Renal and CV Outcomes with Losartan in those with T2DM and Nephropathy[1]

RENAAL – Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan Study - Trial Summary

SUMMARY

- In patients with T2DM and nephropathy, the ARB losartan reduced the rate of renal decline and progression to end-stage renal disease (ESRD). However, this benefit did not translate into a reduction in mortality; CV events were far more prominent than renal events.
  - NNT/year to prevent one patient from progressing to ESRD=17

BACKGROUND

- Diabetic nephropathy is a leading cause of ESRD. This trial assessed the effect of losartan (an angiotensin receptor blocker) on both renal and cardiovascular (CV) outcomes in patient s with type-2 diabetes. Previous studies with ACEI had demonstrated beneficial effects on proteinuria, but not necessarily the superiority of ACEI or ARB in delaying progression to ESRD.

RENAAL TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE FOR FULL CRITERIA)

DESIGN:

- Randomized, double-blind, placebo controlled trial; uncertain if allocation concealed; ITT; stopped early after mean of 3.4 years due to an ACEI RCT showing CV benefit in renal impairment.[2] Stratification by baseline proteinuria.
- 6 week screening phase: patients received standard antihypertensive unless taking ACEI or ARB (replaced by alternative open label meds)
- Funding and non-voting participation by sponsoring pharmaceutical company (Merck).

POPULATION: (Inclusion and Exclusion):

- **INCLUSION:** patients, age 31-70, with T2DM and nephropathy (ACR ratio ≥300, or proteinuria 0.6g/day) and SCr between 1115-265 umol/L.
- **EXCLUSIONS included:** if T1DM, non-diabetic renal disease, renal-artery stenosis, previous MI, coronary bypass in last month, cerebrovascular accident, angioplasty in previous 6 months, TIA in past year, or any history of HF.
- **POPULATION at baseline (some imbalance between groups, given the relatively small cohorts):**
  - **n=1513 enrolled, age ~60,** 62% male, current smoker ~18%
  - 85% CVD (secondary prevention), ~93%% on hypertensive meds, 50% with neuropathy, ~63% retinopathy, LDL=3.7, TG=2.5,
  - Mean SCr=88 umol/L, mean BP=153/82 mmHg
  - ~48% white, ~18% Hispanic, ~15% Black, ~16% Asian

INTERVENTION/COMPARISON:

- **Losartan 50mg once daily, then increasd to 100mg once daily at 4 weeks, vs placebo; (background of conventional antihypertensive therapy)**
  - Follow-up

OUTCOMES – evaluated over median follow-up of 3.4 years:

- **Primary:** composite of doubling of SCr, ESRD, or death
- **Secondary, select**: composite of morbidity and mortality from CV cause, proteinuria, rate of progression of renal disease

RESULTS – over 3.4 years – ITT analysis

	Losartan 100mg (No/100patient-yr) **n=751**	**Placebo** (No/100patient-yr) **n=762**	**Relative Risk Reduction** 95% CI	**ARR** (Per 100 patient-yr), **NNT** per year	**Comments**
1° Endpoint (doubling of SCr, ESRD, death)	327 (15.9)	359 (18.1%)	16% 2-28%	2.2 **NNT≈45** per year	Of interest, risk reduction in RCT was calculated using a Cox regression model as opposed to the crude rate of events; if crude rate had been used, the 1° outcome would not be stat significant. {43.5% vs 47.1%, RR 0.924; p=0.16; NNT≈28 (-69 – 12) over 3.4 yrs.} However, the 2° endpoints were evaluated using crude rates. The decrease in risk of primary endpoint was similar after adjustment for blood pressure, overall. Renal protection from Losartan is beyond that accounted for by differences in BP. Per protocol analysis saw a little larger, 22% relative risk reduction in the 1°endpoint. Authors estimate that the reduction in ESRD corresponds to a delay of 2 years in the need for dialysis or transplantation. Of interest, reductions in rate of renal function decline are much smaller in RENAAL than those reported for captopril in T1DM.
Doubling of SCr	(7.9)	(10.0)	25%, 8-39%	2.1, **NNT≈48**	
ESRD	(6.8)	(9.1)	28%, 11-42%	5.9%, **NNT≈17**	
Death	(6.8)	(6.6)	-2% NS, -27-19%	-0.7%, NS	
CV related event: morbidity/mortality	32.9%	35.2%	10% $^{p=0.26}$ NS	NS	
MI	6.7%	8.9%	28% $^{p=0.08}$ NS	NS	
HF, 1st hospitalization	11.9%	16.7%	32% $^{p=0.005}$	4.8, **NNT≈21**	
Proteinuria, uACR	↓ ~35-40%	↑ ~5-10%	-	-	
Decline in eGFR* median	4.4	5.2	15% $^{p=0.01}$	-	
DC due to AE	-	-	-	-	
Serious AE (SAE)	-	-	-	-	

*Decline in eGFR are in mL/minute per 1.73 m^2 units per year; **ACEI**=angiotensin converting enzyme inhibitor **ACR**=albumin/creatinine ratio **AE**=adverse event **ARB**=angiotensin receptor blocker **ARR**=absolute risk reduction **BP**=blood pressure **CHF**=congestive heart failure **CI**=95% confidence interval **CV**=cardiovascular **CVD**=CV disease **DC**=discontinued **DM**=diabetes mellitus **eGFR**=estimated glomerular filtration rate **ESRD**=end-stage-renal-disease **HF**=heart failure **ITT**-intention-to-treat **K+**=potassium **LDL**=low-density lipoprotien **NNT**=number needed to treat **NS**=not-statistically significant **RR**=relative risk **SCr**=serum creatinine **T1DM**=type-1 DM **T2DM**=type-2 DM **TG**=triglycerides **tx**=treatment **uACR**=urinary albumin/creatinine ratio

- It is uncertain if the renal benefit seen here with an ARB can be extrapolated to ACEI.

[1] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; **RENAAL** Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 Sep 20;345(12):861-9. doi: 10.1056/NEJMoa011161. PMID: 11565518.

[2] Mann, JFE, Gerstein, HC, Pogue, J, Bosch, J, Yusuf, S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the **HOPE** randomized trial. *Ann Intern Med* 2001;134:629-636