Is RAAS blockade the "ACE" up your sleeve when it comes to preventing diabetic nephropathy?

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Clinical Question: Does the use of ACE inhibitors (ACEi) or ARBs prevent nephropathy in normotensive, normoalbuminuric patients with Type 1 or Type 2 diabetes mellitus?	
P	Normotensive, normoalbuminuric diabetic patients (Type 1 or Type 2)
I	ACE inhibitors or ARBs
C	Placebo
O	Diabetic nephropathy

Bottom Line: ACEi appears to be effective in the primary prevention of microalbuminuria in normotensive*, normoalbuminuric** patients with diabetes (Type 1 or Type 2) by about 5% over 2-5 years (NNT 20). ARBs do not appear show this effect. There is not enough evidence to confirm that the addition of ACEi will reduce clinically significant outcomes such as end-stage renal disease or mortality in this specific population.

- *Primary patient population included in the analyses would be considered **hypertensive** per current practice standards (**BP > 130/80 mmHg**).
- **Normoalbuminuric was defined as patients **albumin excretion rate (AER) < 30 mg/d**.

Available Evidence:

- Cochrane Review (1): ACEi reduced the risk of new onset of microalbuminuria, macroalbuminuria or both when compared to placebo (8 studies, 11,906 patients: RR 0.71, 95% CI 0.56 to 0.89), with similar benefits in people with and without hypertension
    - ADVANCE trial was heavily weighted in the analysis (45.5%) although the authors found similar results when it was removed (RR 0.63, 95% CI 0.48 to 0.83, P = 0.0009)
        - Primary patient population: avg 66 y.o. with T2DM duration of 8 years, avg BP was **145/81 mmHg**
        - Intervention included perindopril and indapamide
    - difference between normotensive and hypertensive patients not statistically different: P = 0.74
    - No effect was observed for ARBs vs placebo for new microalbuminuria, macroalbuminuria or both (5 studies, 7653 participants: RR 0.90, 95% CI 0.68 to 1.19) or death (5 studies, 7653 participants: RR 1.12, 95% CI 0.88 to 1.41)
    - ACEi reduced the risk of death when compared to placebo (6 studies, 11,350 participants: RR 0.84, 95% CI 0.73 to 0.97); no analysis of hypertensive vs normotensive patients
    - no significant difference in the risk for doubling serum creatinine (5 studies, RR 0.77, 95% CI 0.39 to 1.49; P = 0.13) or ESRD (3 studies; RR 1.94, 95% CI 0.6 to 5.70; P = 0.76)

- EUCLID study (2): There was little beneficial effect in those who started the trial with an AER of 5 μg/min or less; but those who started with microalbuminuria (AER ≥20 μg/min) benefited more from lisinopril than did those in the normoalbuminuric range. Thus, after 2 years, the absolute and relative treatment differences in AER were 34.2 μg/min (49.7%) in the microalbuminuric group; and 1.0 μg/min (12.7%) in the normoalbuminuric group.
    - Normotensive definition in this study does not match what is used in current clinical practice (**SBP < 155 mmHg, DBP 75-90**)
        - Avg BP of pts included was **122/79 mmHg**
    - Benefits primarily shown in microalbuminuric group (not statistically significant) which the study was underpowered to detect outcomes in this group as most patients were normoalbuminuric
    - Type 1 diabetic patients only
    - This study was also included in above Cochrane Review analysis, contributing 20.3% weight
- Candesartan trials (3): Individual and pooled results of the 3 trials showed that candesartan had little effect on risk for microalbuminuria (pooled hazard ratio, 0.95 [95% CI, 0.78 to 1.16]; *P* = 0.60). Pooled results showed that the annual rate of change in albuminuria was 5.53% lower (CI, 0.73% to 10.14%; *P*= 0.024) with candesartan than with placebo over 4-5 y.
    - studies not powered for renal endpoints (retinopathy studies)
    - one of the studies defined controlled hypertension as blood pressure ≤160/90 mm Hg

References:

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3. Bilous R, Chaturvedi N, Sjolie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: Three randomized trials. Ann Intern Med 2009;151:11–20, w3-4