

Renin-Inhibitors: Where do they fit into the RAAS Picture?

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Disclosure Information

- Advisory Board : Astra Zeneca, Bayer Healthcare
- Education and Research Grants : Merck Pfizer Sanofi Aventis - BMS .
- Speaker / Publication : Pfizer, Sanofi Aventis / BMS, Novartis, Astra Zeneca

Learning Objectives

- Review current hypertension treatment in Canada
- Explain the role of direct renin inhibition: mechanism and effects
- Weigh the evidence behind the use of aliskiren for the treatment of hypertension
- Review other potential benefits of direct renin inhibitors.

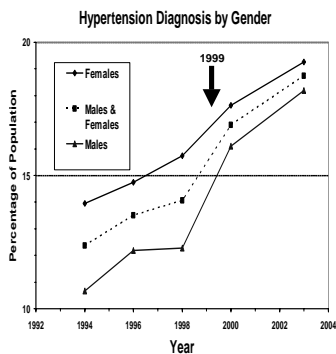
Background

- In 2006 hypertension was the most common diagnosis accounting for over 20 million patient visits to physician offices in Canada
- Hypertension is a risk factor for cerebrovascular disease, coronary artery disease, congestive heart failure, renal failure, peripheral vascular disease, dementia and atrial fibrillation.

http://hypertension.ca/chap/wp-content/uploads/2008/03/chap_2008background-final-draft_jan28.ppt#560,3 Hypertension as a Risk Factor

http://www.imshealthcanada.com/vgn/images/portal/ot_4000087343/11/79014602Trends06_En_07CORR.pdf

Changes in Diagnosis of Hypertension in Canada



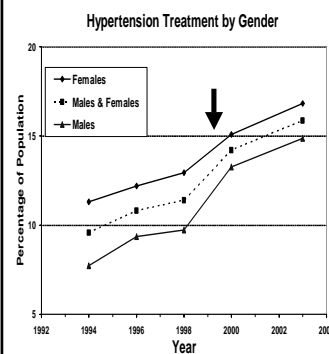
Post 1999 compared to pre 1999

- Marked increase in the rate of diagnosis of hypertension
- Closing of the gender gap

NPHS, CCHS

Onysko J, Hypertension 2006;48:853-64

Changes in Treatment of Hypertension in Canada



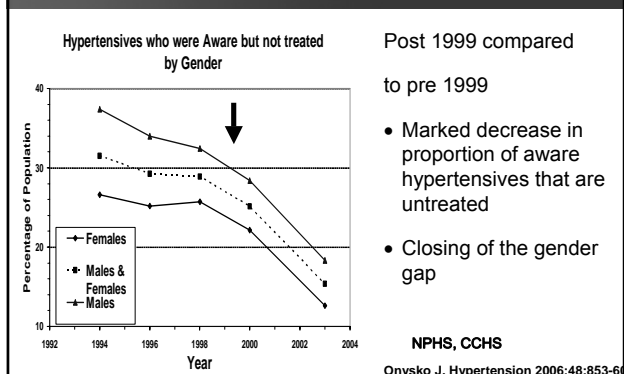
Post 1999 compared to pre 1999

- Doubling of the rate of treatment of hypertension
- Closing of the gender gap

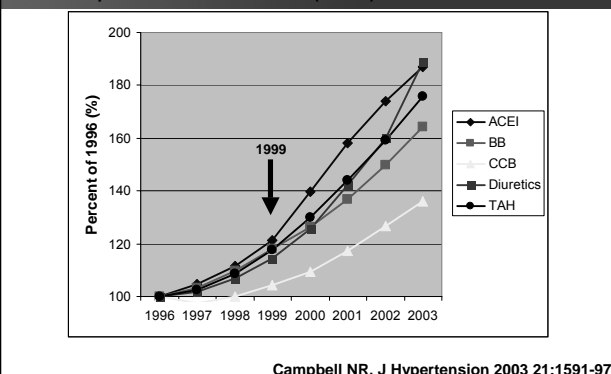
NPHS, CCHS

Onysko J, Hypertension 2006;48:853-64

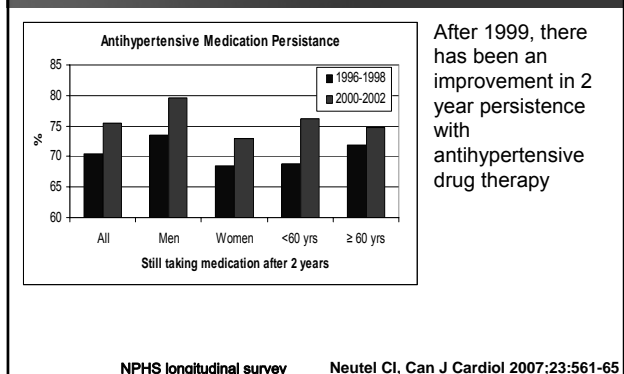
Changes in proportion of aware hypertensive Canadians not treated with antihypertensive drugs



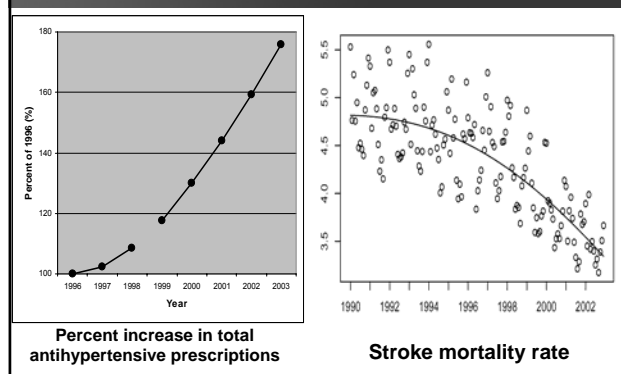
Percent Increase in Antihypertensive Prescriptions in Canada (IMS)



Increased persistence with antihypertensive therapy after initial diagnosis



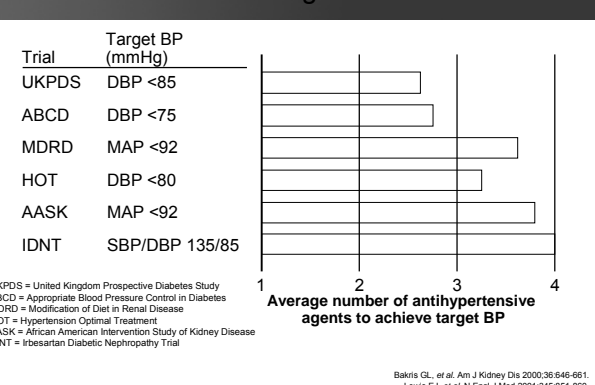
Proportional Changes in Antihypertensive Prescriptions and Changes in Stroke Death in Canada

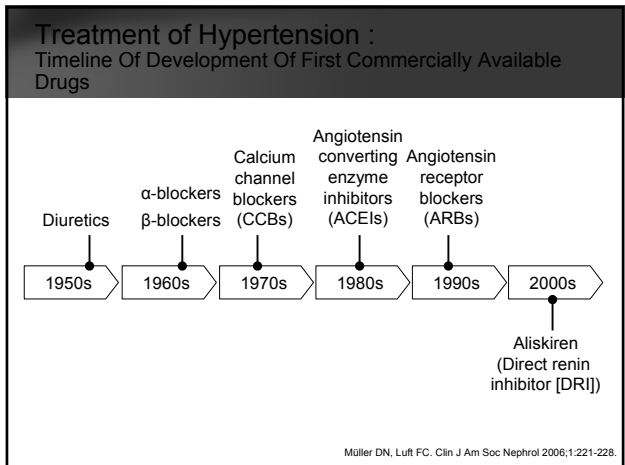


Treatment of Hypertension Canada versus USA

- USA 2004
 - Awareness 66.5% (33.5% unaware)
 - Treatment 53.7%
 - 81% of aware hypertensive Americans are on drug therapy
 - **Control 33.1%**
- Canada 2003
 - 85% of aware hypertensive Canadians are on drug therapy
 - **Control unknown**

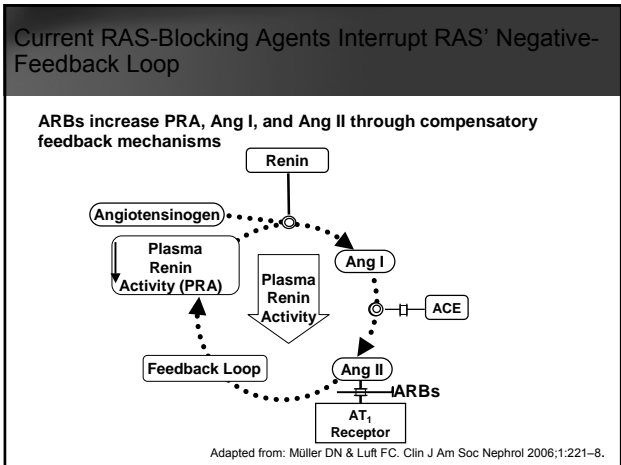
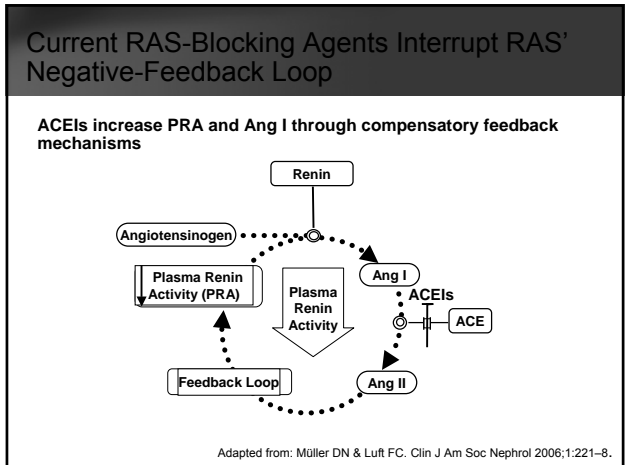
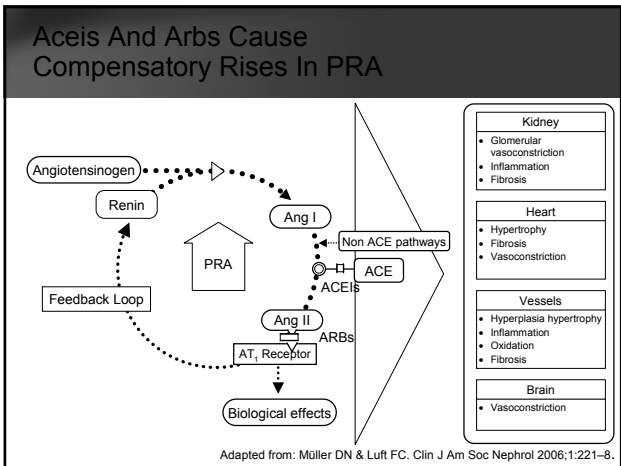
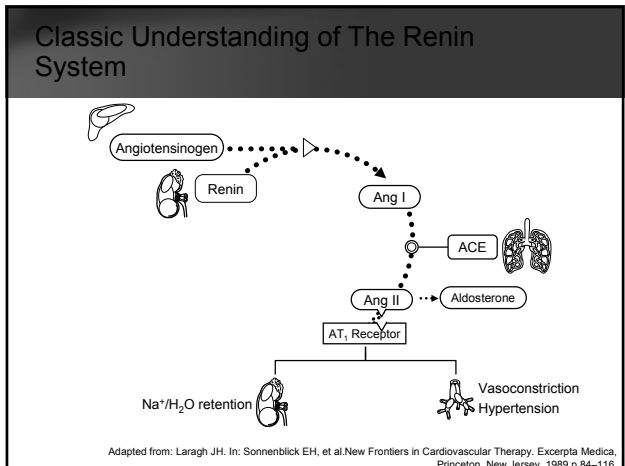
Multiple Antihypertensive Agents Are Needed To Achieve Target BP

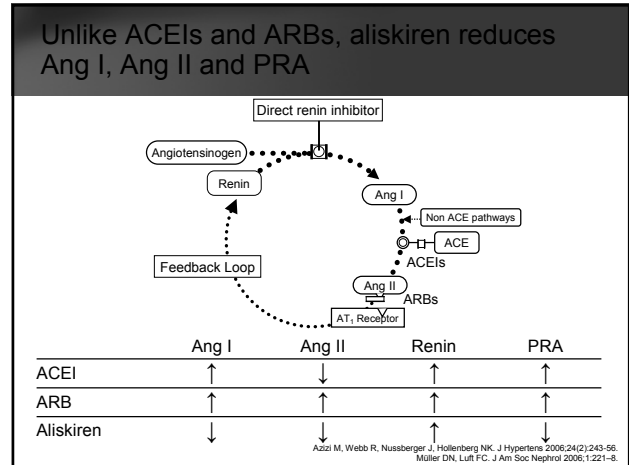
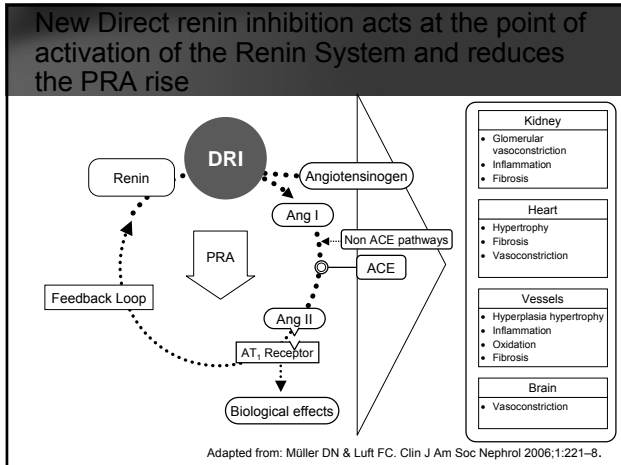




History of Aliskiren

- Search for an antihypertensive agent aimed at the top of the renin-angiotensin system
- Oral renin inhibitor – Novartis
- Dr Alice Huxley (Speedel) bought the drug
- “Alis” kiren
- Drug sold back to Novartis





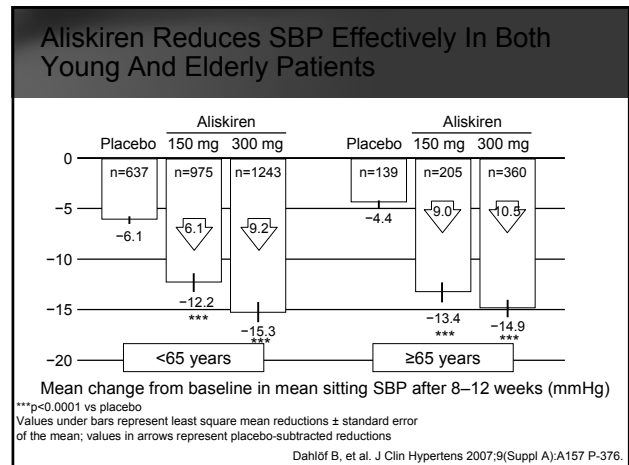
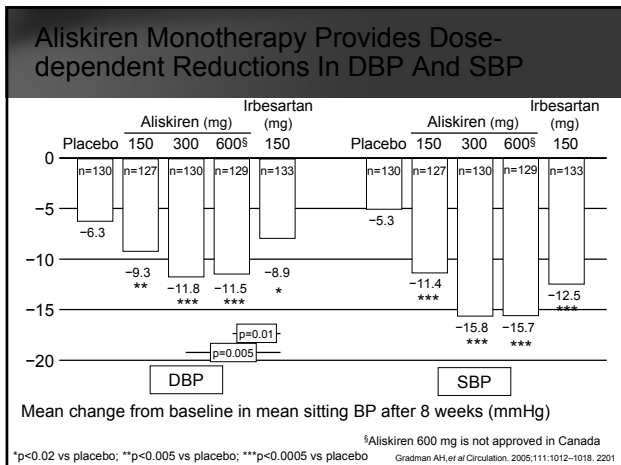
Aliskiren Has Greater Oral Bioavailability Compared With Previous Direct Renin Inhibitors

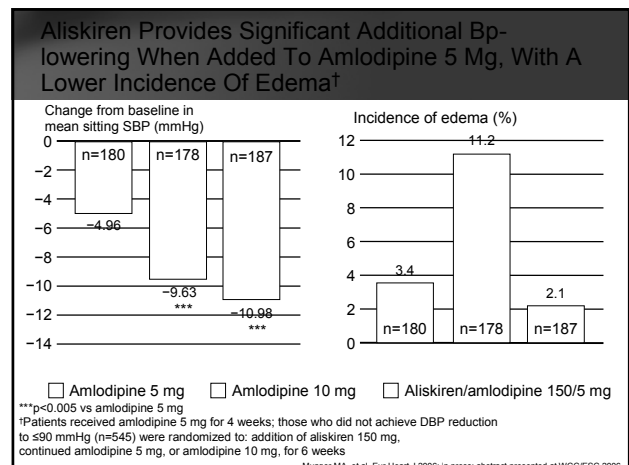
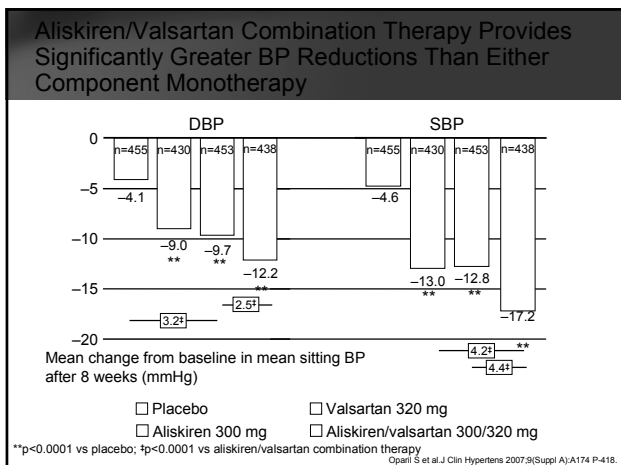
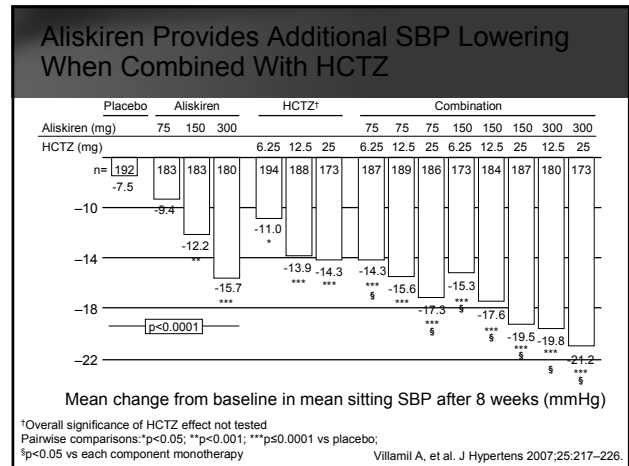
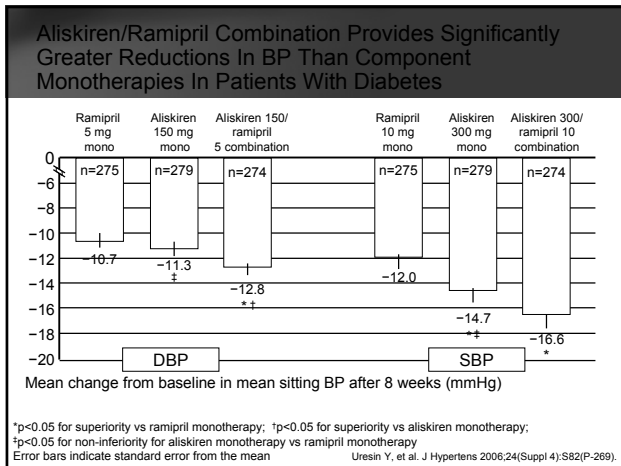
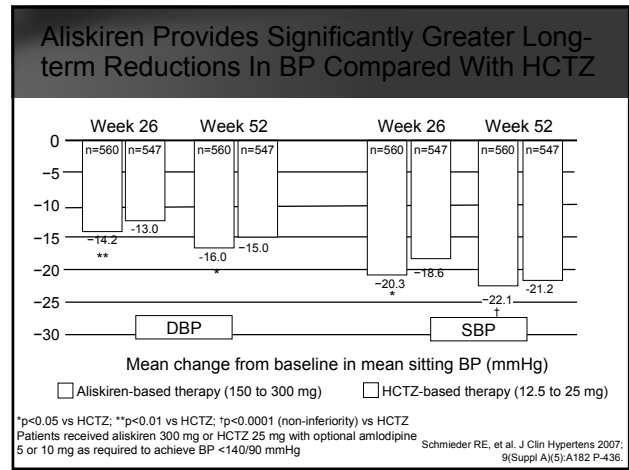
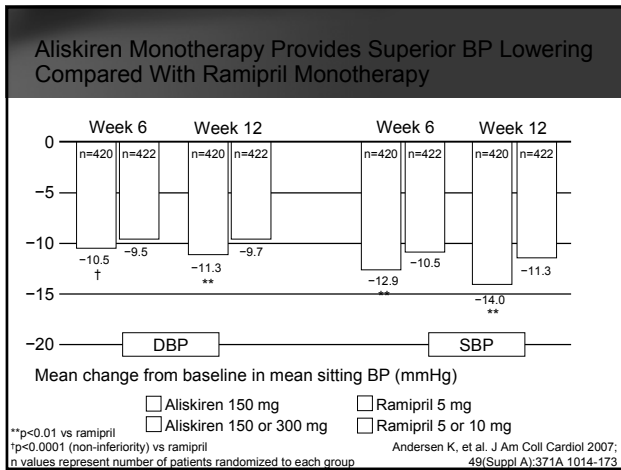
- The oral bioavailability of aliskiren is approximately 2.6%
 - this is an improvement on older direct renin inhibitors, which have lower oral bioavailability (generally <1%)
- Peak plasma concentrations are reached within 1 to 3 hours
- Plasma steady-state concentrations are reached after 5 – 8 days (t_{1/2} 40 hours)
- Approximately 1.4% of the dose is metabolized
- Aliskiren is not metabolized to any significant extent by cytochrome P450 isoenzymes and has no significant effect on cytochrome P450 isoenzyme activity
- Aliskiren is a substrate of P-glycoprotein, but does not inhibit its activity
- Aliskiren is eliminated primarily unchanged in the faeces; approximately 0.6% of the dose is recovered in the urine

Aliskiren Product Monograph. Novartis Pharmaceuticals Canada Inc. [2007].

Efficacy with Aliskiren Hypertension Trials

- The efficacy of Aliskiren was extensively studied alone or in combination with other antihypertensive agents
- Monotherapy trials were done vs.:
 - Placebo
 - Active Control:
 - ♦ Irbesartan
 - ♦ Ramipril
 - ♦ Hydrochlorothiazide (HCTZ)
- Combination trials were done with:
 - Ramipril
 - Valsartan
 - HCTZ
 - Amlodipine





Aliskiren Monotherapy Exhibits Placebo-like Tolerability Up To 300 Mg Once Daily

	Placebo n=781	Aliskiren 75 mg ^s n=478	Aliskiren 150 mg n=774	Aliskiren 300 mg n=768	Aliskiren 600 mg ^s n=296
Any SAE, n (%)	5 (0.6)	3 (0.6)	3 (0.4)	4 (0.5)	1 (0.3)
Any AE, n (%)	314 (40.2)	193 (40.4)	290 (37.5)	309 (40.2)	130 (43.9)
Discontinuations due to AE, n (%)	27 (3.5)	8 (1.7)	12 (1.6)	20 (2.6)	5 (1.7)
Adverse events, reported by ≥2% of patients for aliskiren monotherapy overall, n (%)					
Headache	68 (8.7)	31 (6.5)	42 (5.4)*	44 (5.7)*	15 (5.1)
Nasopharyngitis	45 (5.8)	34 (7.1)	33 (4.3)	29 (3.8)	5 (1.7)**
Diarrhoea	9 (1.2)	6 (1.3)	9 (1.2)	18 (2.3)	28 (9.5)†

AE, adverse event; SAE, serious adverse event. †p<0.05; **p<0.01; †p<0.0001 vs placebo

^sAliskiren 75 mg and 600 mg doses are not approved in Canada

Weir MR, et al. Eur Heart J 2006;27(Suppl):299-1796.

Aliskiren Has A Low Potential For Drug Interactions And No Initial Dose Adjustment Is Required In Patients With Renal Or Hepatic Impairment

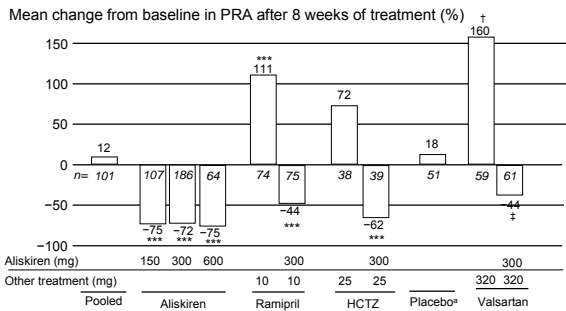
- Low potential for drug-drug interactions
- No initial dose adjustment in renal impairment²
- No initial dose adjustment in hepatic impairment³

Aliskiren Product Monograph. Novartis Pharmaceuticals Canada Inc. [2007].

2. Vaidyanathan S, et al. J Clin Pharmacol 2006;46:1072 P50.

3. Vaidyanathan S, et al. J Clin Pharmacol 2006;46:1072 P-49.

Aliskiren Neutralizes The Rise In PRA Induced By Agents That Stimulate Renin Release



^sPlacebo from aliskiren/valsartan study

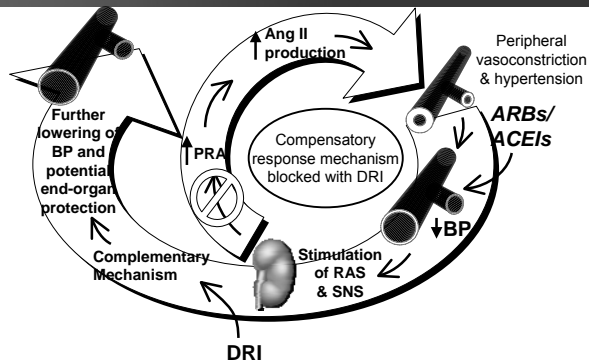
***p<0.0001 vs pooled placebo; †p<0.001, †p<0.0001 vs placebo^s

Taylor AA, et al. J Am Coll Cardiol 2007;49 (9 Suppl A):370A P-1014-170.

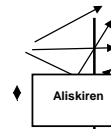
Aliskiren In Hypertension Clinical Summary

- Aliskiren 150–300 mg:
 - provides dose-dependent reductions in DBP and SBP as monotherapy
 - ♦ BP reductions from baseline greater than HCTZ and ramipril and similar to irbesartan
 - provides additional BP lowering when combined with other antihypertensives
 - ♦ HCTZ, ramipril, valsartan and amlodipine
 - has a placebo-like tolerability profile
 - uniquely lowers PRA in monotherapy and combination

Rationale For ARB/ACEI + DRI Combinations



New Drug Combinations



Aliskiren is approved for the treatment of mild to moderate essential hypertension. It may be used alone or concomitantly with thiazide diuretics, angiotensin converting enzyme inhibitors or dihydropyridine calcium channel blockers.

Rasilez[®] (Aliskiren) Product Monograph. Novartis Pharmaceuticals Canada Inc. [2007]

Conclusions

- Treatment of hypertension improving in Canada
- Many patients will require drug combinations
- Aliskiren first new class of drugs in greater than 15 years
- Effective for blood pressure lowering
- Future - outcome trials

Getting More Data Toward Organ Protections Clinical Trials Overview



AVOID study – Design

Study design:	Double-blind, randomized, placebo-controlled
Study population:	496 patients
Inclusion criteria:	Mild-to-moderate hypertension Type 2 diabetes Proteinuria
Treatment period:	24 weeks
Study status*:	Completed

*Study status as of May 2007

Clinicaltrials.gov 2006; Data on File, Novartis 2007

AVOID study – Objectives

Primary objective:

- Percentage change in urinary albumin-to-creatinine ratio (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 include:

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

Clinicaltrials.gov 2006; Data on File, Novartis 2007

ALOFT study – Design

Study design:	Double-blind, randomized, placebo-controlled study
Study population:	280 patients
Inclusion criteria:	Hypertension Stable HF B-type natriuretic peptide (BNP) levels >100 pg/mL
Treatment period:	12 weeks
Study status*:	Completed

*Study status as of May 2007

Clinicaltrials.gov 2006; Data on File, Novartis 2007

ALOFT study – Objectives

Primary objective:

- Evaluate the safety and tolerability of aliskiren 150 mg when given in addition to standard therapy in patients with hypertension and stable HF

Secondary objectives include:

- Effect of aliskiren on BNP, N-terminal proBNP (NT-proBNP) and aldosterone
- Effect of aliskiren on echocardiographic measures of left ventricular (LV) function
- Effect of aliskiren on improvement in signs and symptoms of HF
- Effect of aliskiren on BP

Clinicaltrials.gov 2006; Data on File, Novartis 2007

ALLAY Study – Design

Study design:	Double-blind, randomized, active-controlled
Study population:	480 patients
Inclusion criteria:	Mild-to-moderate hypertension Body mass index (BMI) >25 kg/m ² Left ventricular wall thickness ≥1.3 cm
Treatment period:	36 weeks
Study status*:	Ongoing
Anticipated completion:	Quarter 4, 2007

*Study status as of April 2007

Clinicaltrials.gov 2006; Data on File, Novartis 2007

ALLAY Study – Objectives

Primary objective:

- To evaluate the effect of aliskiren/losartan combination therapy on LVH regression, by measuring the change in LVMI using magnetic resonance imaging (MRI)

Secondary objectives include:

- Assessments of the effect of all treatments on LVMI and other measures of LVH
- Evaluation of the relationship between reduction in 24-hour ambulatory BP monitoring and LVH regression
- Safety and tolerability

Clinicaltrials.gov 2006; Data on File, Novartis 2007