Renal Effects of Enalapril and Losartan in Type 1 Diabetes

Clinical Question: Mr. A, a 54 y/o M with well-controlled type 2 diabetes and mild hypertension, presents to the UNC internal medicine clinic for a new-patient visit after losing his health insurance. During the visit he has no complaints – he has been taking metformin and norvasc without any problems. He is mildly overweight with BMI of 28. Blood pressure is 128/75 and physical exam is normal. His creatinine is at baseline 0.7, and a UPC ratio shows no evidence of protein. He inquires about whether changing his norvasc to an ACEI would be beneficial to his kidneys.

Background: Much has been written on the impact of ACEIs and ARBs on the development of diabetic nephropathy. Although it is well-established that these renin-angiotensin system (RAS) inhibitors are preferred for the treatment of established diabetic nephropathy, there is debate about their role in primary prevention of the condition – that is in patients without evidence of microalbuminuria. Previous studies, namely HOPE, BENEDICT, and ADVANCE, have shown a primary benefit, however their patient populations had poorly-controlled hypertension at baseline. Blood pressure optimization may have played a larger role than any special benefit of RAS inhibition. Earlier this month, data from the DIRECT-Protect 2 trial addressed primary prevention of diabetic nephropathy with candesartan in type 2 diabetics with either normotension or well-controlled hypertension. No significant benefit was found after 5 years of treatment when compared with placebo.


Prospective, triple-blind, multi-center randomized-controlled trial. Enalapril, Losartan, and placebo were compared with respect to their ability to prevent progression of renal biopsy findings consistent with diabetic nephropathy.

Are the results valid?

Was the assignment of patients to treatments randomized?

285 patients (mean age 30 y/o, 46% men)
1. Inclusion criteria: Type 1 diabetics recruited via advertising and discussion at local diabetes clinics.
2. Exclusion criteria:
   a. Hypertension >135/85
   b. Albumin excretion rate >20 ug per minute (UPC ratio >.030)
   c. GFR of < 90.
3. Power calculations based on assumption that the treatment group would have a 50% reduction in mesangial fractional volume with a statistical power of 80% and a significance (alpha) of 5%. From this the authors calculated at least 86 patients would be needed in each group.
4. The patients were randomized into 1 of 3 groups but method for this was not discussed.
More on Power

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<tr>
<th>Treatment</th>
<th>Power</th>
<th>Confidence</th>
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<tbody>
<tr>
<td>does not work</td>
<td>95% - confidence (1-alpha)</td>
<td>5% - type 1 error (alpha)</td>
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<tr>
<td>really works</td>
<td>20% - type 2 error (beta)</td>
<td>80% - power (1-beta)</td>
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Power – How *sensitive* is this study going to be for evaluating whether or not ACEI/ARBs work. Confidence – How *specific* is the study for this evaluation.

Were all the patients who entered the trial properly accounted for and attributed at its conclusion? Primary endpoint was by intention to treat:

Were all patients, health workers, and study personnel masked to treatment?
1. Yes, Patients, physicians, and pathologists were all blinded.
2. Merck (maker of enalapril and losartan) did provide financial support for the trial but had no censoring/advisory power.

Were the groups similar at the start of the trial? Were the groups treated equally? In general the groups were quite similar. Main differences:
1. Placebo group had a slightly higher glycolated hemoglobin, but not statistically different
2. Age, diabetes duration, BMI, %male, race, median albumin excretion, and GFR were all very similar.

What are the results?

1. The primary outcome was a significant change in the fraction of glomerular volume occupied by mesangium.

2. Secondary end points:
   a. Albumin excretion rate – Losartan group had 14 ug/min compared to placebo 5.3 ug/min, which has a p-value of 0.007, otherwise no significant difference.
   b. GFR – no significant differences between the groups.

3. Retinopathy – increase in retinopathy by 2 or more steps; there was a significant difference

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<th>Primary Outcome</th>
<th>Secondary End points</th>
<th>Retinopathy</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>28/74 (38%)</td>
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<tr>
<td>Enalapril</td>
<td>19/77 (25%)</td>
<td>p = 0.02</td>
<td>RRR 37%, ARR 13%, NNT 7.6</td>
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<tr>
<td>Losartan</td>
<td>15/72 (21%)</td>
<td>p = 0.008</td>
<td>RRR 45%, ARR 17%, NNT 5.9</td>
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Will the results help me in caring for my patients?

Can the results be applied to my patient care?

1. Overall feel that mesangial expansion is an objective and clinically relevant end-point that would be a quite sensitive indicator of early nephropathy.
   a. Mesangial expansion has been linked to renal dysfunction
   b. Use of “death” and “need for dialysis,” as end points would require many more years to achieve enough events. Their use would also not answer the specific question at hand.

2. Though technically well-performed, the study was vastly underpowered, and that may have contributed to its negative result. The concurrently positive study for retinopathy is consistent with prior studies, and it does validate that the medications were being dosed appropriately.

3. This patient population (that is type 1 diabetics with good glycemic control, no comorbidities, and normoalbuminuria after 10 years of disease) is much healthier than the typical UNC patient. The study population is also healthier than the patient above (who has type 2 diabetes complicated by mild hypertension)

The study would have made quite an impact had it been positive, as it would have provided a new indication for ACEI and ARB use for primary prevention of diabetic nephropathy. However it was negative, underpowered, and performed in an especially healthy group of diabetics. In the end, it should not change much about what we do for our patient population. As the ACEs and ARBs do not appear to do harm, changing Mr. A’s norvasc to enalapril for blood pressure control would be a reasonable but not mandatory action. Without the baseline mild hypertension there would be little reason to initiate an ACE or ARB in him for primary prevention of diabetic nephropathy.