Aliskiren

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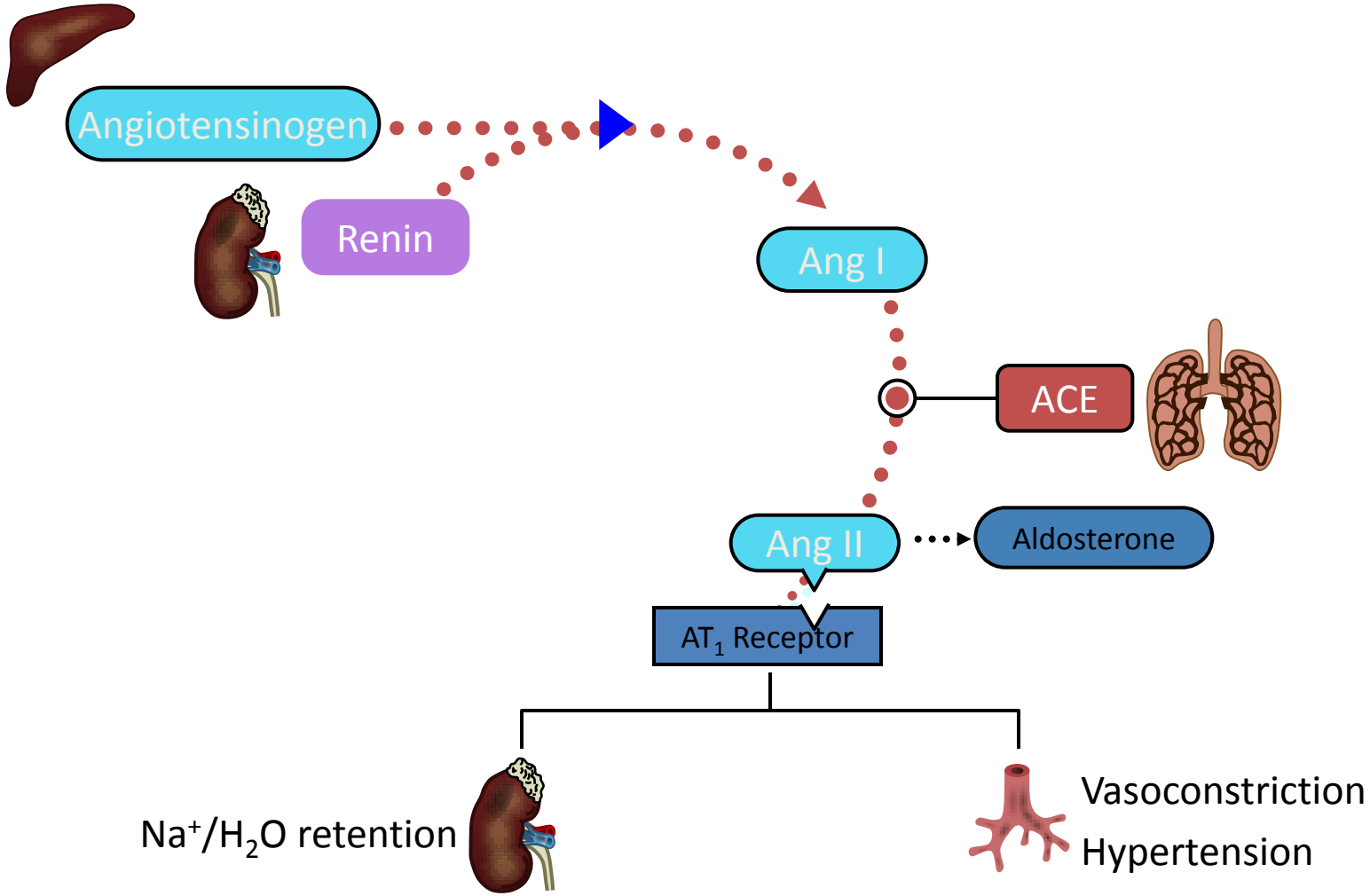
Outline

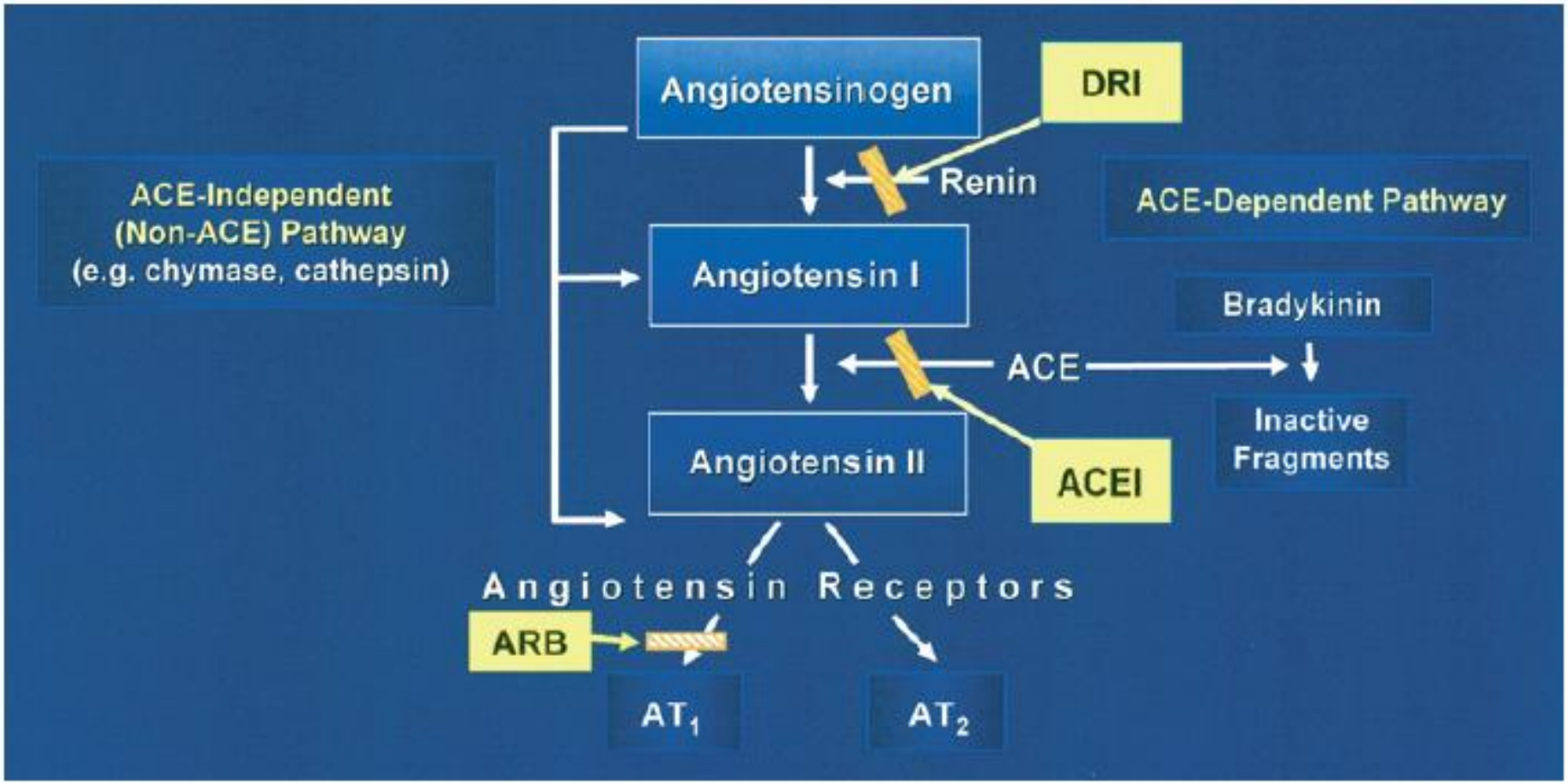
- 1 Development of Aliskiren and review of Renin-angiotensin system
- 2 Some clinical data about aliskiren

Classic understanding of the Renin System



Gibbons GH. 1998; Adapted from: Müller DN & Luft FC. 2006

3 Available Approaches to Pharmacological inhibition of Production or Action of Angiotensin II



(J Am Coll Cardiol 2008;51:519–28)

Why Renin Inhibitor?

- Renin determines the rate-limiting step of synthesis of angiotensins.
- ACE escape
- Aldosterone breakgthrough

ACE Escape

- Renin and Ang I accumulate during ACE inhibition, and might overcome the ability of an ACEI to effectively suppress ACE activity.

- There is also data suggesting that 30 – 40% of Ang II formation in the healthy human during RAAS activation is formed via renin-dependent, but ACE-independent, pathways.

- Moreover, ACE gene polymorphisms contribute to the modulation and adequacy of the neurohormonal response to long-term ACE inhibition, at least in patients with CHF (up to 45% of CHF patients have elevated Ang II levels despite the long-term use of an ACEI) or diabetes.

Expert Opin. Pharmacother. **(2007)**

Aldosterone Breakthrough

- The most important agonists for ALDO secretion are Ang II, potassium, adrenocorticotropic hormone (ACTH) and endothelin-1.
- Aldosterone polymorphism
- Increased endothelin in patients of CHF
- LDL stimulation on mesengial cell
- AT2 receptor dependent

***Expert Opin. Pharmacother.* (2007)**

Renin

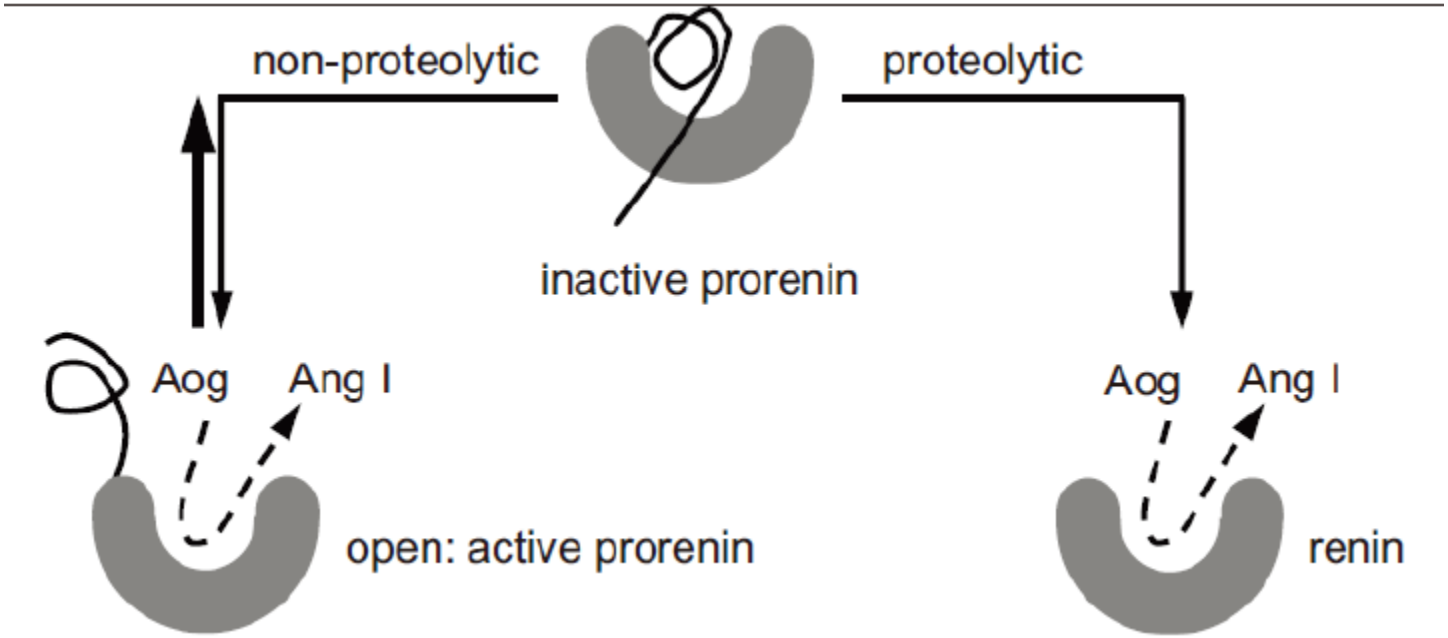
- Renin is an **aspartyl protease synthesized as prorenin**, a proenzyme that contains an additional 43–amino acid N-terminal fragment.

- In human, pro-renin level is about 10 fold of renin but its activity is <3% of renin.

- Renin has **high substrate specificity**, **and its only known substrate is angiotensinogen.**

J. Clin. Invest. 109:1417–1427 (2002).

Renin and Prorenin



Low PH 3.3, low temp 4℃

J Hypertens, 2006. **24(3): p. 529-34.**

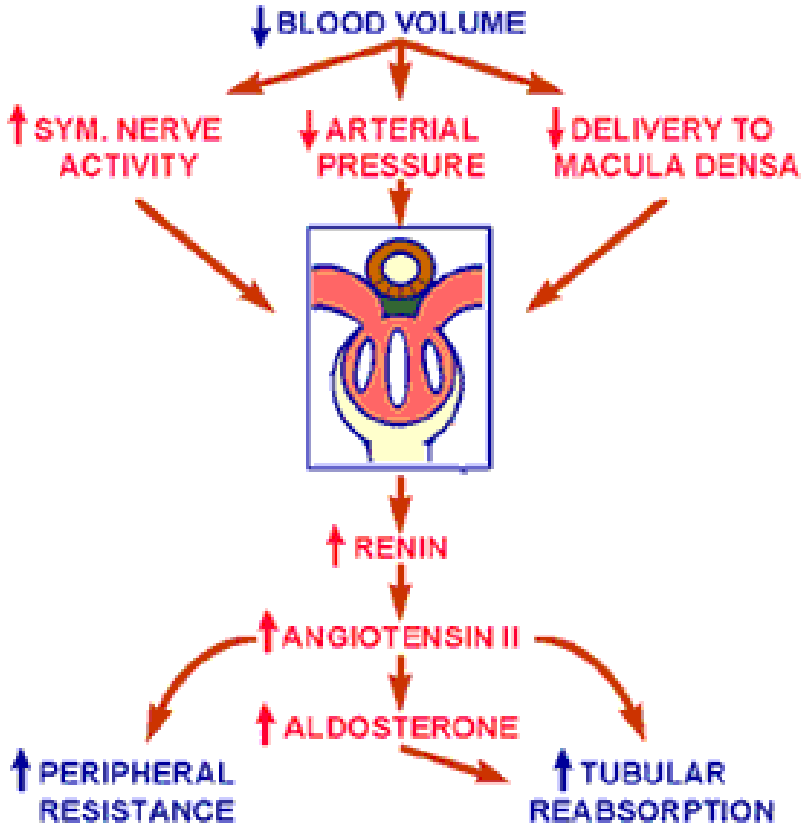
Regulation of Prorenin

- Prorenin may be secreted in **constitutive** pathway or **regulated** pathway.
- In the **constitutive** pathway, prorenin is secreted from JG cells constitutively.
- In **regulated** pathway, prorenin is converted to renin (by proconvertase 1 and cathepsin B) in dense secretary granules in the JG cells and stored. Renin is secreted upon cellular stimulation.

Nephrol Dial Transplant. 2007 May;22(5)

Hypertension. 1996;27:514-517

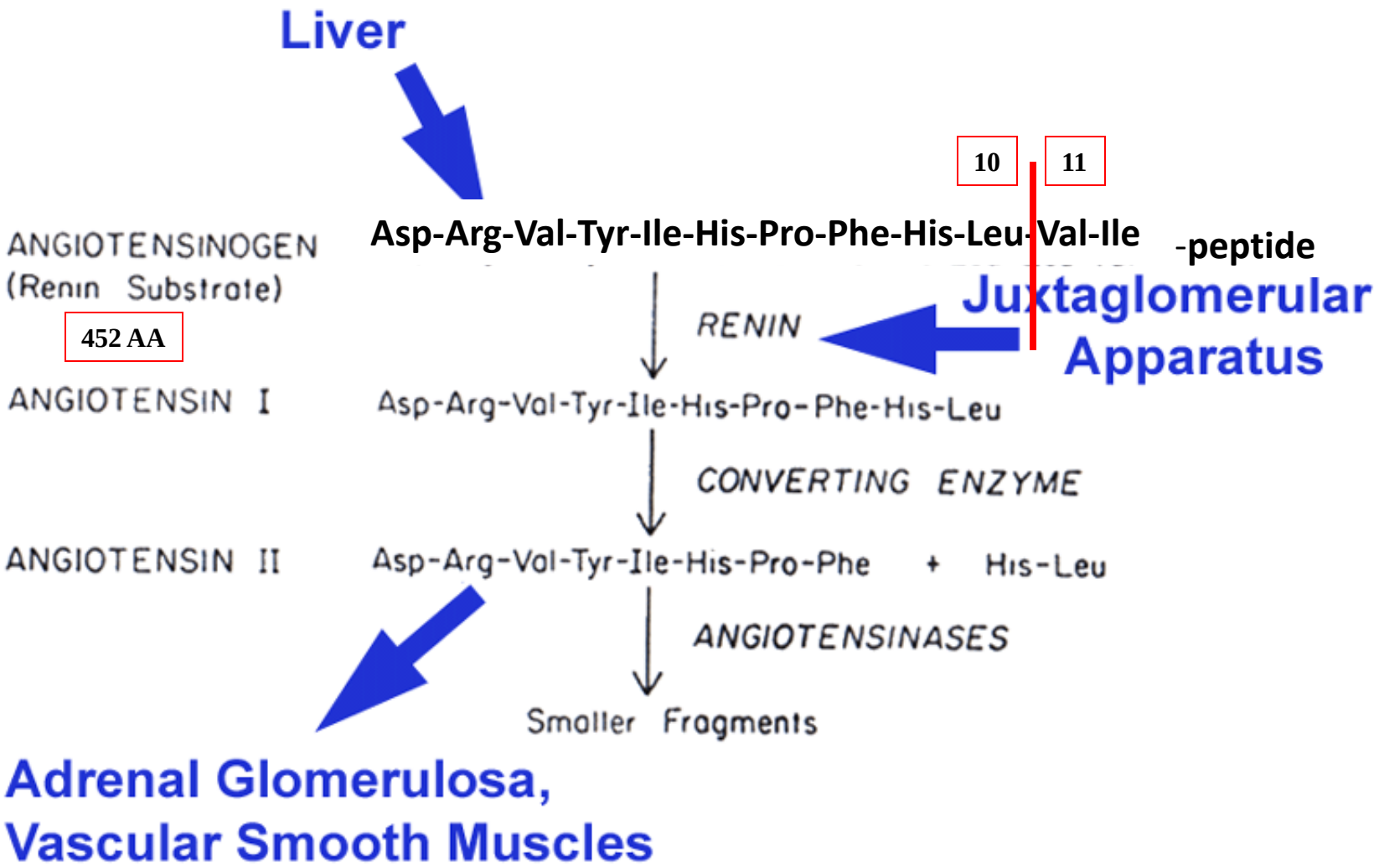
Secretion of Renin



The enzyme is secreted by the kidneys from specialized cells called juxtaglomerular (JG) cells in response to:

(1) A decrease in arterial blood pressure
(2) A decrease in sodium chloride levels in the ultra-filtrate .
(3) Sympathetic nervous system activity acting through the β_1 adrenergic receptors.

Angiotensin Metabolism



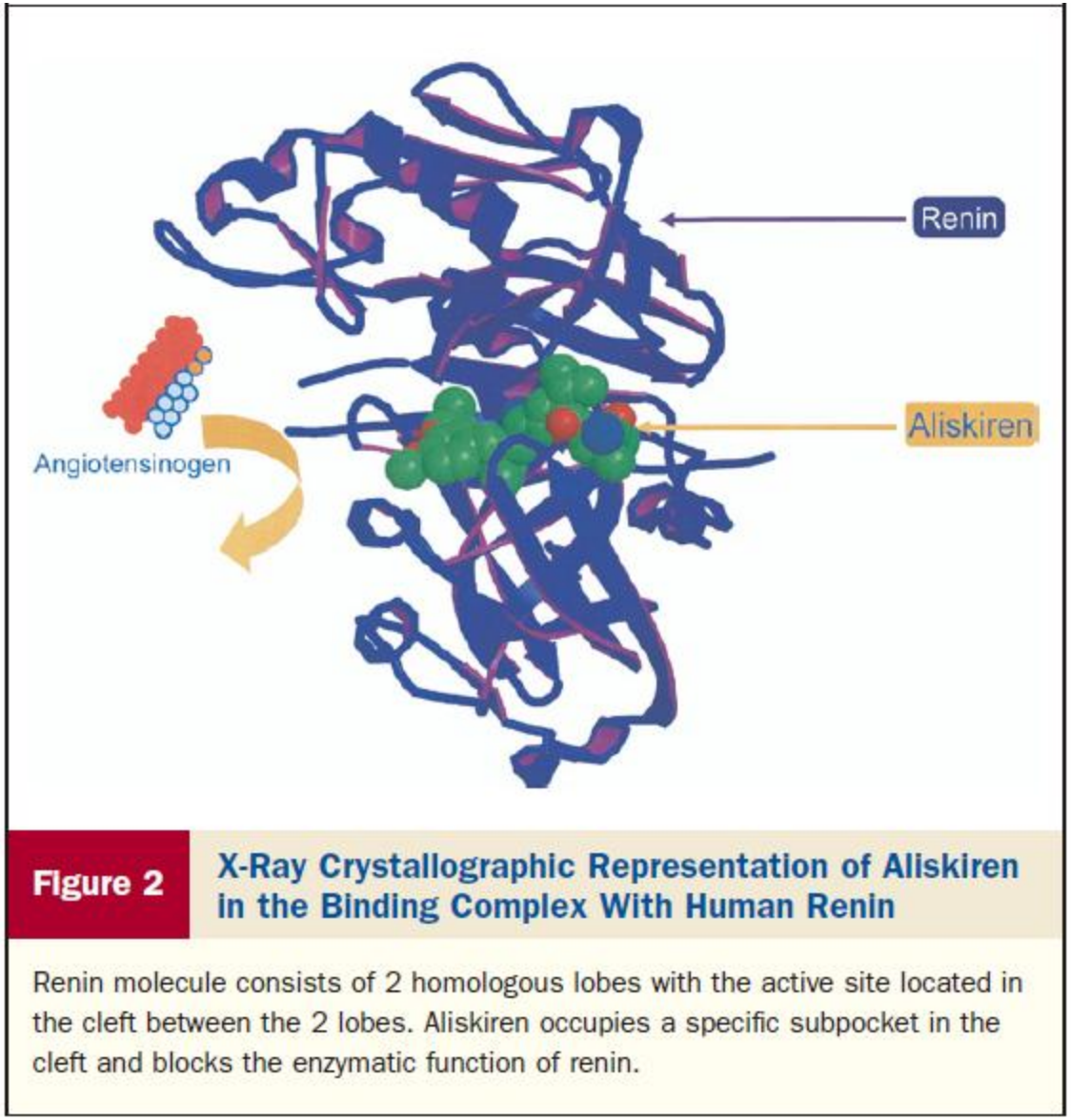


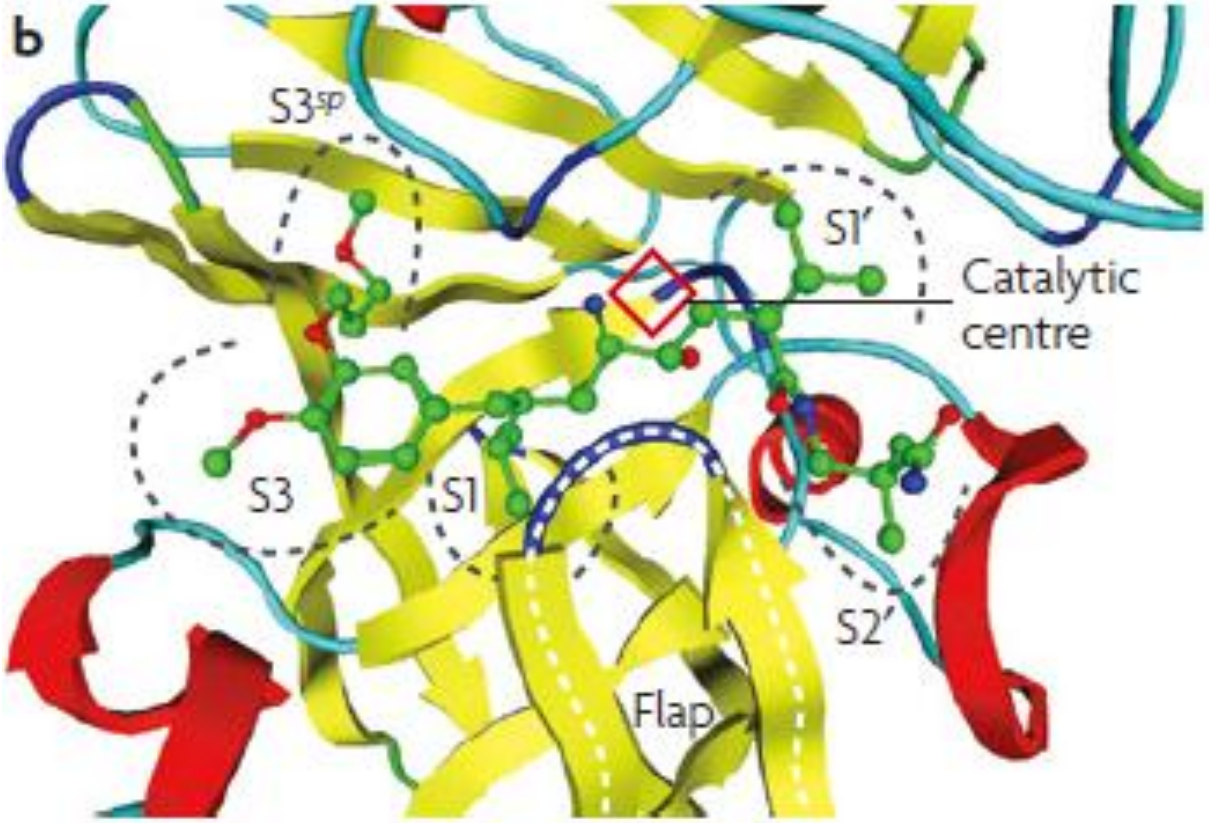
Figure 2 **X-Ray Crystallographic Representation of Aliskiren in the Binding Complex With Human Renin**

Renin molecule consists of 2 homologous lobes with the active site located in the cleft between the 2 lobes. Aliskiren occupies a specific subpocket in the cleft and blocks the enzymatic function of renin.

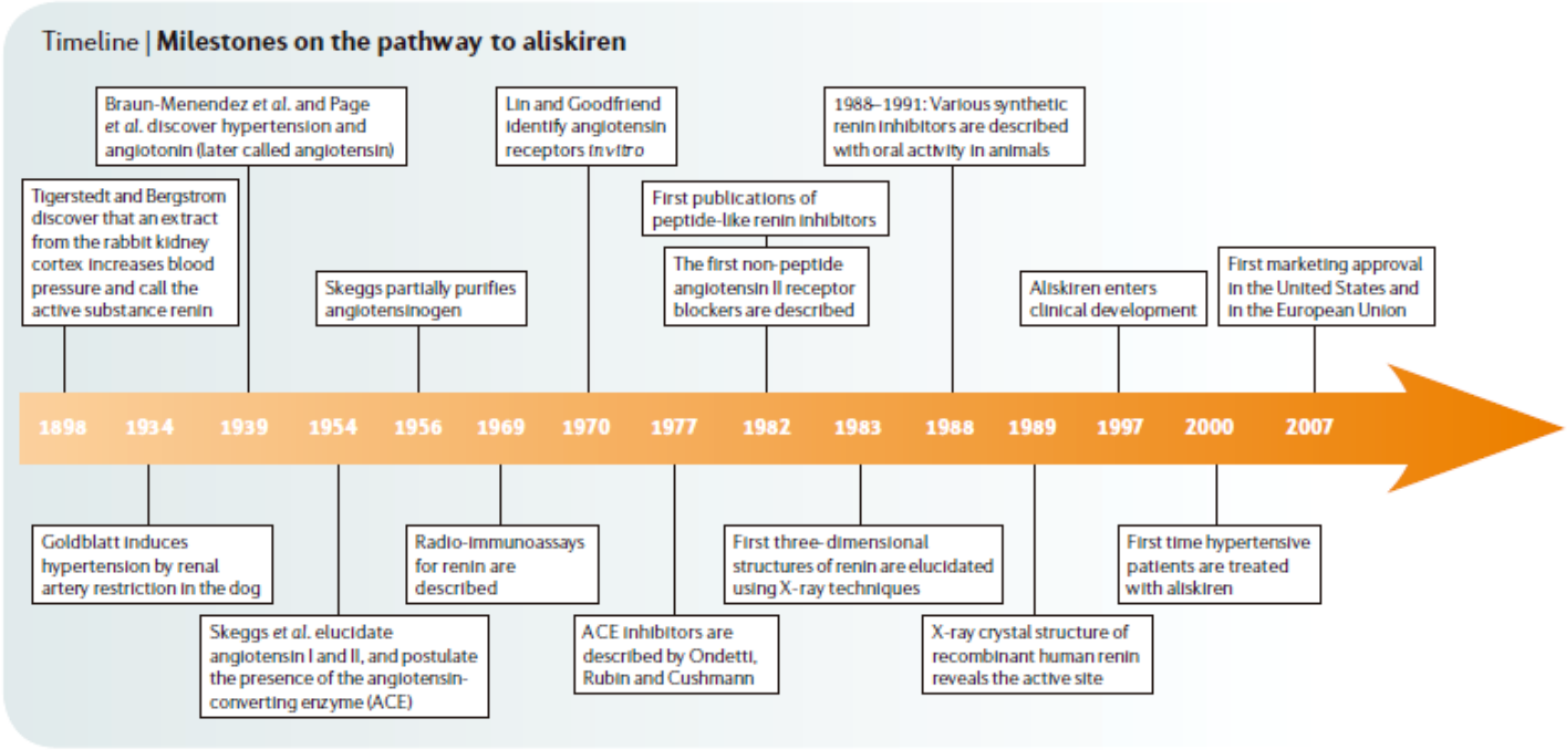
The catalytic activity of the active site is due to 2 aspartic acid residues, 1 located in each lobe of the renin molecule.
A key component of the active site is a distinct subpocket (S3sp), which is specific to renin and unique among the aspartate proteases .
The active site can accommodate 7 amino acid units of the substrate, angiotensinogen, and cleaves the Leu10-val11 peptide bond within angiotensinogen to generate angiotensin I (A I).

J Am Coll Cardiol 2008

Binding Sites for Aliskiren to Renin



Nature Reviews Drug Discovery


Timeline | Milestones on the pathway to aliskiren
Braun-Menendez et al. and Page et al. discover hypertension and angiotonin (later called angiotensin)
Tigerstedt and Bergstrom discover that an extract from the rabbit kidney cortex increases blood pressure and call the active substance renin
Skeggs partially purifies angiotensinogen
Lin and Goodfriend identify angiotensin receptors in vitro
First publications of peptide-like renin inhibitors
The first non-peptide angiotensin II receptor blockers are described
1988–1991: Various synthetic renin inhibitors are described with oral activity in animals
Aliskiren enters clinical development
First marketing approval in the United States and in the European Union
1898
1934
1939
1954
1956
1969
1970
1977
1982
1983
1988
1989
1997
2000
2007
Goldblatt induces hypertension by renal artery restriction in the dog
Skeggs et al. elucidate angiotensin I and II, and postulate the presence of the angiotensin-converting enzyme (ACE)
Radio-immunoassays for renin are described
ACE inhibitors are described by Ondetti, Rubin and Cushmann
First three-dimensional structures of renin are elucidated using X-ray techniques
X-ray crystal structure of recombinant human renin reveals the active site
First time hypertensive patients are treated with aliskiren

Development of Aliskiren

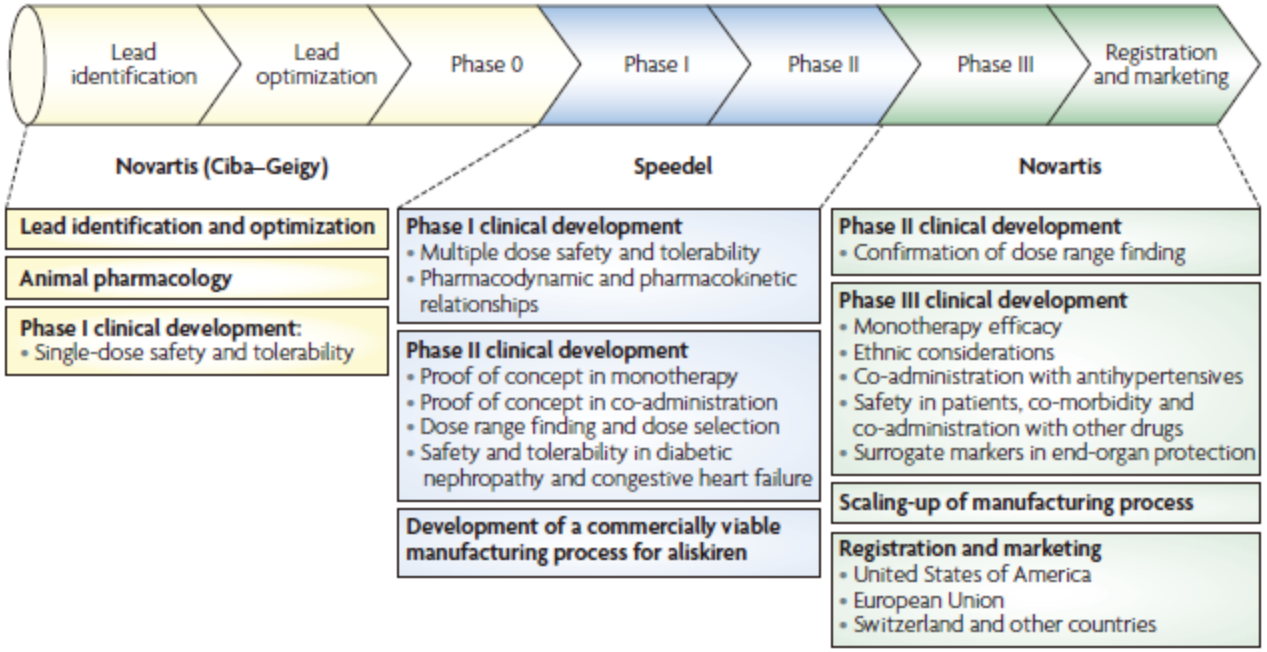
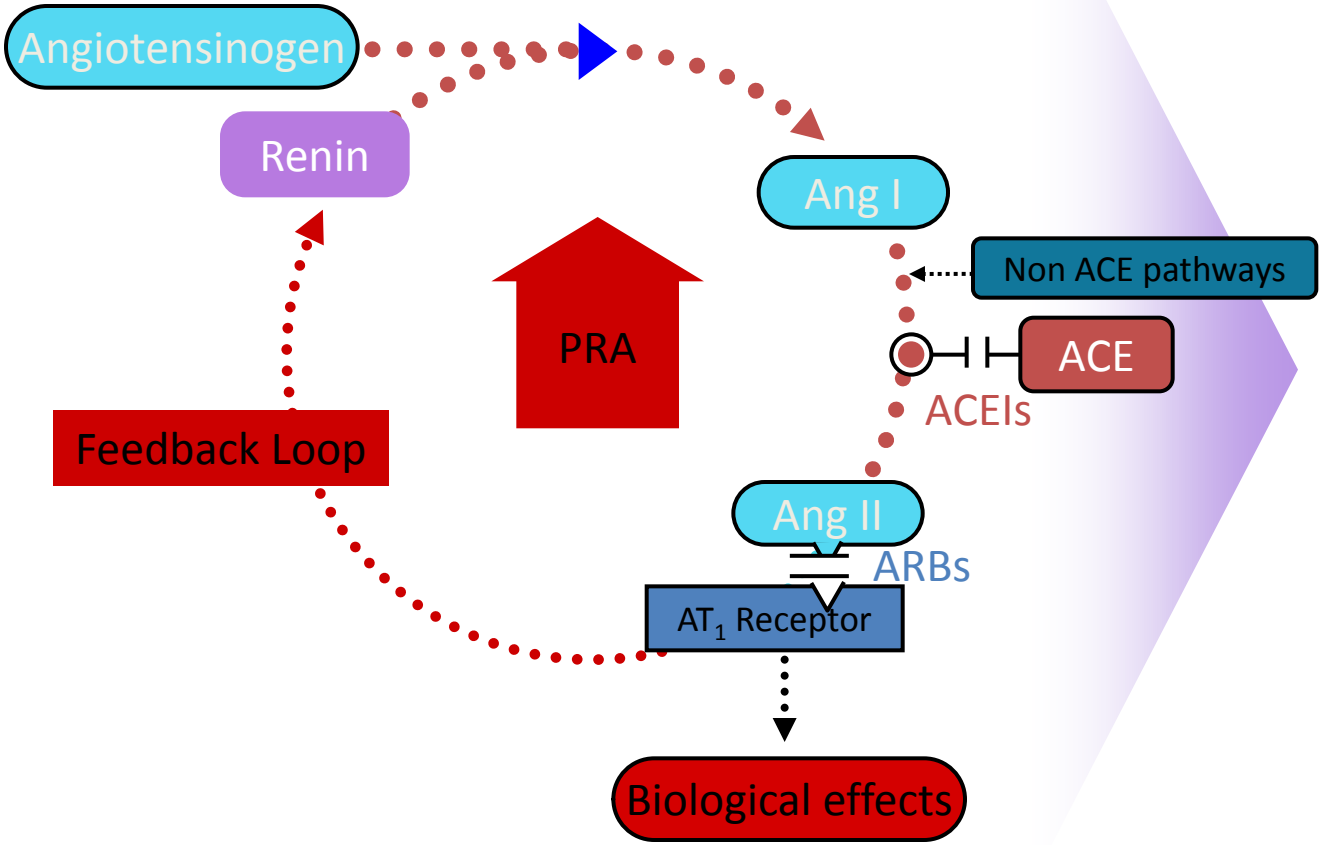


Figure 1 | **Aliskiren: from bench to marketplace.** The discovery and optimization of aliskiren using X-ray crystallography techniques, biochemical and animal pharmacological characterization was performed at Ciba–Geigy[32,33]. A single-dose safety and tolerability study was performed in healthy subjects that showed the potential of the compound. However, the synthesis of aliskiren remained a central problem — it was simply too expensive for the marketplace. Novartis out-licensed the compound to Speedel in 1999 for Phase I and Phase II development and to invent a new synthesis process. Speedel successfully overcame this major technical hurdle, which was critical for advancing the development of aliskiren. During the period 1999–2002, Speedel also established the clinical efficacy of aliskiren in over 500 subjects with mild-to-moderate hypertension in 18 Phase I and II trials and selected the doses to be used later in the Phase III studies. Novartis licensed back the compound in June 2002. The subsequent clinical programme carried out by Novartis, which included over 8,000 patients, provided the evidence for the safety and efficacy of aliskiren in treating hypertension, leading to its regulatory approval in the United States and Europe in 2007.

ACEIs and ARBs cause compensatory rises in PRA



Kidney
- Glomerular vasoconstriction
- Inflammation
- Fibrosis

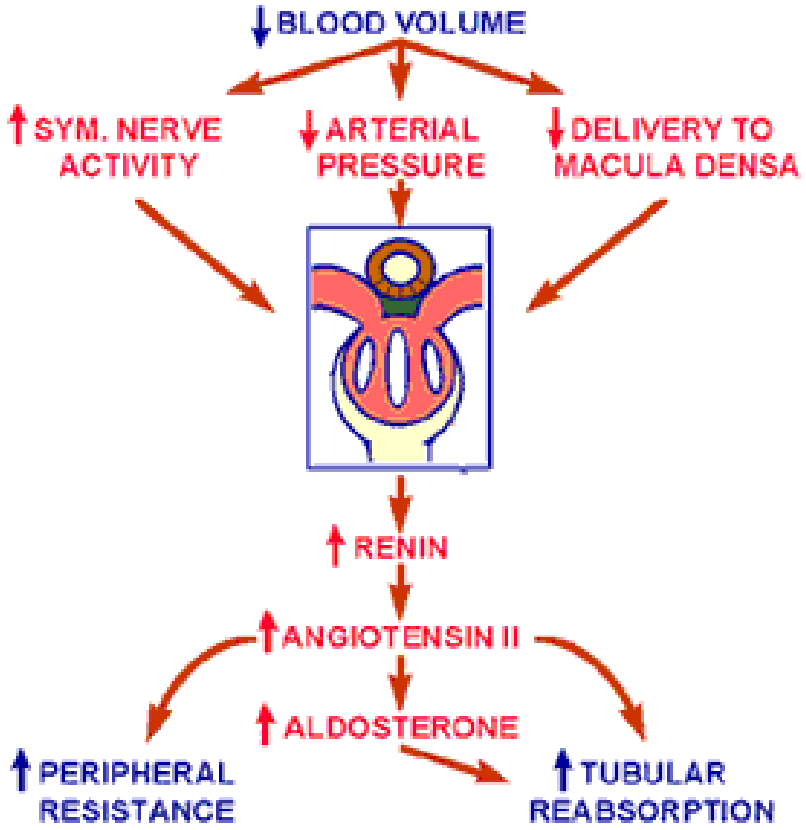
Heart
- Hypertrophy
- Fibrosis
- Vasoconstriction

Vessels
- Hyperplasia hypertrophy
- Inflammation
- Oxidation
- Fibrosis

Brain
- Vasoconstriction

Clin J Am Soc Nephrol 2006

Secretion of Renin



The enzyme is secreted by the kidneys from specialized cells called juxtaglomerular (JG) cells in response to:

(1) A decrease in arterial blood pressure
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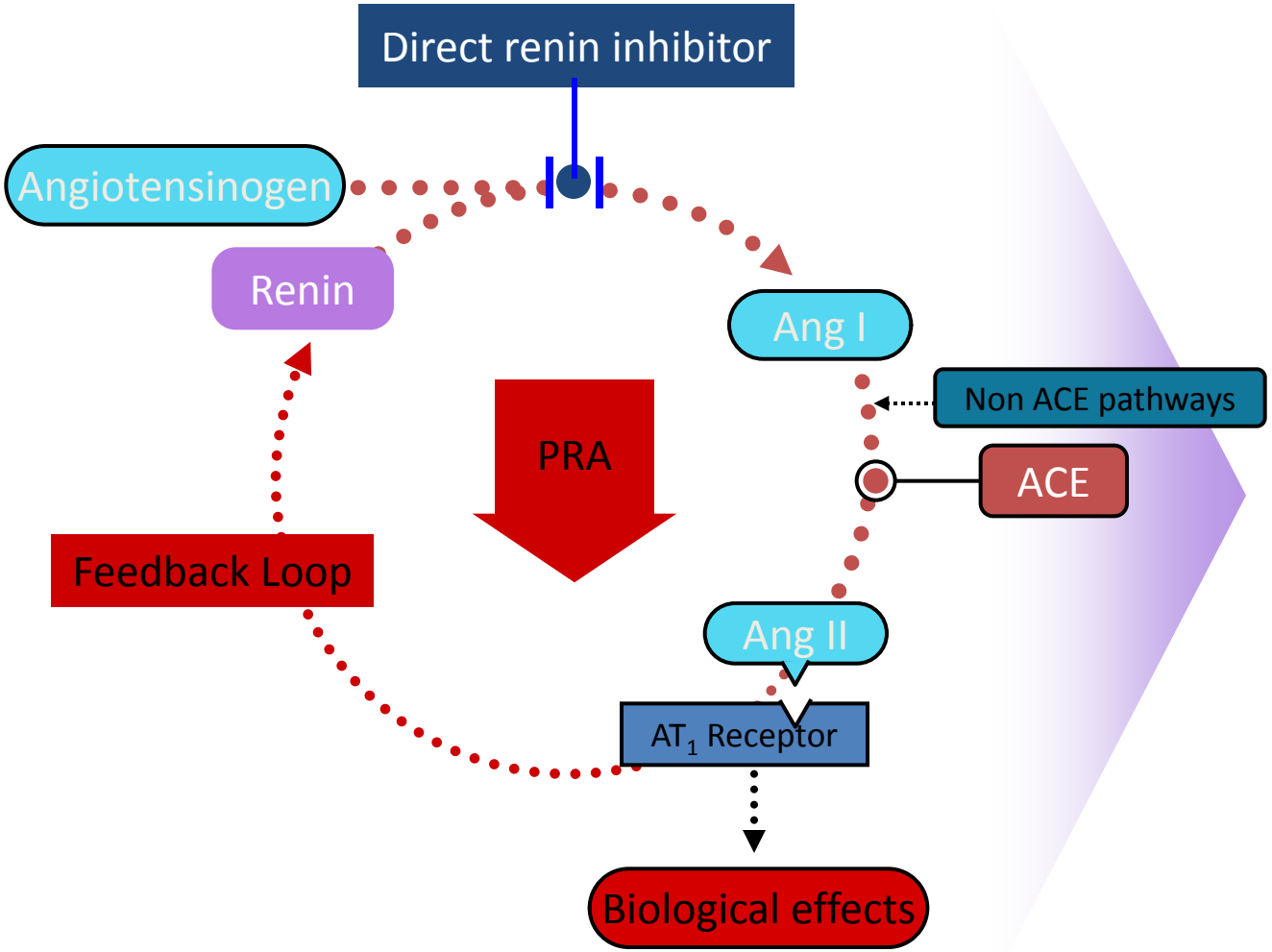
(3) Sympathetic nervous system activity acting through the β_1 adrenergic receptors.

Direct renin inhibition acts at the point of activation of the Renin System and neutralizes the PRA rise



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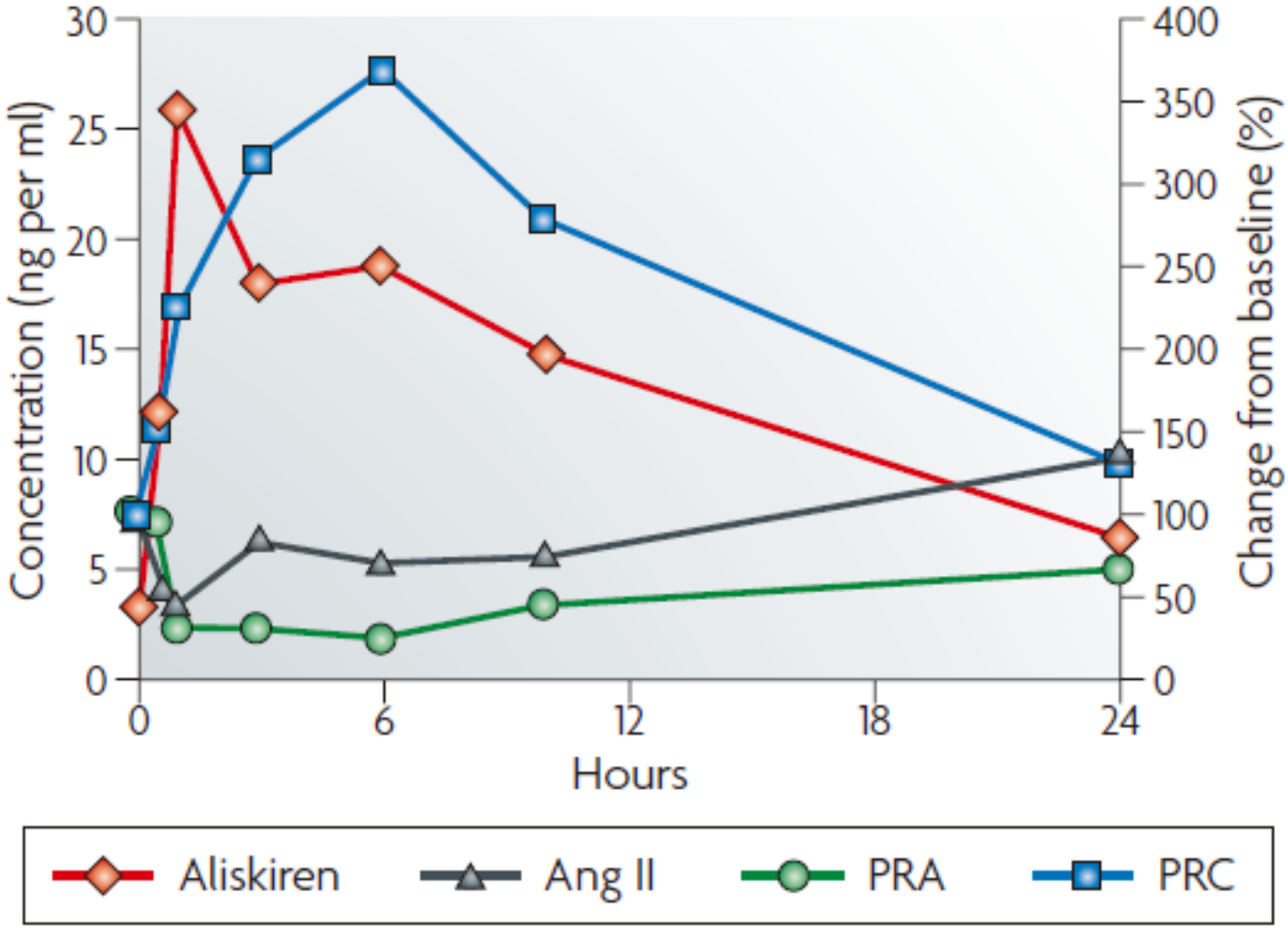
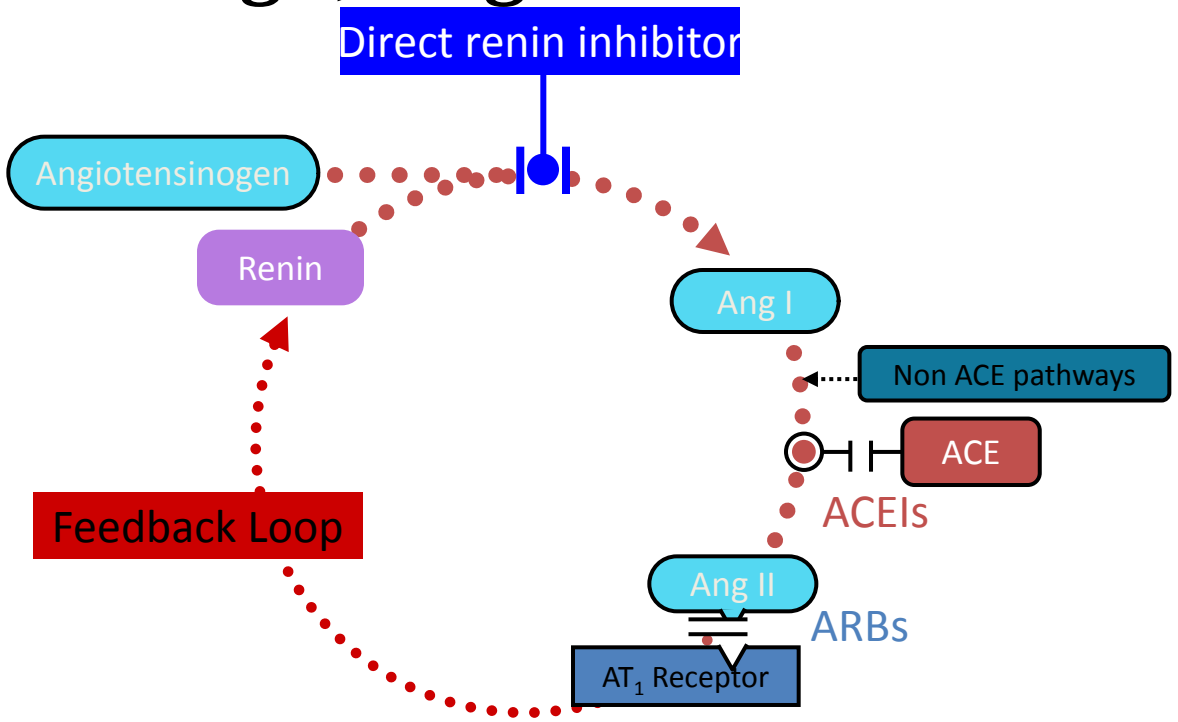
Clin J Am Soc Nephrol 2006



Nature Reviews Drug Discovery | AOP, published online 14 May 2008; doi:10.1038/nrd2550

Unlike ACEIs and ARBs, Aliskiren reduces Ang I, Ang II and PRA



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

J Hypertens 2006;Clin J Am Soc Nephrol 2006

Clinical Research

- The dose–response relationship of aliskiren in decreasing BP.
- Its efficacy as monotherapy
- Its efficacy in combination with other antihypertensives agents.
- The safety and efficacy of aliskiren in various patient populations (the elderly, different racial groups, diabetic patients, obese patients and patients with reduced renal and hepatic function).
- The pharmacokinetics of aliskiren and the potential for drug–drug interactions.
- Its effect on surrogate markers of end-organ disease, such as diabetic kidney disease and congestive heart failure.

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Does Response in The Range of 150-600 mg/day

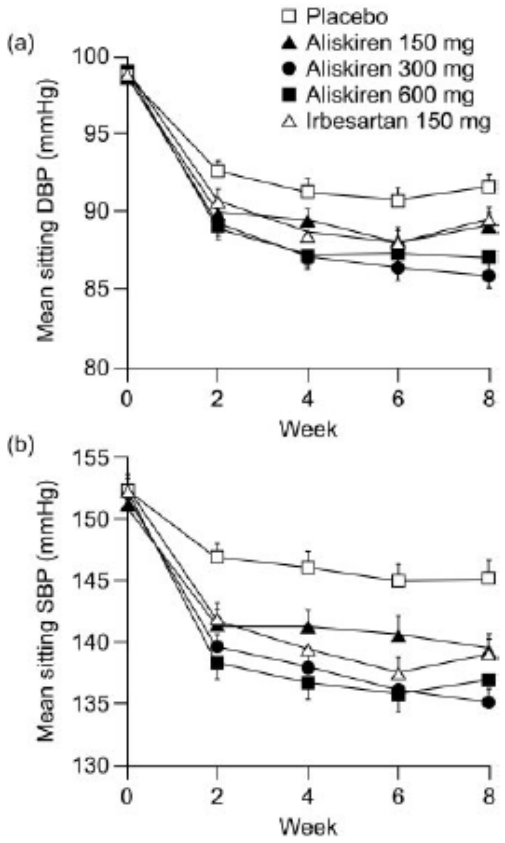

Figure 3. Effect of study treatment on trough mean sitting DBP and SBP throughout active treatment phase in patients with mild-to-moderate hypertension. Data represent absolute mean values of (a) trough sitting DBP and (b) SBP at 2-week intervals after treatment with placebo, aliskiren 150, 300, or 600 mg or irbesartan 150 mg. Data are presented as mean±SEM.

Circulation 2005

Safety and Tolerability

TABLE 5. Safety and Tolerability of Study Treatment

Adverse Event by MedDRA Class	Placebo (n=131)	Aliskiren 150 mg (n=127)	Aliskiren 300 mg (n=130)	Aliskiren 600 mg (n=130)	Irbesartan 150 mg (n=134)
All adverse events	42 (32.1)	34 (26.8)	47 (36.2)	43 (33.1)	49 (36.6)
Discontinuation because of adverse event	3 (2.3)	5 (3.9)	4 (3.1)	3 (2.3)	3 (2.2)
Blood/lymphatic	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.7)
Cardiac	2 (1.5)	2 (1.6)	0 (0.0)	2 (1.5)	1 (0.7)
Ear/labyrinth	1 (0.8)	1 (0.8)	5 (3.8)	0 (0.0)	3 (2.2)
Eye	1 (0.8)	0 (0.0)	0 (0.0)	2 (1.5)	1 (0.7)
Gastrointestinal	5 (3.8)	5 (3.9)	12 (9.2)	12 (9.2)	9 (6.7)
General	5 (3.8)	2 (1.6)	6 (4.6)	9 (6.9)	5 (3.7)
Immune system	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Infections	14 (10.7)	8 (6.3)	4 (3.1)	8 (6.2)	11 (8.2)
Injury/procedures	0 (0.0)	2 (1.6)	1 (0.8)	1 (0.8)	2 (1.5)
Investigations	1 (0.8)	2 (1.6)	0 (0.0)	2 (1.5)	1 (0.7)
Metabolism/nutrition	1 (0.8)	2 (1.6)	0 (0.0)	1 (0.8)	1 (0.7)
Musculoskeletal	4 (3.1)	8 (6.3)	12 (9.2)	10 (7.7)	11 (8.2)
Nervous system	12 (9.2)	8 (6.3)	13 (10.0)	10 (7.7)	9 (6.7)
Psychological	8 (6.1)	3 (2.4)	2 (1.5)	2 (1.5)	2 (1.5)
Renal/urinary	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	2 (1.5)
Reproductive	2 (1.5)	0 (0.0)	3 (2.3)	1 (0.8)	0 (0.0)
Respiratory	5 (3.8)	4 (3.1)	5 (3.8)	4 (3.1)	6 (4.5)
Skin/subcutaneous	2 (1.5)	2 (1.6)	5 (3.8)	3 (2.3)	2 (1.5)
Surgical procedures	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.7)
Vascular	1 (0.8)	1 (0.8)	2 (1.5)	2 (1.5)	1 (0.7)

Data are presented as the number (%) of patients reporting adverse events.

Most common side effects are headache , dizziness and diarrhea

Circulation 2005

Aliskiren Monotherapy Does Not Cause Paradoxical Blood Pressure Rises

Meta-Analysis of Data From 8 Clinical Trials

Alice V. Stanton, Alan H. Gradman, Roland E. Schmieder, Juerg Nussberger,
Ramesh Sarangapani, Margaret F. Prescott

Abstract—Angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and diuretics all cause reactive rises in plasma renin concentration, but particularly high levels have been reported with aliskiren. This prompted speculation that blockade of plasma renin activity with aliskiren could be overwhelmed, leading to paradoxical increases in blood pressure. This meta-analysis of data from 4877 patients from 8 randomized, double-blind, placebo- and/or active-controlled trials examined this hypothesis. The analysis focused on the incidence of paradoxical blood pressure increases above predefined thresholds, after ≥4 weeks of treatment with 300 mg of aliskiren, angiotensin receptor blockers (300 mg of irbesartan, 100 mg of losartan, or 320 mg of valsartan), 10 mg of ramipril, 25 mg of hydrochlorothiazide, or placebo. There were no significant differences in the frequency of increases in systolic (>10 mm Hg; $P=0.30$) or diastolic (>5 mm Hg; $P=0.65$) pressure among those treated with aliskiren (3.9% and 3.1%, respectively), angiotensin receptor blockers (4.0% and 3.7%), ramipril (5.7% and 2.6%), or hydrochlorothiazide (4.4% and 2.7%). Increases in blood pressure were considerably more frequent in the placebo group (12.6% and 11.4%; $P<0.001$). None of the 536 patients with plasma renin activity data who received 300 mg of aliskiren exhibited an increase in systolic pressure >10 mm Hg that was associated with an increase in plasma renin activity >0.1 ng/mL per hour. In conclusion, the incidence of blood pressure increases with aliskiren was similar to that during treatment with other antihypertensive drugs. Blood pressure rises on aliskiren treatment were not associated with increases in plasma renin activity. This meta-analysis found no evidence that aliskiren uniquely causes paradoxical rises in blood pressure. (***Hypertension*. 2010;55:00-00.**)

Key Words: ACE inhibitor ■ aliskiren ■ angiotensin receptor blocker ■ direct renin inhibitor ■ diuretic ■ renin ■ plasma renin activity

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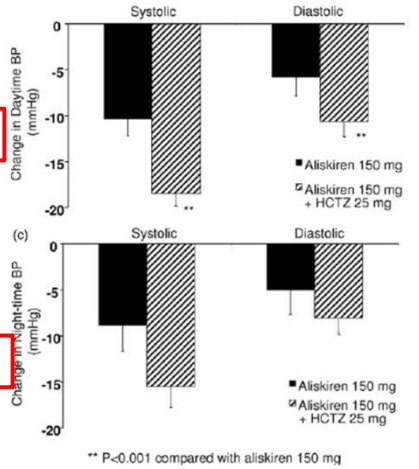
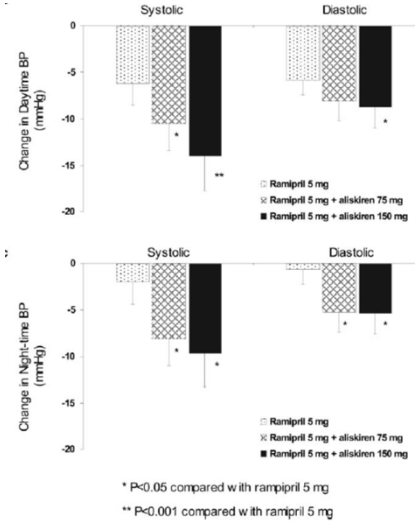
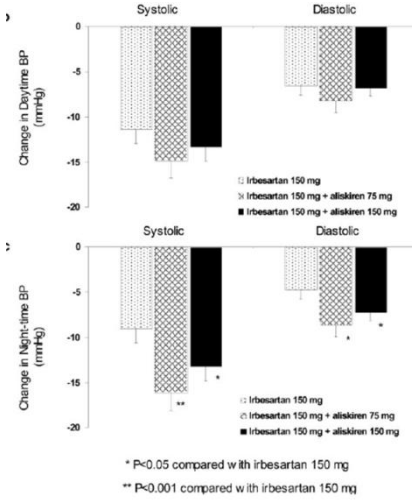
Aliskiren Combined with Thiazide, Ramipril and Irbesartan

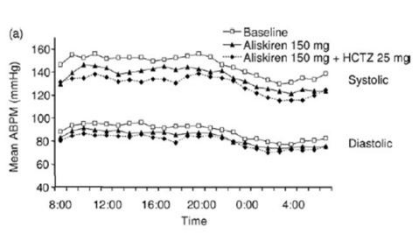
Day time

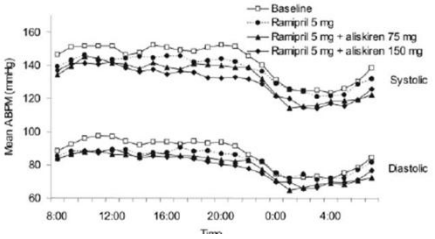
Night time

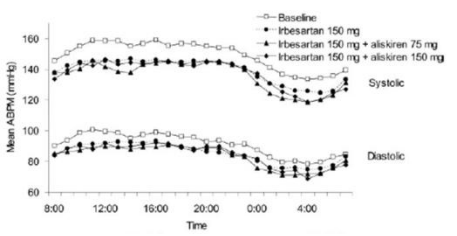






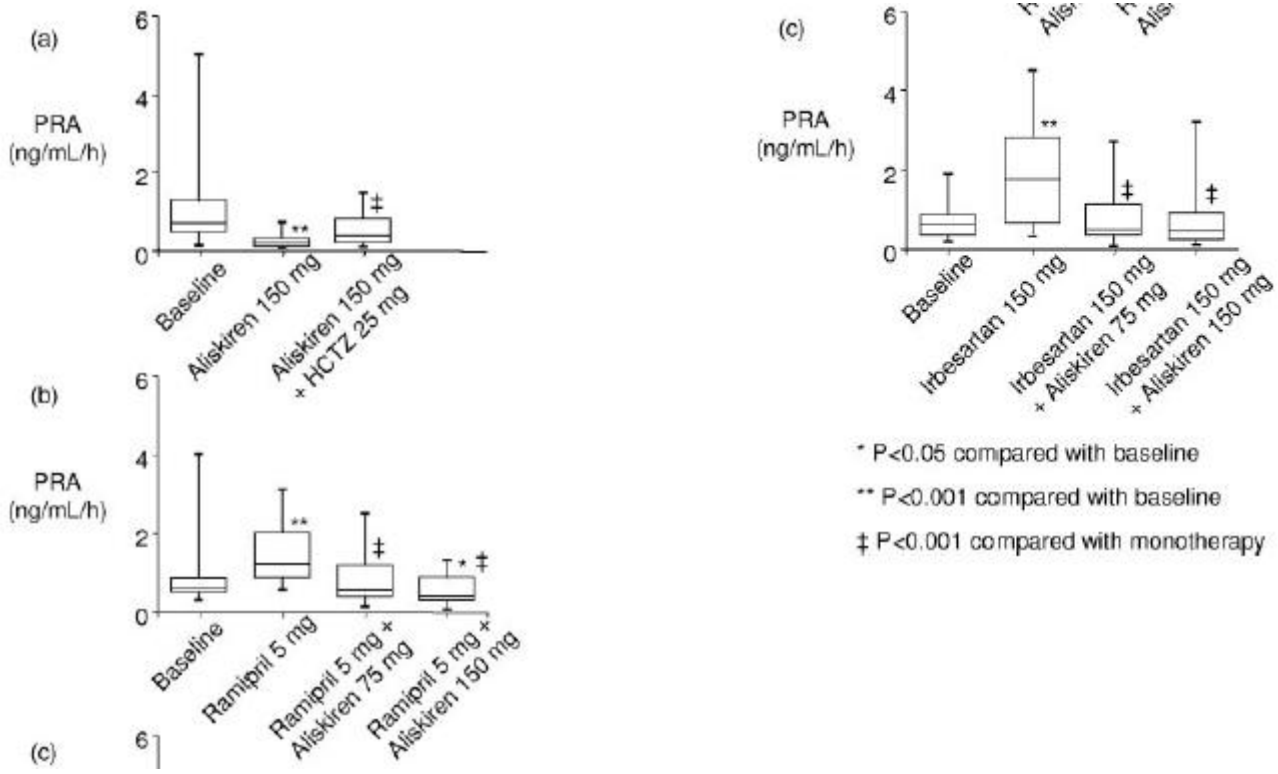






Hypertension 2007

Plasma Renin Activity After Aliskiren and Combination with Thiazide, ACEI and ARB



Hypertension 2007

Aliskiren Combined with Valsartan

Aliskiren 300mg Valsartan 320 mg

Sys

Dia

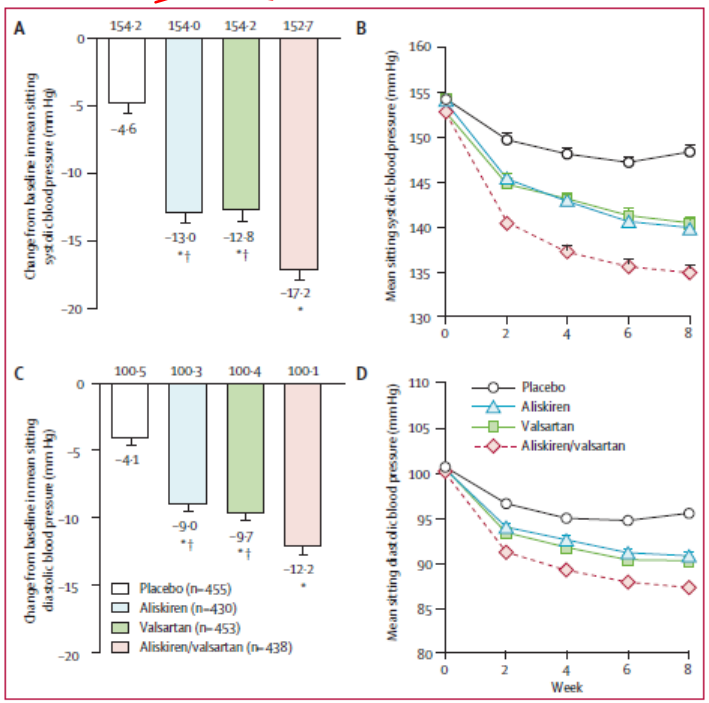


Figure 2: **Effect of study treatments on (A, B) mean sitting systolic blood pressure and (C, D) mean sitting diastolic blood pressure**

Data in (A) and (C) are presented as the least-squares mean (SE). *p<0·0001 *vs* placebo. †p<0·0001 *vs* aliskiren/valsartan combination. Data on x-axes of (A) and (C) are mean baseline blood pressures for the intention-to-treat population.

PRC

PRA

Aldo

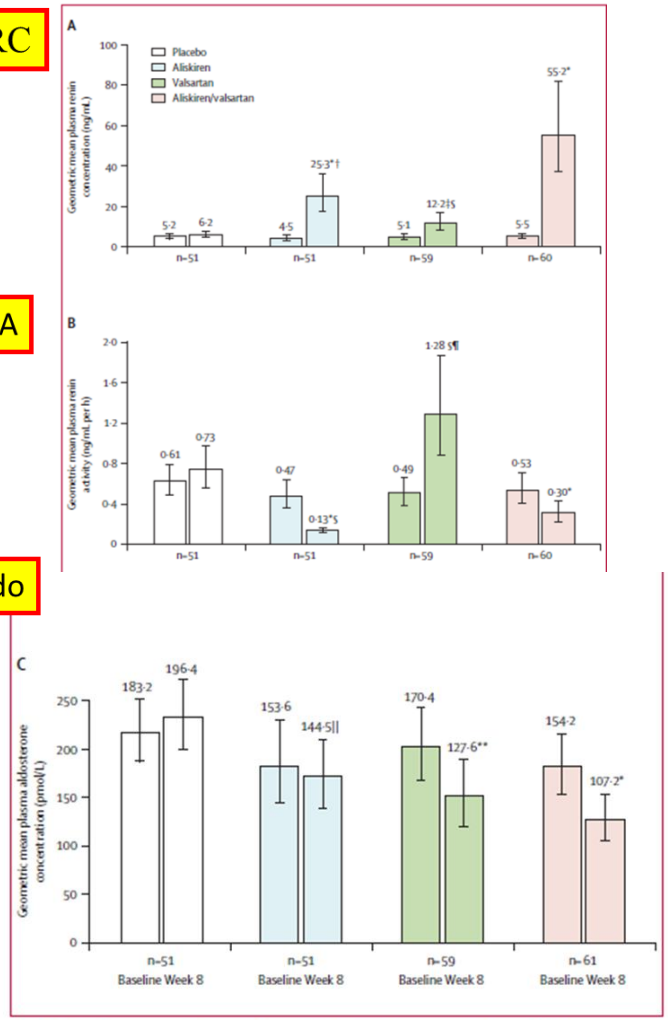


Figure 4: **Geometric mean (A) plasma renin concentration, (B) plasma renin activity, and (C) plasma aldosterone concentration at baseline and at week 8**

Data are geometric mean values and 95% CI. *p<0·0001 *vs* placebo. †p=0·0014 *vs* combination. ‡p=0·0002 *vs* placebo. §p<0·0001 *vs* combination. ¶p=0·0003 *vs* placebo. ||p=0·0071 *vs* combination. **p=0·0007 *vs* placebo.

Lancet 2007; 370: 221–29

Aliskiren Combined with Valsartan

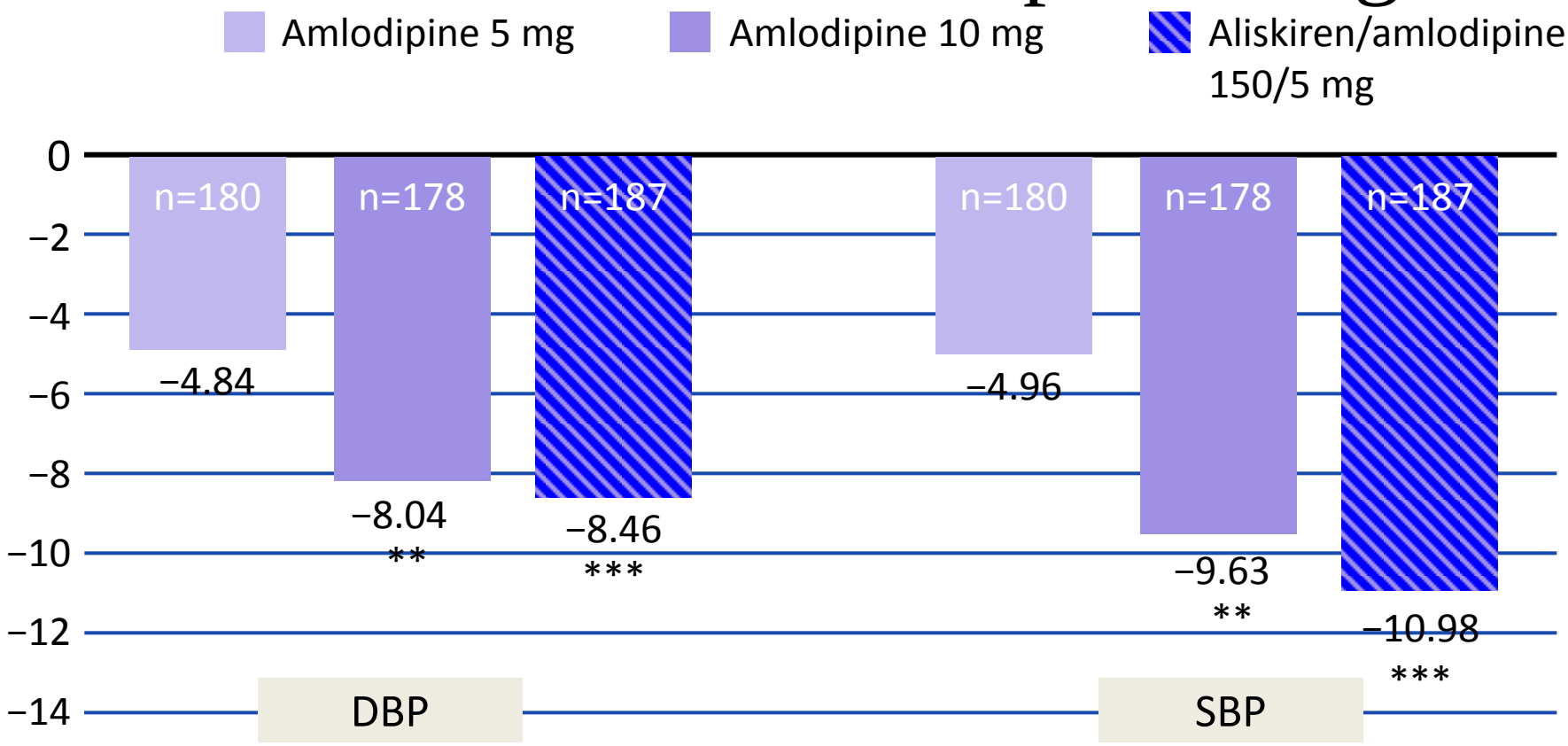
	Placebo (n=458*)	Aliskiren (n=437)	Valsartan (n=455)	Aliskiren/valsartan (n=446)
Adverse events				
Any adverse event	168 (37%)	149 (34%)	167 (37%)	156 (35%)
Any serious adverse event	5 (1%)	8 (2%)	6 (1%)	3 (0·7%)
Discontinuations due to adverse events	10 (2%)	11 (3%)	11 (2%)	7 (2%)
Most frequent adverse events (≥2% in any treatment group)				
Headache	41 (9%)	14 (3%)	25 (5%)	19 (4%)
Nasopharyngitis	9 (2%)	16 (4%)	20 (4%)	12 (3%)
Dizziness	9 (2%)	8 (2%)	11 (2%)	8 (2%)
Fatigue	5 (1%)	4 (1%)	10 (2%)	8 (2%)
Nausea	11 (2%)	6 (1%)	7 (2%)	7 (2%)
Laboratory abnormalities				
Serum potassium†				
<3·5 mmol/L	17 (4%)	11 (3%)	20 (4%)	12 (3%)
>5·5 mmol/L‡	12 (3%)	7 (2%)	7 (2%)	18 (4%)
≥6·0 mmol/L	6 (1%)	4 (1%)	5 (1%)	2 (0·5%)
Creatinine§				
>176·8 µmol/L	0	1 (0·2%)	2 (0·4%)	4 (0·9%)
Blood urea nitrogen§				
>14·3 mmol/L	0	1 (0·2%)	1 (0·2%)	0

Data are n (%). *One randomised patient did not take double-blind medication before discontinuation. †n=445 for placebo, 416 for aliskiren, 443 for valsartan, 424 for aliskiren/valsartan. ‡Of the 18 patients with increases in serum potassium >5·5 mmol/L during double-blind treatment, 13 had potassium concentrations within the normal range at the end of the study without the need for treatment disruption. §n=446 for placebo, 417 for aliskiren, 445 for valsartan, 426 for aliskiren/valsartan.

Table 2: **Safety and tolerability of study treatments**

Lancet 2007; 370: 221–29

Aliskiren significantly lowers BP when combined with amlodipine 5 mg



Mean change from baseline in mean sitting BP at Week 6 (mmHg)

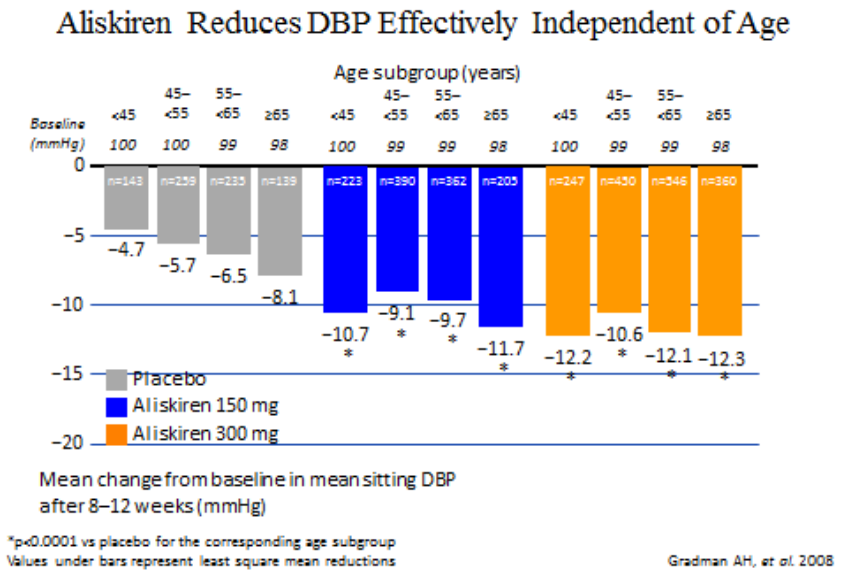
J. Clin. Hypertens. (2007).

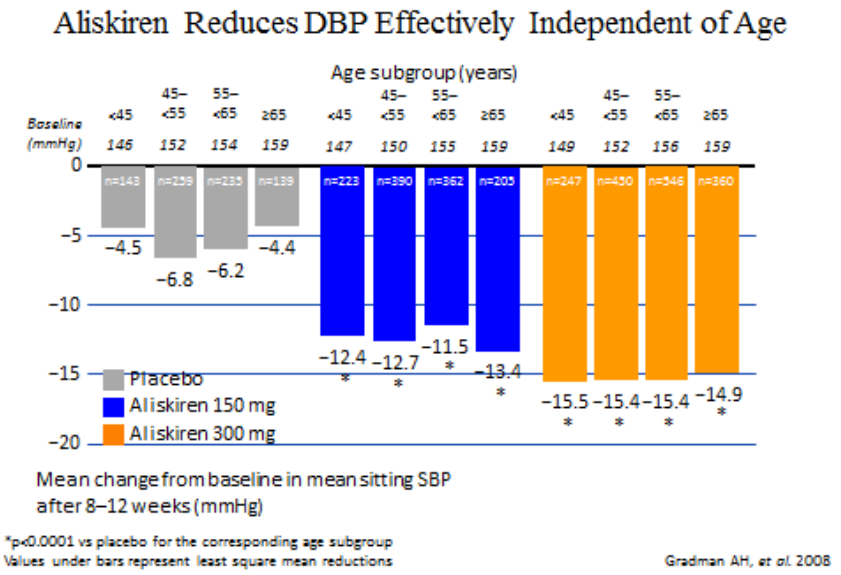
**p=0.0002 and ***p<0.0001 vs. amlodipine 5 mg

Clinical Research

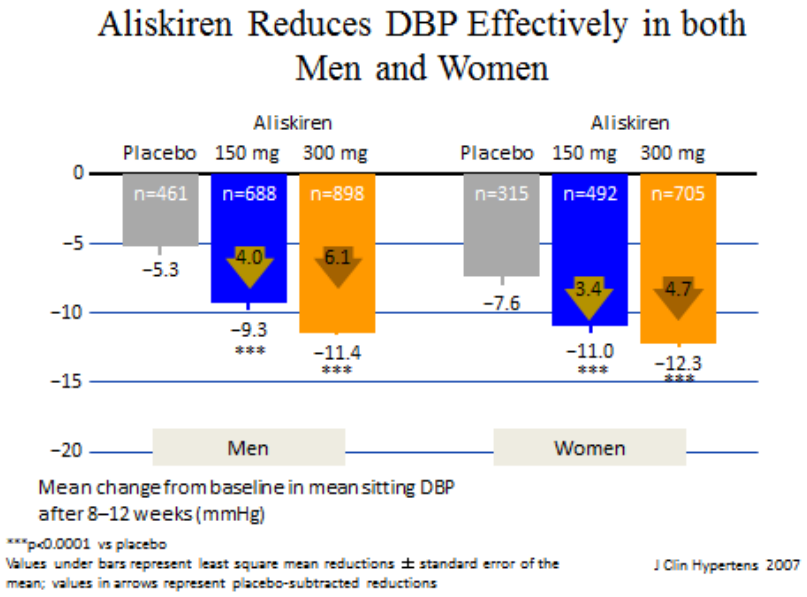
- The dose–response relationship of aliskiren in decreasing BP.
- Its efficacy as monotherapy
- Its efficacy in combination with other antihypertensives.
- The safety and efficacy of aliskiren in various patient populations (the elderly, different racial groups, diabetic patients, obese patients and patients with reduced renal and hepatic function).
- The pharmacokinetics of aliskiren and the potential for drug–drug interactions.
- Its effect on surrogate markers of end-organ disease, such as diabetic kidney disease and congestive heart failure.

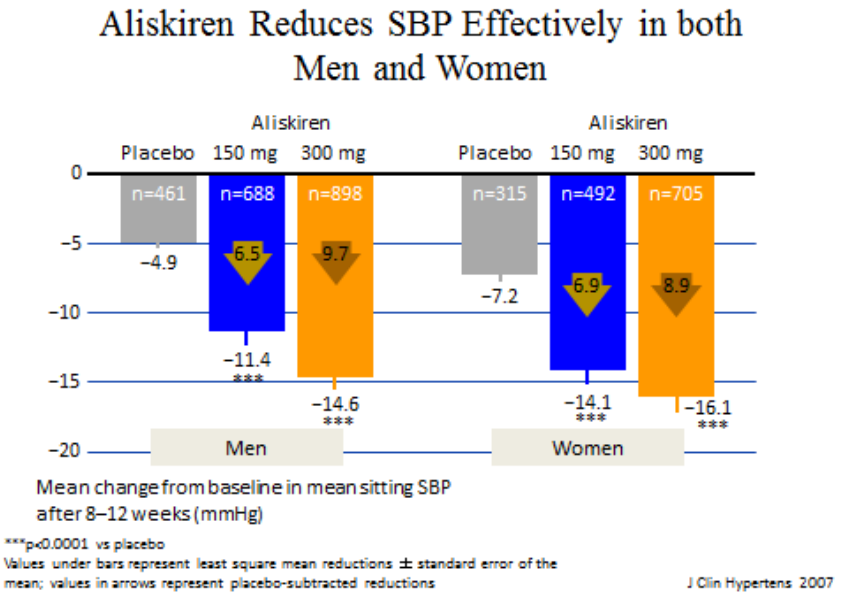
Aliskiren Reduce both SBP and DBP Independent of Age



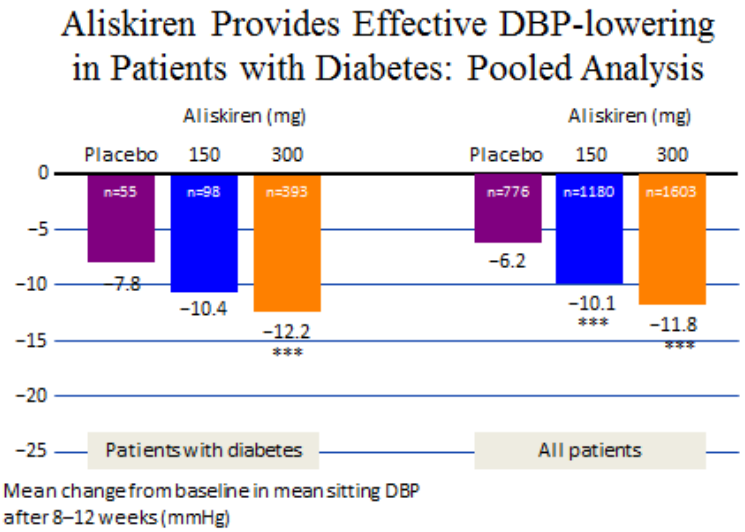


Aliskiren Reduce SBP and DBP Irrespective of Male or Female



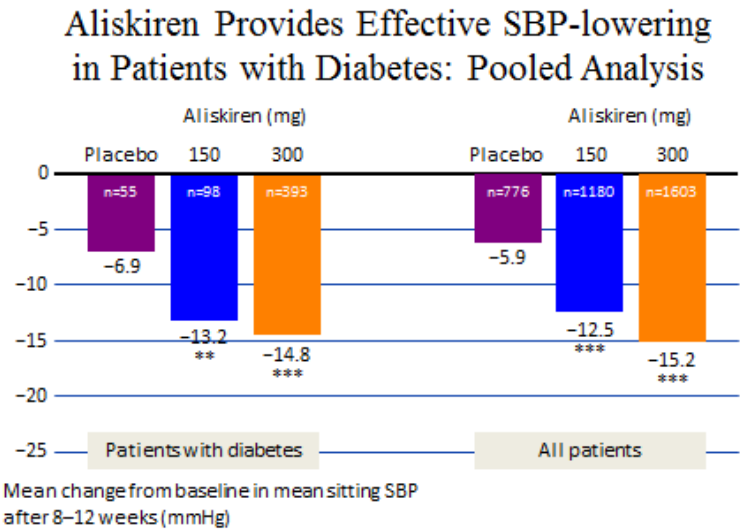


Aliskiren Reduce SBP and DBP Irrespective of DM or not



***p<0.001 vs placebo

Taylor AA, *et al.* 2007



**p<0.01; ***p<0.001 vs placebo

Taylor AA, *et al.* 2007

Aliskiren Monotherapy Results in the Greatest and the Least Blood Pressure Lowering in Patients With High- and Low-Baseline PRA Levels, Respectively

Alice V. Stanton[1], Patrick Dicker[2] and Eoin T. O'Brien[3]

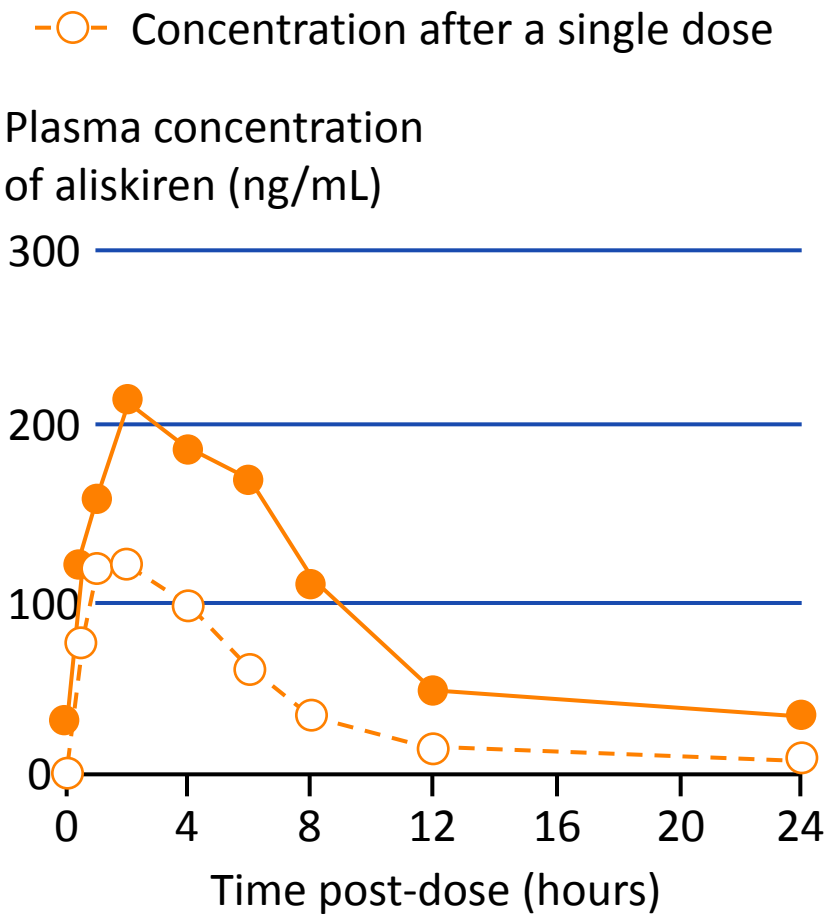
Hypertensive patients with low-baseline plasma renin activity (PRA) are known to respond best to natriuretic drugs, and those with high PRA respond best to renin–angiotensin system (RAS) blockade. However, there has been recent speculation that blood pressure (BP)–lowering responses to the renin inhibitor, aliskiren, might also be blunted in some patients with medium-to-high baseline PRA. It has been suggested that treatment resistance in these patients may result from excessive reactive increases in renin secretion, such that aliskiren's blockade of PRA is overwhelmed. In order to test for evidence in support of this hypothesis, we conducted a reanalysis of original data from three published clinical trials of aliskiren. When aliskiren was administered as a monotherapy, or in combination with other blockers of the RAS, changes in PRA were closely correlated with baseline PRA. Patients with low-baseline PRA demonstrated small reductions or rises in PRA, rather than patients with medium-to-high baseline PRA. We confirmed that ambulatory BP-lowering responses to full dose aliskiren monotherapy were greatest and least among patients with high- and low-baseline PRA, respectively. However no such association was demonstrated during aliskiren combination therapy. With either monotherapy or combination therapy, no patient with a baseline PRA >0.65 ng/ml/h was observed to have a rise in both PRA and BP. We conclude, therefore, that there is only evidence for one type of resistance to aliskiren—as with all blockers of the RAS, lesser BP-lowering responses to aliskiren occur in those with the least renin to block.

Am J Hypertens 2009; **22**:954-957

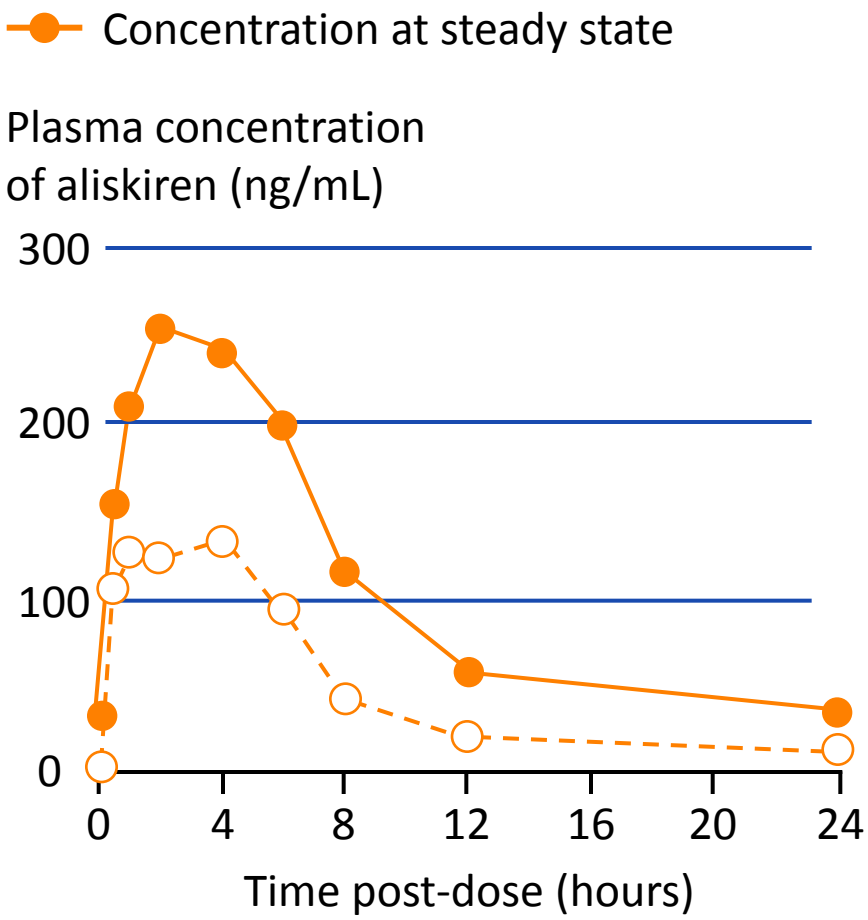
Clinical Research

- The dose–response relationship of aliskiren in decreasing BP.
- Its efficacy as monotherapy
- Its efficacy in combination with other antihypertensives.
- The safety and efficacy of aliskiren in various patient populations (the elderly, different racial groups, diabetic patients, obese patients).
- The pharmacokinetics of aliskiren and the potential for drug–drug interactions.
- Its effect on surrogate markers of end-organ disease, such as diabetic kidney disease and congestive heart failure.

Aliskiren demonstrates predictable steady-state pharmacokinetics and no accumulation in healthy volunteers



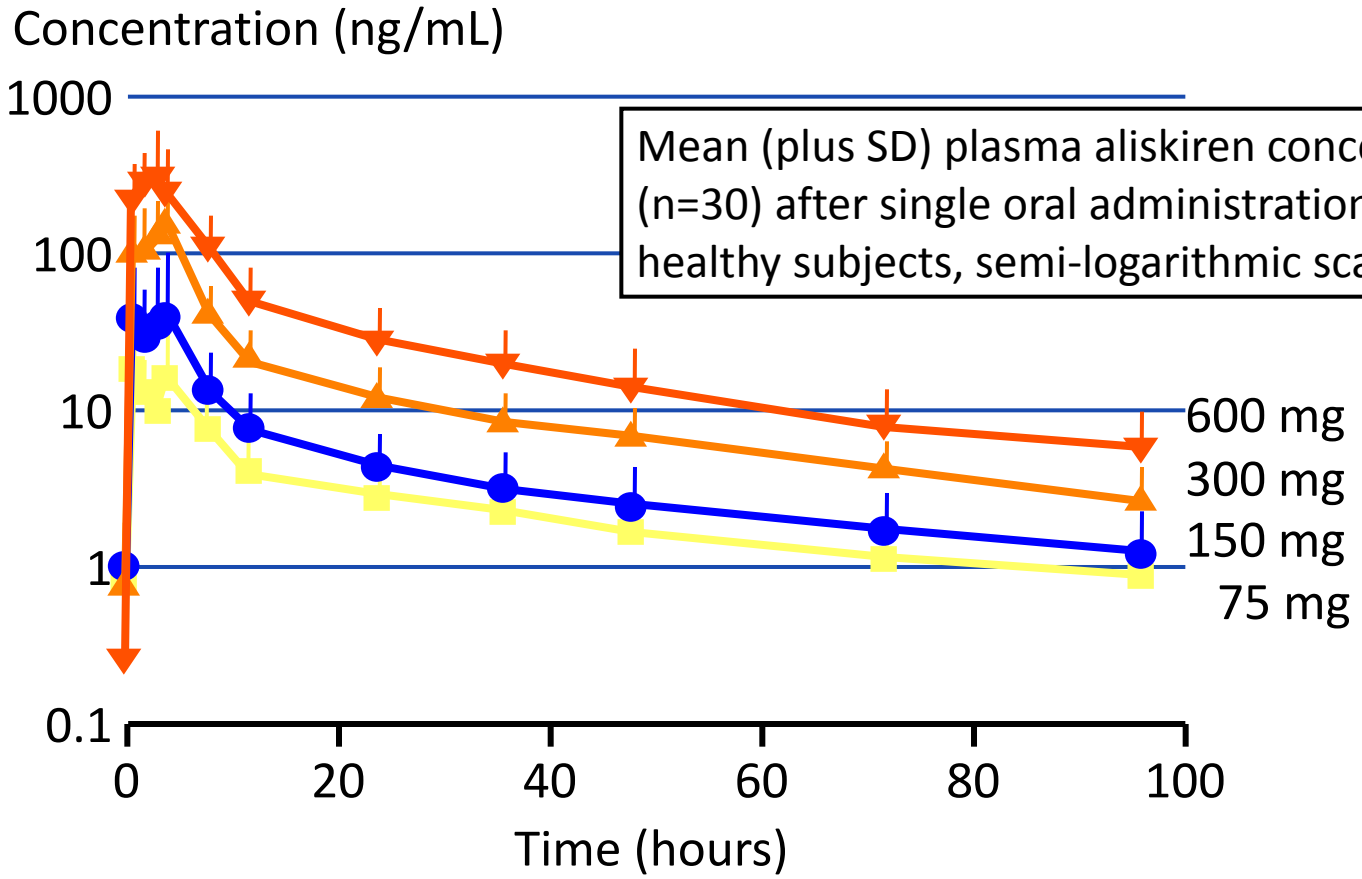
Caucasian volunteers (n=19)



Japanese volunteers (n=19)

Basic Clin Pharmacol Toxicol 2007

Aliskiren Has a Half-life of Approximately 40 Hours, Making it Suitable for Once-daily Dosing



Mean (plus SD) plasma aliskiren concentration profiles (n=30) after single oral administration of aliskiren to healthy subjects, semi-logarithmic scale

90% of the absorbed dose was eliminated by the faecal route and less than0.6% was recovered in the urine

Clin Pharmacol Ther 2006

Journal of Human Hypertension (2010) 24, 93–103

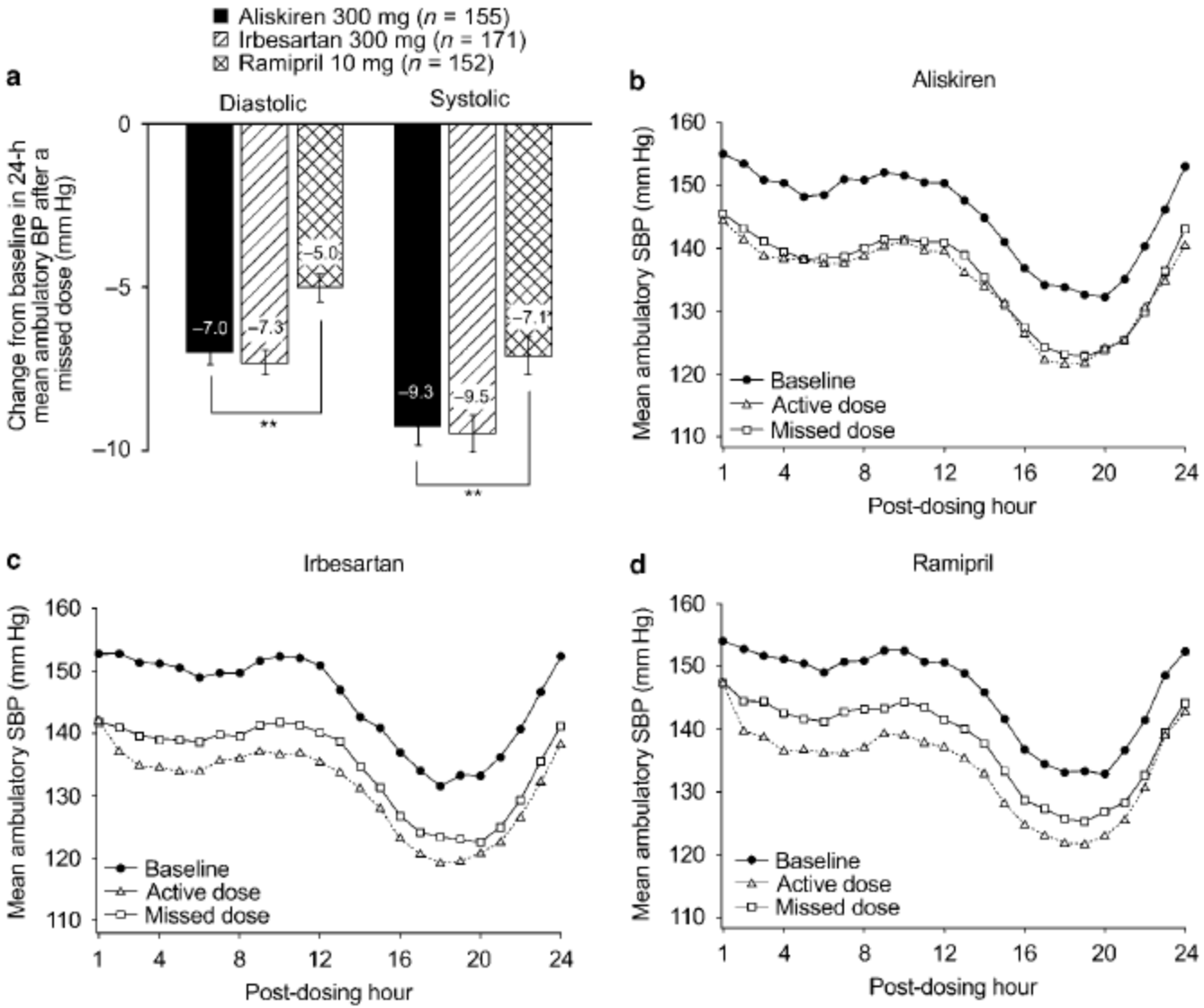
www.nature.com/jhh

ORIGINAL ARTICLE

Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irbesartan or ramipril: results of a randomized, double-blind study

P Palatini[1], W Jung[2], E Shlyakhto[3], J Botha[4], C Bush[5] and DL Keefe[5]
[1]*Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy;* [2]*Department of Cardiology, Academic Hospital Villingen, Villingen-Schwenningen, Germany;* [3]*Scientific Research Institute of Cardiology, Saint Petersburg, Russia;* [4]*Novartis Pharma AG, Basel, Switzerland and* [5]*Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA*

Most patients inadvertently miss an occasional dose of antihypertensive therapy, and hence drugs that provide sustained blood-pressure (BP) reduction beyond the 24-h dosing interval are desirable. The primary objective of this study was to compare the 24-h mean ambulatory BP reductions from baseline after a simulated missed dose of the direct renin inhibitor aliskiren, irbesartan or ramipril. In this double-blind study, 654 hypertensive patients (24-h mean ambulatory diastolic BP (MADBP) ⩾85 mm Hg) were randomized 1:1:1 to once-daily aliskiren 150 mg, irbesartan 150 mg or ramipril 5 mg. Doses were doubled after 2 weeks. At day 42, patients were again randomized equally within each group to receive 1 day of placebo ('missed dose') on either day 42 or day 49. Patients with a successful 24-h ambulatory BP measurement at baseline and on day 42/49 were included in the analyses. The 24-h mean ambulatory systolic BP (MASBP)/MADBP reductions from baseline after a missed dose of aliskiren 300 mg (9.3/7.0 mm Hg) were similar to irbesartan 300 mg (9.5/7.3 mm Hg) and significantly larger than ramipril 10 mg (7.1/5.0 mm Hg, $P \leqslant 0.008$). Loss of BP-lowering effect with aliskiren in the 24 h after a missed dose (1.0/0.7 mm Hg for 24–48-h vs 0–24-h MASBP/MADBP) was significantly lower than with irbesartan (3.6/2.2 mm Hg, $P < 0.01$) or ramipril (4.0/2.6, $P < 0.0001$). This equates to maintenance of 91/91% of the MASBP/MADBP-lowering effect with aliskiren, greater than irbesartan (73/77%) or ramipril (64/65%). The incidence of adverse events was similar across treatments (32.9–36.0%), although ramipril treatment was associated with an increased incidence of cough (ramipril, 6.1%; aliskiren, 0.5%; irbesartan, 1.8%). Aliskiren 300 mg provided a sustained BP-lowering effect beyond the 24-h dosing interval, with a significantly smaller loss of BP-lowering effect in the 24–48 h period after dose than irbesartan 300 mg or ramipril 10 mg.
Journal of Human Hypertension (2010) **24**, 93–103; doi:10.1038/jhh.2009.38; published online 21 May 2009



2010/12/22

楊登堯 Journal of Human Hypertension (2010)

Alis 40, irb 11-15,rami 2-4

No Dose Adjustment of Aliskiren is Necessary in Patients with Renal Impairment

- In patients with renal impairment:
  - there was a modest (~2-fold) increase in exposure to aliskiren
  - changes in aliskiren exposure did not correlate with the severity of renal disease or with creatinine clearance
  - steady-state clearance of aliskiren was 60–70% of the values for matched healthy control subjects
  - renal clearance of aliskiren predictably decreased with increasing severity of renal impairment
  - aliskiren was well tolerated
- As renal impairment has only a modest effect on aliskiren exposure, adjustment of the aliskiren dose is not likely to be necessary in patients with hypertension and renal impairment

Clin Pharmacokinetic 2007

No Dose Adjustment of Aliskiren is Necessary in Patients with Hepatic Impairment

- In patients with hepatic impairment:
  - plasma concentration–time profiles were similar to those in matched healthy subjects
  - aliskiren exposure was similar to that in matched healthy subjects
  - there was no significant correlation between aliskiren exposure and severity of hepatic impairment
  - aliskiren was well tolerated
- As the pharmacokinetics of aliskiren are not significantly affected by hepatic impairment, and aliskiren has no significant hepatic metabolism, dose adjustment of aliskiren will not be required in the treatment of patients with hypertension and hepatic impairment

J Clin Pharmacol 2007

Aliskiren has a low potential for drug interactions

- **Effects of other drugs on aliskiren**:
  - Co-administration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.
  - Co-administration of atorvastatin resulted in about a 50% increase in aliskiren C_{max} and AUC after multiple dosing.
  - Co-administration of 200 mg twice-daily ketoconazole with aliskiren resulted in an approximate 80% increase in plasma levels of aliskiren. A 400 mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.
- Effects of aliskiren on other drugs:
  - Co-administration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.
  - The effects of aliskiren on warfarin pharmacokinetics have not been evaluated in a well-controlled clinical trial.
  - When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively.

Br J Clin Pharmacol 2004, Int J Clin Pharmacol Ther 2005, Clin Pharmacol Ther 2007, Clin Pharmacol Ther 2007, Clin Pharmacol Ther 2006, J Clin Pharmacol 2006, Clin Pharmacol Ther 2007; Clin Pharmacol Ther 2007.

Clinical Research

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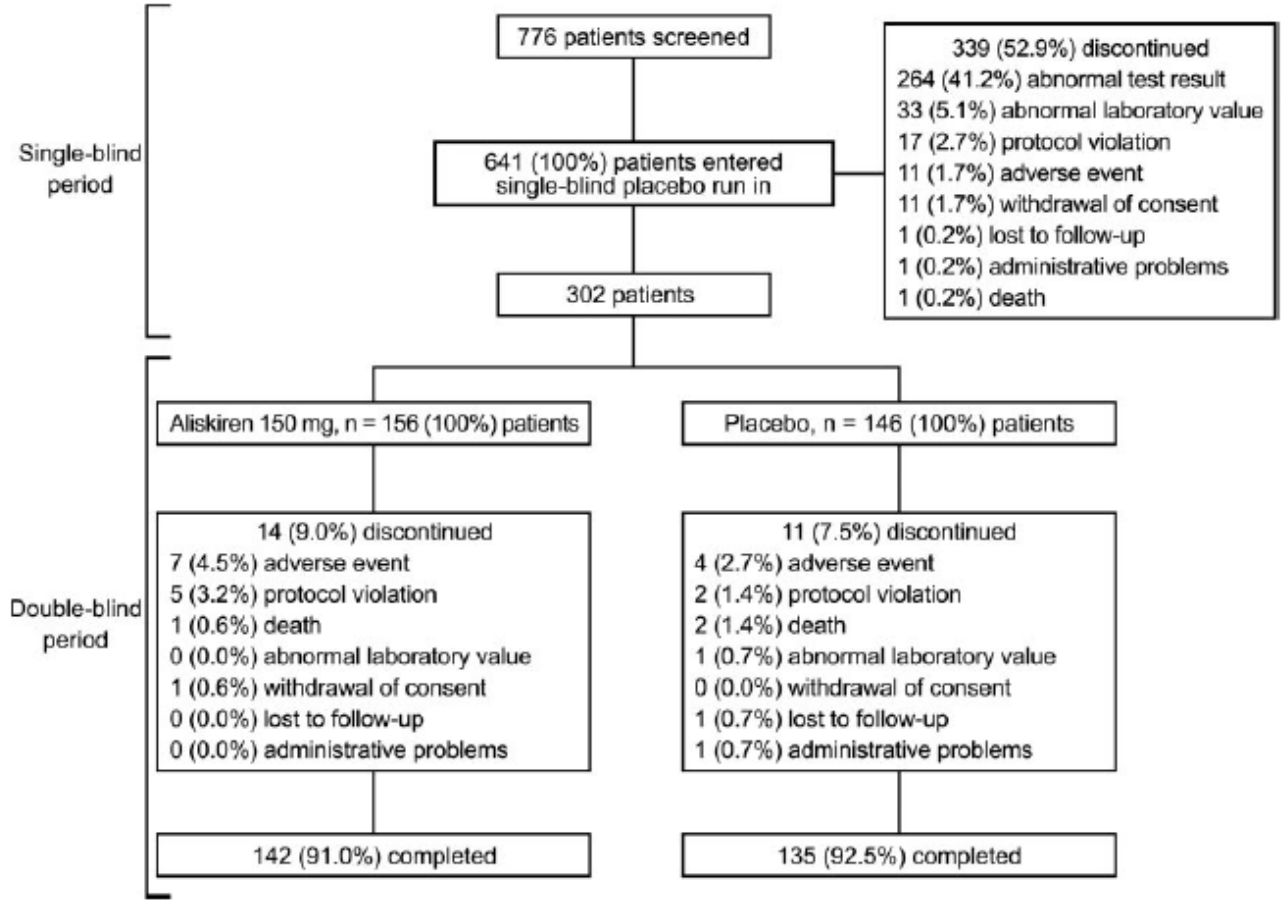
Effects of the Oral Direct Renin Inhibitor Aliskiren in Patients With Symptomatic Heart Failure (ALOFT)



Circ Heart Fail. 2008

BNP Lowered if Aliskiren was Added to Standard Therapy for Heart Failure

Table 2. Neurohumoral Measurements (Plasma Unless Stated Otherwise)

Neurohumoral Measure	Baseline Mean±SD	Baseline Geometric Mean (95% CI)	End of Study Mean±SD	End of Study Geometric Mean (95% CI)	Ratio: End of Study/Baseline Geometric Mean (95% CI)	Ratio: Aliskiren/Placebo (95% CI)	*P*
NT-proBNP, pg/mL							
Aliskiren	2158±2269	1389 (1159, 1664)	1915±2373	1087 (888, 1331)	0.73 (0.57, 0.93)	0.75 (0.61, 0.94)	0.0106
Placebo	2123±3858	1233 (1019, 1492)	2885±6393	1419 (1190, 1691)	0.96 (0.75, 1.24)		
BNP, pg/mL							
Aliskiren	301±269	204 (175, 240)	240±307	135 (112, 163)	0.64 (0.48, 0.84)	0.75 (0.59, 0.95)	0.0160
Placebo	273±246	189 (162, 220)	261±272	168 (141, 200)	0.85 (0.64, 1.12)		
Aldosterone, pmol/L							
Aliskiren	334±364	208 (176, 247)	285±281	184 (157, 216)	0.99 (0.81, 1.22)	0.99 (0.93, 1.18)	0.9064
Placebo	307±316	190 (159, 226)	276±273	177 (149, 210)	1.00 (0.82, 1.23)		
Urinary aldosterone, nmol/d							
Aliskiren	38±43	24 (20, 28)	29±33	18 (16, 21)	0.81 (0.65, 1.00)	0.79 (0.66, 0.96)	0.0150
Placebo	37±41	23 (19, 27)	31±33	21 (18, 24)	1.02 (0.82, 1.26)		
Plasma renin concentration, ng/L							
Aliskiren	69±112	26 (20, 33)	155±177	63 (49, 81)	2.61 (1.87, 3.63)	2.60 (1.97, 3.44)	<0.0001
Placebo	79±120	31 (24, 39)	74±116	28 (22, 37)	1.00 (0.73, 1.38)		
Plasma renin activity, $ng \cdot mL^{-1} \cdot h^{-1}$							
Aliskiren	7.32±11.70	1.80 (1.32, 2.46)	1.61±3.47	0.42 (0.33, 0.54)	0.18 (0.12, 0.26)	0.23 (0.17, 0.31)	<0.0001
Placebo	8.38±12.98	2.24 (1.65, 3.05)	7.42±11.54	2.04 (1.50, 2.76)	0.78 (0.54, 1.13)		

Circ Heart Fail. 2008

No Significant Adverse Event When Aliskiren Added to Standard Therapy for Heart Failure

Table 4. Prespecified Safety Assessments and Adverse Events

	Placebo (n=146)	Aliskiren (n=156)
Prespecified safety assessment, n (%)		
Renal dysfunction‡	2 (1.4)	3 (1.9)
Symptomatic hypotension†§	2 (1.4)	5 (3.2)
Hyperkalemia‖	7 (4.8)	10 (6.4)
Any of the above¶	11 (7.5)	17 (10.9)
Adverse events occurring in ≥3% of patients, n (%)*		
Nasopharyngitis	4 (2.7)	6 (3.8)
Asthenia	2 (1.4)	5 (3.2)
Diarrhea	2 (1.4)	5 (3.2)
Hyperuricemia	2 (1.4)	5 (3.2)
Hypotension	1 (0.7)	5 (3.2)
Nausea	0 (0.0)	5 (3.2)
Cardiac failure	6 (4.1)	4 (2.6)
Dyspnea	5 (3.4)	3 (1.9)
Dizziness	5 (3.4)	2 (1.3)

No statistically significant differences were found in any assessment.

*In either treatment group.

†Orthostatic hypotension (defined as a decrease of ≥10 mm Hg diastolic or ≥20 mm Hg in systolic blood pressure when changing from the sitting to the standing position) occurred in 25 (17.4%) placebo-treated and 27 (17.4%) aliskiren-treated patients at any time after randomization.

Fisher exact test *P* for ‡1.000, §0.4495, ‖0.4989, and ¶0.3294; all nonsignificant.

Circ Heart Fail. 2008

Patients with acute coronary syndromes and elevated levels of natriuretic peptides: the results of the AVANT GARDE-TIMI 43 Trial

Benjamin M. Scirica[1,2]*, David M. Morrow[1,2], Christoph Bode[3], Witold Ruzyllo[4], Mikhail Ruda[5], Anthonius J.M. Oude Ophuis[6], Jose Lopez-Sendon[7], Karl Swedberg[8], Michal Ogorek[9], Nader Rifai[10], Valentina Lukashevich[11], Mojdeh Maboudian[11], Christopher P. Cannon[1,2], Carolyn H. McCabe[1,2], and Eugene Braunwald[1,2]

[1]TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA; [2]Harvard Medical School, Boston, MA, USA; [3]Medizinische Universitatsklinik, Freiburg, Germany; [4]Institute of Cardiology, Warsaw, Poland; [5]Cardiology Research Center, Moscow, Russia; [6]Canisiud Wilhelmina Ziekenhuis, Nijmegen, The Netherlands; [7]Hospital Universitario La Paz, Madrid, Spain; [8]Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [9]Samodzielny Szpital Wojewódzki, Piotrków Trybunalski, Poland; [10]Children's Hospital, Boston, MA, USA; and [11]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Received 21 January 2010; revised 29 April 2010; accepted 11 May 2010

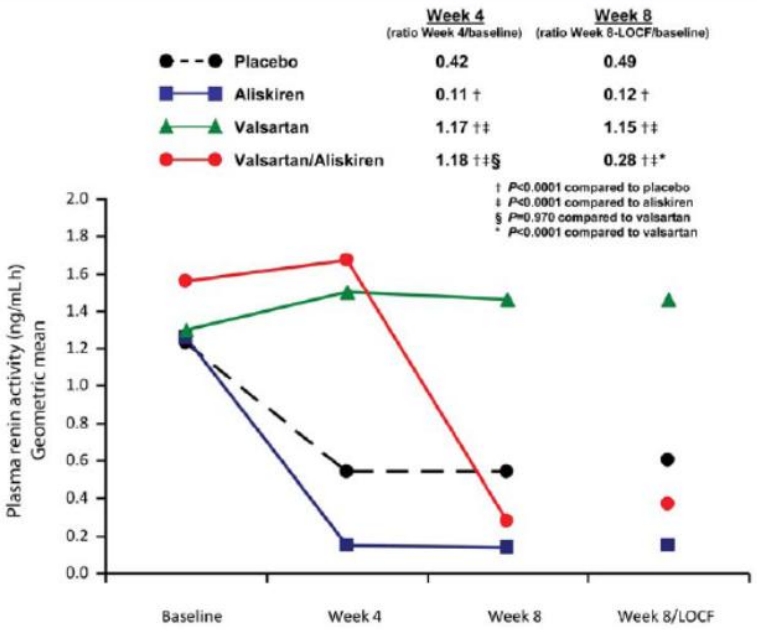
Aims Elevated natriuretic peptides (NPs) are associated with an increased cardiovascular risk following acute coronary syndromes (ACSs). However, the therapeutic implications are still undefined. We hypothesized that early inhibition of renin–angiotensin–aldosterone system (RAAS) in patients with preserved left ventricular function but elevated NPs but following ACS would reduce haemodynamic stress as reflected by a greater reduction NP compared with placebo.

Methods and results AVANT GARDE-TIMI 43 trial, a multinational, double-blind trial, randomized 1101 patients stabilized after ACS *without* clinical evidence of heart failure or left ventricular function ≤40% but *with* an increased level of NP 3–10 days after admission to aliskiren, valsartan, their combination, and placebo. The primary endpoint was the change in NT-proBNP from baseline to Week 8. NT-proBNP declined significantly in each treatment arm, including placebo, by Week 8, though there were no differences in the reduction between treatment strategies (42% in placebo, 44% in aliskiren, 39% in valsartan, and 36% in combination arm). Although several subgroups had higher baseline levels of NP and greater reductions over the study period, there were no differences among treatment groups in any subgroup. There were no differences in clinical outcomes but there were more adverse events, including serious events and adverse events leading to early study drug discontinuation, in patients treated with active therapy.

Conclusion In this study of a high-risk population with elevated levels of NPs but relatively preserved systolic function and no evidence of heart failure following ACS, there was no evidence for a benefit of early initiation of inhibition of RAAS with valsartan, aliskiren, or their combination compared with placebo with respect to a reduction in NP over 8 weeks of therapy. Moreover, adverse events were reported more frequently in patients assigned to active therapy.

Keywords Natriuretic peptides • Acute coronary syndrome • Renin–angiotensin–aldosteron system

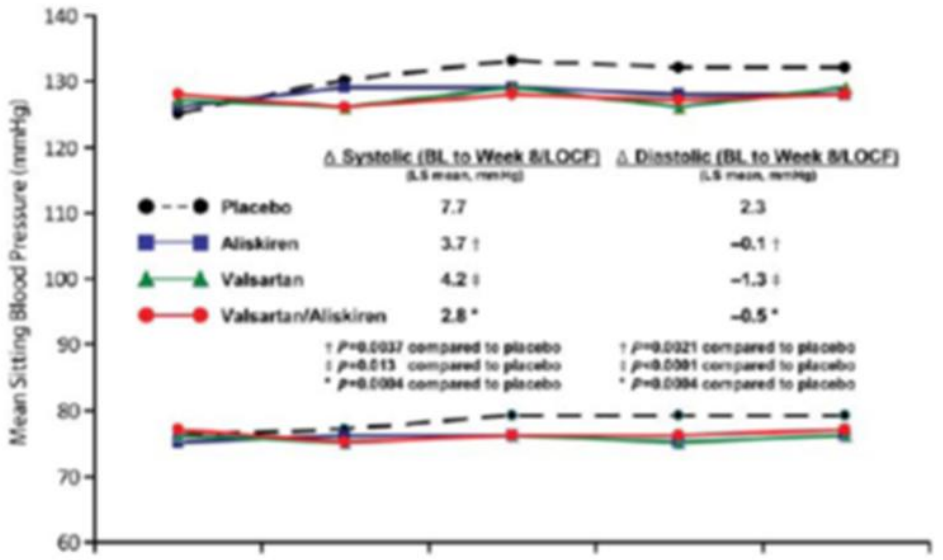
Plasma Renin Activity



	Baseline Geometric mean (95% CI)	Week 4 Geometric mean (95% CI)	Week 8 Geometric mean (95% CI)	Week 8/ End of study Geometric mean (95% CI)
Placebo	1.23 (1.00, 1.51)	0.54 (0.451, 0.656)	0.54 (0.45, 0.66)	0.60 (0.50, 0.72)
Aliskiren	1.26 (1.03, 1.54)	0.15 (0.131, 0.163)	0.14 (0.12, 0.15)	0.15 (0.14. 0.17_
Valsartan	1.30 (1.07, 1.58)	1.50 (1.67, 1.91)	1.46 (1.13, 1.89)	1.46 (1.15, 1.86)
Valsartan/ Aliskiren	1.56 (1.29, 1.90)	1.66 (1.29, 2.14)	0.28 (0.23, 0.35)	0.37 (0.30, 0.46)

2010 Eur Heart J

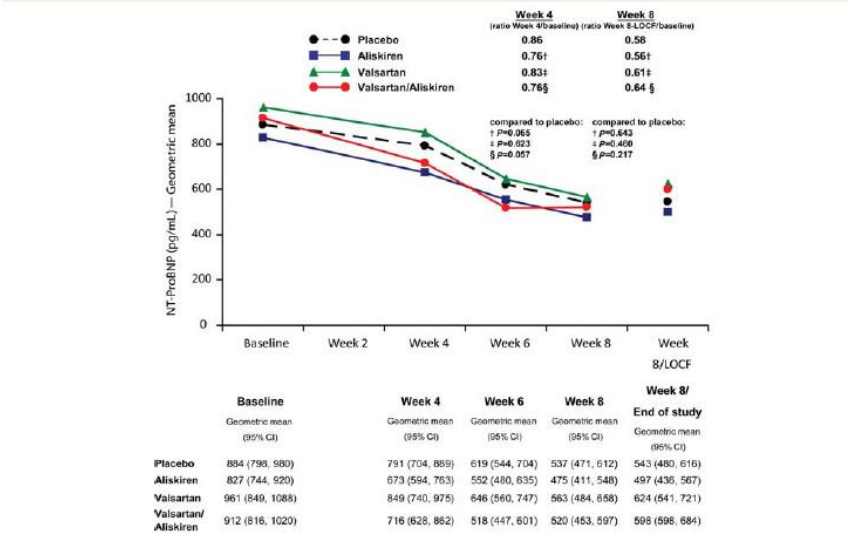
Blood Pressure Changes



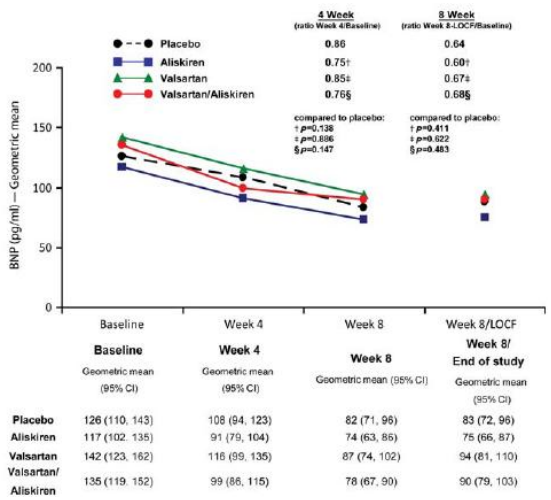
	Baseline	Week 2	Week 4	Week 6	Week 8	Week 8/ End of Study
Placebo	125/76	130/77	133/79	132/79	132/79	132/79
Aliskiren	126/75	129/76	129/76	128/75	128/76	128/76
Valsartan	127/76	126/75	129/76	129/75	129/76	129/76
Valsartan/ Aliskiren	128/77	126/75	128/76	126/76	128/77	128/77

2010 Eur Heart J

BNP and NT-Pro BNP



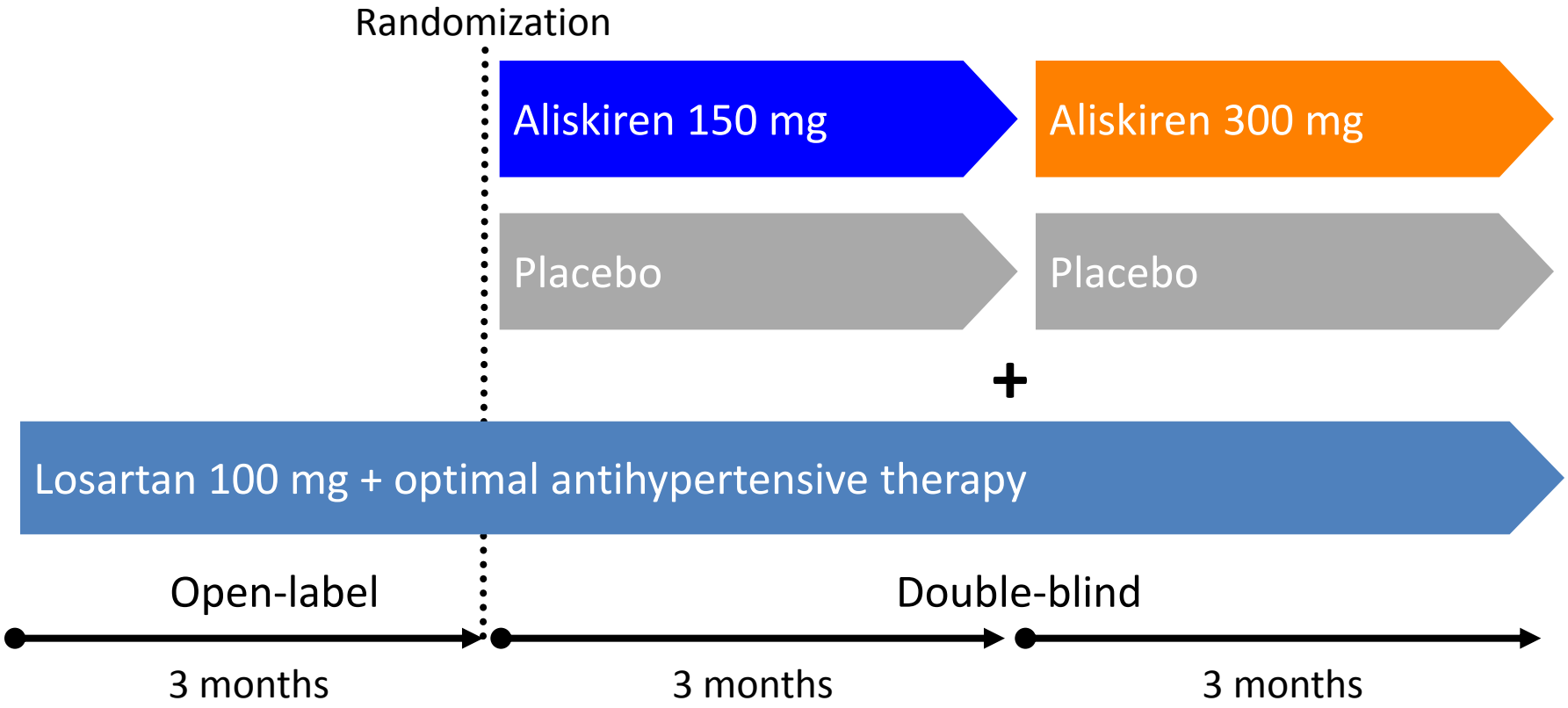
	Baseline Geometric mean (95% CI)	Week 4 Geometric mean (95% CI)	Week 6 Geometric mean (95% CI)	Week 8 Geometric mean (95% CI)	Week 8/ End of study Geometric mean (95% CI)
Placebo	884 (798, 980)	791 (704, 889)	619 (544, 704)	537 (471, 612)	543 (480, 616)
Aliskiren	827 (744, 920)	673 (594, 763)	552 (480, 635)	475 (411, 548)	497 (436, 567)
Valsartan	961 (849, 1088)	849 (740, 975)	646 (560, 747)	563 (484, 658)	624 (541, 721)
Valsartan/ Aliskiren	912 (816, 1020)	716 (628, 862)	518 (447, 601)	520 (453, 597)	598 (598, 684)



	Baseline Geometric mean (95% CI)	Week 4 Geometric mean (95% CI)	Week 8 Geometric mean (95% CI)	Week 8/ End of study Geometric mean (95% CI)
Placebo	126 (110, 143)	108 (94, 123)	82 (71, 96)	83 (72, 96)
Aliskiren	117 (102, 135)	91 (79, 104)	74 (63, 86)	75 (66, 87)
Valsartan	142 (123, 162)	116 (99, 135)	87 (74, 102)	94 (81, 110)
Valsartan/ Aliskiren	135 (119, 152)	99 (86, 115)	78 (67, 90)	90 (79, 103)

2010 Eur Heart J

Aliskiren in the eValuation of prOteinuria In Diabetes (AVOID) study – Study design overview



- All patients continue to receive open-label losartan 100 mg and optimal antihypertensive therapy during the double-blind period
- Patients force-titrated after 3 months
- All treatments administered once daily

NEJM 2008

AVOID
Population and Objectives

Study population:

- Patients with mild-to-moderate hypertension, type 2 diabetes and nephropathy (UACR 200–3500 mg/g)

Primary objective:

- Change in UACR from baseline to study end with aliskiren when added to losartan 100 mg once daily and optimal antihypertensive therapy, compared with placebo

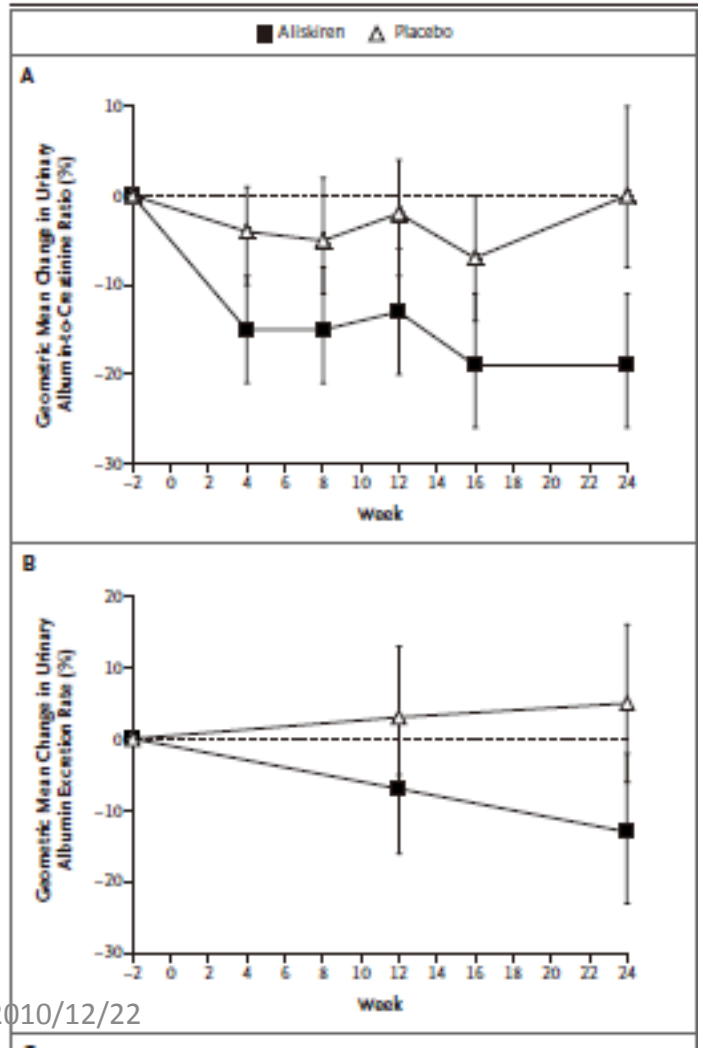
Secondary objectives included:

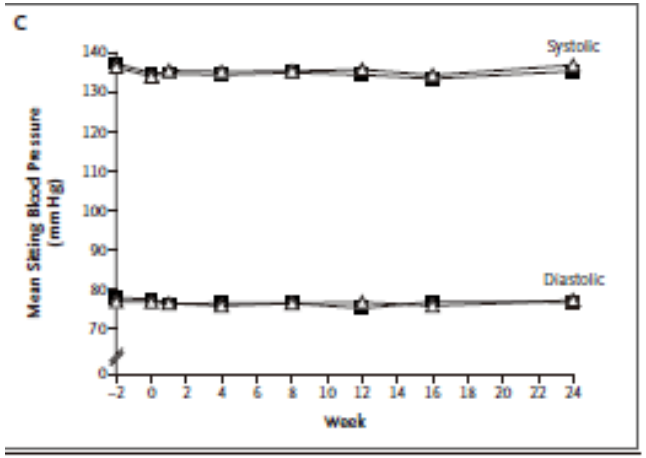
- Proportion of patients with ≥50% reduction in UACR at study end
- Effect of treatment on BP
- Safety and tolerability

UACR – urinary albumin-to-creatinine ratio

NEJM 2008

Urinary Albumin Decrease Dose-dependently but BP was Similar among Groups





(p=0.07)

(p=0.08)

NEJM 2008

Diabetes Care Publish Ahead of Print, published online August 6, 2010

Impact of Baseline Renal Function on the Efficacy and Safety of Aliskiren Added To Losartan in Patients with Type 2 Diabetes and Nephropathy

Impact of eGFR in the AVOID study

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**The investigators who participated in the AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes) study are listed in the Online Appendix available at http://care.diabetesjournals.org.*

Objective: Proteinuric diabetic patients with reduced GFR are at high risk of renal and cardiovascular disease progression and treatment-related adverse events. This post-hoc analysis assessed the efficacy and safety of aliskiren added to maximal recommended dose of losartan according to baseline estimated GFR (CKD stage 1-3).

Research Design and Methods: In the AVOID study, 599 hypertensive patients with type 2 diabetes and nephropathy received 6 months' aliskiren (150 mg daily titrated to 300 mg daily after 3 months) or placebo added to losartan 100 mg and optimal antihypertensive therapy. Exclusion criteria included eGFR <30 ml/min/1.73 m^2 and serum potassium >5.1 mmol/l.

Results: Baseline characteristics were similar between treatment groups in all CKD stages. The antiproteinuric effects of aliskiren were consistent across CKD stages (19%, 22% and 18% reduction). In the stage 3 group, baseline serum creatinine levels were equal but renal dysfunction, prespecified as a post randomization serum creatinine elevation >176.8. µmol/l (2.0 mg/dl) occurred more frequently in the placebo group (29.2% vs. 13.6%, p=0.032). Serum potassium elevations >5.5 mmol/l (based on a single measurement) were more frequent with aliskiren (22.5% vs. 13.6%) in stage 3 CKD. Adverse event rates were similar between treatments, irrespective of CKD stage.

Conclusions: Aliskiren added to losartan reduced albuminuria and renal dysfunction and was well tolerated, except for hyperkalemia (stage 3), independent of baseline CKD stage in patients with type 2 diabetes, hypertension and nephropathy.

Addition of Aliskiren to Losartan and Optimal Antihypertensive Therapy was Generally Well Tolerated during The Study

	Optimal antihypertensive therapy +	
	Aliskiren (n=301)	Placebo (n=298)
Any adverse event (AE), n (%)	201 (66.8)	200 (67.1)
Any serious AE, n (%)	27 (9.0)	28 (9.4)
Discontinuations due to AEs, n (%)	17 (5.6)	19 (6.4)
Deaths, n (%)	0	2 (0.7)
AEs 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)
Hyperkalaemia	15 (5.0)	17 (5.7)
Peripheral oedema	13 (4.3)	23 (7.7)

NEJM 2008

Effect of Study Treatments on Laboratory Values

		Optimal antihypertensive therapy + Aliskiren (n=299)	Optimal antihypertensive therapy + Placebo (n=297)
Potassium	<3.5 mmol/L, n (%)	15 (5.0)	11 (3.7)
	>5.5 mmol/L, n (%)	41 (13.7)	32 (10.8)
	≥6.0 mmol/L, n (%)	14 (4.7)	5 (1.7)
Creatinine	>2.0 mg/dL, n (%)	37 (12.4)	54 (18.2)
BUN	>40.0 mg/dL, n (%)	65 (21.7)	66 (22.2)

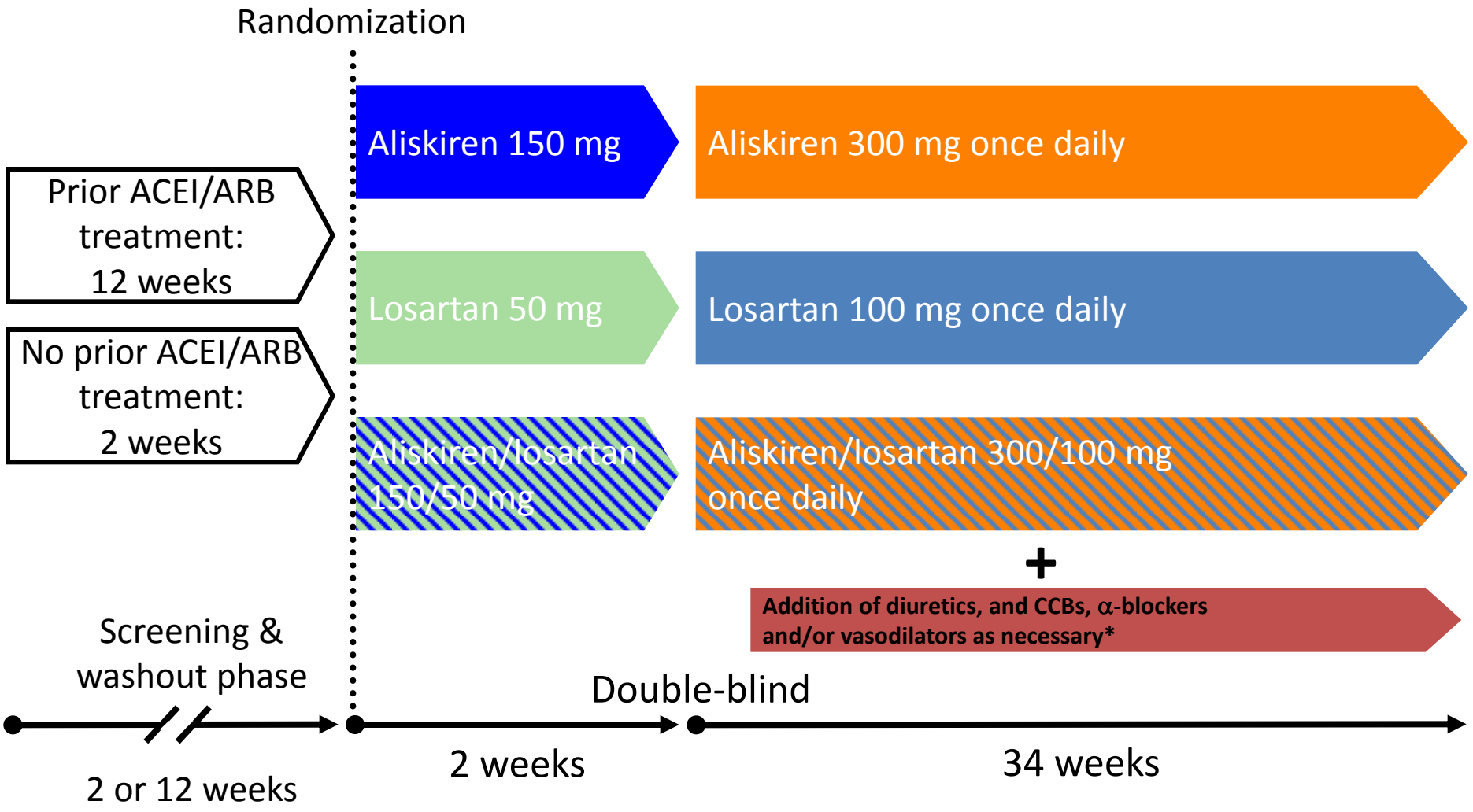
- The incidence of serum potassium >6.0 mEq/L was numerically, but not significantly greater with aliskiren compared with placebo (p=0.06)

BUN – blood urea nitrogen

Data are presented as number of patients with pre-specified abnormal laboratory values at any time during the double-blind period

NEJM 2008

ALiskiren in Left ventriculAr hypertrophY (ALLAY) – Study design overview



*To achieve BP <140/90 mmHg (<130/80 mmHg for patients with diabetes)

Circulation 2009

ALLAY
Population and objectives

Study population:

- Patients with a history of hypertension or newly diagnosed hypertension (SBP 140 to <180 mmHg; DBP 90 to <110 mmHg), body mass index (BMI) >25 kg/m^2 and left ventricular wall thickness ≥1.3 cm[†]

Primary objective:

- To evaluate whether aliskiren/losartan combination therapy was superior to losartan monotherapy in reducing LVH, by measuring the change in LVMI using CMR

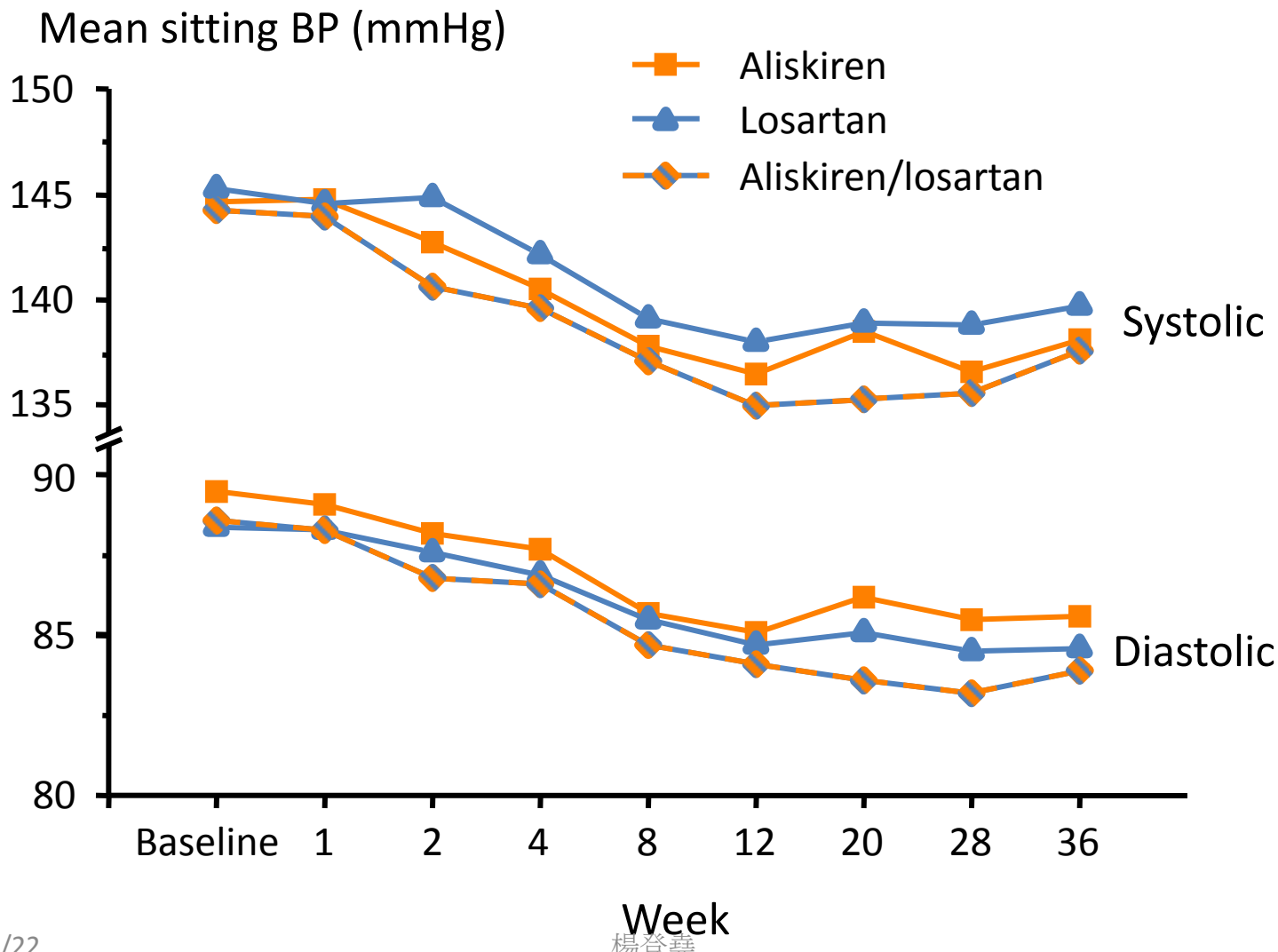
Key secondary objectives include:

- Evaluate whether aliskiren monotherapy was non-inferior to losartan monotherapy in reducing LVMI
- Safety and tolerability

[†]Confirmed by central echocardiography core laboratory assessments

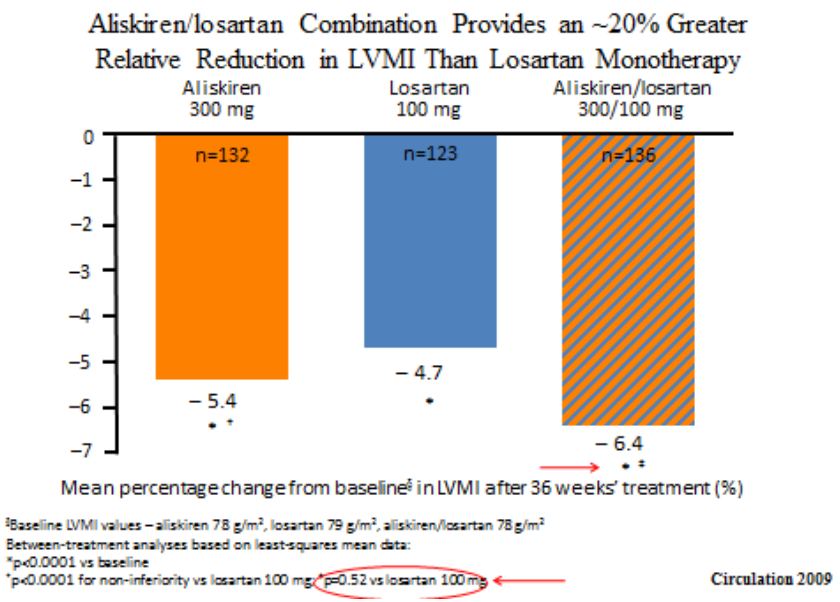
Circulation 2009

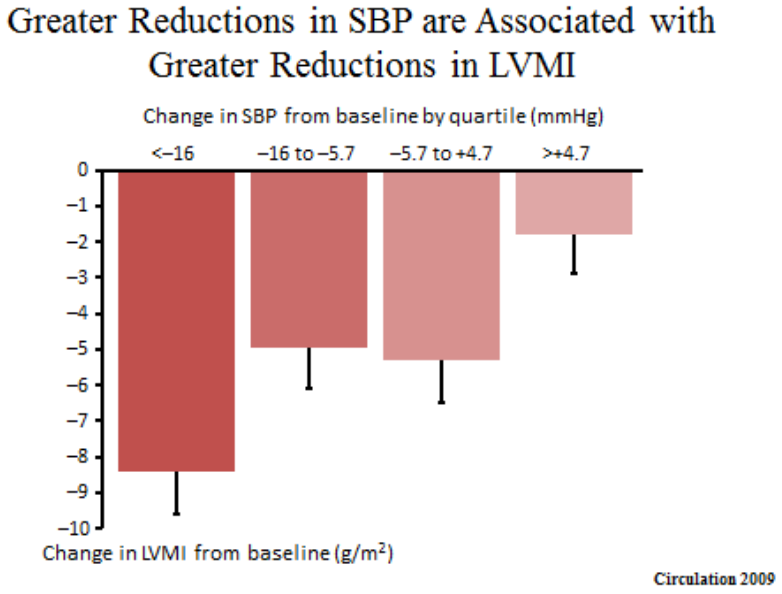
Aliskiren/losartan Combination Therapy was Associated with lower BP Compared with either Monotherapy at all Time points Post-baseline



Circulation 2009

Effect on LVMI





No Evidence of an Elevated Incidence of Hyperkalaemia with Aliskiren/losartan Combination Therapy

	Aliskiren (n=154)	Losartan (n=152)	Aliskiren/losartan (n=154)
Serum potassium			
<3.5 mEq/L, n (%)	12 (8.1)	11 (7.3)	7 (4.6)
>5.5 mEq/L, n (%)	4 (2.7)	5 (3.3)	5 (3.3)
≥6.0 mEq/L, n (%)	3 (2.0)	1 (0.7)	1 (0.7)
BUN			
>40.0 mg/dL, n (%)	1 (0.7)	2 (1.3)	0
Serum creatinine			
>2.0 mg/dL, n (%)	0	1 (0.7)	1 (0.7)

Data are shown for the safety population; BUN – blood urea nitrogen

Circulation 2009

Conclusion (1)

1 Aliskiren is the first one drug of the new class of anti-hypertensive drug (renin inhibitor)

2 It has a dose-dependent Bp lowering effect from 75 to 300mg.

3 The peak serum concentration happens 1-3 hours after drug administration, and the half life is about 40 hours

(one missing dose will not affect the BP significantly).

4 90% of the drug is eliminated from the faces and no dosage adjustment is needed in liver or renal failure patient; no frequent severe adverse events.

Conclusion (2)

5 Patients with high baseline renin activity respond to aliskiren better?

6 It will reduce BP further when combined with thiazide, ACEI,ARB and CCB.

7 Similar effects among different age, gender, race, with or without DM and obesity.

8 No significant drug-drug interactions. (Atorvastatin, Ketoconazole; lasix, warfarin)

9 Aliskiren may improve some surrogate marker for target organ damage (BNP, proteinuria).