Renal Outcomes with Telmisartan, Ramipril, or Both, in People at High Vascular Risk[1]

ONTARGET – Renal Outcomes - Trial Summary

SUMMARY

- Compared to either alone, combination ACEI-ARB (ramipril+telmisartan) was more harmful for renal outcomes in high-renal risk patients
- Tolerability – hypotension resulting in discontinuation was an issue, especially for the combination, 406/8576 (4.7%).
- Compared to the strictly CV outcomes in same RCT, renal events were much less frequent; consider prioritizing CV interventions.

BACKGROUND

- Angiotensin receptor blockers (ARB) and angiotensin converting enzyme inhibitors (ACEI) reduce proteinuria. This RCT assessed the effect of each individually, and in combination, on renal outcomes in high-CV-risk patients (age ≥55, atherosclerotic vascular disease, or diabetes with end-organ damage). What would be the net benefit/harm of a combination of ARB + ACEI, versus either alone?

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

DESIGN:

- randomized, double-blind, active controlled trial; allocation concealed; intention-to-treat (ITT) analysis used; p-values two sided for all renal outcomes; sensitivity analysis compared those who took study drugs for <50% of the study period; only 0.2% lost to follow-up; funding by manufacturer; independent coordination and analysis
- 3-4 week run-in period with escalating doses of ramipril (2.5mg, 5mg) partially overlapping with telmisartan (40mg)
  - ~64% were taking and ACEI or ARB prior
  - 11.7% were excluded following run in (3.9% poor compliance, 1.7% symptomatic hypotension, 0.8% elevated K+, 0.2% ↑SCr)

POPULATION: (Inclusion and Exclusion: Full criteria online)[2]

- **INCLUSION:** patients, age ≥55, with vascular disease (coronary, peripheral, or cerebrovascular), or diabetes with end-organ damage
- **EXCLUSIONS included:** poor compliance at run-in, hypotension symptoms, hyperkalemia; known hypersensitivity or intolerance to ACE or ARB; variety of cardiac complications (e.g. symptomatic HF, uncontrolled hypertension eg. BP>160/100); significant renal artery disease, SCr >265umol/L proteinuria (?TRANSCEND ONLY), hepatic disfunction, uncorrected volume or sodium depletion;
- **POPULATION at baseline (recruitment 2001-2007; well balanced):**
  - **n=25,620 enrolled (~8500 each arm)**; mean age 65 yrs, ~72% male, 85%
  - 85% CVD (secondary prevention), 69% hypertension, 38% diabetes, ~21% stroke or TIA; LDL=2.9, TG=1.7,
  - Mean SCr=94 umol/L, K+ 4.4mmol/L (80.9% with eGFR ≥60; ~1%with eGFR <30); microalbuminuria ~13%; mean BP=141.8/82.1
  - 73% European, 14% Asian, 9% Aboriginal; ~50% past smoker, ~12% current smoker
  - at baseline, most patients on statins ~62%, antiplatelet tx ~80%, beta-blockers ~57%

INTERVENTION/COMPARISON:

- **Ramipril titrated to 10mg daily, vs telmisartan 80mg daily, vs combination (ramipril + telmisartan); follow-up at 6wks, & q6months**
  - Follow-up for those taking ACEI or ARB over time (@1yr, @end of study):
    - Ramipril group: 93%/1%, 85%/3%; Telmisartan group: 94%/3%, 86%/6%

OUTCOMES – evaluated over median follow-up of 56 months:

- **Primary (renal):** composite of dialysis, doubling of SCr, and death.
- **Secondary, select**: dialysis or doubling of SCr; eGFR rate of decline, increase in proteinuria (urinary albumin excretion).

RESULTS – over 56 months

	Ramipril 10mg/day n=8576	**Telmisartan** 80mg/day n=8542	**Combo** Ramipril+Telmisartan n=8502	**Telmisartan Vs Ramipril Risk ratio** NNT/H @56months	**Combo Vs Ramipril Risk ratio** NNT/H @56months	**Comments**
1° Renal Outcome: dialysis, renal transplant, doubling of SCr, or death.	13.4%	13.4%	14.5%	1.00, 0.92-1.09	1.09, 1.01-1.18 NNH≈91	For renal outcomes: ramipril and telmisartan similar; combo worse
Note: inclusion of all-cause death in this endpoint increases the number of events significantly however, most more likely to have CV cause given the CV data in the parallel CV publication (exaggerates renal outcome given it is a non-renal outcome.						Subgroups consistent (combo ↑ harm in low risk; no benefit in high-risk,)
2° Renal Outcome: any dialysis or SCr doubling	2.03	2.21	2.49	1.09, 0.89-1.34	1.24, 1.01-1.51 NNH≈217	Renal abnormalities more common in combo group 13.5%, vs ramipril 10.2% & telmisartan 10.6%; acute dialysis ↑in combo vs ramipril;
All-cause death	11.8%	11.6%	12.5%	0.98, 0.90-1.07	1.07, 0.98-1.16	Doubling of SCr: similar: all 3 groups
BP – mean ↓ at 6wks	↓6.4/4.3 mmHg	↓7.4/5.0 mmHg	↓9.8/6.3 mmHg	-	-	BP: trends continued through study;
Hypotension, leading →discontinuation	1.7%	2.7%	4.8%	NNH≈100 p<0.001	NNH=32 p<0.001	Vs ramipril, combo group also had more syncope (0.3% vs 0.2%, p=0.03), and diarrhea (0.5% vs 0.1%).
K+ >5.5mmol/L	3.3%	3.4%	5.6%	NS	1.69 $_{p<0.001}$; NNH≈44	K+ at baseline: 4.4±0.4
eGFR: change 0-6wks	-2.14	-2.51	-4.01	P=0.07	p <0.0001	SCr baseline=93.7 (SD 22.8)
eGFR: change: 0-end	-2.82	-4.12	-6.11	P <0.0001	p <0.0001	eGFR=73.6mL/min (SD 19.6)
Progression micro- to macro-albuminuria	2.12%	1.77%	1.61%	HR=0.83, 0.67-1.04	HR=76, 0.60-0.96 NNT≈196	Other of note: ↑cough in ramipril vs telmisartan (4.2% vs 1.1%), and ↑angioedema (0.3% vs 0.1%).
Renal impairment →DC	0.7%	0.8%	1.1%	NS	1.58, p<0.001	
1° CV Outcome: CV death,MI,stroke,HF hosp	16.5%	16.7%	16.3%	1.01, 0.94-1.09 NS	0.99, 0.92-1.07 NS	Separately published CV results[3]; telmisartan non-inferior to ramipril.

Microalbuminuria defined as 3.4mg/mmol – 33.9 mg/mmol: was present in 29.7% of those with diabetes, 9.2% in those without; **Macroalbuminuria**: was present in 12.2% of those with diabetes, 1.4% in those without. **Risk of developing new microalbuminuria, macroalbuminuria, or both** during the trial not different between telmisartan and ramipril (11.1% vs 11.7%), but lower with combination therapy vs ramipril (10.4% vs 11.7%)

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 **hosp**=hospitalization **ITT**-intention-to-treat **K+**=potassium **LDL**=low-density lipoprotien **NNH**=number needed to harm **NNT**=number needed to treat **RR**=relative risk **SCr**=serum creatinine **T1DM**=type-1 DM **T2DM**=type-2 DM **TG**=triglycerides **tx**=treatment **uACR**=urinary albumin/creatinine ratio

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[1] Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, et al; **ONTARGET** investigators. **Renal** outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008 Aug 16;372(9638):547-53. doi: 10.1016/S0140-6736(08)61236-2. PMID: 18707986.

[2] Teo K, Yusuf S, Sleight P, Anderson C, Mookadam F, Ramos B, et al; **ONTARGET/TRANSCEND** Investigators. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. Am Heart J. 2004 Jul;148(1):52-61. doi: 10.1016/j.ahj.2004.03.020. PMID: 15215792.

[3] ONTARGET Investigators; Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. (**CV Outcomes**) N Engl J Med. 2008 Apr 10;358(15):1547-59. doi: 10.1056/NEJMoa0801317. Epub 2008 Mar 31. PMID: 18378520.