The Effects of Ramipril on Cardiovascular and Microvascular Outcomes in those with T2DM[1]

MICRO-HOPE Substudy – with an Additional Focus on Renal/Microvascular Outcomes - Trial Summary

SUMMARY

- In older, high-CV risk patients with diabetes, the ACEI ramipril reduced both major CV events and microvascular events. The impact on CV events was relatively more than that on microvascular events over 4.5yrs (RR ↓25%, NNT≈23 vs RR ↓16%, NNT≈40, respectively).
- Risk of development of overt nephropathy was specifically reduced by 24% (NNT≈53).
- All benefits were more than would be expected from BP reduction alone. Harms, other than cough (↑5%), were uncommon.

BACKGROUND

- The HOPE/MICRO-HOPE Sub-study evaluated the role of ACE inhibitors (ACEI) in a broad group of patients with diabetes, specifically looking at the delay/prevention of microvascular/renal outcomes (e.g. overt nephropathy) and key overall CV outcomes.

HOPE & MICROHOPE PRESPECIFIED SUBSTUDY - TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE FOR FULL CRITERIA)

DESIGN:

- Randomized, double-blind, placebo controlled trial; uncertain if allocation concealed; ITT; stopped 6 months early after median of 4.5 years.
- Run-in period: 2.5mg ramipril daily x 7-10 days, then matching placebo x10-14 days; 80% compliant, tolerated (no side effects), maintaining </=SCr 200umol/L and K+ </= 5.5mmol/L.
- 2x2 factorial design (ramipril 10mg/day vs placebo, and vitamin D 400IU/day vs placebo); Cox's regression models used in statistical analysis.

POPULATION: (Inclusion and Exclusion):

- **INCLUSION:** patients, age 55+, with a history of diabetes and CV disease or at lease 1 other CV risk factor {total cholesterol >5.2, HDL <0.9, hypertension (taking antihypertensives or BP >160/90mmHg), known microalbuminuria, current smoker}.
- **EXCLUSIONS included:** dipstick positive proteinuria or established diabetic nephropathy, other severe renal disease, hyperkalemia, CHF, ejection fraction <0.4, uncontrolled hypertension, recent MI or stroke (<4 weeks); use of, or hypersensitivity to vitamin E or ACEI.
- **POPULATION at baseline:**
  - **n=3577 enrolled** (a diabetes subset of the 9541 participants in the HOPE study)**, age ~66,** 63% male, current smoker ~15%
  - 70% CVD (mostly secondary prevention ~60% CAD)), ~56%% on hypertensive meds
  - Mean SCr=94 umol/L, mean BP=142/80 mmHg
  - Population base in North and South America and Europe

INTERVENTION/COMPARISON:

- **Ramipril 10mg day, vs placebo; (background of conventional antihypertensive therapy)**

  Still on assigned medication, ramipril or placebo: a) at 1 yr: 84% & 88%; b) at end of study: 65% & 66%; at 4yrs ~12-15% on open-label ACEI

OUTCOMES – evaluated over median follow-up of 4.5 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 median 4.5 years – ITT analysis

	Ramipril 10mg (No/100patient-yr) **n=1808**	**Placebo** (No/100patient-yr) **n=1769**	**Relative Risk Reduction** (95% CI)	**Absolute Risk** NNT / 4.5yrs	**Comments**
1° Endpoint (MI, stroke, CV death)	15.3%	19.8%	25% (12-36)	4.5%, NNT≈23	**Authors calculation**, CV & microvascular endpoints: NNT≈15/4.5yrs **Subgroups**: ramipril benefit appears consistent across subgroups **Microvascular endpoints**: most effect on overt nephropathy 6.5 vs 8.4% p=0.027; small uncertain effect on laser tx (retinopathy) 9.4 vs 10.5% p=0.24; trivial or no effect on dialysis 5 vs 5% . **Risk of nephropathy:** ramipril lowered risk in those who did, & those who did not have microalbuminuria; ramipril led to a lower ACr ratio than placebo at 1yr and at end of study; in those without microalbuminuria at baseline, risk of new microalbuminuria was not significantly reduced. Ramipril led to lower rate of overt proteinuria (7 vs 8%). **AE/Reasons for DC** (discontinuing drug vs placebo): cough 7 vs 2%, hypotension/dizziness 2 vs 1%, angioedema 0.3 vs 0.1%, hypertension 3 vs 5%, clinical event 8% vs 10%, other ~28%; unfortunately SAE not reported. **BP change at end of study (in mmHg): (cuff BP; ? in evening)** - Systolic: -1.9 vs +0.55 - Diastolic: -3.3 vs -2.3 - (both statistically significant although small difference) **Outcome benefits for ramipril appear to be greater than would be expected from ↓ in BP alone (consistent with other ACEI RCTs.)**
MI	10.2%	12.9%	22% (6-36)	2.7%, NNT≈37	
Stroke	4.2%	6.1%	33% (10-50)	1.9%; NNT≈53	
CV death	6.2%	9.7%	37% (21-51)	3.5%, NNT≈29	
Total Mortality	10.8%	14.0%	24% (8-37)	3.2%, NNT≈32	
Hospitalization: for HF; for unstable angina	4.5% 11.8%	4.5% 11.7%	- -	- -	
Revascularization	14%	16.4%	17% (2-30%)	2.4%, NNT≈42	
Overt nephropathy	6.5%	8.4%	24% (3-40)	1.9%, NNT≈53	
Microvascular: overt nephropathy, laser tx fo retinopathy, or dialysis.	15.1%%	17.6%%	16% (1-29)	2.5%, NNT≈40	
DC due to Cough	7%	2%	-	-	
DC due to Angioedema	0.3%	0.1%	-	-	
DC anytime	37%	37%	-	-	
Serious AE (SAE)	?	?	-	-	

Microalbuminuria = a ratio of ≥2mg/mmol; ***Overt Nephropathy*** = as 24h urine albumin ≥ 300mg, or total urine protein excretion ≥ 50mg/day, or A/C ratio ≥36mg/mmol (without other 24hr urine result)
ACEI=angiotensin converting enzyme inhibitor **ACR**=albumin/creatinine ratio **AE**=adverse event **BP**=blood pressure **CHF**=congestive heart failure **CI**=95% confidence interval **CV**=cardiovascular **CVD**=CV disease **DC**=discontinued **DM**=diabetes mellitus **ESRD**=end-stage-renal-disease **HF**=heart failure **ITT**-intention-to-treat **K+**=potassium **NNT**=number needed to treat **SCr**=serum creatinine **tx**=treatment

[1] Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet. 2000 Jan 22;355(9200):253-9. Erratum in: Lancet 2000 Sep 2;356(9232):860