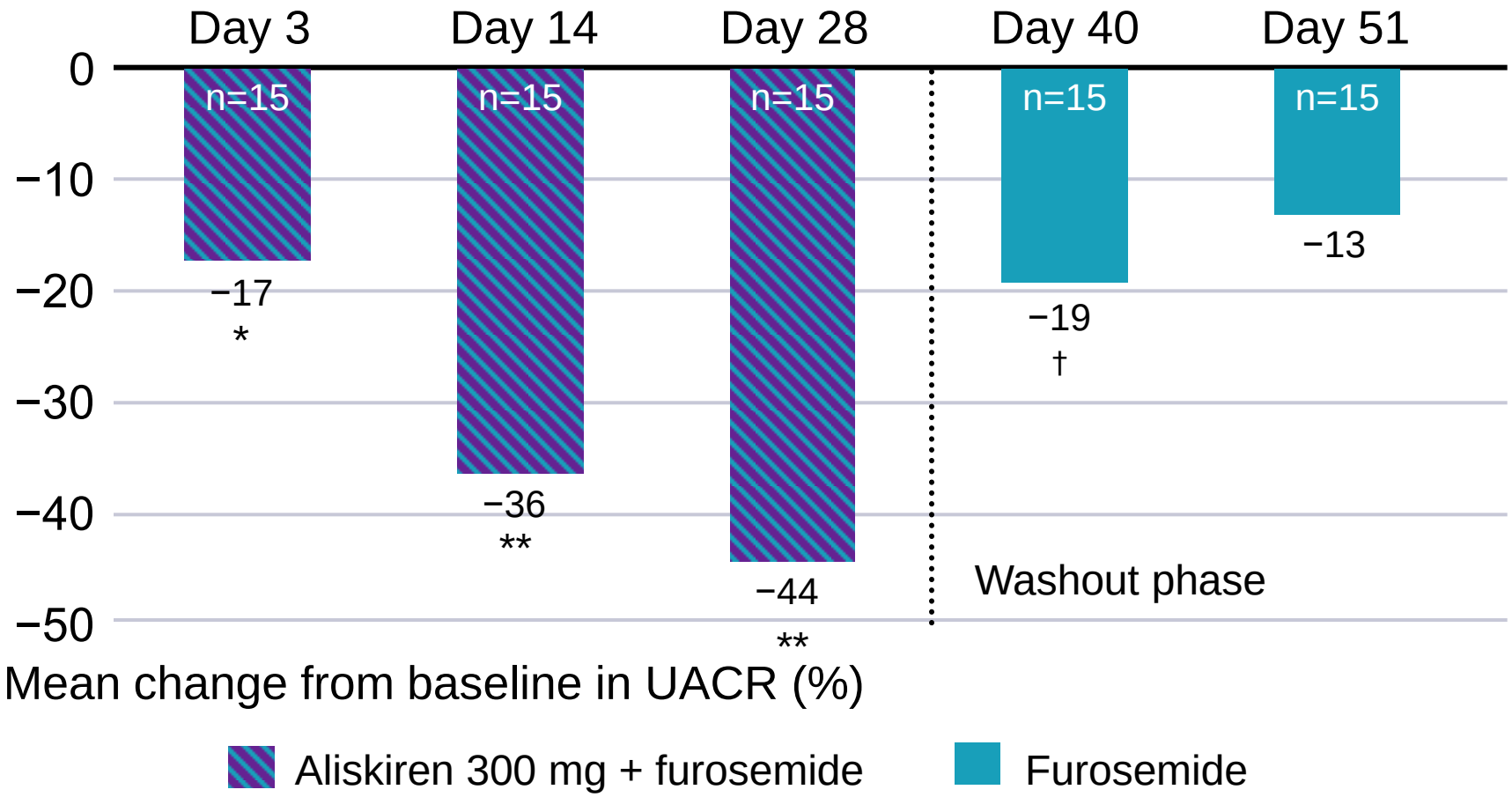


ALOFT
ALiskiren Observation of Heart Failure Treatment

Pre-specified safety assessments

Assessment, n (%)	Placebo (n=146)	Aliskiren 150 mg (n=156)
Renal dysfunction	2 (1.4)	3 (1.9)
Symptomatic hypotension	2 (1.4)	5 (3.2)
Hyperkalaemia	7 (4.8)	10 (6.4)
Any of the above	11 (7.5)	17 (10.9)

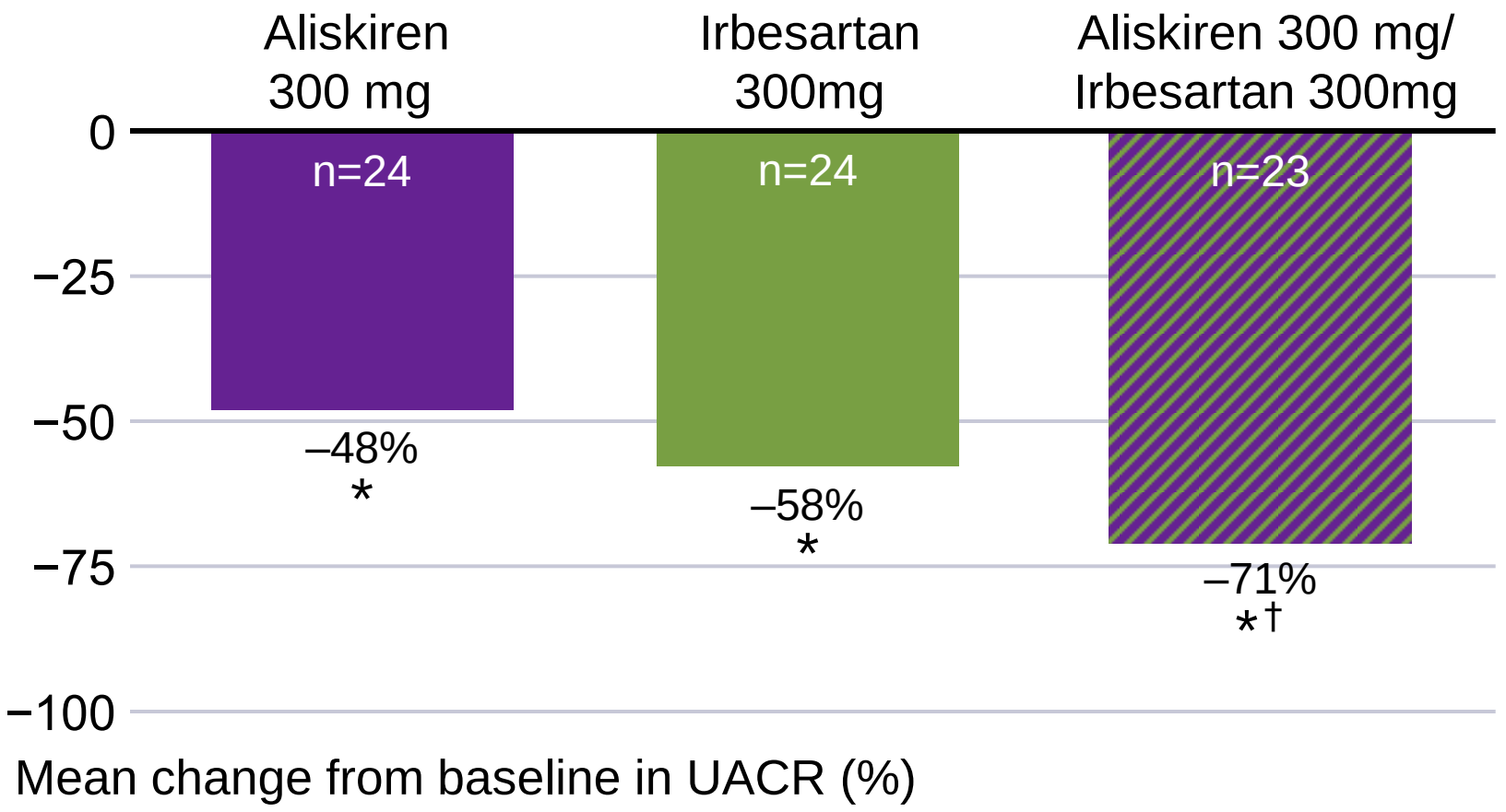
Aliskiren significantly reduces UACR from baseline in patients with diabetes and albuminuria



*p=0.04; **p<0.001; †p=0.02 vs baseline

Persson *et al*. 2007

Study 2243 primary endpoint: Change from baseline in UACR



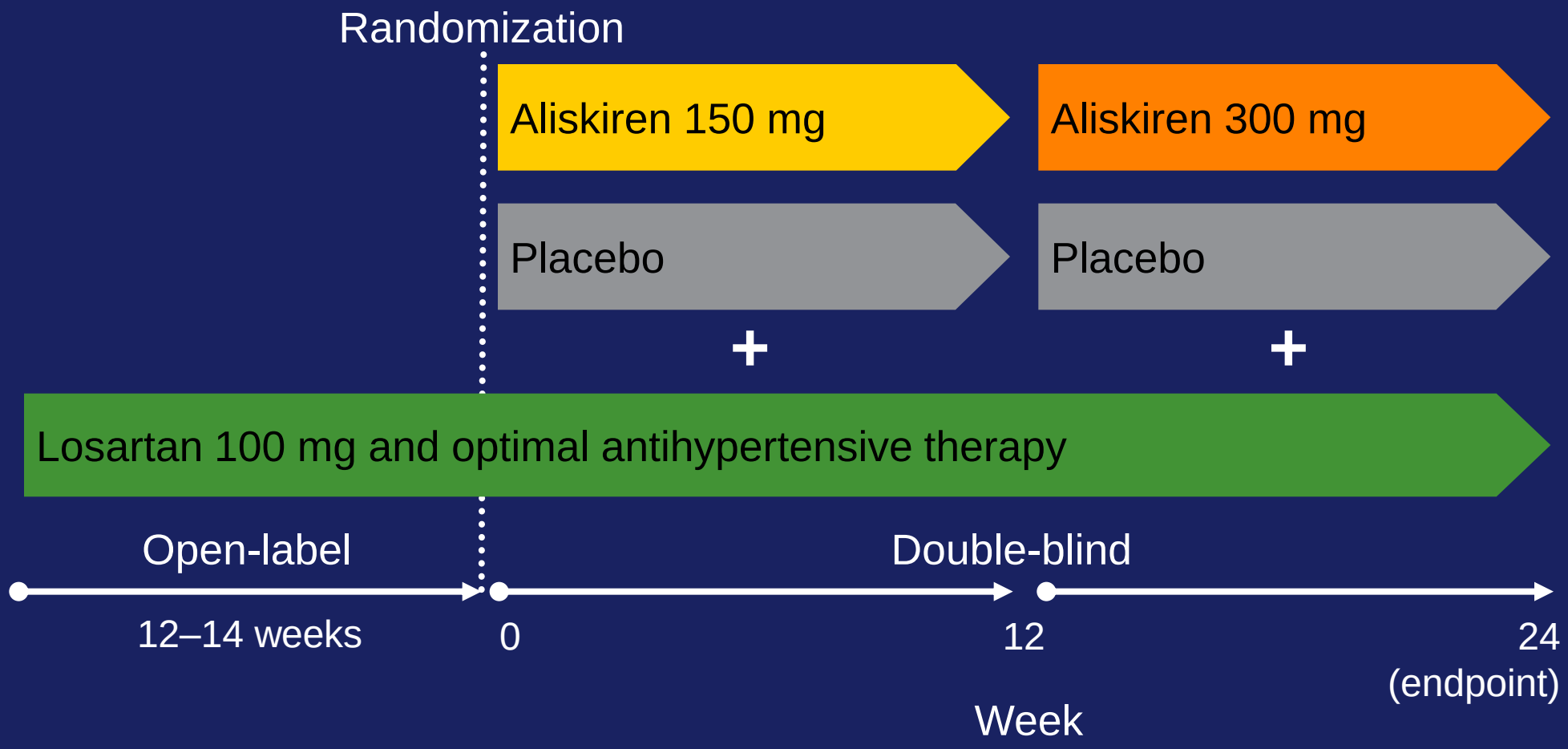
*p<0.001 vs placebo; †p<0.05 vs component monotherapies

Novartis, data on file 2008 (Study 2243)


AVOID
Aliskiren in the EValuation of PrOteinuria In Diabetes

NOVARTIS

A double-blind, randomized, placebo-controlled study in hypertensive patients with type 2 diabetes and nephropathy



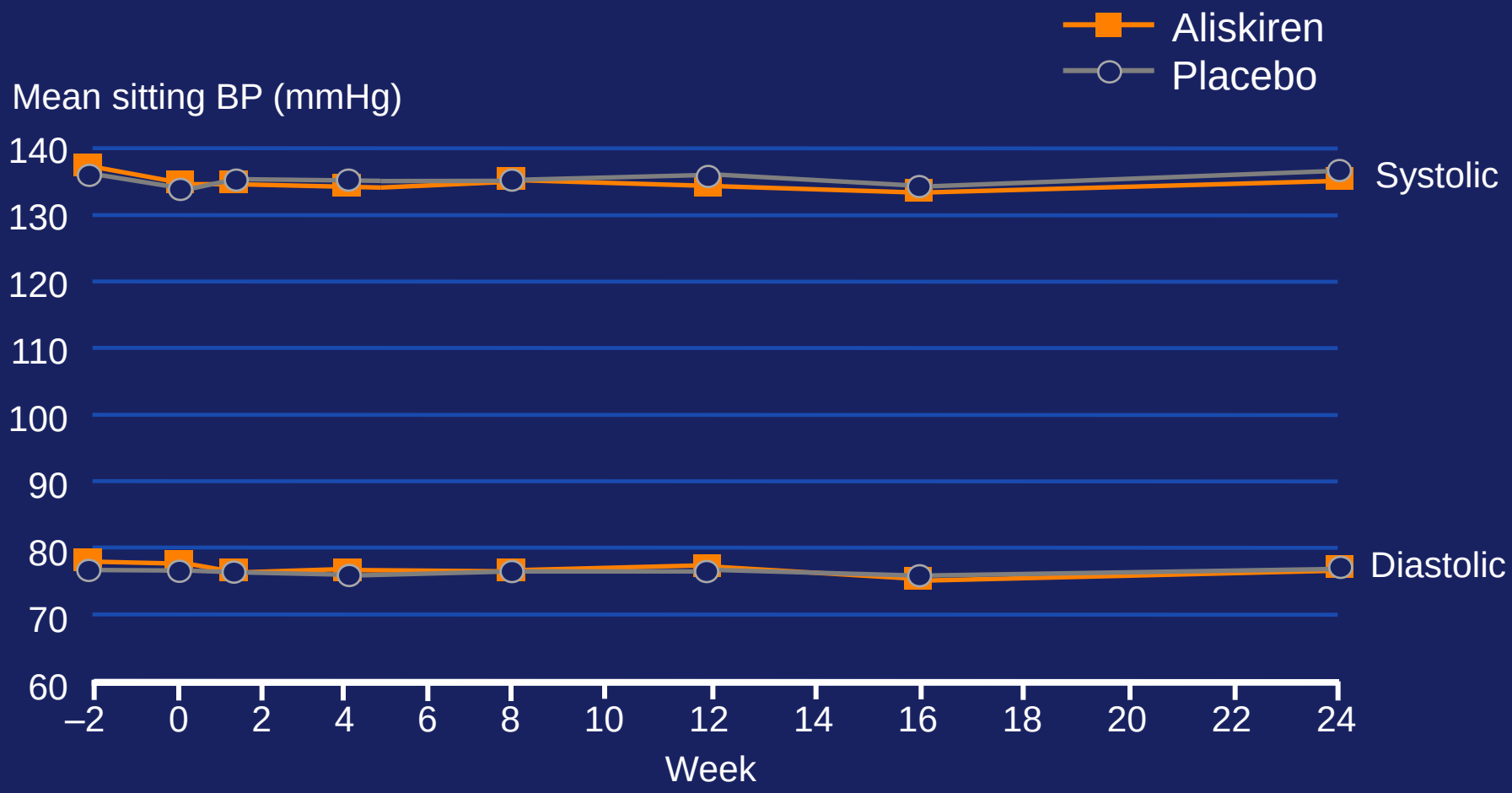
Forced titration at week 12
All doses were administered once daily

Baseline laboratory variables were similar in the two treatment groups

Characteristic	Aliskiren (n = 301)	Placebo (n = 298)
Mean sitting blood pressure, mmHg		
Systolic	135 ± 12	134 ± 12
Diastolic	78 ± 8	77 ± 9
UACR, mg/g	513 (463–569)	553 (502–609)
UAER, µg/min	495 (440–557)	520 (469–576)
Estimated GFR, mL/min/1.73 m^2	68.5 ± 25.7	66.8 ± 24.5

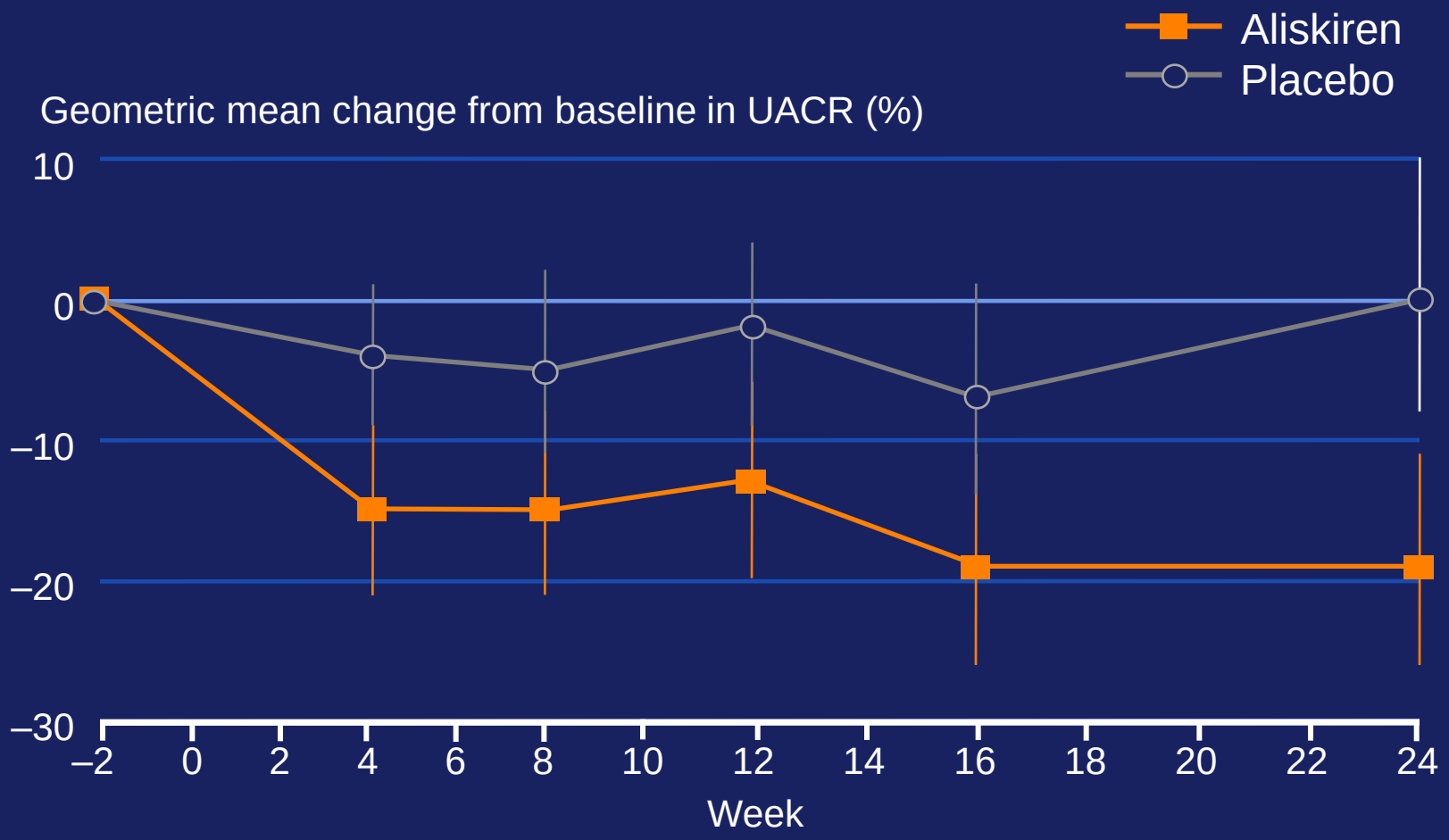
Data are presented as mean ± SD, except for UACR and UAER which are shown as geometric mean (95% CI)
GFR values were calculated using the Modification of Diet in Renal Disease formula
GFR, glomerular filtration rate; UACR, urinary albumin:creatinine ratio; UAER, urinary albumin excretion rate

Effect of aliskiren and placebo on blood pressure throughout the course of the study



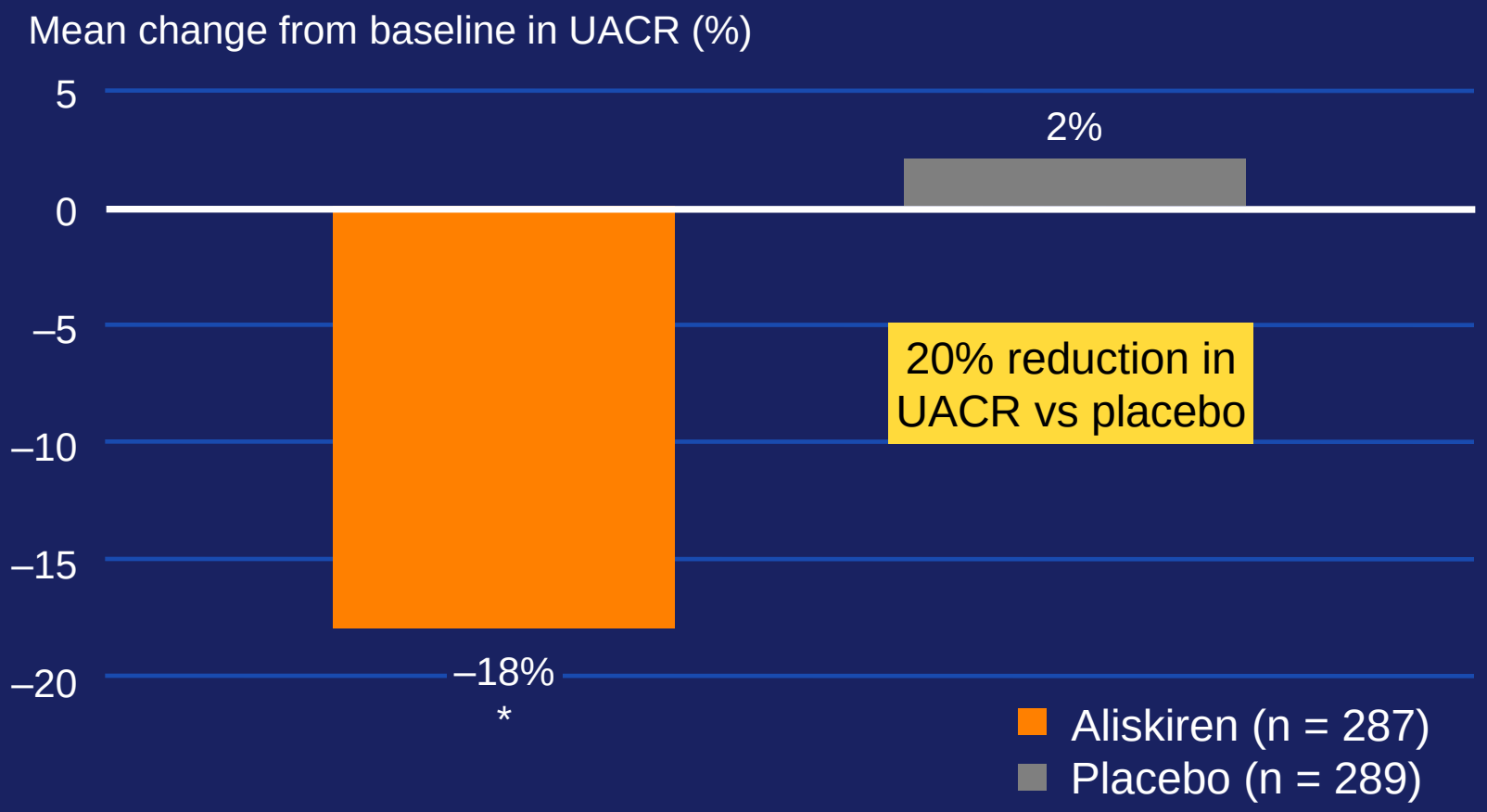
Date are shown as mean ± SEM
Baseline was the week 0 (Day 1) value
BP, blood pressure

Changes in UACR with aliskiren and placebo throughout the course of the study



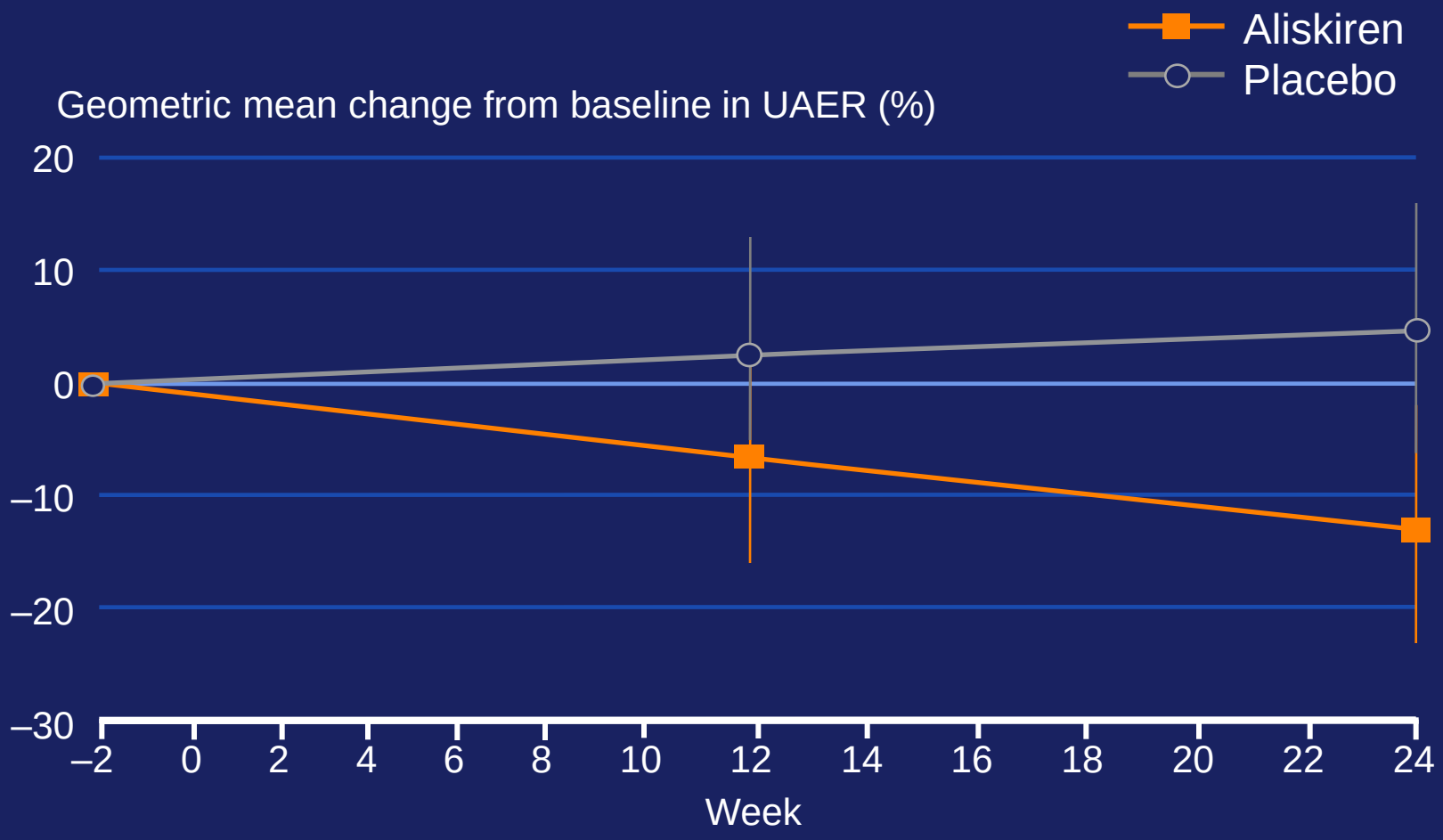
Data are shown as change from baseline in geometric mean (95% CI)
Baseline was the week –2 value
UACR, urinary albumin:creatinine ratio

Aliskiren significantly reduced UACR from baseline to week 24 endpoint compared with placebo



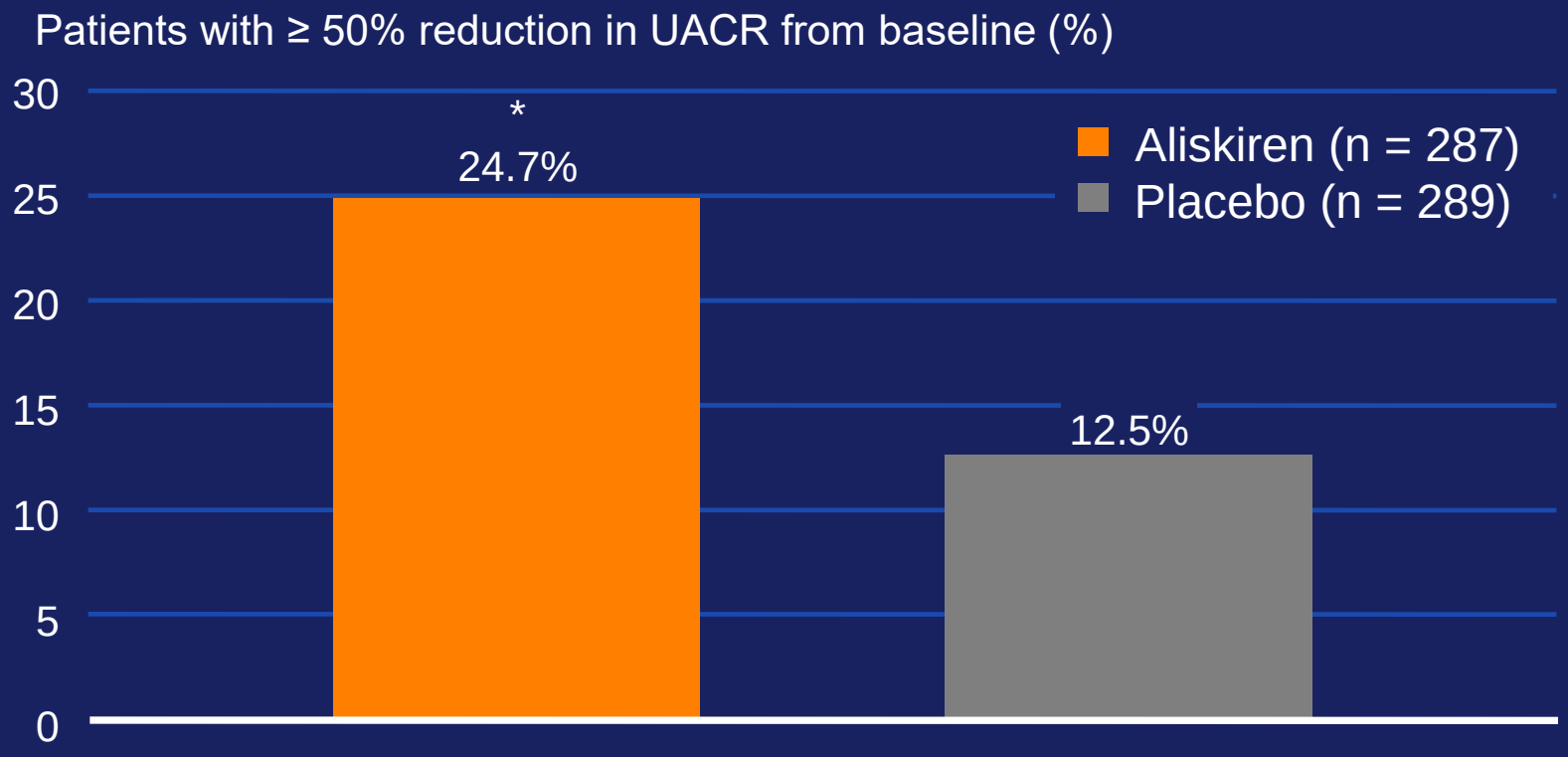
*p = 0.0009
Data are shown as percentage change in geometric mean
Baseline was week −2 value
UACR, urinary albumin:creatinine ratio

Changes in UAER with aliskiren and placebo throughout the course of the study



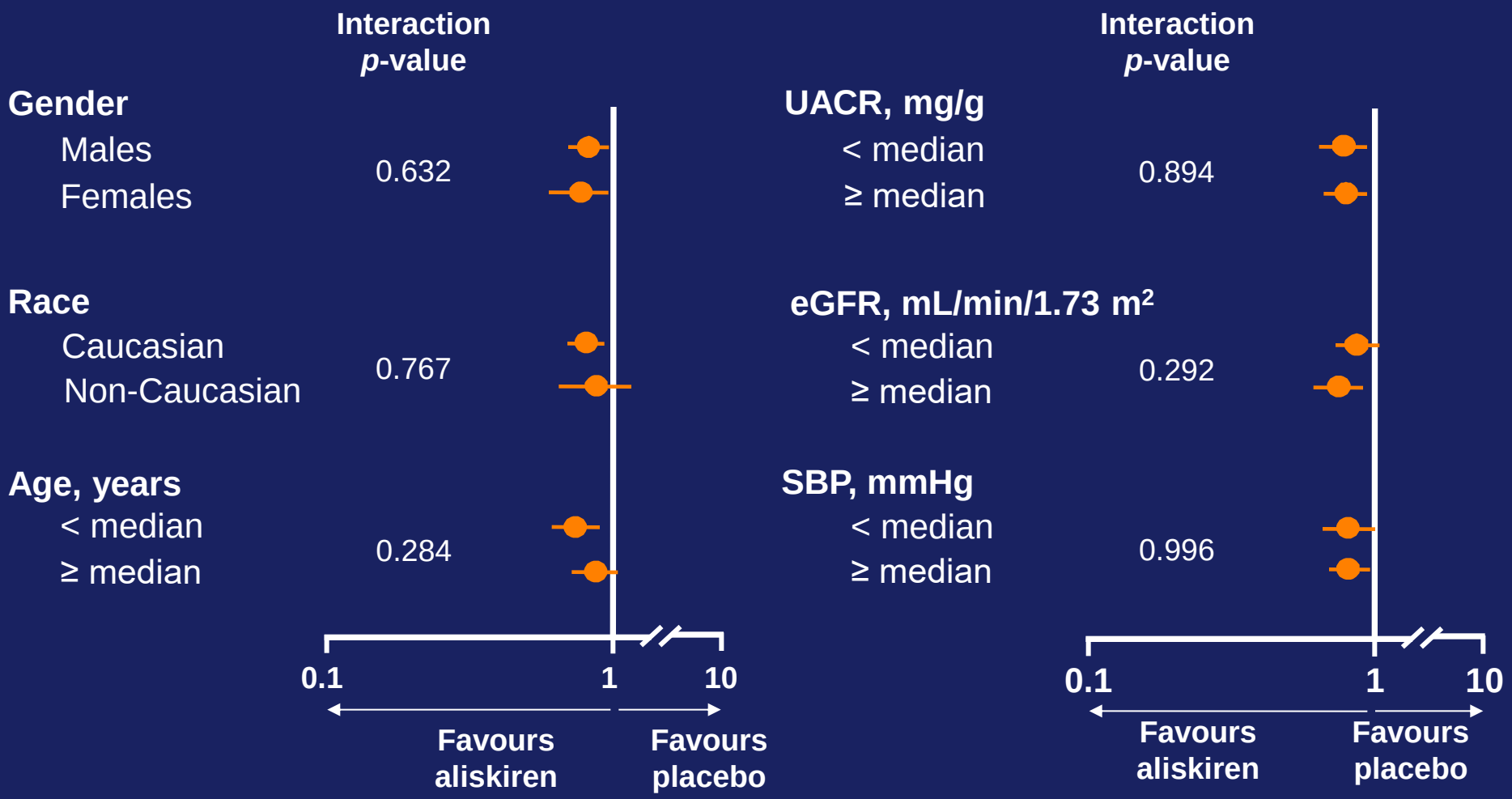
Data are shown as change from baseline in geometric mean (95% CI)
Baseline was the week –2 value
UAER, urinary albumin excretion rate

Aliskiren enabled significantly more patients to achieve a ≥ 50% reduction in UACR from baseline compared with placebo



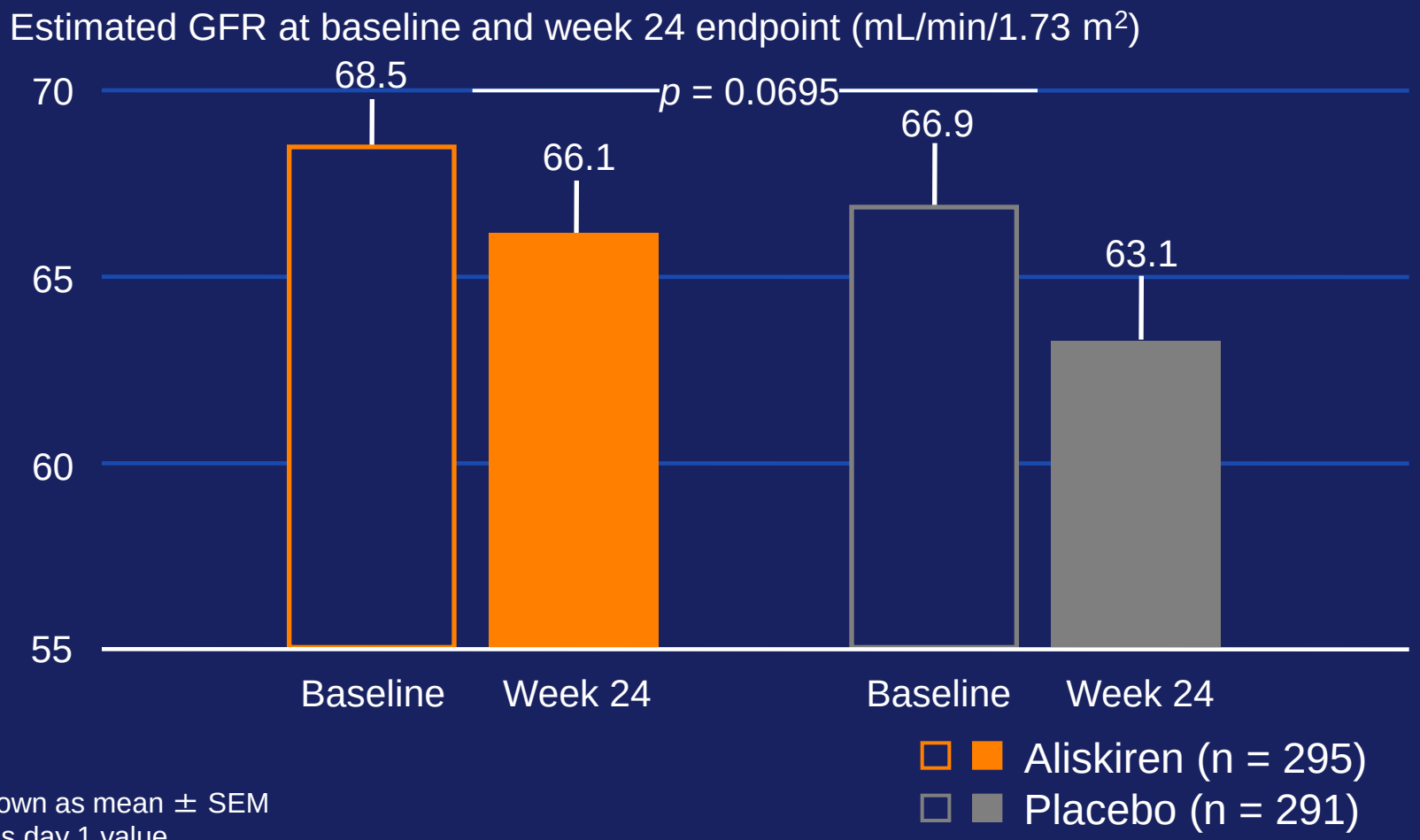
*p = 0.0002 vs placebo
Baseline was week –2 value
UACR, urinary albumin:creatinine ratio

Aliskiren provided greater reductions in UACR than placebo across different patients subgroups



Data are shown as geometric mean with 95% CI for the ratio of the treatment effect for aliskiren:placebo
GFR was calculated using the Modification of Diet in Renal Disease formula
eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary creatinine:albumin ratio

Aliskiren treatment preserved estimated GFR during the study



Data are shown as mean ± SEM
Baseline was day 1 value
GFR values were calculated using the Modification of Diet in Renal Disease formula
GFR, glomerular filtration rate

Addition of aliskiren to losartan and optimal antihypertensive therapy was generally well tolerated during the study

	Aliskiren (n = 301)	Placebo (n = 298)
Any adverse event, n (%)	201 (66.8)	200 (67.1)
Any serious adverse event, n (%)	27 (9.0)	28 (9.4)
Discontinuations due to adverse events, n (%)	17 (5.6)	19 (6.4)
Deaths, n (%)	0	2 (0.7)
Adverse events reported by ≥ 5% of patients in either treatment group, n (%)		
Headache	18 (6.0)	11 (3.7)
Nasopharyngitis	18 (6.0)	15 (5.0)
Dizziness	15 (5.0)	10 (3.4)
Hyperkalemia	15 (5.0)	17 (5.7)
Peripheral edema	13 (4.3)	23 (7.7)

Data are shown for the double-blind period

Aliskiren provides renoprotective benefits in hypertensive type 2 diabetes patients with nephropathy, independent of BP lowering

- The study met its primary objective – aliskiren + losartan provided a significant additional 20% reduction in UACR at week 24 endpoint compared with losartan + placebo
  - At week 12, aliskiren 150 mg significantly reduced UACR by 11% ($p < 0.02$) compared with losartan + placebo
- Aliskiren + losartan resulted in 25% of patients achieving a UACR reduction of ≥ 50% compared with 12.5% receiving placebo + losartan
- Aliskiren was generally well tolerated
  - The frequency of serum creatinine > 2.0 mg/dL was significantly higher in the placebo group than in the aliskiren group, whereas hyperkalemia (≥ 6.0 mEq/L) was higher with aliskiren than placebo
- BP was similar between treatment groups, suggesting that the renoprotective effects of aliskiren were independent of BP lowering

ARB, angiotensin receptor blocker; BP, blood pressure; UACR, urinary albumin:creatinine ratio; UAER, urinary albumin excretion rate

The Steno-2 Study

IMPACT OF TARGET DRIVEN MULTIFACTORIAL INTERVENTION ON CARDIOVASCULAR DISEASE IN MICROALBUMINURIC PATIENTS WITH TYPE 2 DIABETES

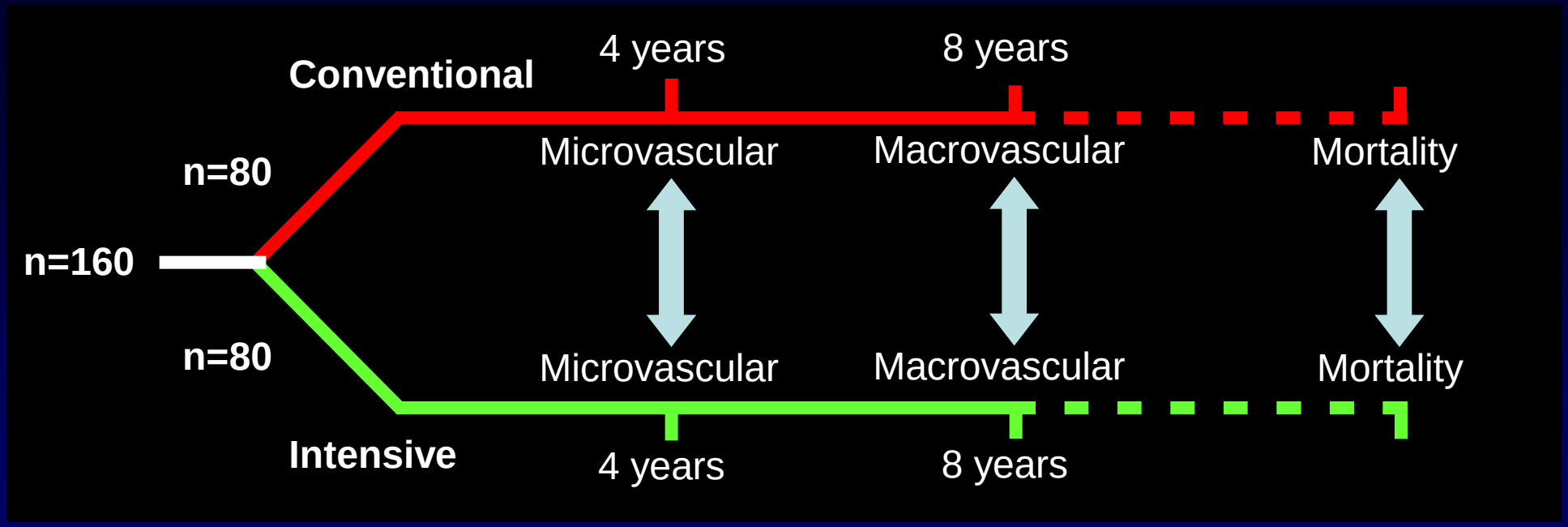
Peter Gæde
Pernille Vedel
Nicolai Larsen
Gunnar VH Jensen
Hans-Henrik Parving
Oluf Pedersen

Steno Diabetes Center

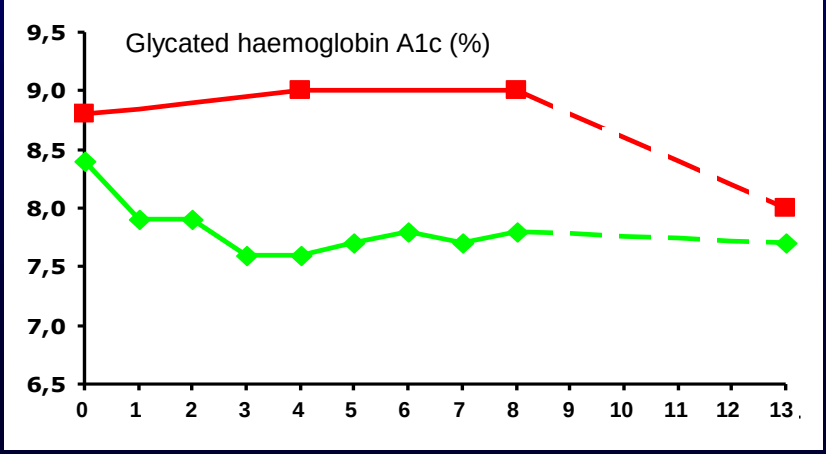
Gæde P et al. N Engl J Med 2003;348:383-93

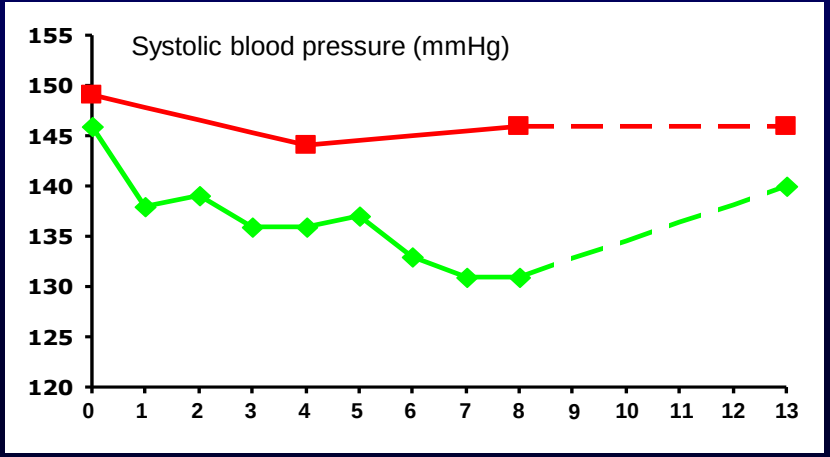
Steno-2: Design

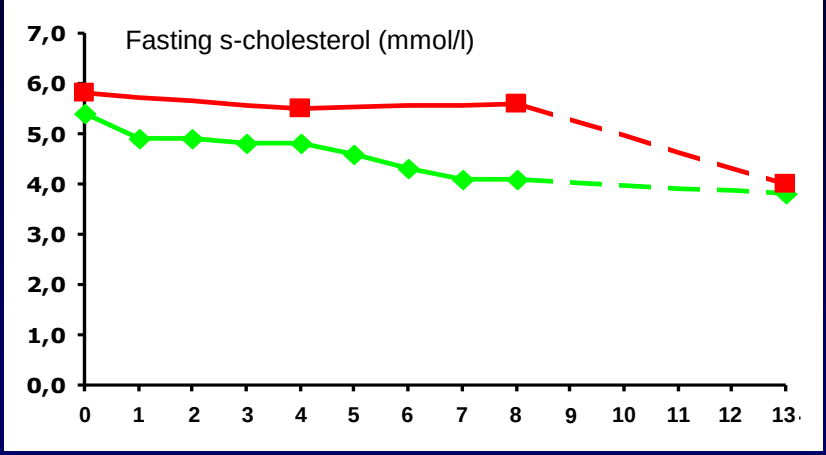
- **Pre-planned endpoint examinations at 4, 8 years after randomization and after 60 cases of mortality**
- **Interventional part of study ended after 8 years**

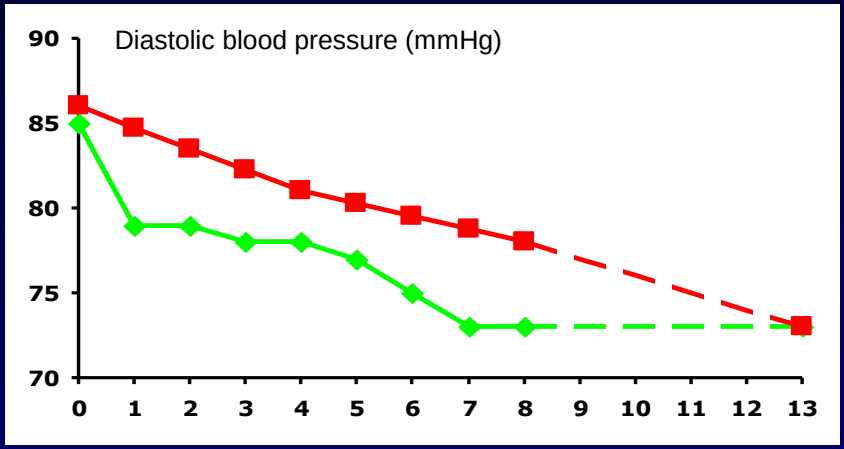


Risk markers during follow-up



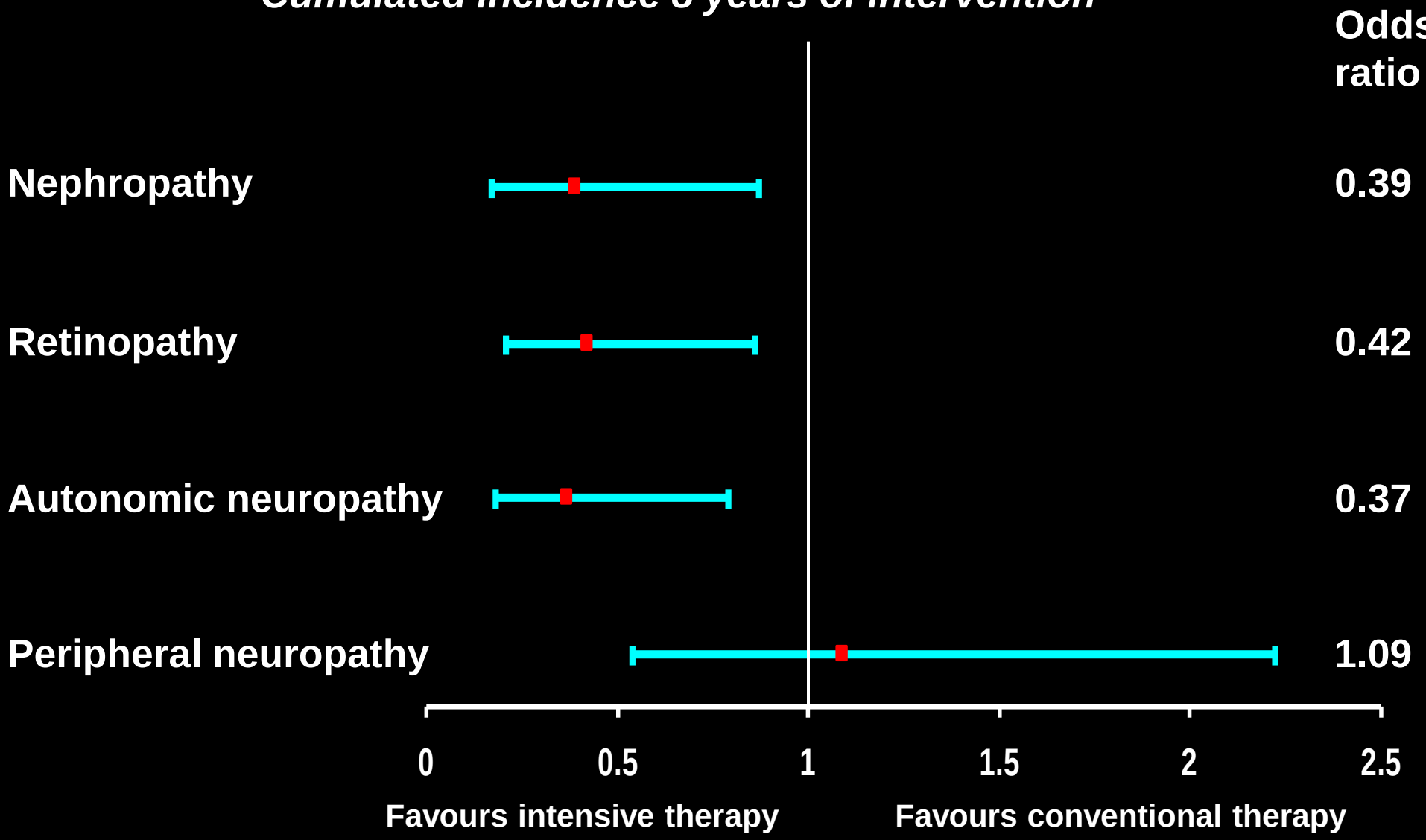




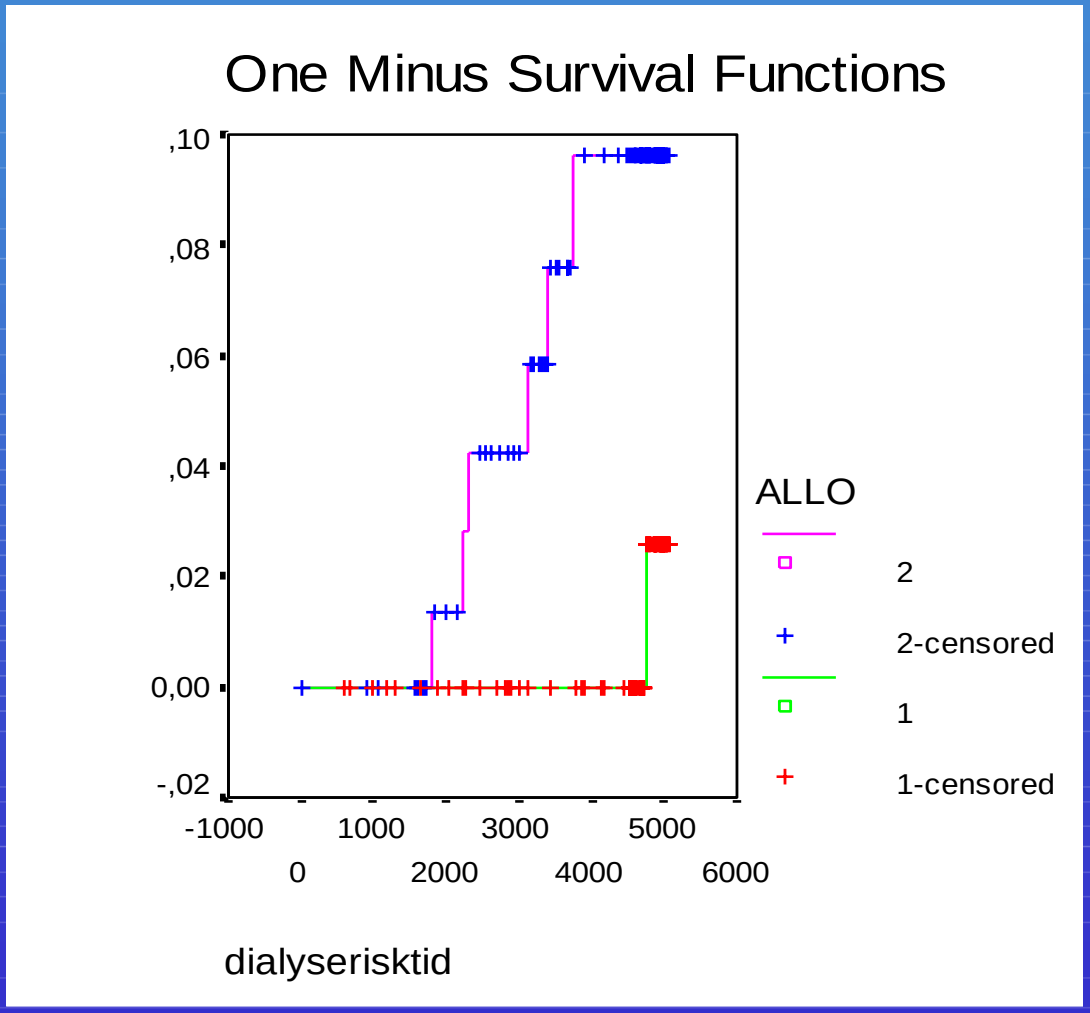


Microvascular complications

Cumulated incidence 8 years of intervention



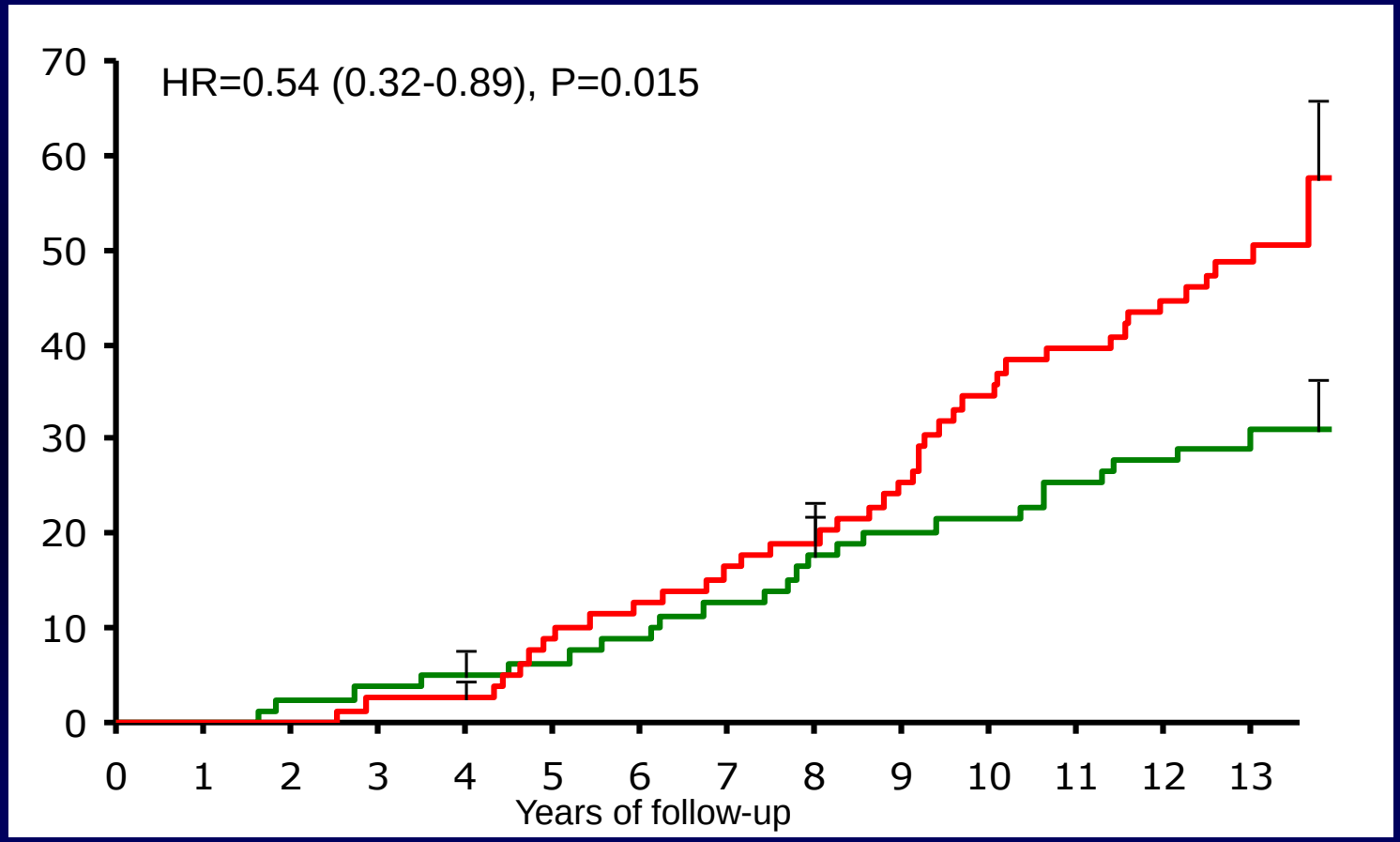
End-stage renal failure requiring dialysis



6 patients in the original conventionally treated group versus 1 patient in the intensively treated group progressed to end-stage renal disease requiring dialysis treatment

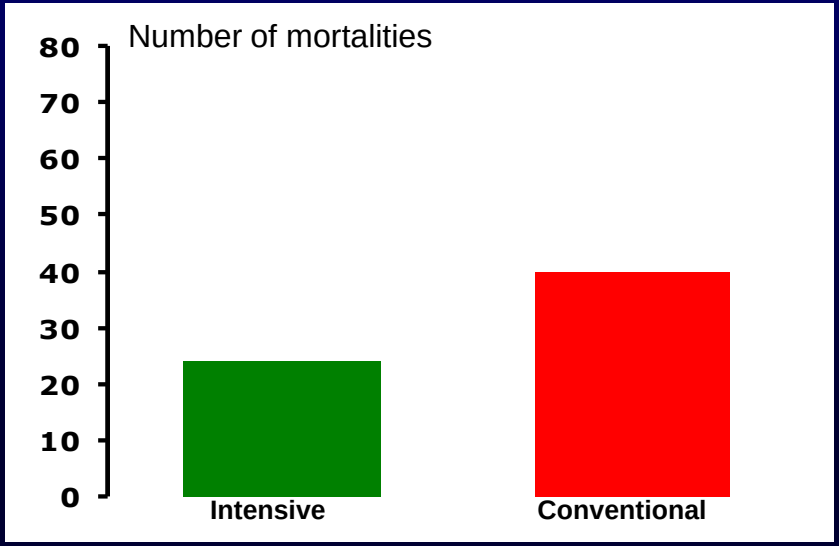
log-rank p=0.039

Steno-2 Extension Study: Mortality



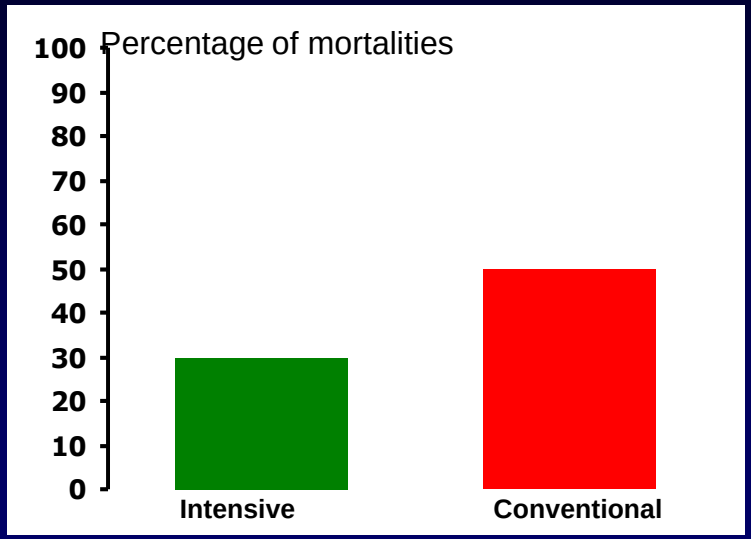
Numbers at risk								
Conventional	80	80	77	69	63	51	43	30
Intensive	80	78	75	72	65	62	57	39

Steno-2 Extension Study: Mortality



24 patients died in the intensive group compared to 40 patients in the conventional group

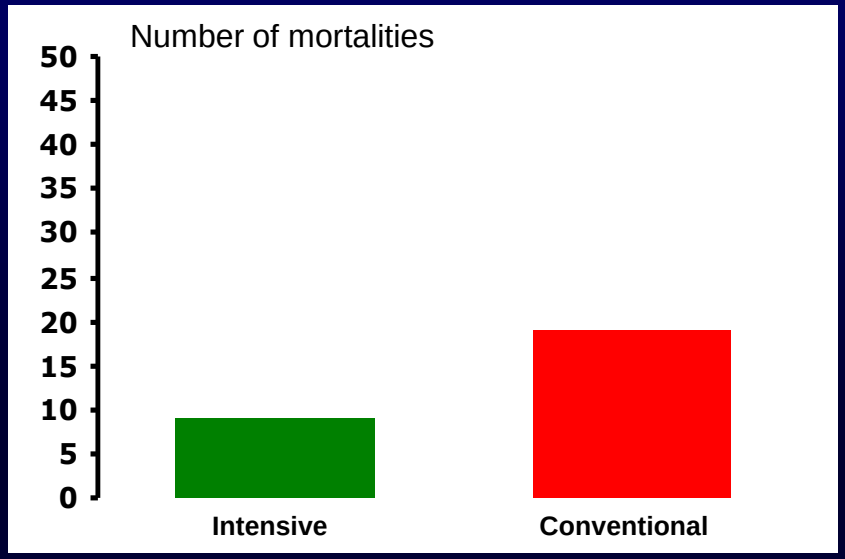
HR = 0.54 (0.32-0.89), P=0.015



30% of patients died in the intensive group compared to 50% of patients in the conventional group

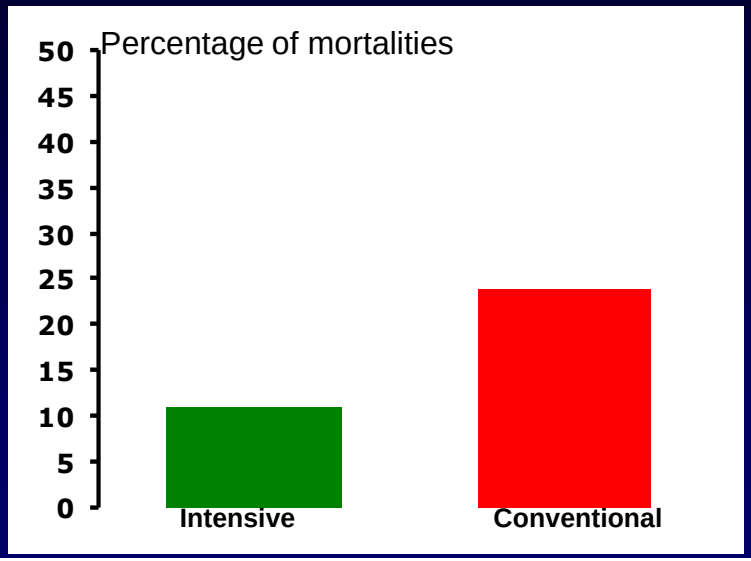
Absolute risk reduction = 20%

Steno-2 Extension Study: CVD Mortality



9 patients died of CVD in the intensive group compared to 19 patients in the conventional group

HR = 0.43 (0.19-0.95), P=0.036

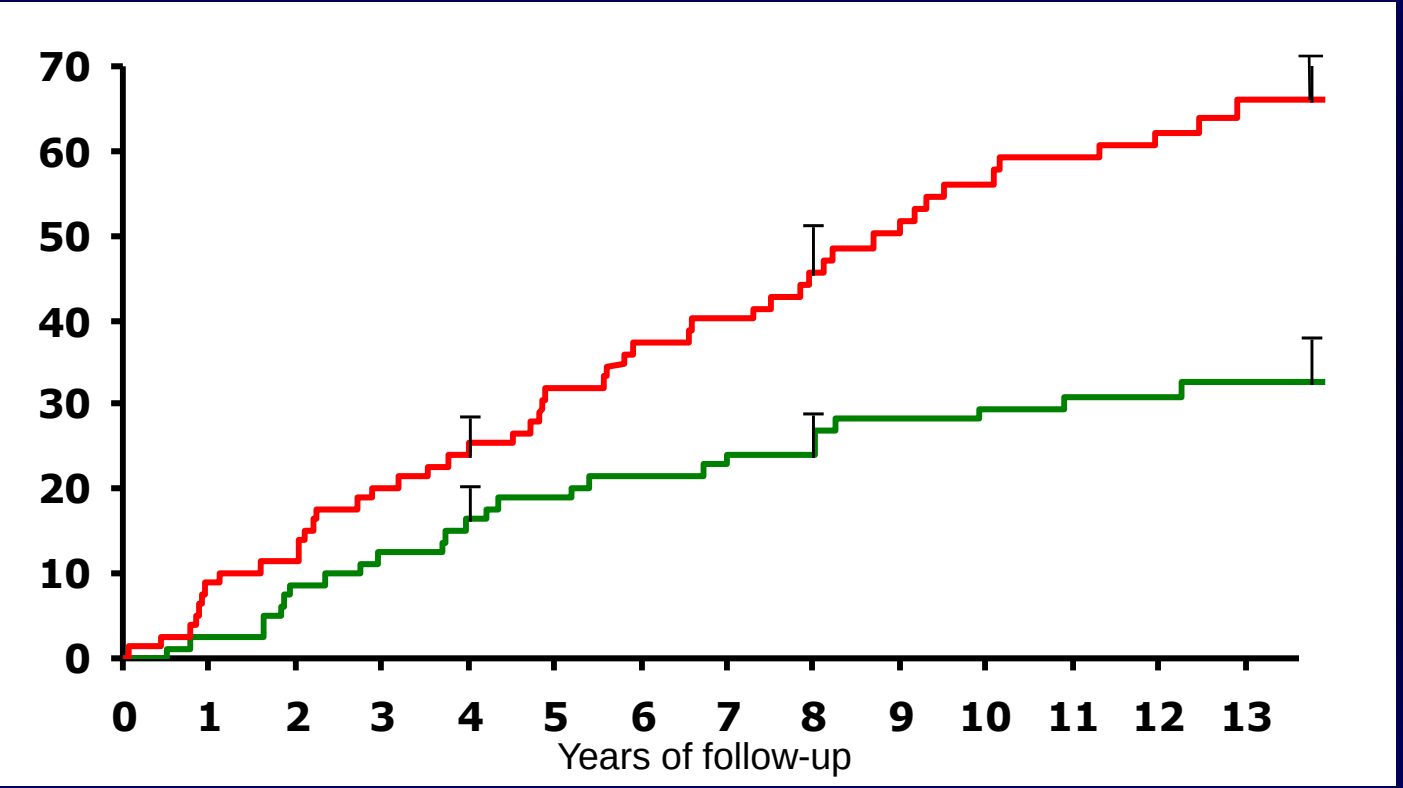


11% of patients died in the intensive group compared to 24%of patients in the conventional group

Absolute risk reduction = 13%

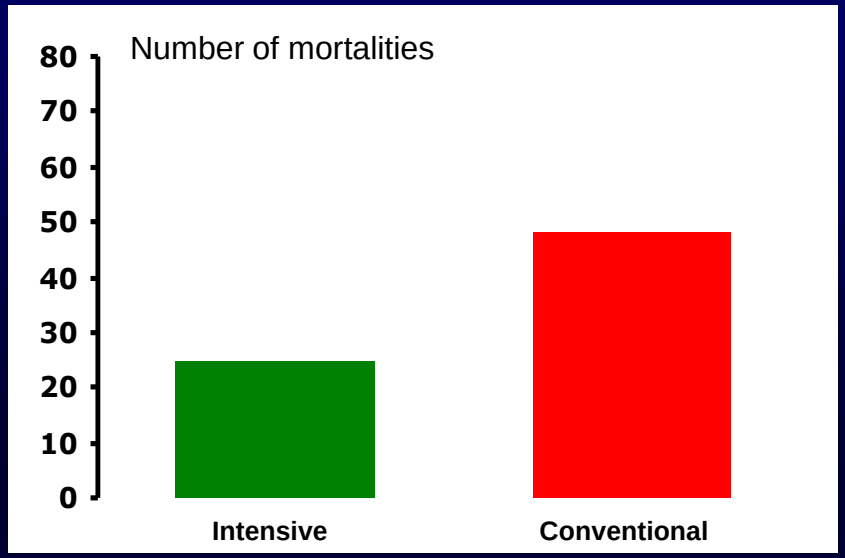
Steno-2 Extension Study: Any CVD

Percentage of patients with a major CVD event during follow-up



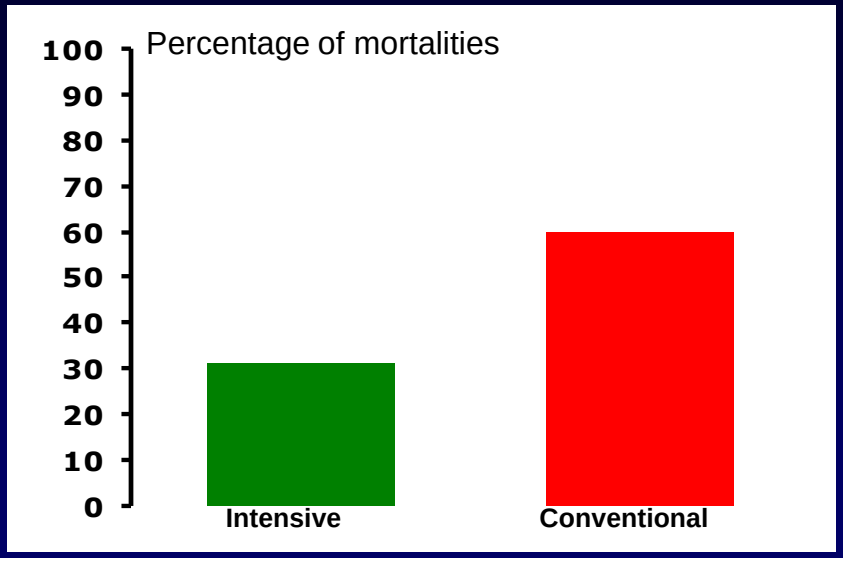
Numbers at risk								
Conventional	80	70	606	46	38	29	25	14
Intensive	80	72	5	61	56	50	47	31

Steno-2 Extension Study: Any CVD



25 patients had a CVD event in the intensive group compared to 48 patients in the conventional group

HR = 0.41 (0.25-0.67), P=0.0003

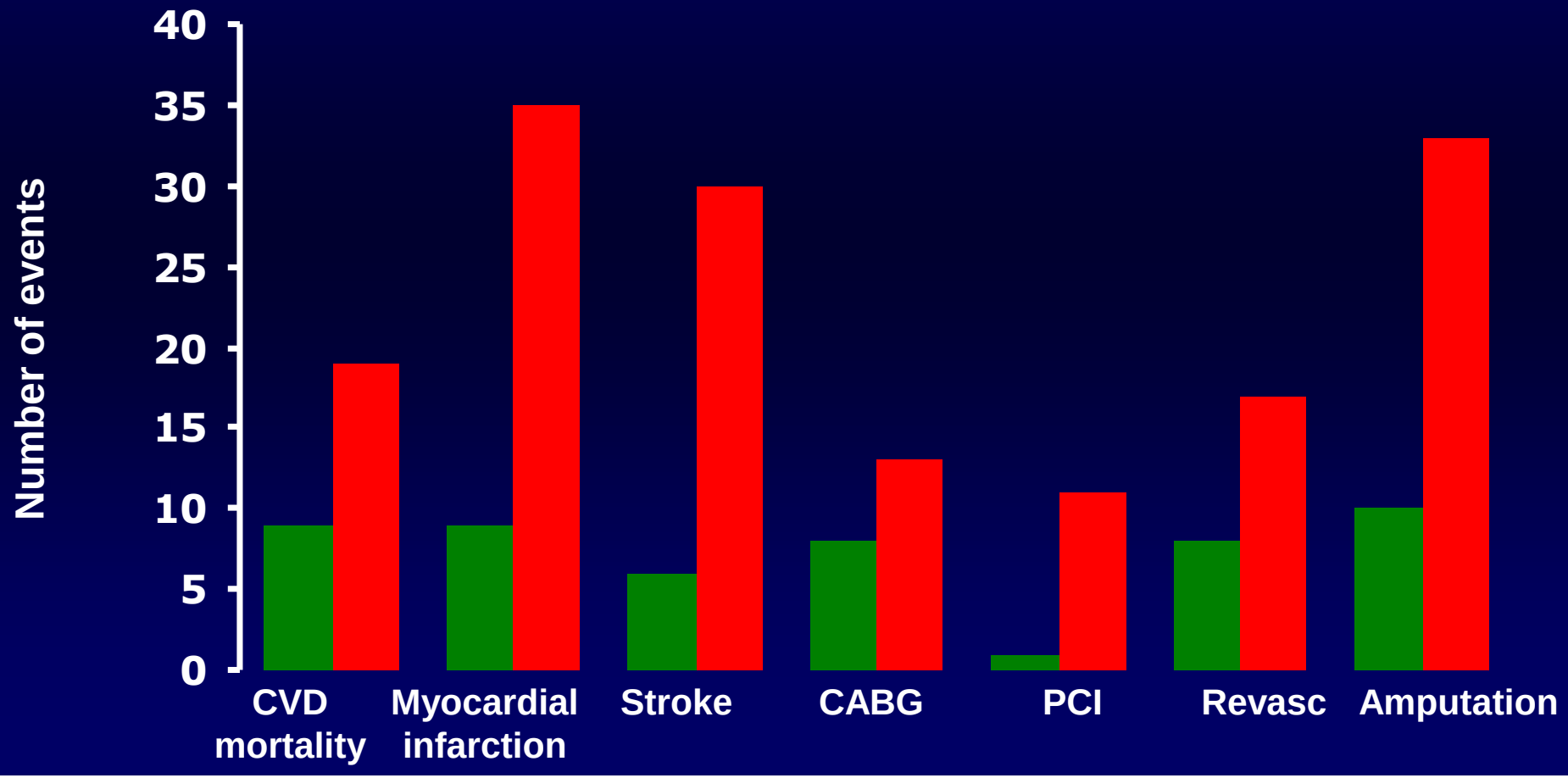


31% of patients had a CVD event in the intensive group compared to 60%of patients in the conventional group

Absolute risk reduction = 29%

Steno-2 Post Trial: Any CVD

51 major CVD events in 25 patients (31%) occurred in the intervention group compared to 158 events in 48 patients (60%) in the conventional group



Steno-2: Number needed to treat

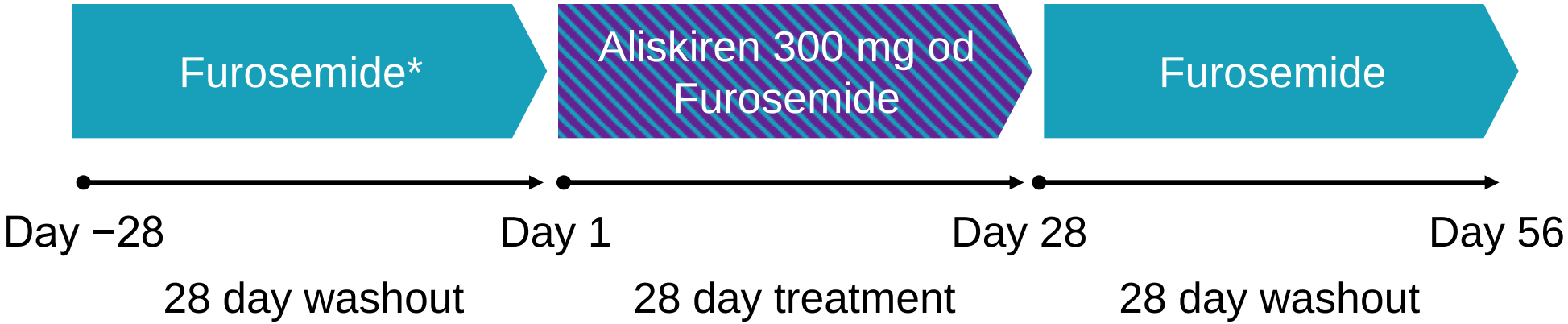
Number of patients with type 2 diabetes needed to treat for 13.3 years to prevent one …..

Death	*5 patients*
Cardiovascular death	*8 patients*
Major cardiovascular event	*3 patients*
Progression to nephropathy	*5 patients*
Dialysis	*16 patients*
Laser treatment	*7 patients*

Steno-2: Major clinical results

- A 50 % relative risk reduction in microvascular disease after 4 years of intervention maintained throughout the rest of follow-up
- A 50 % relative risk reduction in major cardiovascular events after 8 years of intervention maintained throughout the rest of follow-up
- A 50 % relative reduction in mortality after 13 years of follow-up

Study 2242 – Design



Patients with type 2 diabetes, hypertension and albuminuria received stable doses of furosemide throughout the study

UACR: Morning spot urine on Day 1–56

24-hour BP: Day 3, 7, 14, 28, 31, 35, 42, 56

Mean baseline UACR = 173 mg/day

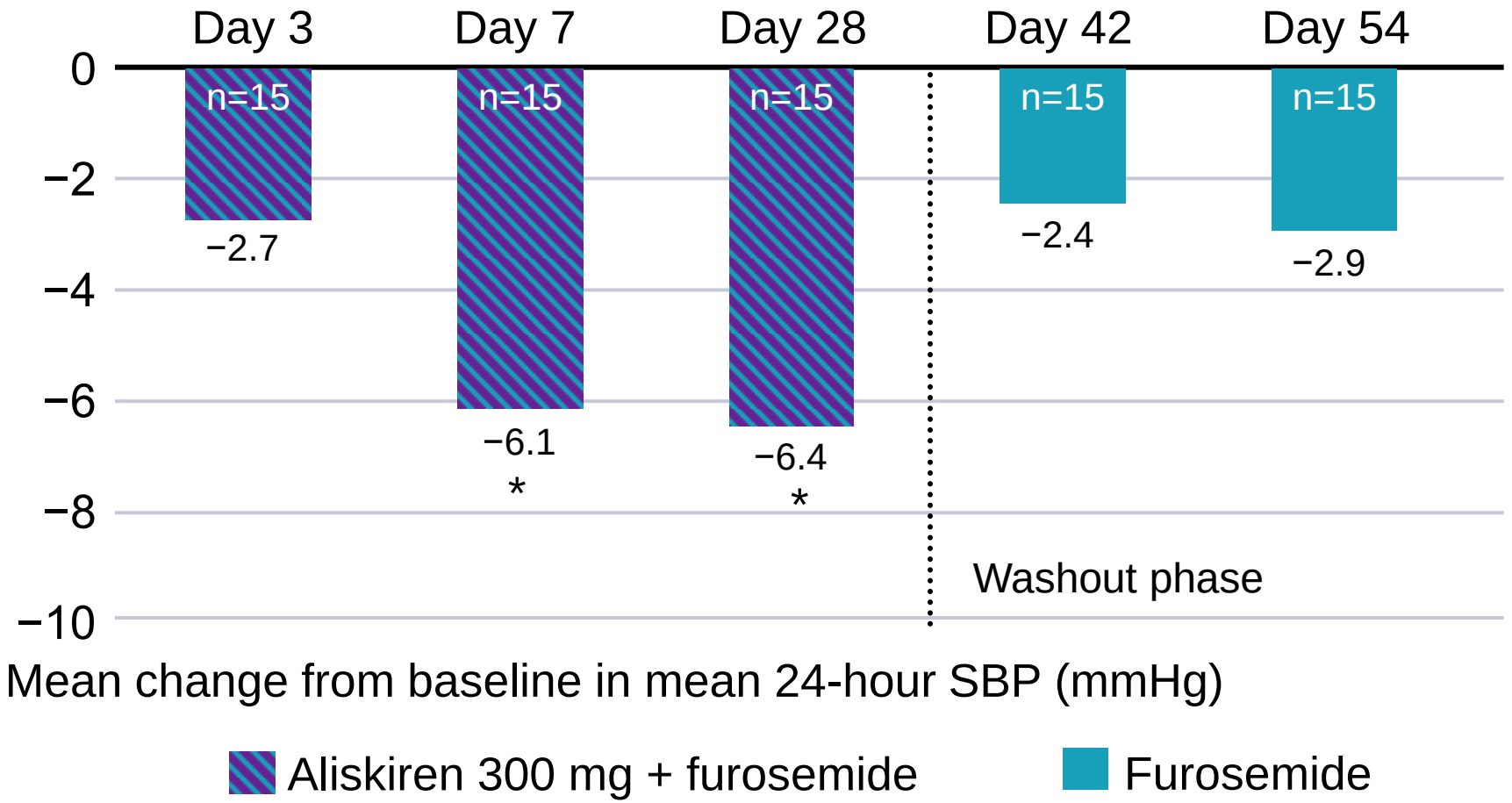
*slow-release furosemide in stable dose

Persson F, *et al*. 2007 (Study 2242)

Additional data in diabetic patients

Study 2242:
Anti-proteinuric effect of aliskiren in patients with hypertension and Type 2 diabetes

Study 2242 – Aliskiren provides significant reductions from baseline in mean 24-hour SBP



*p<0.05 vs baseline

Persson F, *et al*. 2007 (Study 2242)