

# Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

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## Background

- Diabetic nephropathy is characterized by progressive proteinuria, hypertension, decline in renal function, and risk of cardiovascular disease
- The pathogenesis and progression of diabetic nephropathy is multifactorial. The RAAS plays an important role.
- Persistent proteinuria is the hallmark of diabetic nephropathy and suggests declining glomerular filtration rate.
- Reduction in proteinuria is associated with a slowing of the progression to end-stage renal disease and has been used as a surrogate endpoint for renal protection.

## Hypothesis

- The direct renin inhibitor, *aliskiren*, added to standard maximum renoprotective therapy with losartan 100 mg daily confers additional renoprotection than losartan alone. Reduction in urinary albumin:Cr ratio is a marker of renoprotective effects.

## Study Design and Methods

- Design: multinational, randomized, double-blind placebo controlled trial
- Inclusion criteria: adults 18-85 years with hypertension, type 2 diabetes, and nephropathy (early morning urinary albumin:Cr of >300 mg/g or >200 mg/g in patients already on an ACE-I or ARB)
- Exclusion criteria: non-diabetic kidney disease, urinary albumin:Cr >3500 mg/g, eGFR < 30 ml/min, chronic UTI, [K<sup>+</sup>] > 5.1, severe hypertension, major cardiovascular disease within the previous 6 months
- Randomization: 1892 patients meeting inclusion criteria were screened
  - 805 patients entered 3 mo. open label period during which all previous inhibitors of the RAAS were discontinued and replaced with losartan 100 mg daily; patients continued previous antihypertensives and started on additional medications to achieve <130/80
  - 206 patients excluded → 599 underwent randomization:
    1. Losartan 100 mg daily + aliskiren 150 mg daily for 3 months, then 300 mg daily for 3 months (N=301) or
    2. Losartan 100 mg daily + placebo 1 daily for 3 months, then placebo 2 daily for 3 months (N=298)
- Patient characteristics (Table 1): except for age, patient demographic, clinical, and laboratory characteristics were similar b/t groups. population is overwhelmingly white, extremely obese; up to 20% continued to smoke; < 50% were taking ASA
- Primary efficacy endpoints: percentage reduction in morning urinary albumin:Cr at 6 months
- Primary safety endpoints: total number of adverse and serious adverse events

## Results

- Primary outcome: reduction in urinary albumin:Cr
  - Figure 2A. Aliskiren reduced mean morning urine albumin:Cr by 20% at 6 mo (95% CI, 9-30; P<0.001) compared to placebo. Approximately half of this effect was seen at 3 mo (11% reduction from baseline, 95% CI, 2-20; P=0.02)
  - Figure 3. Subgroup analysis showed no differences in reduction
- Secondary outcomes: overnight urinary albumin excretion rate and blood pressure
  - Figure 2B. Reduction in overnight excretion of albumin by 18% in aliskiren group (95% CI, 5-30; P=0.009) compared to placebo.
  - Figure 2C. BP identical between groups at baseline. There were non-significant trends in greater reduction of systolic (P=0.07) and diastolic pressures (P=0.08) in the aliskiren group. Though mean absolute reduction was minimal (2/1 mmHg), this may confer significant difference in cardiac outcomes by ALLHAT data
- Primary safety outcome: adverse events
  - Table 3. Adverse events (66.8% aliskiren and 67.1% placebo) and serious adverse events (9.0% aliskiren and 9.4% placebo) were not different between groups. Similar numbers of patients withdrew from each group because of these.
  - Non-significant trend (P=0.06) towards increased incidence of [K<sup>+</sup>] >6.0 in aliskiren group (4.7%) vs. placebo (1.7%); this is higher than in RALES trial

## Conclusions

- Big picture and take home: similar to ACE-Is and ARBs, the direct renin inhibitor aliskiren may have renoprotective effects independent of blood pressure-lowering effects (i.e. Figs 2A and 2C) in diabetics with nephropathy
- This strategy of dual blockade could be more efficacious than simultaneous use of ACE-I and ARB
- Results described here warrant a multicenter prospective extended outcomes study

## Limitations/Criticisms

- Authors did not differentiate between use of DHP and non-DHP CCB which can affect proteinuria
- Does short-term reduction in proteinuria really confer long-term benefits in delay to ESRD?

