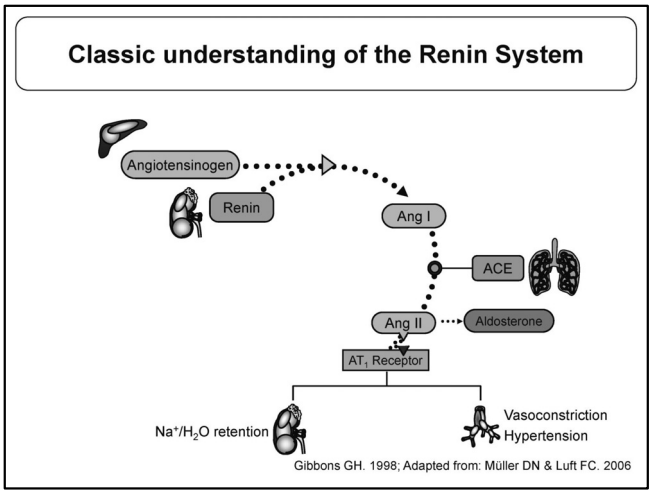
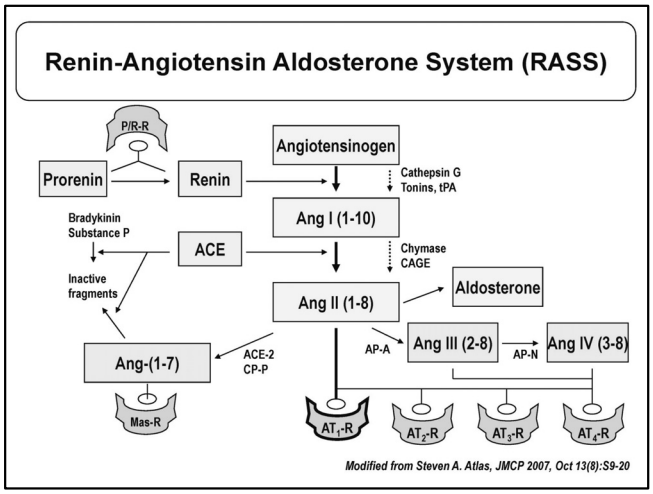
[연수강좌]

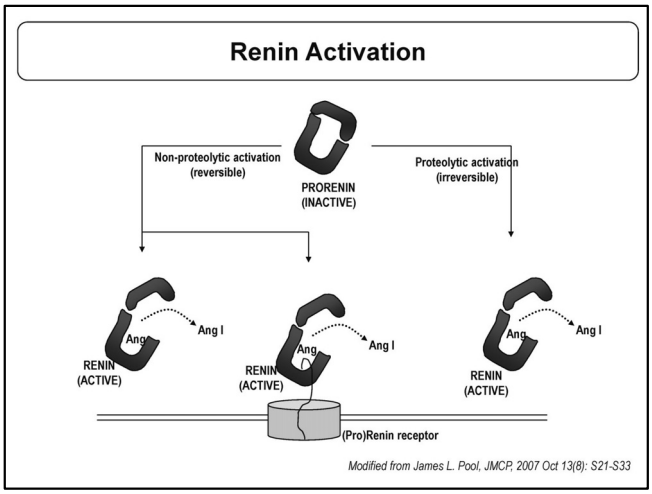
새로운 항고혈압제제인 Direct Renin Inhibitor의 효과

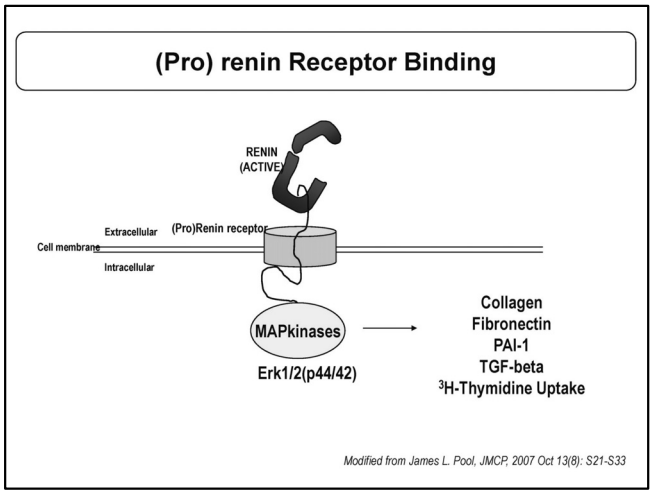
차 대 룡

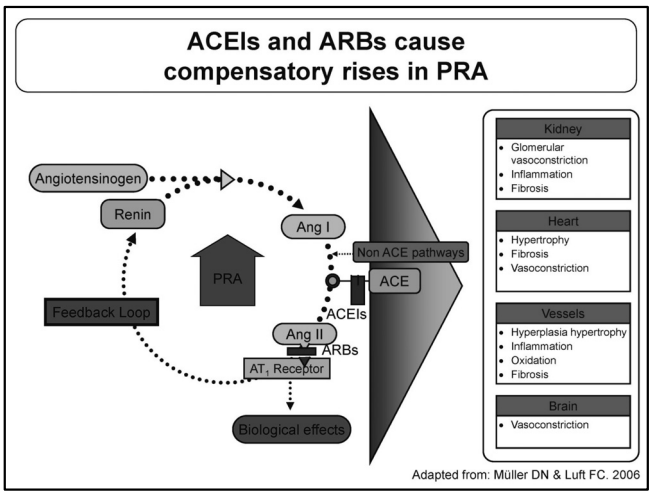
고려의대 내과학교실

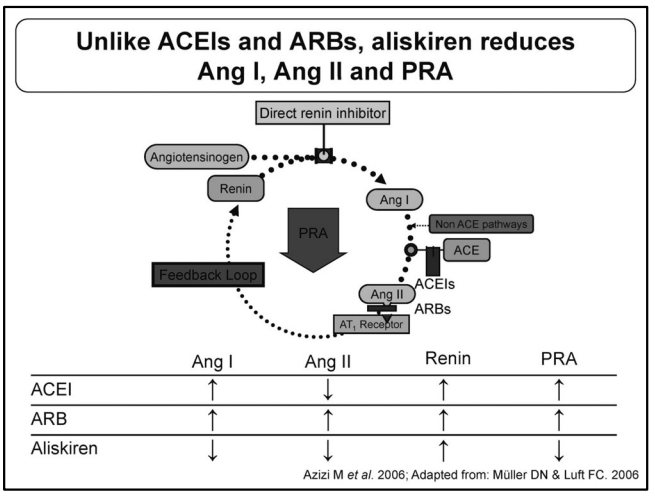


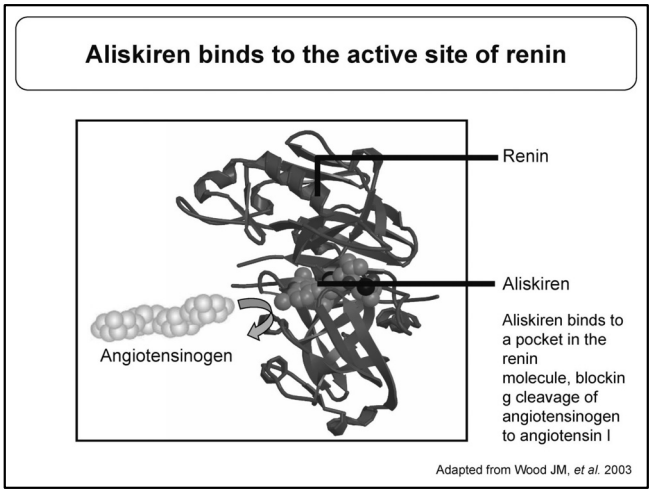


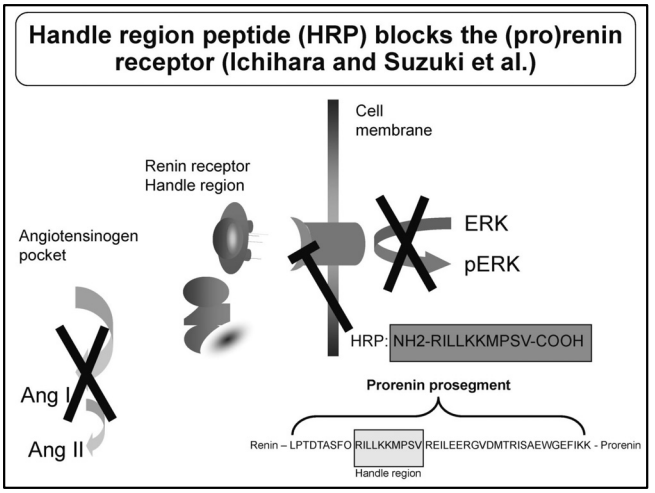


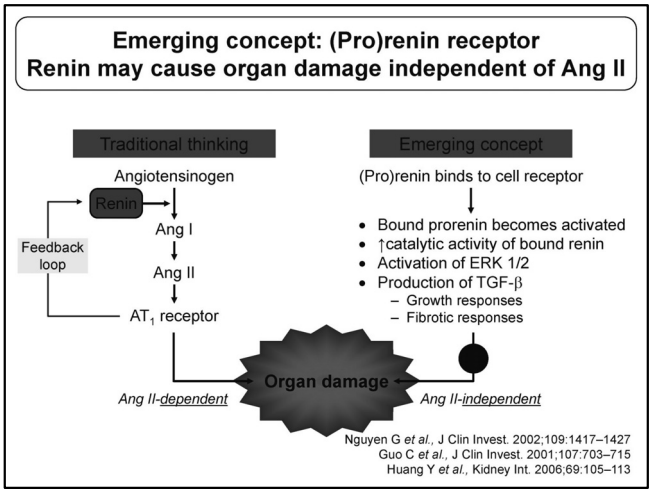


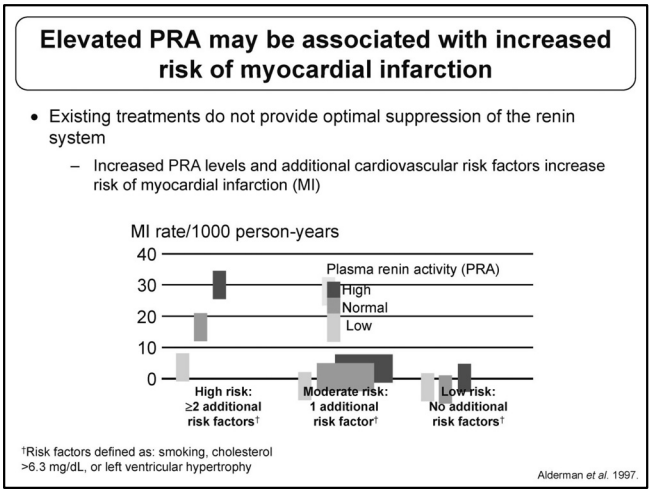

ACEIs and ARBs cause compensatory rises in PRA
Angiotensinogen
Renin
Ang I
Non ACE pathways
PRA
ACE
Feedback Loop
ACEIs
Ang II
ARBs
AT1 Receptor
Biological effects
Kidney
Glomerular vasoconstriction
Inflammation
Fibrosis
Heart
Hypertrophy
Fibrosis
Vasoconstriction
Vessels
Hyperplasia hypertrophy
Inflammation
Oxidation
Fibrosis
Brain
Vasoconstriction
Adapted from: Müller DN & Luft FC. 2006


Unlike ACEIs and ARBs, aliskiren reduces Ang I, Ang II and PRA
Direct renin inhibitor
Angiotensinogen
Renin
Ang I
Non ACE pathways
PRA
ACE
Feedback Loop
ACEIs
Ang II
ARBs
AT1 Receptor
Ang I
Ang II
Renin
PRA
ACEI
ARB
Aliskiren
Azizi M et al. 2006; Adapted from: Müller DN & Luft FC. 2006


Aliskiren binds to the active site of renin
Renin
Aliskiren
Angiotensinogen
Aliskiren binds to a pocket in the renin molecule, blocking cleavage of angiotensinogen to angiotensin I
Adapted from Wood JM, et al. 2003


Handle region peptide (HRP) blocks the (pro)renin receptor (Ichihara and Suzuki et al.)
Cell membrane
Renin receptor Handle region
Angiotensinogen pocket
ERK
pERK
HRP: NH2-RILLKKMPSV-COOH
Ang I
Ang II
Prorenin prosegment
Renin – LPTDTASFO RILLKKMPSV REILEERGVDMTRISAEWGEFIKK - Prorenin
Handle region


Emerging concept: (Pro)renin receptor Renin may cause organ damage independent of Ang II
Traditional thinking
Angiotensinogen
Renin
Ang I
Ang II
AT1 receptor
Feedback loop
Emerging concept
(Pro)renin binds to cell receptor
Bound prorenin becomes activated
↑catalytic activity of bound renin
Activation of ERK 1/2
Production of TGF-β
– Growth responses
– Fibrotic responses
Ang II-dependent
Organ damage
Ang II-independent
Nguyen G et al., J Clin Invest. 2002;109:1417–1427
Guo C et al., J Clin Invest. 2001;107:703–715
Huang Y et al., Kidney Int. 2006;69:105–113

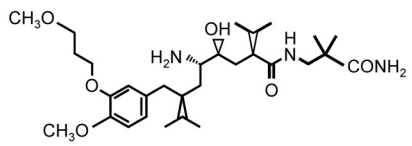

Elevated PRA may be associated with increased risk of myocardial infarction
Existing treatments do not provide optimal suppression of the renin system
– Increased PRA levels and additional cardiovascular risk factors increase risk of myocardial infarction (MI)
MI rate/1000 person-years
40
30
20
10
0
Plasma renin activity (PRA)
High
Normal
Low
High risk: ≥2 additional risk factors†
Moderate risk: 1 additional risk factor†
Low risk: No additional risk factors†
†Risk factors defined as: smoking, cholesterol >6.3 mg/dL, or left ventricular hypertrophy
Alderman et al. 1997.

Development of direct renin inhibitors has been challenging

- Numerous renin inhibitors have been synthesized and studied previously, including H142, ditekiren, enalkiren, zankiren and remikiren
- However, these agents were not clinically effective due to:
  - lack of oral availability
  - low efficacy
  - short half-life
  - high cost of synthesis

Luther R, *et al.* 1991; Stanton A. 2003; Wood JM, *et al.* 2003

Aliskiren: the first orally available direct renin inhibitor



- Molecular weight = 609.8
- High solubility in water and biological fluids
- Non-peptide drug suitable for oral administration

Wood JM, *et al.* 2003

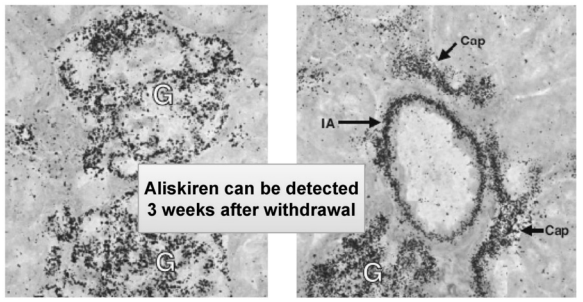
Aliskiren has a high specificity for human renin

Renin isoform	IC_{50} (nM)
Human	0.6
Marmoset	2
Dog	7
Rabbit	11
Guinea pig	63
Rat	80
Pig	150
Cat	8500

- Aliskiren has a high specificity for human renin and is thus challenging to study in animal models
- Animal model developed to test human renin inhibitors: *double TransGenic Rat (dTGR)*
  - expresses genes for human renin and human angiotensinogen
  - animals develop severe hypertension and end-organ damage

Wood JM, *et al.* 2003; Bohlender J, et al. 1997

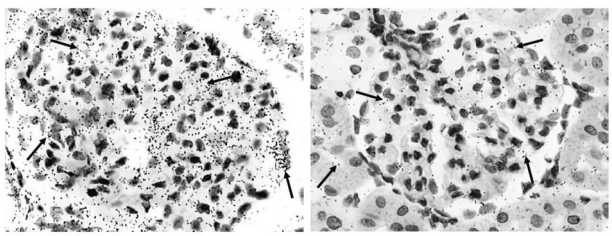
Aliskiren localizes in the kidney



G = glomerulus
IA = interlobular artery
Cap = Capillaries

Feldman *et al.* J Clin Hypertens 2006;8:A80-81 P178

Aliskiren decreases the glomerular expression of the (pro)renin receptor in a rat model of diabetic nephropathy



Vehicle | Aliskiren 10 mg/kg/d

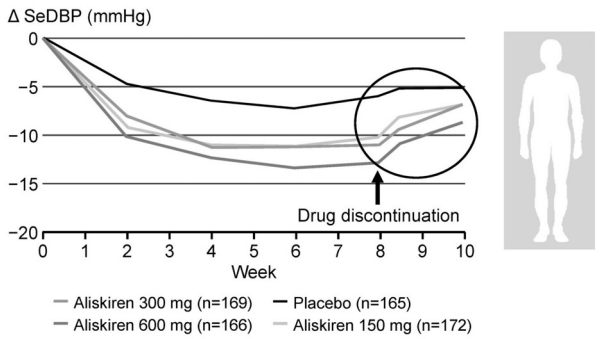
Arrows indicate (pro)renin receptor expression (small dark circles)

Nguyen G, *et al.* 2007

Clinical PK/PD profile

- Formulation: 150/300mg tablet
- Dose linear PK
- Predictable steady state
- No accumulation
- Half life :40 hrs (once daily dosing)

Aliskiren demonstrates persistence of effect after discontinuation



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

Aliskiren has a low potential for drug interactions and no initial dose adjustment is required in patients with renal or hepatic impairment

- Low potential for drug-drug interactions
  - no known clinically relevant interactions with drugs commonly used to treat hypertension or diabetes[1]
  - when co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by ~30% and ~50%, respectively[1]
- No initial dose adjustment in renal impairment[2]
- No initial dose adjustment in hepatic impairment[3]

Rasilez® (aliskiren) Summary of Product Characteristics (SPC) 2007;
[2]Vaidyanathan S, *et al.* 2006 (Study 2209); [3]Vaidyanathan S, et al. 2006 (Study 2210)

Diabetes and hypertension are the leading causes of end-stage renal disease

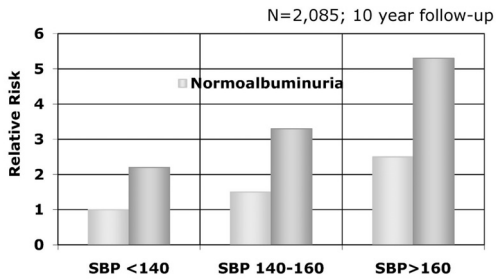
- Diabetes is a growing global health concern; the worldwide prevalence of diabetes is predicted to rise from 171 million in 2000 to 366 million in 2030[2]
  - Diabetes is the leading cause of nephropathy in developed countries[1]
- Hypertension is a common co-morbidity in diabetes, affecting 74% of patients[4]
  - Hypertension increases the risk of developing kidney disease and accelerates its progression to kidney failure[3]
- Diabetes and hypertension are the most common causes of end-stage renal disease (44% and 28% of patients, respectively)[4]
  - In the US, more than 100,000 patients each year are diagnosed with kidney failure[4]
  - Kidney failure represents a significant economic burden – care in the US cost $27 billion in 2003

[1]KDOQI 2007;49(Suppl 2):S12–154;
[2]Wild *et al.*, 2004;27:1047–53; [3]NKUDIC, 2006;
[4]Selby *et al.*, 2004;10:163–70; [5]Berthoux *et al.*, 1999;14:2332–42

Proteinuria

- Microalbuminuria and proteinuria:
  - can represent the early stages of CKD, which can progress to ESRD
  - are independent risk factor for cardiovascular disease
  - can indicate an increased risk of death
- The level of proteinuria has prognostic implications – higher levels are associated with faster progression of kidney disease and greater risk of cardiovascular disease
- Renin system suppression shows the greatest benefit for slowing progression of renal disease in Type 2 diabetic nephropathy (RENAAL and IDNT trials)
- More complete renin system suppression provides more effective reduction in proteinuria (COOPERATE and CALM trials)
- Animal studies with Aliskiren show reduction and prevention of onset of albuminuria
- There may be potential advantages of direct renin inhibition in the management of proteinuria to be confirmed by the results of trials currently in progress

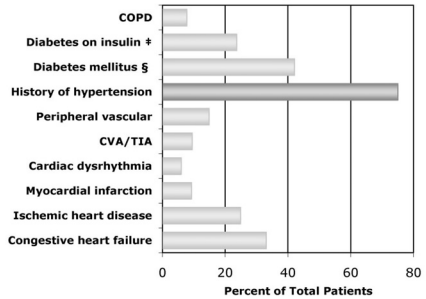
Risk of Ischemic Heart Disease Related to SBP and Microalbuminuria



Borch-Johnsen K, et al. Arterioscler Thromb Vasc Biol. 1999;19(8):1992-1997. With permission from Lippincott Williams & Wilkins.

Comorbidities in Renal Disease Patients (1999)

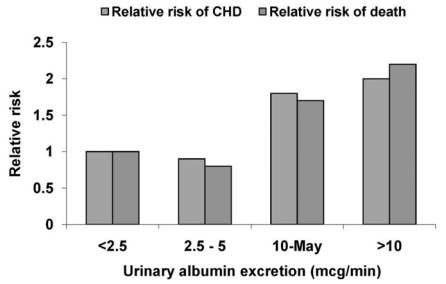
Hypertension and Diabetes are the leading co-morbidities in renal patients



§ Diabetes mellitus as a primary or contributing diagnosis.
‡ Diabetes mellitus that requires insulin treatment, which is a subset of the diabetes category.

United States Renal Data System (USRDS) 2000 Annual Data Report • WWW.USRDS.ORG

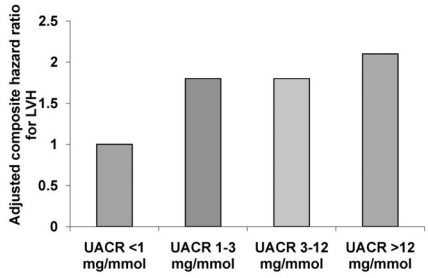
Microalbuminuria as low as 5 mcg/min (~7 mg albumin/day) is related to increased CV risk



- Cohort subset study, Copenhagen, Den mark
- 1,734 subjects with hypertension, microalbu minuria and no CHD at entry to trial
- 8-year follow-up study for CHD; 12 year follow up for death

CHD: congestive heart disease; CV: cardiovascular
Klausen KP et al. Hypertension 2005;46:33-7.

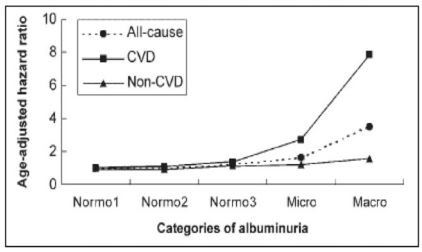
An increase in UACR (urine albumin concentration ratio) is correlated with the risk of LVH



- Multicenter study 1,063 patients with hypertension, diabetes, L VH (LIFE study)
- UACR measured for 4.7 years

LVH: left ventricular hypertrophy; UACR: urine albumin concentration/urinary creatinine concentration ratio
Ibsen H et al. Diabetes Care 2006;29:595-600.

Microalbuminuria is predictive of all-cause and CVD mortality – EPIC-NORFOLK STUDY

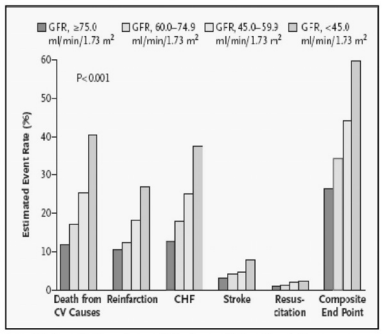


Age-adjusted HRs of all-cause, CVD, and non-CVD mortality

UACR (mg/mmol): Normo 1 (0.00-0.40), Normo 2 (0.41-0.90), Normo 3 (0.91-2.40), Micro (2.50 – 25.00), Macro (>25)

Fuyun et al., Int. J. Epidemiology 2004; 33, 189

Even mild reduction in renal function is a major risk factor for CV complications in post-MI patients (VALIANT)



Kaplan-Meier Estimates of Rates of Death at three years from CV causes, reinfarction, CHF, stroke, resuscitation after cardiac arrest, and the composite endpoint according to eGFR Anavekar et al., NEJM 2004; 351, 1285

The Dual Significance of Proteinuria

- Proteinuria (albuminuria) results from injury to glomerular circulation
  - Increased proteinuria (albuminuria) is associated with progressive kidney disease
- In diabetes and hypertension, proteinuria (albuminuria) is also an indicator of injury in the systemic circulation
  - Proteinuria (albuminuria) is associated with increased cardiovascular risk

Treatment guidelines for patients with hypertension, diabetes and nephropathy

- Annually check for proteinuria, albuminuria, serum creatinine and calculate the estimated glomerular filtration rate (eGFR)[1,2]
- In patients with proteinuria, albuminuria or reduced eGFR:
  - use angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) titrated to the maximum tolerated dose[1,2]
  - intensify management of blood pressure (BP) to achieve target of <130/80 mmHg[1,2]
  - monitor progression of nephropathy[1,2]
  - advise limiting protein intake to 0.8 g/kg daily in patients with proteinuria[1]
  - intensify other renal and cardiovascular protection measures (e.g. smoking cessation, aspirin therapy and lipid-lowering therapy)[1]

1. IDF 2005; 2. ADA 2006

Evidence for use of antihypertensive agents (UKPDS data)

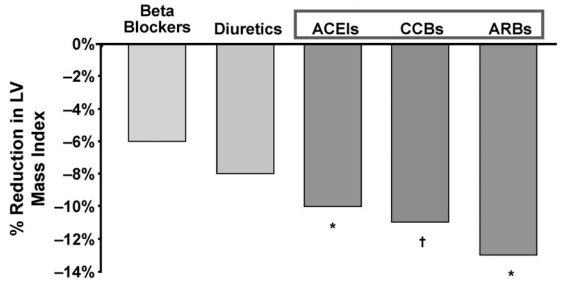
- Intensive control of BP using a target BP <150/85 mmHg in patients with diabetes significantly reduced* the risk of:
  - all diabetes complications by 24%[1]
  - diabetes-related deaths by 32%[1]
  - stroke by 44%[1]
  - heart failure by 56%[1]
  - microvascular complications by 37%[1]
- Agents targeting the Renin System may offer additional renal protection beyond BP-lowering efficacy
  - the ARBs irbesartan and losartan are approved for the treatment of nephropathy in patients with Type 2 diabetes and hypertension[2,3]

*Compared with less intensive control (target BP <180/105 mmHg)

1. UKPDS 1998
2. Avapro® (irbesartan) US prescribing information
3. Cozaar® (losartan) US prescribing information

Regression of LVH

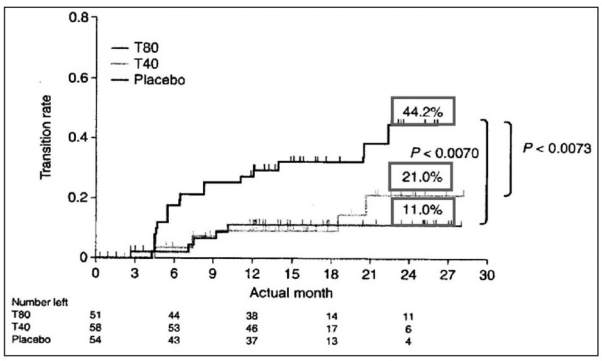
A Meta-analysis of 80 Studies Involving 3,767 Patients With Equivalent Blood Pressure Lowering



* = $P < 0.05$ vs beta blockers.
† $P < 0.09$ vs beta blockers.

(Am J Med , 2003)

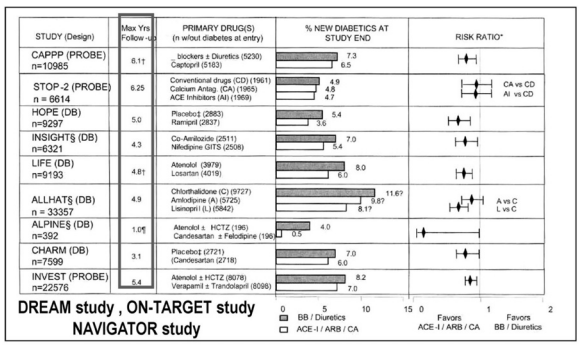
INNOVATION (incipient to overt : ARB investigation on type 2 diabetic nephropathy)



Type 2 diabetic Japanese pts, 1yr F/U

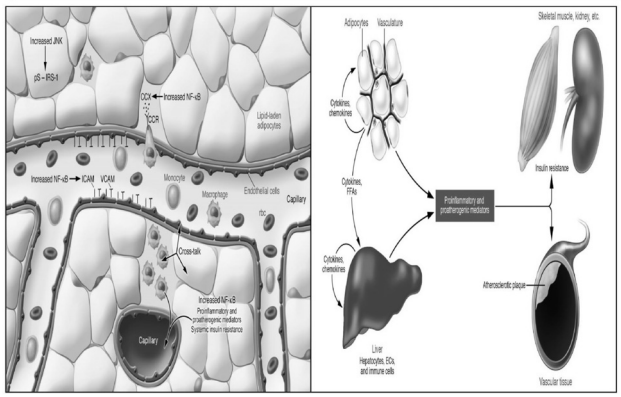
(Makino et al, Diabetes Care, 2007)

Effect of new onset diabetes with different anti-hypertensive medication



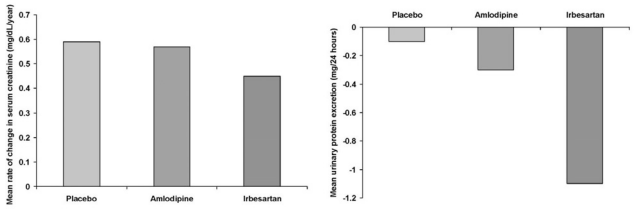
14-34% reduction of new onset diabetes with RAS blockade

Role of adipose tissue in insulin resistance



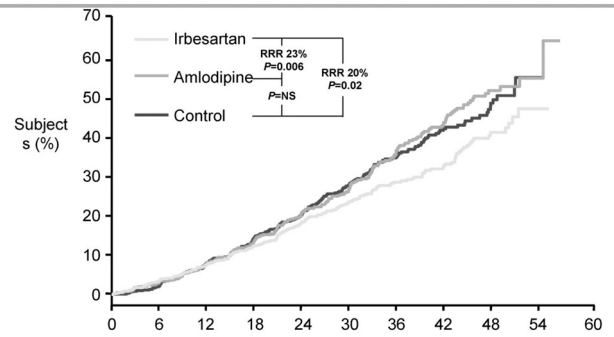
The IDNT study showed that ARBs conferred better renoprotection compared to CCBs

- Randomized, double-blind multinational study
- 1,715 hypertensive subjects with Type 2 diabetes and nephropathy; Mean follow up 2.6 years
- Irbesartan was more effective than placebo ($p<0.01$) and amlodipine ($p<0.02$) in reducing progression of nephropathy



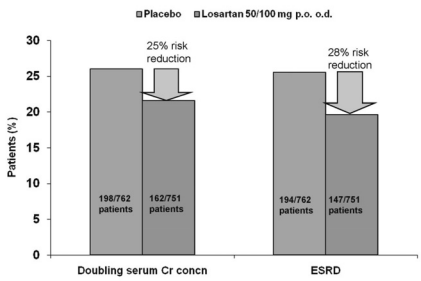
ARBs: angiotensin receptor blockers; CCB: calcium channel blockers; IDNT: Irbesartan Diabetic Nephropathy Trial
Lewis EJ et al. N Engl J Med 2001;345:851-60.

IDNT Primary Endpoint
Time to Doubling of Serum Creatinine, ESRD, or Death



Lewis EJ et al. *N Engl J Med* 2001;345:851-860.

The RENAAL study showed ARBs reduced progression of nephropathy

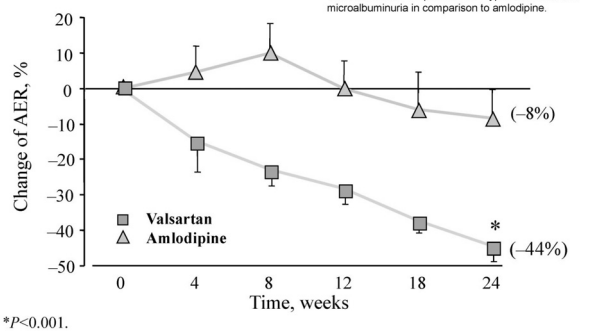


- Randomized, double-blind multinational study
- 1,513 subjects with Type 2 diabetes and nephropathy; Mean follow up 3.4 years
- Losartan was more effective than placebo in reducing progression of nephropathy (p=0.006) and ESRD (p=0.002)

ARBs: angiotensin receptor blockers; ESRD: end stage renal disease;
RENAAL: Reduction of Endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Study
Brenner BM et al. N Engl J Med 2001; 345:861-9.

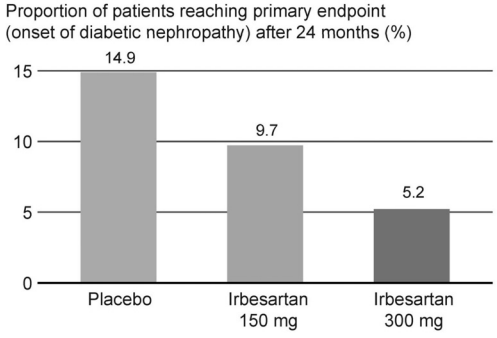
MARVAL: ARBs Significantly Lowers AER

•Multicenter, double-blind, randomized, active-controlled, parallel group study to assess the short-term effects of valsartan on AER in patients with type 2 diabetes and microalbuminuria in comparison to amlodipine.

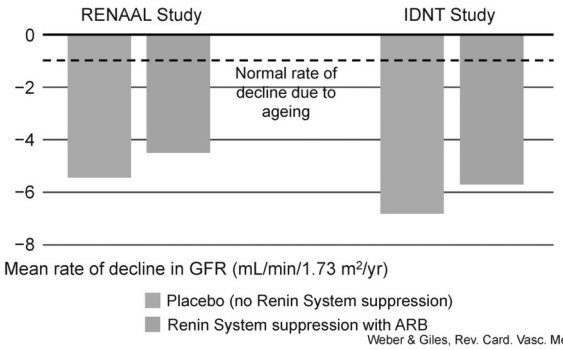


*$P<0.001$.
Viverti etal., Circulation 2004

Existing antihypertensives have limitations: Onset of diabetic nephropathy is delayed but not halted by ARBs



Existing antihypertensives have limitations: Despite treatment with ARBs, the rate of decline in renal function is still higher than expected due to ageing



Weber & Giles, Rev. Card. Vasc. Med. 2006

Evidence for improving renal function by combining ACEIs and ARBs is limited

- While combining ACEIs and ARBs has been suggested as a potentially beneficial approach to improving renoprotection,[1] few studies have been conducted and the results are inconclusive:
- The IMPROVE study[2]
  - Patients: 405 patients with microalbuminuria, elevated CV risk and hypertension who had received ACEI therapy for 2 months prior to enrolment
  - Result: after 20 weeks, ramipril/irbesartan 10/300 mg combination therapy failed to provide a significant improvement in albuminuria* compared with ramipril alone
- The COOPERATE study[3]

  Patients: 336 Japanese patients with non-diabetic renal disease

  Result: after 3 years, trandolapril/losartan 3/100 mg combination therapy reduced the risk of doubling of serum creatinine concentration or end-stage renal disease by ~60% compared with component monotherapies

  However, the results of the COOPERATE study are controversial and the robustness of the data has been questioned[4–6]

*Assessed by measuring albumin excretion rate

1. Weber & Giles 2006; 2. Bakris *et al.* 2007; 3. Nakao *et al.* 2003
4. Bidani 2006; 5. Kruger *et al.* 2003; 6. Halbekath & Schenk 2003

Evidence for improving renal and cardiac function by aliskiren (animal and human data)

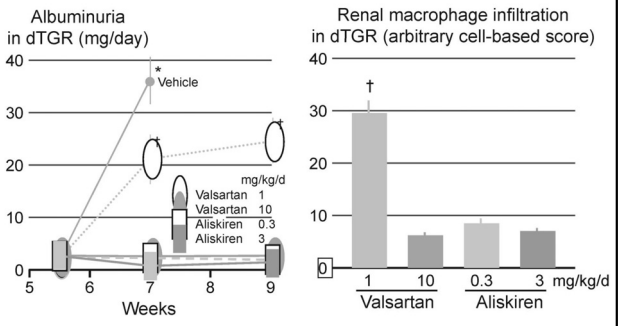
- More complete inhibition of RAS system by aliskiren : decrease in PRA
  - - may be more beneficial than classical RAS blockade
- Problem of high human specificity of aliskiren
  - - transgenic rat model, but may be useful in higher dose
- Representative human experiment : hypertension, diabetes study

Transgenic Rats overexpressing the human renin and angiotensinogen genes dTGR:

a suitable model for testing human renin inhibitors

Feldman

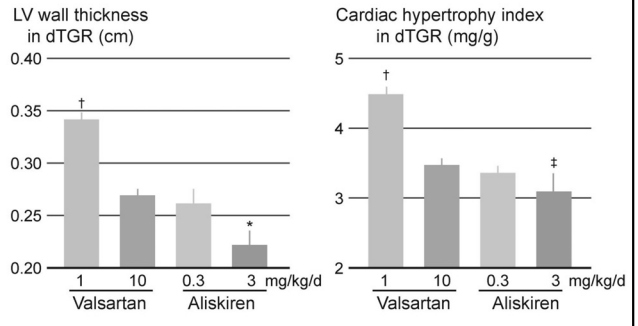
Aliskiren prevents albuminuria and inhibits renal inflammation in dTGR



*p<0.05 vs all other groups; †p<0.05 vs other groups
Untreated rats died by Week 8

Pilz B, *et al.* 2005

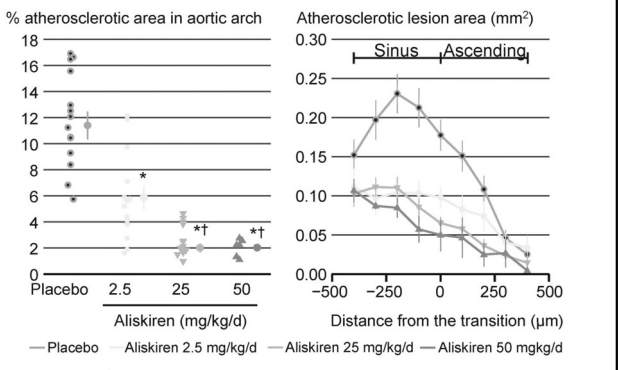
Aliskiren reduces LV mass and prevents LVH in dTGR



*p<0.05 vs all other groups; †p<0.05 vs all other groups; ‡p<0.05 vs valsartan 10 mg.
dTGR, double-transgenic rats. Untreated rats died by Week 8

Pilz B, *et al.* 2005

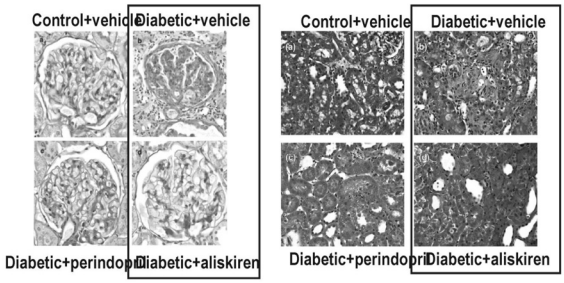
Aliskiren reduces atherosclerosis induced by hypercholesterolaemia in LDL receptor -/- mice



*p<0.0001 vs vehicle; †p<0.01 vs aliskiren 2.5 mg/kg/d

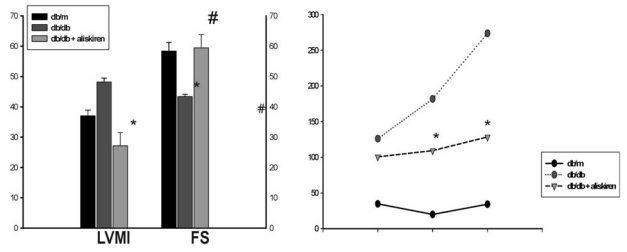
Lu H, *et al.* 2008

The effect of Aliskiren in advanced DN



D.J.Kelly, Y.Zang et al. Diabetologia(2007) 50:2398-2404

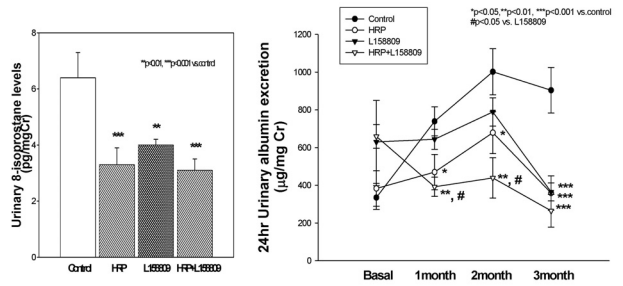
Aliskiren decrease LVMI and improves systolic function and decrease UAE excretion in type 2 diabetic mice



LVMI: left ventricular mass index (mg/10gr)
FS: fractional shortening (%)

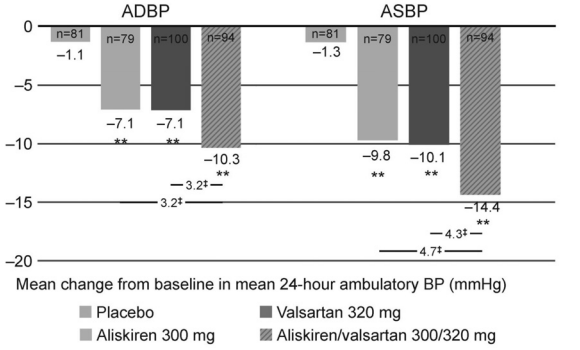
(unpublished data)

HRP reduces urinary albumin excretion and decrease urinary excretion of 8-isoprostane and combination with ARB shows further beneficial effect in type 2 diabetic mice



The ASPIRE HIGHER clinical study programme Overview

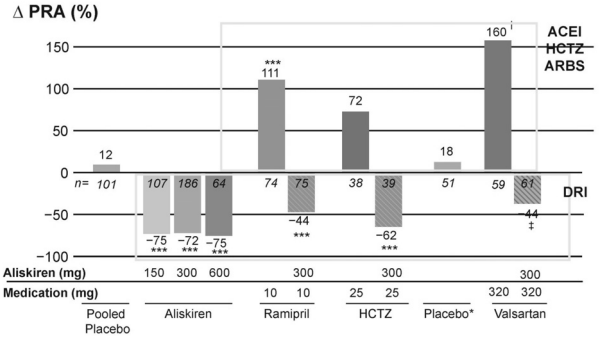
Aliskiren/Valsartan significantly lowers 24-hour ambulatory BP compared with monotherapies



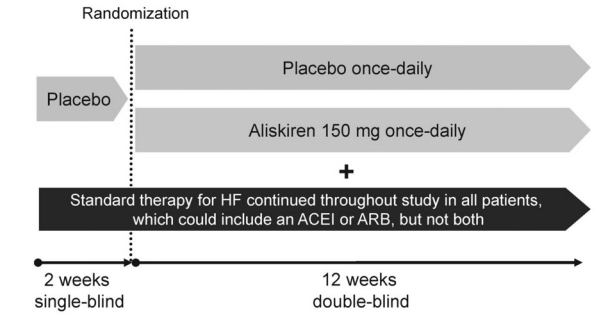
**p<0.0001 vs placebo; ‡p<0.0001 vs aliskiren/valsartan combination

Oparil S, *et al.* 2007

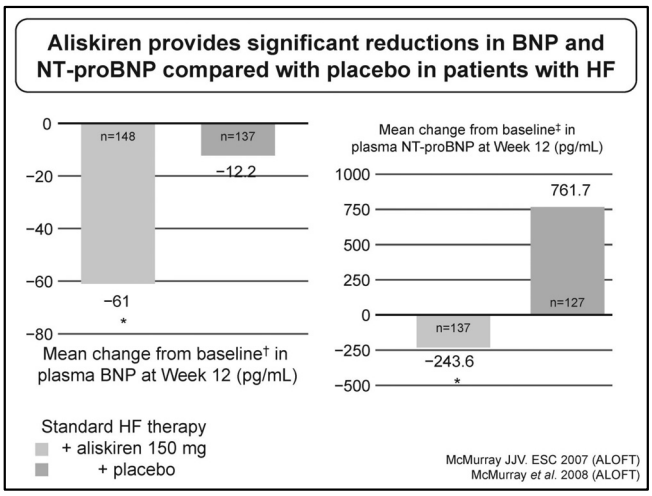
Aliskiren inhibits PRA Rise

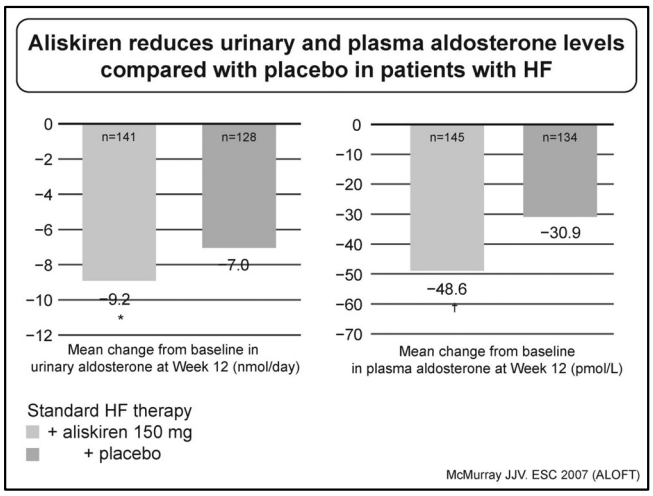


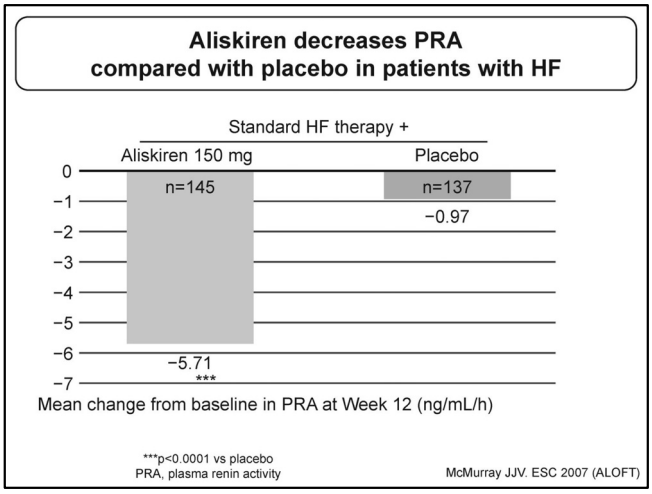
ALiskiren Observation of heart Failure Treatment (ALOFT) – Study design overview

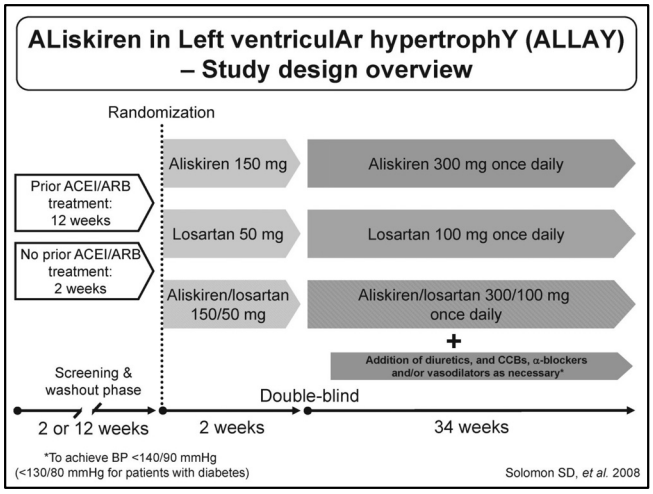


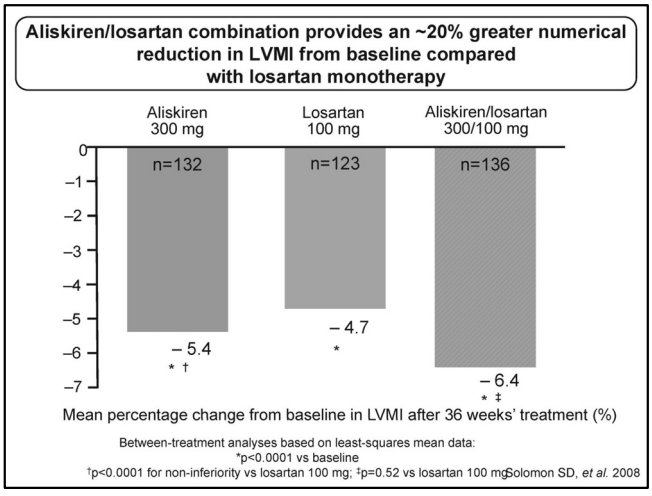
McMurray JJV. ESC 2007 (ALOFT)

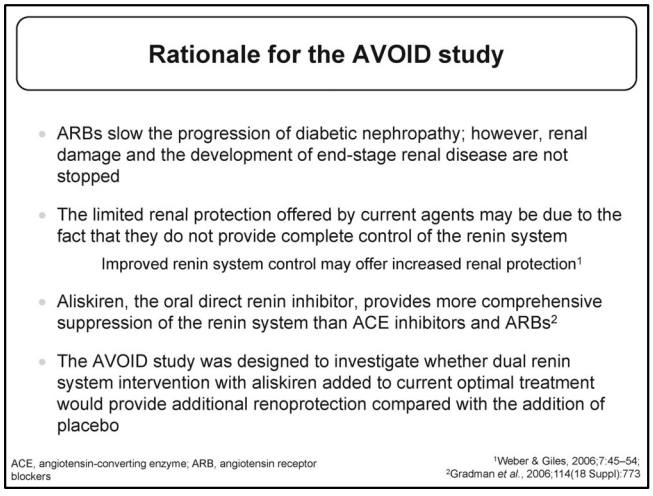

Aliskiren provides significant reductions in BNP and NT-proBNP compared with placebo in patients with HF
n=148
n=137
−12.2
−61
*
Mean change from baseline† in plasma BNP at Week 12 (pg/mL)
Mean change from baseline‡ in plasma NT-proBNP at Week 12 (pg/mL)
761.7
n=127
n=137
−243.6
*
Standard HF therapy
+ aliskiren 150 mg
+ placebo
McMurray JJV. ESC 2007 (ALOFT)
McMurray et al. 2008 (ALOFT)


Aliskiren reduces urinary and plasma aldosterone levels compared with placebo in patients with HF
n=141
n=128
−7.0
−9.2
*
Mean change from baseline in urinary aldosterone at Week 12 (nmol/day)
n=145
n=134
−30.9
−48.6
†
Mean change from baseline in plasma aldosterone at Week 12 (pmol/L)
Standard HF therapy
+ aliskiren 150 mg
+ placebo
McMurray JJV. ESC 2007 (ALOFT)

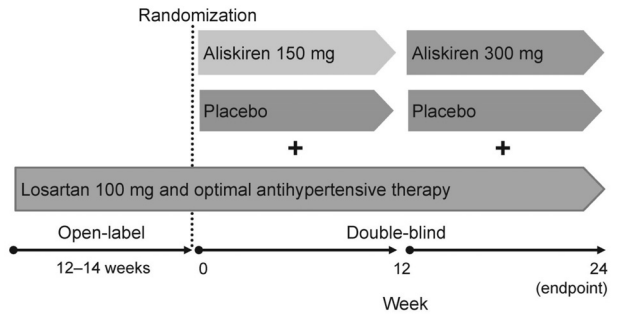

Aliskiren decreases PRA compared with placebo in patients with HF
Standard HF therapy +
Aliskiren 150 mg
Placebo
n=145
n=137
−0.97
−5.71
***
Mean change from baseline in PRA at Week 12 (ng/mL/h)
***p<0.0001 vs placebo
PRA, plasma renin activity
McMurray JJV. ESC 2007 (ALOFT)


ALiskiren in Left ventriculAr hypertrophY (ALLAY) – Study design overview
Randomization
Prior ACEI/ARB treatment: 12 weeks
No prior ACEI/ARB treatment: 2 weeks
Aliskiren 150 mg
Aliskiren 300 mg once daily
Losartan 50 mg
Losartan 100 mg once daily
Aliskiren/losartan 150/50 mg
Aliskiren/losartan 300/100 mg once daily
+
Addition of diuretics, and CCBs, α-blockers and/or vasodilators as necessary*
Screening & washout phase
Double-blind
2 or 12 weeks
2 weeks
34 weeks
*To achieve BP <140/90 mmHg (<130/80 mmHg for patients with diabetes)
Solomon SD, et al. 2008


Aliskiren/losartan combination provides an ~20% greater numerical reduction in LVMI from baseline compared with losartan monotherapy
Aliskiren 300 mg
Losartan 100 mg
Aliskiren/losartan 300/100 mg
n=132
n=123
n=136
– 5.4
* †
– 4.7
*
– 6.4
* ‡
Mean percentage change from baseline in LVMI after 36 weeks' treatment (%)
Between-treatment analyses based on least-squares mean data:
*p<0.0001 vs baseline
†p<0.0001 for non-inferiority vs losartan 100 mg; ‡p=0.52 vs losartan 100 mg
Solomon SD, et al. 2008


Rationale for the AVOID study
ARBs slow the progression of diabetic nephropathy; however, renal damage and the development of end-stage renal disease are not stopped
The limited renal protection offered by current agents may be due to the fact that they do not provide complete control of the renin system
Improved renin system control may offer increased renal protection[1]
Aliskiren, the oral direct renin inhibitor, provides more comprehensive suppression of the renin system than ACE inhibitors and ARBs[2]
The AVOID study was designed to investigate whether dual renin system intervention with aliskiren added to current optimal treatment would provide additional renoprotection compared with the addition of placebo
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers
[1]Weber & Giles, 2006;7:45–54;
[2]Gradman et al., 2006;114(18 Suppl):773

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



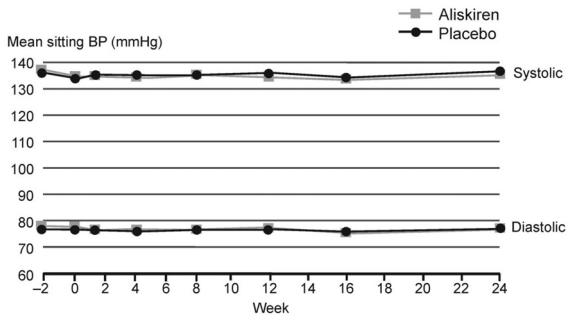
Forced titration at week 12
All doses were administered once daily

Study objectives

- Primary objective:
  - change in UACR from baseline to week 24 endpoint with aliskiren added to losartan 100 mg once daily and optimal antihypertensive therapy, compared with addition of placebo
- Secondary objectives include:
  - proportion of patients with ≥ 50% reduction in UACR at week 24 endpoint
  - effect of treatment on UAER
  - effect of treatment on BP
  - effect of treatment on estimated GFR
  - safety and tolerability of study treatments

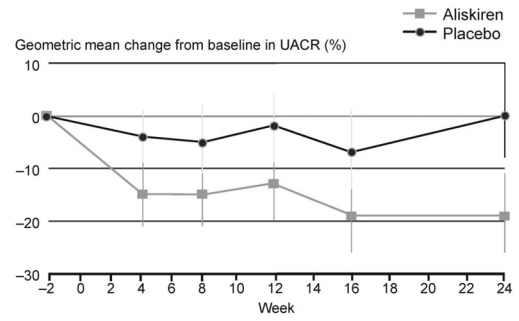
BP, blood pressure; GFR, glomerular filtration rate;
UACR, urinary albumin:creatinine ratio; UAER, urinary albumin excretion rate

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



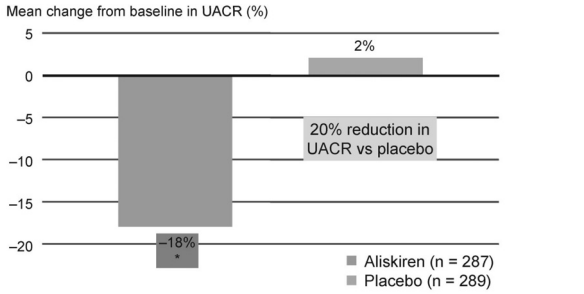
Date are shown as mean ± SEM
Baseline was the week 0 (Day 1) value
BP, blood pressure

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



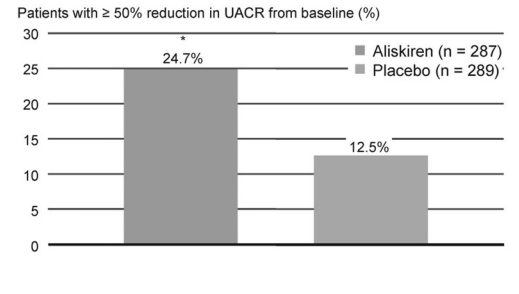
Data are shown as change from baseline in geometric mean (95% CI)
Baseline was the week –2 value
UACR, urinary albumin:creatinine ratio

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



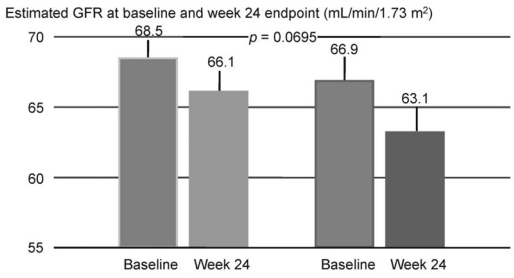
*p = 0.0009
Data are shown as percentage change in geometric mean
Baseline was week –2 value
UACR, urinary albumin:creatinine ratio

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 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)

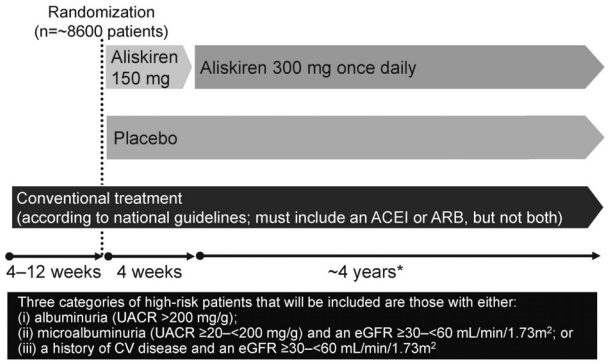
Data are shown for the double-blind period

Rationale for the ALiskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints (ALTITUDE)

- Losartan and irbesartan have been shown to reduce the rate of progression of nephropathy in patients with type 2 diabetes, diabetic nephropathy and a history of hypertension
  - however, renal damage and ESRD are delayed, but not stopped
- No drugs that influence the renin system have been shown to reduce CV morbidity or mortality in this patient population
- Furthermore, no evidence exists for a beneficial effect of drugs that target the renin system in patients whose diabetic nephropathy is characterized by a low estimated GFR
- A potential reason for the limited cardio- and reno-protection offered by current agents is that they are unable to provide complete control of the renin system
  - greater protection may be offered by improved renin system control[1]
- Aliskiren, the novel direct renin inhibitor, provides more complete control of the renin system than ACEIs and ARBs[2]
- The ALTITUDE study is designed to investigate whether addition of aliskiren to conventional therapy provides additional cardio- and reno-protection compared with addition of placebo in patients with type 2 diabetes at high risk of developing clinical events

1. Weber & Giles, 2006; 2. Gradman *et al.* 2006

ALTITUDE – Design overview



Three categories of high-risk patients that will be included are those with either:
(i) albuminuria (UACR >200 mg/g);
(ii) microalbuminuria (UACR ≥20–<200 mg/g) and an eGFR ≥30–<60 mL/min/1.73m²; or
(iii) a history of CV disease and an eGFR ≥30–<60 mL/min/1.73m²

*ALTITUDE is an event driven study

Parving H-H, *et al.* 2007 (Study 2337E)

ALTITUDE – Objectives

Primary objective:

- to determine whether aliskiren, when added to conventional treatment delays the occurrence of CV and renal complications in patients with type 2 diabetes at high risk for CV and renal events
  - occurrence is defined as the first event of the following composite primary endpoint: (1) CV death; (2) resuscitated sudden death; (3) non-fatal MI; (4) non-fatal stroke; (5) unplanned hospitalization for HF; (6) onset of ESRD or renal death; and (7) doubling of baseline serum creatinine concentration, sustained for at least one month

Secondary objectives:

- to determine whether aliskiren, when added to conventional treatment:
  - delays the occurrence of CV complications
  - delays the occurrence of renal complications

Parving H-H, *et al.* 2007 (Study 2337E)