Is there a Role for Direct Renin Inhibitors?

Frederik Persson, MD

Steno Diabetes Center, Denmark

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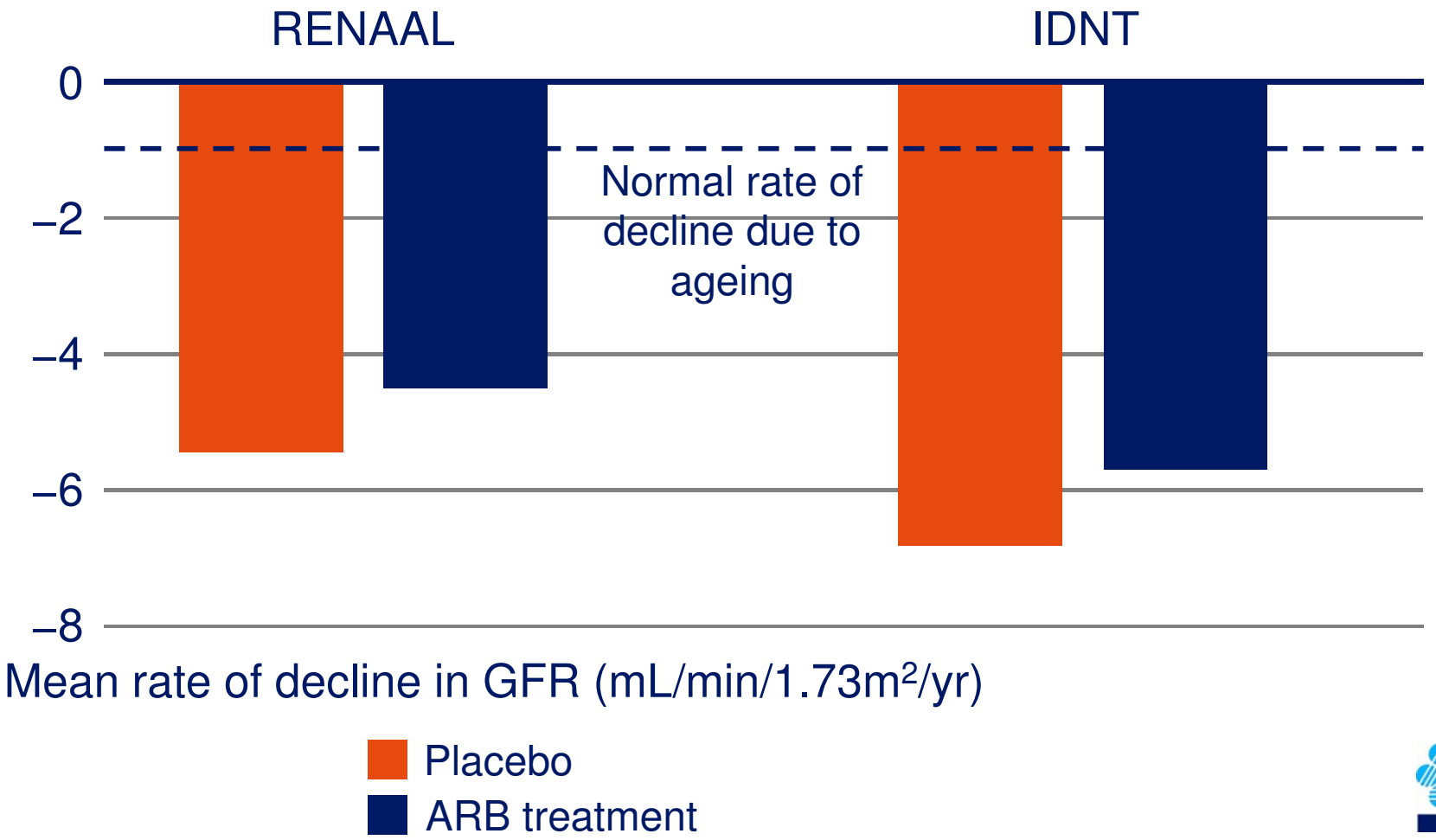
Unmet need for improved treatment



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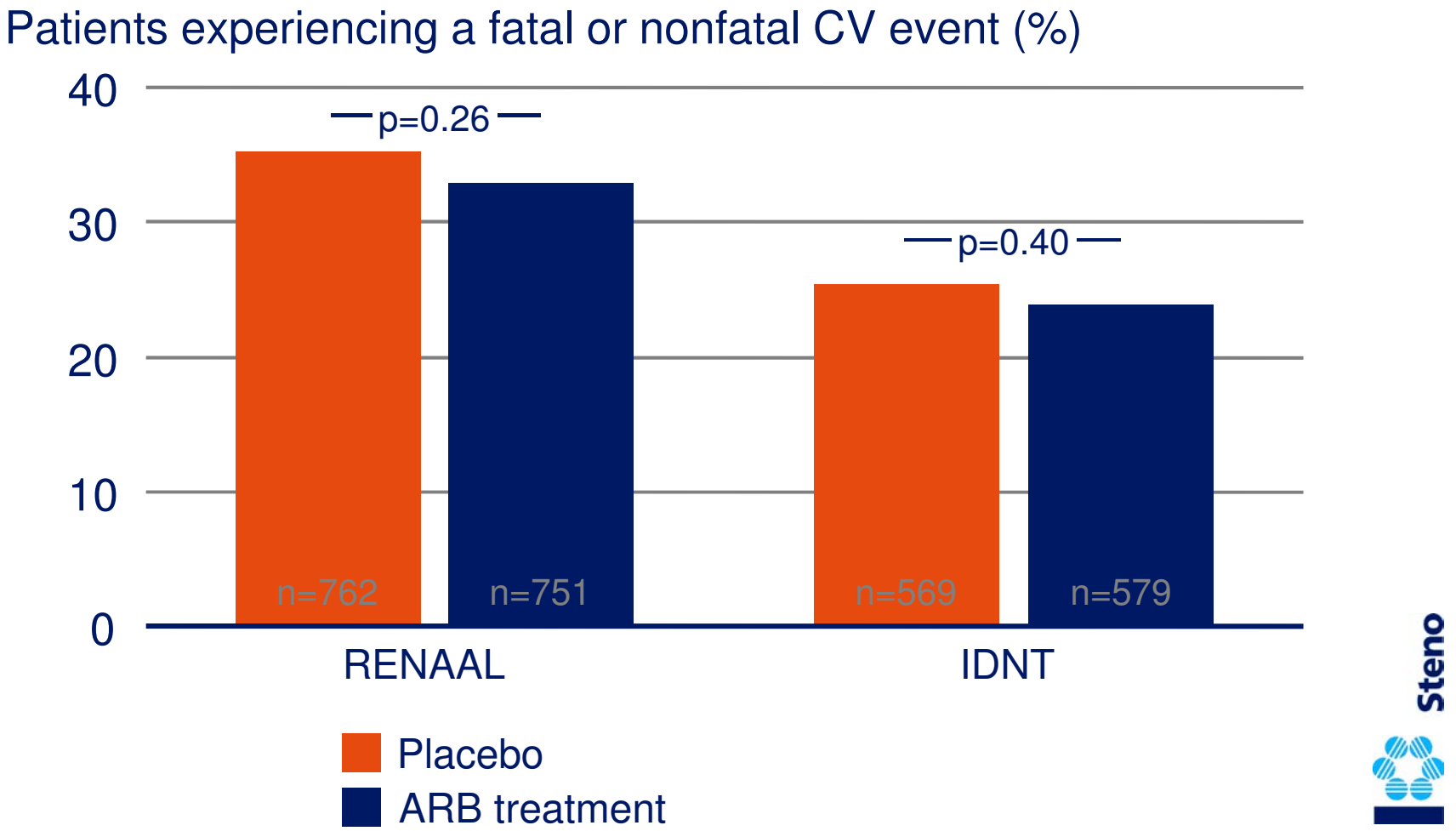
Brenner *et al*. 2001; Lewis *et al*. 2001

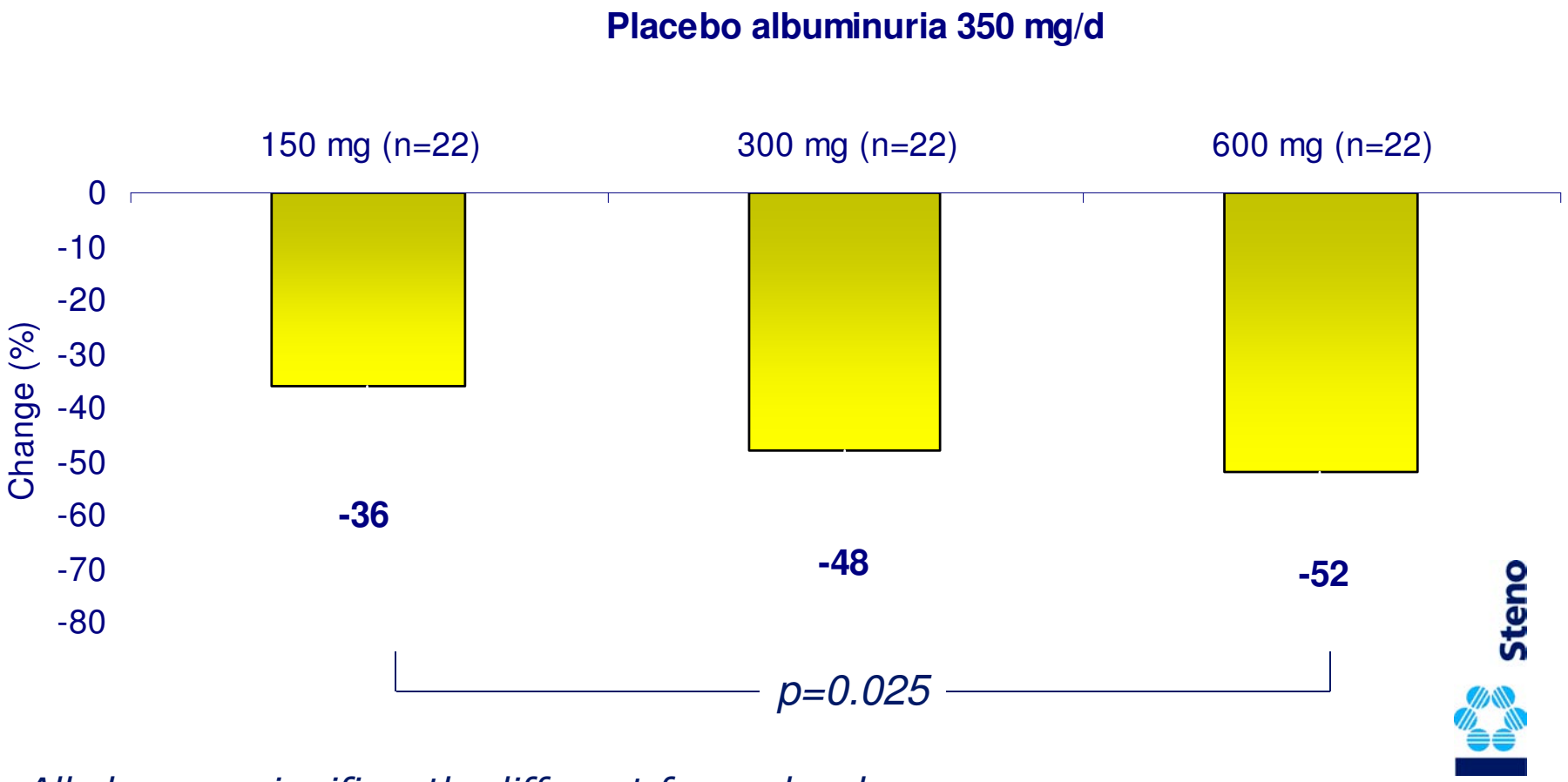
Even more in CVD



Brenner *et al*. 2001; Lewis *et al*. 2001

Change in albuminuria vs. placebo

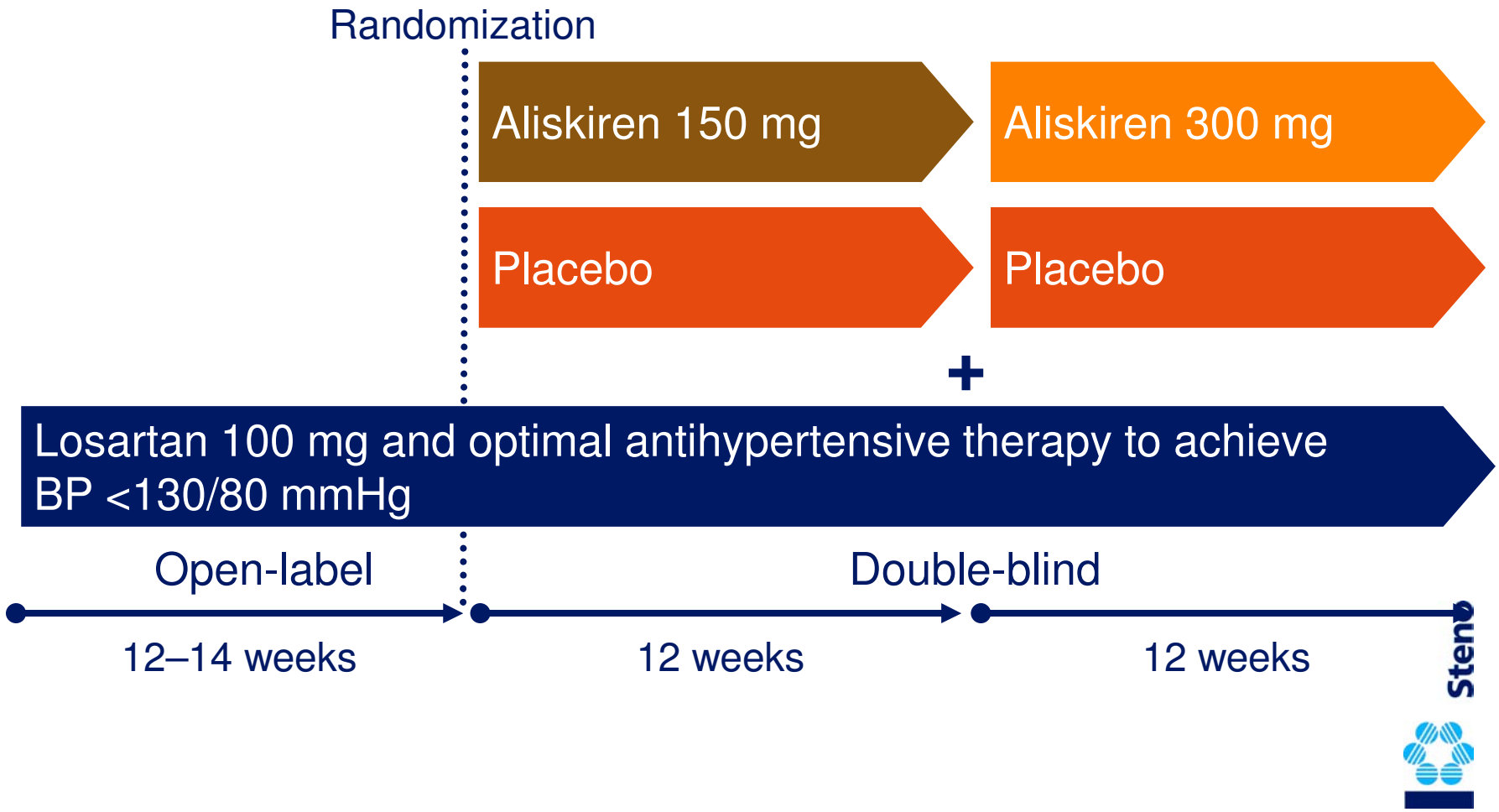
Patients with type 2 diabetes, hypertension and albuminuria



All changes significantly different from placebo.

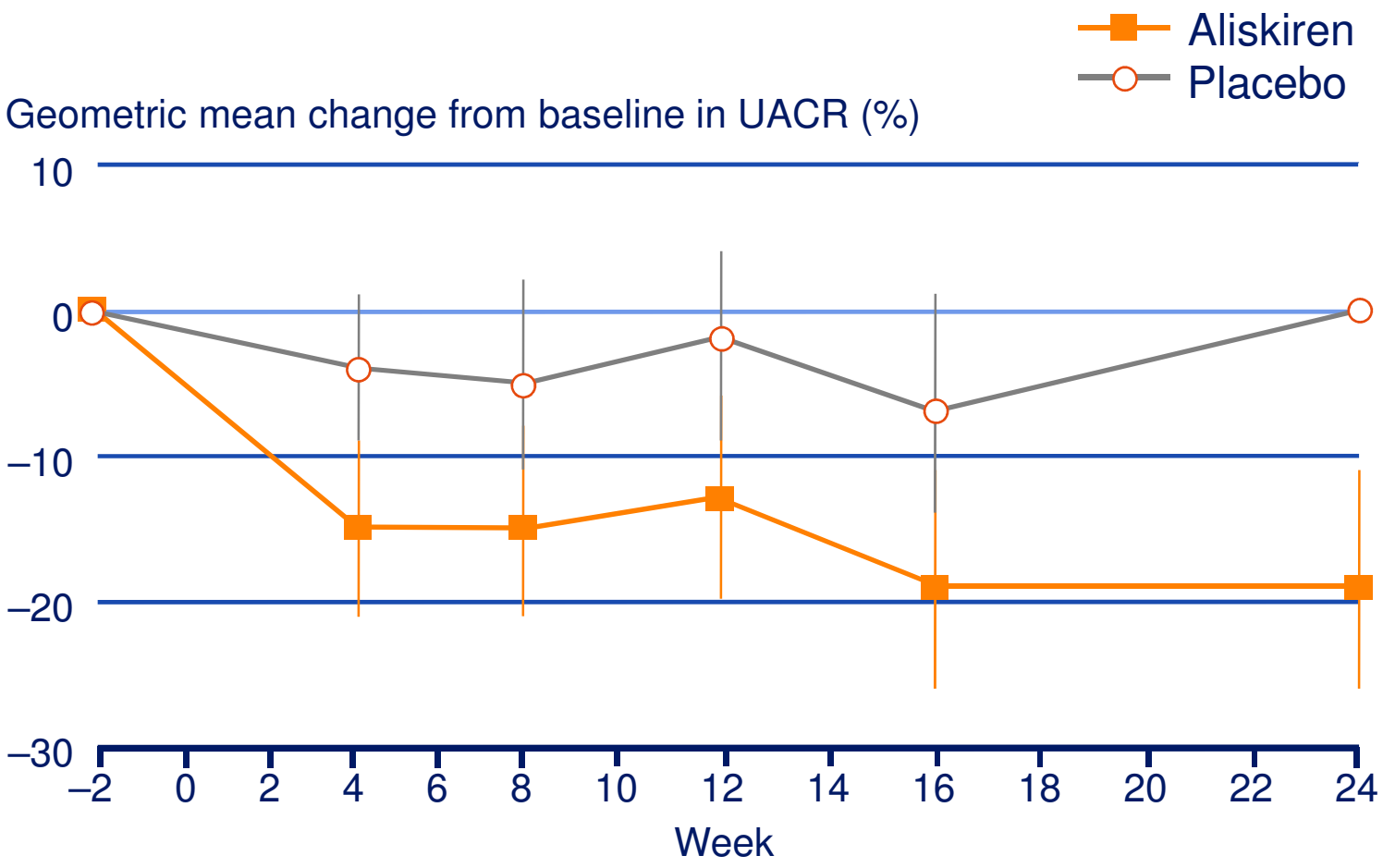
Persson et al. Diabetologia 2010

Aliskiren in patients with hypertension, Type 2 diabetes and proteinuria



Parving et al. NEJM 2008

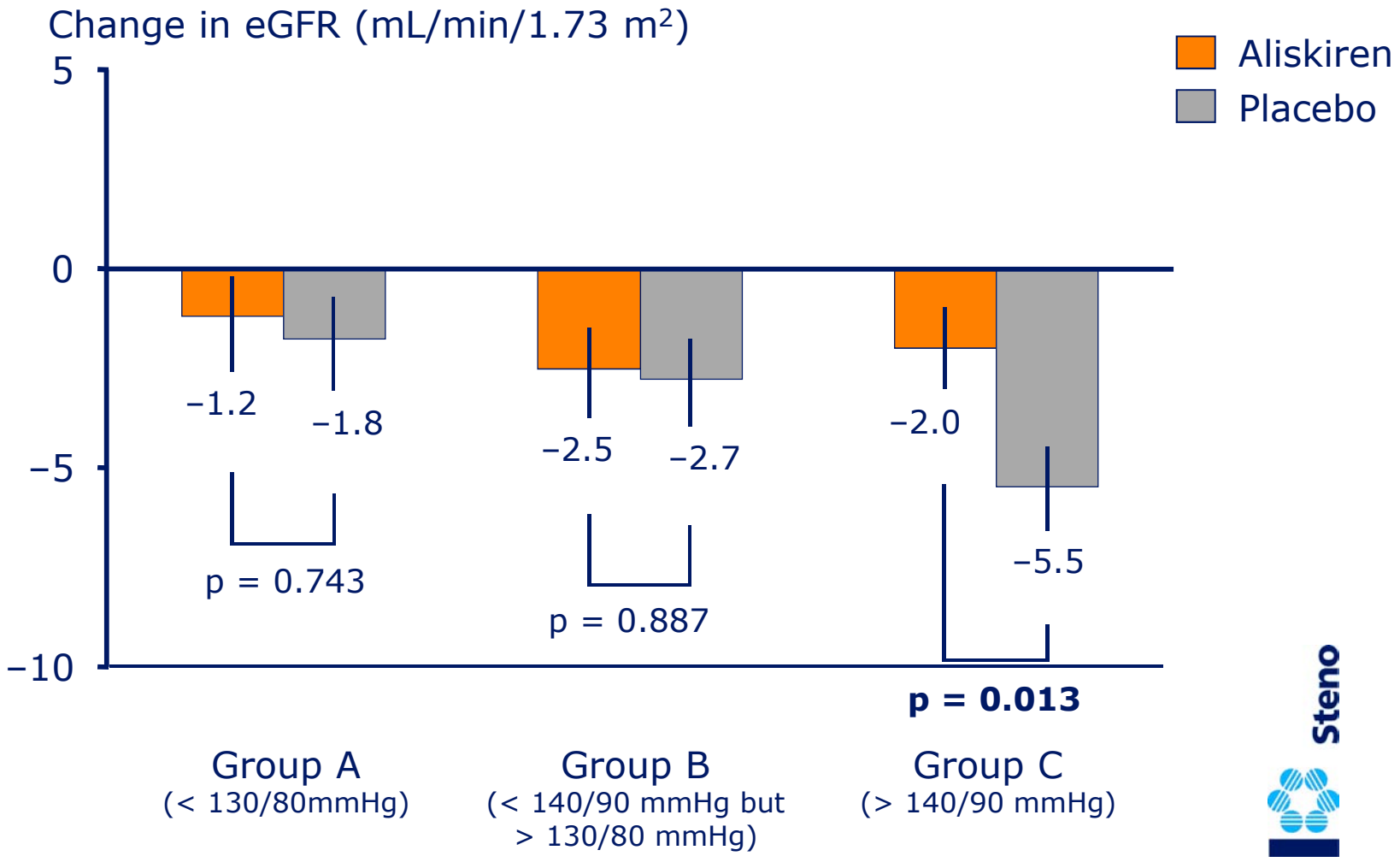
Changes in UACR with aliskiren and placebo in the AVOID study



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

Parving et al. NEJM 2008

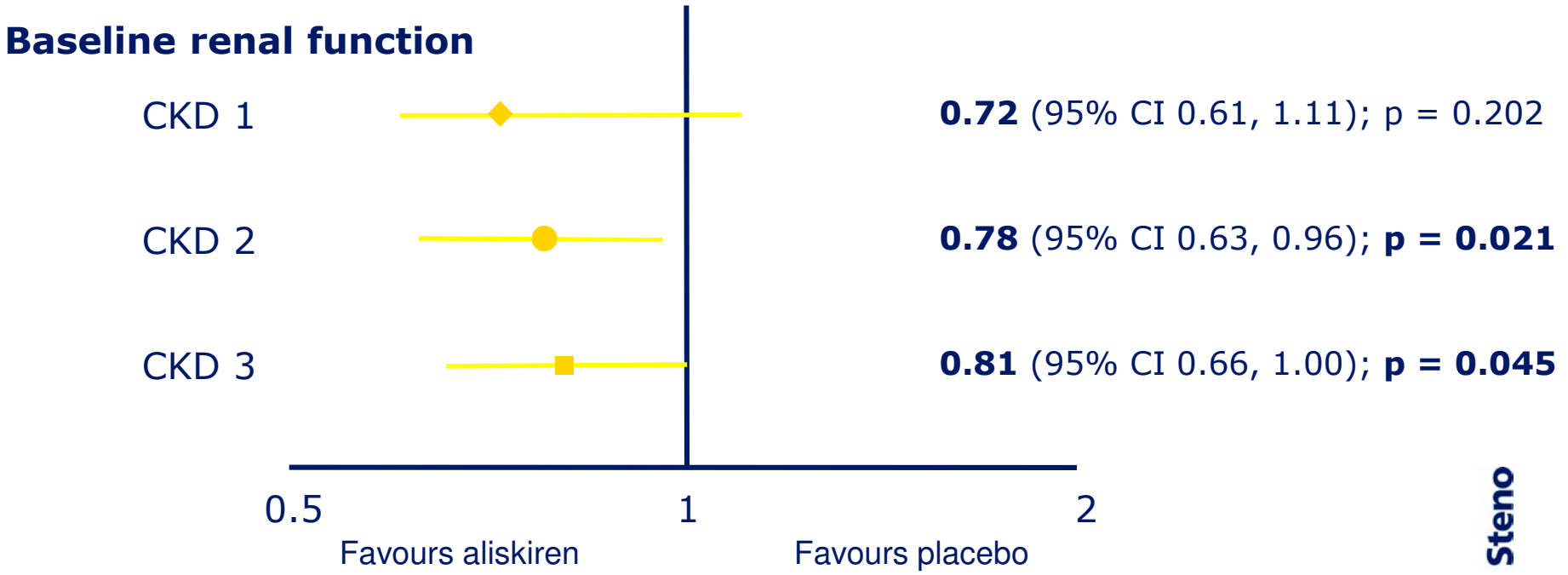
eGFR change from baseline at week 24
according to BP subgroups



Persson et al. CJASN 2011

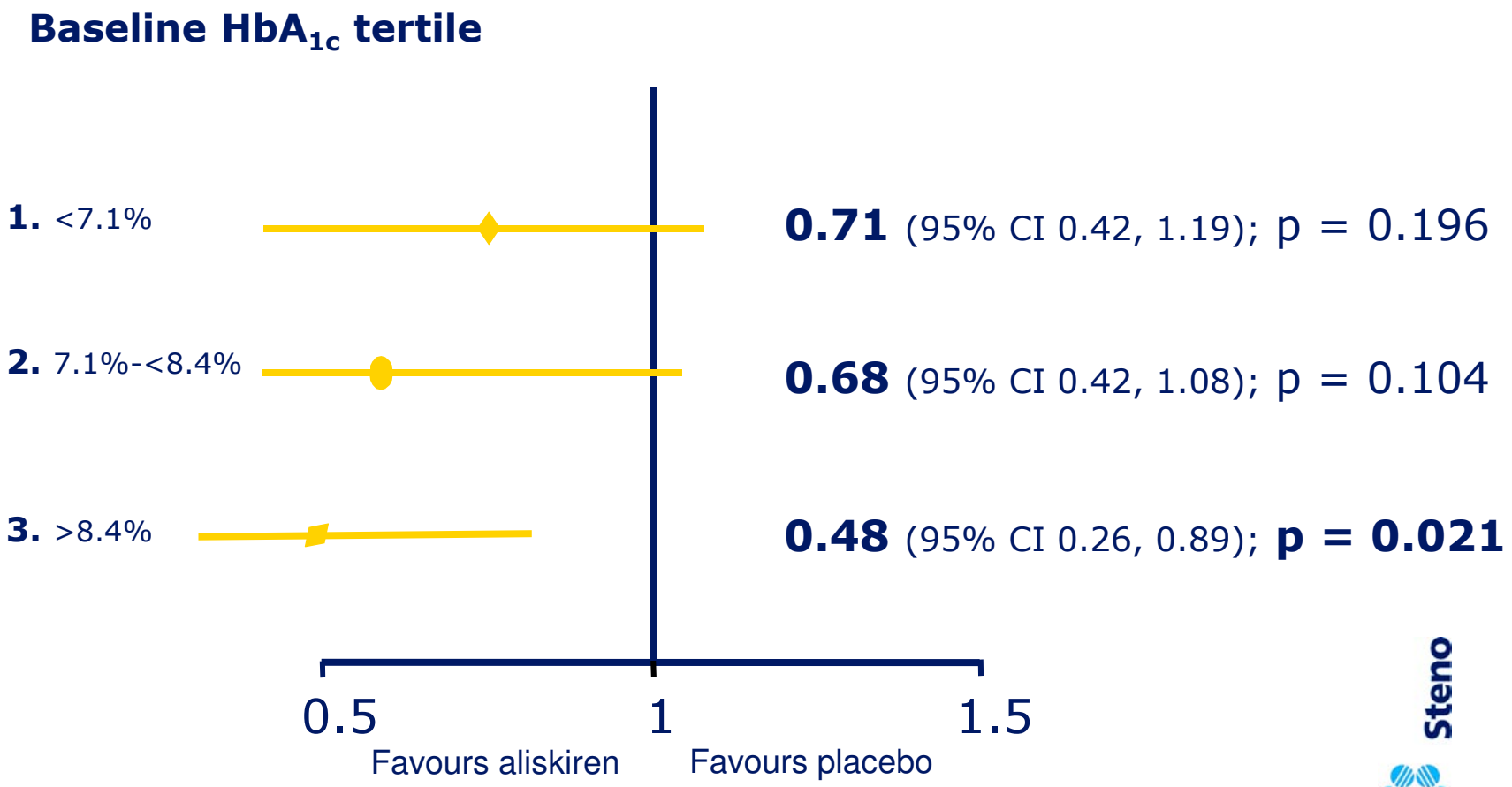
Efficacy

UACR reduction at 24 weeks



Persson et al. Diabetes Care 2010

Efficacy in relation to glycemia



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Persson et al. JRAAS 2012

Hyperkalemia

defined as a *single* serum potassium value above 5.5 mmol/L

	Aliskiren	Placebo	P
CKD 3 n (%)	29 (22.5)	16 (13.6)	0.07
CKD 2 n (%)	10 (9.6)	14 (11.5)	0.65
CKD 1 n (%)	2 (3.2)	2 (3.9)	1.00

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Persson et al. Diabetes Care 2010

Hypotension
Investigator defined

	Aliskiren	Placebo	P
CKD 3 n (%)	5 (3.9)	1 (0.8)	0.215
CKD 2 n (%)	5 (4.8)	1 (0.8)	0.097
CKD 1 n (%)	2 (3.1)	0	0.502

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Persson et al. Diabetes Care 2010

Hypotension
investigator defined

	Aliskiren		Placebo		
BP group					
	n	%	n	%	*p*-value
Group A (<130/80 mmHg)	7	**9.2**	0	0	**0.005**
Group B (<140/90 mmHg but >130/80 mmHg)	2	2.1	1	1.1	0.621
Group C (>140/90 mmHg)	3	2.3	2	1.7	0.999

No differences between the subgroups for hyperkalemia or renal dysfunction

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Persson et al. CJASN 2011

ALTITUDE study – Design

Study design:	Randomized, double-blind, placebo-controlled study
Study population:	8606 patients
Inclusion criteria:	Type 2 diabetes 1.Persistent macroalbuminuria (UACR ≥200 mg/g) and eGFR ≥30 mL/min/1.73 m^2 2.Persistent microalbuminuria (UACR ≥20 mg/g and <200 mg/g) and a mean eGFR ≥30 and <60 mL/min/1.73 m^2 3. A history of cardiovascular disease (e.g. myocardial infarction, stroke, heart failure or coronary artery disease) and a mean eGFR ≥ 30 and <60 mL/min/1.73 m^2 Concomitant treatment must include an ACEI or an ARB

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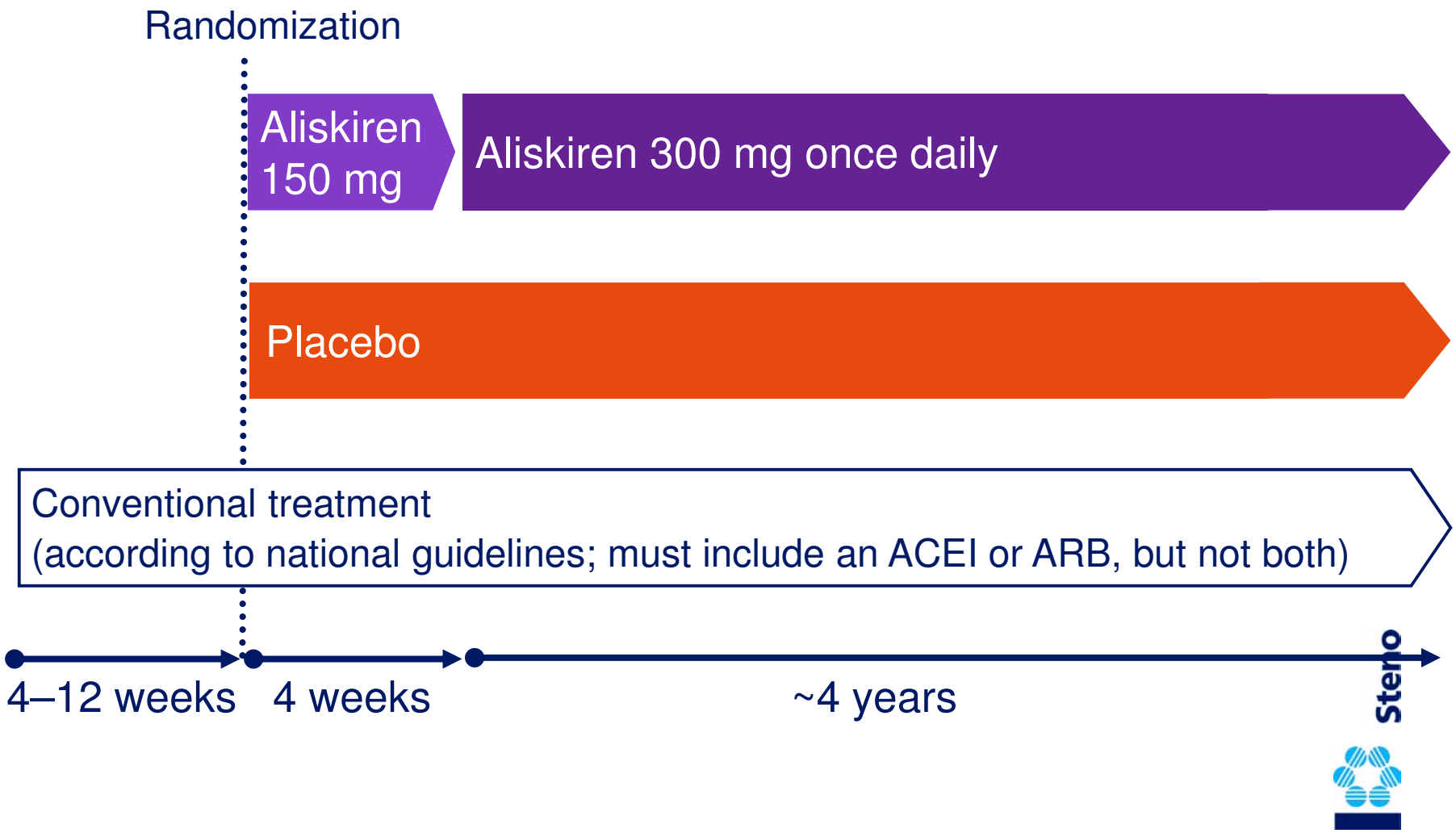
ALTITUDE study – Design overview



ALTITUDE– Primary endpoint

Composite of:

cardiovascular (CV) death, resuscitated sudden death, non-fatal myocardial infarction (MI), non-fatal stroke, unplanned hospitalization for heart failure, ESRD or renal death (death attributable to kidney failure, need for renal replacement therapy with no dialysis or transplantation available or applied) or doubling of baseline serum creatinine concentration, sustained for at least a month.

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Parving et al. NDT 2009

ALTITUDE baseline

Variable	Total (*N* = 8606)
Age, years	65.0 (58, 72)
Male, *n* (%)	5851 (68.0)
Race, *n* (%)	
White	4873 (56.6)
African American	280 (3.3)
Asian	2726 (31.7)
Native American	10 (0.1)
Other	703 (8.2)
Pacific island	14 (0.2)
Body mass index (kg/m^2)	29.1 (25.7, 33.2)
Known duration of diabetes, *n* (%)	
≤ 1 year	288 (3.3)
> 1–5 years	1229 (14.3)
≥ 5 years	7086 (82.3)
Retinopathy, %	36.8

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Parving et al. JRAAS 2012

ALTITUDE baseline

Any of the following cardiovascular diseases, *n* (%)	4118 (47.9)
Congestive heart failure or hospitalization for congestive heart failure	960 (11.2)
Unstable angina pectoris	830 (9.6)
Myocardial infarction	1434 (16.7)
Prior percutaneous coronary intervention	1224 (14.2)
Prior coronary artery bypass graft	1067 (12.4)
Stroke	852 (9.9)
Transient ischaemic attack	353 (4.1)
Amputation of toe/foot/leg	341 (4.0)

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ALTITUDE baseline

Diastolic blood pressure, mmHg	74.3 (67.3, 80.7)
Systolic blood pressure, mmHg	134.7 (126.0, 149.7)
Pulse pressure, mmHg	62.0 (52.0, 73.3)
Serum creatinine, µmol/L	115.0 (91.0, 137.0)
eGFR, ml/min per 1.73 m^2	51.7 (41.9, 64.9)
eGFR, ml/min per 1.73 m^2 category, *n* (%)	
< 30	220 (2.6)
≥ 30 to < 45	2574 (29.9)
≥ 45 to < 60	3024 (35.1)
≥ 60	2781 (32.3)

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Event adjudication – Dec 20th 2011

- 1123 adjudicated events - 69%
- 581 events (13.6%) with aliskiren vs. 542 (12.6%) placebo
- Hazard ratio 1.09 (0.97, 1.22), for primary composite endpoint
- Hazard ratio 1.14 (0.99, 1.30) for secondary cardiovascular endpoint
- Hazard ratio 1.34 (1.01, 1.34) p=0.044 for stroke

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Secondary renal endpoint -Dec 20th 2011

- Hazard ratio 0.93 (0.76, 1.15)
- Doubling of Screa – 141 vs. 159
- ESRD or renal death – 72 vs. 60

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Adverse events - Dec 20th 2011

- Renal serious adverse events – 201 vs. 142, $p<0.001$
- Serious adverse events of hyperkalemia – 46 vs. 14, $p<0.001$

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Continued studies

- ATMOSPHERE - aliskiren vs. ramipril vs. combination in heart failure

- APOLLO – aliskiren in the elderly

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