Diabetic nephropathy: Do all patients with Diabetes Mellitus benefit from an ACE-I or ARB?

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Objectives:

1. Explain the screening, diagnosis, and pathophysiology of diabetic nephropathy
2. Describe the renin-angiotensin-aldosterone system (RAAS) and the mechanism of action and effects of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB)
3. Review the current guidelines and treatment recommendations for diabetic nephropathy
4. Evaluate the available literature regarding the effects of RAAS on diabetic nephropathy in normoalbuminuric patients

I. Introduction

a. Diabetes Mellitus (DM)[1]
   i. Type 1 (T1DM)
      1. Insulin-dependent DM (IDDM)
      2. Autoimmune destruction of β cells in pancreas
      3. Accounts for 5-10% of all diagnosed cases of DM
   ii. Type 2 (T2DM)
      1. Non-insulin dependent DM (NIDDM)
      2. Insulin resistance and relative deficiency in insulin secretion
      3. Accounts for 90-95% of all diagnosed cases of DM

b. Prevalence of diagnosed and undiagnosed diabetes in the United States, all ages, 2007[1]
   i. Affects nearly 24 million people in the United States → 8% of population
   ii. Diagnosed: 17.9 million people
   iii. Undiagnosed: 5.7 million people

c. Prevalence of diagnosed and undiagnosed diabetes in the United States, ≥ 20 years old, 2007[1]
   i. Age ≥ 20 years: 23.5 million people
   ii. Age ≥ 60 years: 12.2 million people

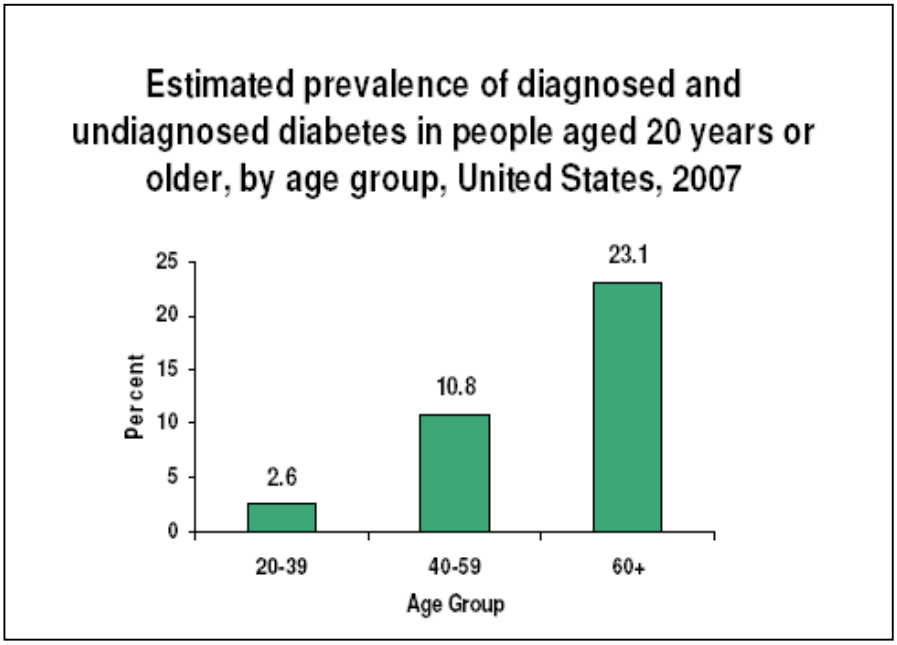

Figure 1. Estimated prevalence of diagnosed and undiagnosed diabetes in ≥ 20 year olds[1]

d. Incidence of diagnosed diabetes among people aged ≥ 20 years old, 2007[1]
   i. About 1.6 million new cases

e. Estimated costs of DM in 2007[1]
   i. Total (direct and indirect): $174 billion
   ii. Managing diabetic nephropathy[2]
      1. T1DM: $1.9 billion
      2. T2DM: $15 billion

f. Complications of DM[1]
    i. Microvascular
        1. Nephropathy
        2. Retinopathy
            a. Leading cause of new cases of blindness among adults aged 20-74 years
            b. Causes 12,000 to 24,000 new cases of blindness each year
        3. Neuropathy
            a. About 60-70% of people have mild to severe forms of nervous system damage
                i. Impaired sensation in hands or feet, slowed digestion of food in stomach, carpal tunnel syndrome, erectile dysfunction
    ii. Macrovascular
        1. Heart disease
            a. Death rates about 2 to 4 times higher than adults without DM
        2. Stroke
            a. Risk of stroke is 2 to 4 times higher among people with DM
g. Preventing complications[1]
    i. Glycemic control
        1. Every percentage point drop in HgbA1c, can reduce risk of microvascular complications by 40%
    ii. Blood pressure (BP) control
        1. Reduces risk of cardiovascular disease (heart disease or stroke) by 33-50%
        2. Reduces risk of microvascular complications by 33%
        3. For every 10 mmHg reduction in systolic blood pressure (SBP), risk of any complication related to DM is reduced by 12%
    iii. Lipid control
        1. Improved control of LDL can reduce cardiovascular complications by 20-50%

II. Diabetic nephropathy

a. Background[3]
    i. Occurs in 20-40% of patients with DM
    ii. Single leading cause of end stage renal disease (ESRD)[1]
        1. 44% of new cases of kidney failure in 2005
    iii. Associated with increased cardiovascular mortality
    iv. Earliest clinical abnormality = microalbuminuria[4]
        1. Occurs between 5-15 years after onset of T1DM or T2DM
    v. Symptomatic kidney failure = worsening albuminuria, increases in BP, and decreasing glomerular filtration rate (GFR) [4]
        1. Around 20 years after onset of T1DM or T2DM

b. Definition[3]
    i. Increased urinary albumin excretion (UAE) in the absence of other renal diseases
    ii. Presumptive diagnosis of kidney disease caused by diabetes
    iii. Categorized into stages[3,5]
        1. Microalbuminuria
            a. Modest elevation of albumin
            b. Associated with stable kidney function
            c. Greater risk of macroalbuminuria and kidney failure
        2. Macroalbuminuria
            a. Higher elevation of albumin
            b. Associated with progressive decline in GFR and increase in systemic blood pressure, and high risk of kidney failure
c. Risk factors[3]
    i. Hyperglycemia
    ii. Elevated blood pressure
    iii. Genetic predisposition
    iv. Hyperlipidemia
    v. Smoking
    vi. Dietary protein intake
d. Pathophysiology[6,7]
    i. Hemodynamic changes
        1. Hyperfiltration and hyperperfusion
            a. Found early in disease process
            b. Elevation in glomerular capillary pressure causes an enhanced transcapillary hydraulic pressure gradient and increase in glomerular plasma blood flow
                i. Decrease in both afferent and efferent arteriole resistance
                    1. Afferent more dilated than efferent → increased glomerular capillary pressure
                    2. Defect in autoregulation
            c. Prostanoids, nitrogen oxide (NO), atrial natriuretic factor, growth hormone, glucagon, insulin, angiotensin II (ANG II)
            d. Elevated intraglomerular pressure linked to an increase in mesangial cell matrix production and thickening of glomerular basement membrane → glomerulosclerosis
            e. Vascular endothelial growth factors (VEGFs) induced by diabetic environment
            f. Cytokines, such as transforming growth factor beta (TGF-β)
                i. Dilatation of vas afferens by inhibiting calcium transients
                ii. Increases NO production
    ii. Inflammation
        1. Up-regulation of genes of inflammatory and vasoactive mediators in proximal tubular cells
        2. Result in renal scarring
    iii. Pathological changes
        1. Hyperglycemia induces mesangial hypertrophy and thickening of glomerular basement membrane
        2. Increased in amount of matrix in mesangium → progresses to sclerosis of glomerular capillaries
            a. Sclerotic changes (usually after ~ 10 years of diabetes) classified by
                i. Diffuse, nodular, or both

3. As glomerulus becomes more fibrotic and scarred → loses function and ESRD results
4. May also see afferent and efferent glomerular arteriolar thickening, tubular basement membrane thickening, and increased volume of interstitium

e. Screening and diagnosis[5,8]

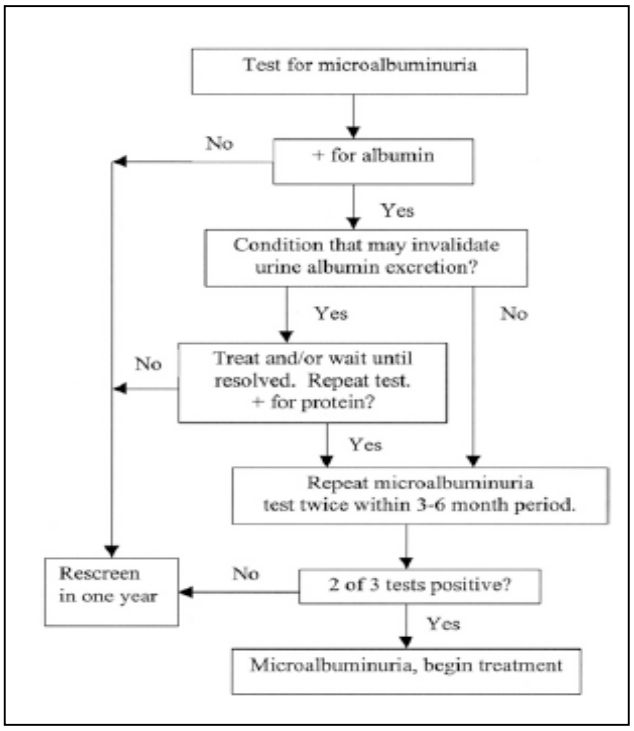

Figure 2. Screening and diagnosis of diabetic kidney disease[5]

i. Assess UAE yearly in
   1. T1DM patients with diabetes ≥ 5 years
   2. T2DM patients at diagnosis
ii. Measure serum creatinine yearly in
   1. All adults with DM regardless of degree of UAE
   2. Used to estimate GFR and stage of chronic kidney disease (CKD), if present
iii. Measure albumin-to-creatinine ratio in random spot collection (preferred method)
   1. Two of three specimens collected within a 3 to 6 month period should be abnormal before a diagnosis or micro- or macroalbuminuria can be made
      a. Some conditions may cause a transient increase in UAE
         i. Exercise within 24 hours, infection, fever, CHF, marked hyperglycemia, hypertension
iv. Can attribute CKD to DM in patients with the following
   1. Presence of macroalbuminuria
   2. Presence of microalbuminuria
      a. In presence of diabetic retinopathy
      b. In T1DM of ≥ 10 years duration

Table 1. Definitions of abnormalities in albumin excretion[5]

Category	Spot collection (mg/g creatinine)	24 hour collection (mg/24 hr)	Timed collection (mcg/min)
Normoalbuminuria	< 30	< 30	< 20
Microalbuminuria	30-300	30-300	20-200
Macroalbuminuria	> 300	> 300	> 200

III. Treatment in Diabetic Nephropathy

a. General recommendations to reduce risk or slow progression of nephropathy[5,8]
   i. Optimize glucose control (HgbA1c < 7%)
   ii. Optimize blood pressure (BP) control (< 130/80 mmHg)

b. Intensive management of glycemic control has been shown to delay the onset of microalbuminuria and progression of microalbuminuria to macroalbuminuria
   i. Preventing development of microalbuminuria

Table 2. Summary of trials: preventing development of microalbuminuria

Trial	Population	N	Renal endpoint	Treatment	Duration	Results
DCCT[9]	T1DM without (1° prevention) and with (2° intervention) retinopathy at baseline; normotensive; normoalbuminuria or microalbuminuria	1441	Occurrence of microalbuminuria	IT (A1c 7.2%) vs CT (A1c 9.1%)	6.5 years	Intensive therapy: reduced by 34% (1° prevention) and 43 % (2° intervention)
EDIC[10]	T1DM Normoalbuminuria at beginning and end of DCCT	1349	Occurrence of new cases of microalbuminuria	IT (A1c 8%) vs CT (A1c 8.2%)	8 year post final DCCT visit	6.8% vs 15.8%
Kumamoto[11]	T2DM without hypertension (1° prevention cohort vs 2° intervention)	110	New onset and progressive diabetic kidney disease	IT (A1c 7.1%) vs CT (A1c 9.4%)	6 years	7.7% vs 28%
UKPDS 33[12]	Newly diagnosed T2DM	3867	Development of microalbuminuria	IT (insulin or sulfonylurea) (A1c 7%) vs CT (diet) (A1c 7.9%)	9 years	24% relative risk reduction
VA Cooperative Study[13]	T2DM with no microalbuminuria	95	Development of microalbuminuria	IT (A1c 7.1%) vs CT (A1c 9.2%)	2 years	17% vs 35%

IT: intensive therapy; CT: conventional therapy

DCCT: 1^0 prevention – no retinopathy and UAE < 28 mcg/min at baseline; 2^0 intervention – background retinopathy with or without microalbumoinuria, but normal GFR

Kumamoto: 1^0 prevention – no retinopathy and UAE < 30 mg/24 hr; 2^0 intervention – simple retinopathy and UAE < 300 mg/24 hr

ii. Preventing development of macroalbuminuria

Table 3. Summary of trials: preventing development of macroalbuminuria

Trial	Population	N	Renal endpoint	Treatment	Duration	Results
DCCT[9]	T1DM without (1° prevention) and with (2° intervention) retinopathy at baseline	1441	Occurrence of macroalbuminuria	IT (A1c 7.2%) vs CT (A1c 9.1%)	6.5 years	0.8% vs 5.6%
EDIC[10]	T1DM	1349	New cases of macroalbuminuria	IT vs CT (A1c ~ 8% in both groups at this time)	8 year post final DCCT visit	1.4% vs 9.4%
Stockholm[14]	T1DM with nonproliferative retinopathy	102	Development of macroalbuminuria	IT (A1c 7.1%) vs CT (A1c 8.5%)	7.5 years	2.1% vs 16.6%
Kumamoto[11]	T2DM without hypertension (1° prevention cohort vs 2° intervention)	110	Progression to macroalbuminuria	IT (A1c 7.1%) vs CT (A1c 9.4%)	6 years	11.5% vs 32%
UKPDS 33[12]	Newly diagnosed T2DM	3867	Development of macroalbuminuria	IT (insulin or sulfonylurea) (A1c 7%) vs CT (diet) (A1c 7.9%)	9 years	33% relative risk reduction+
VA Cooperative Study[13]	T2DM with microalbuminuria	95	Development of macroalbuminuria	IT (A1c 7.1%) vs CT (A1c 9.2%)	2 years	12% vs 36%
ADVANCE[15]	T2DM with h/o macro- or microvascular disease or one other risk factor for vascular disease	11140	Development of macroalbuminuria	IT (A1c 6.5%) vs CT (A1c 7.3%)	5 years	2.9% vs 4.1%

IT: intensive therapy; CT: conventional therapy
+ Not statistically significant

c. Protein restriction[8]
   i. May improve measures of renal function
   ii. In patients with DM and earlier stages of CKD
      1. Reduction of protein intake to 0.8-1 g/kg/day
   iii. In patients with later stages of CKD
      1. Reduction of protein intake to 0.8 g/kg/day

d. Pharmacotherapy
   i. RAAS blockade[8]

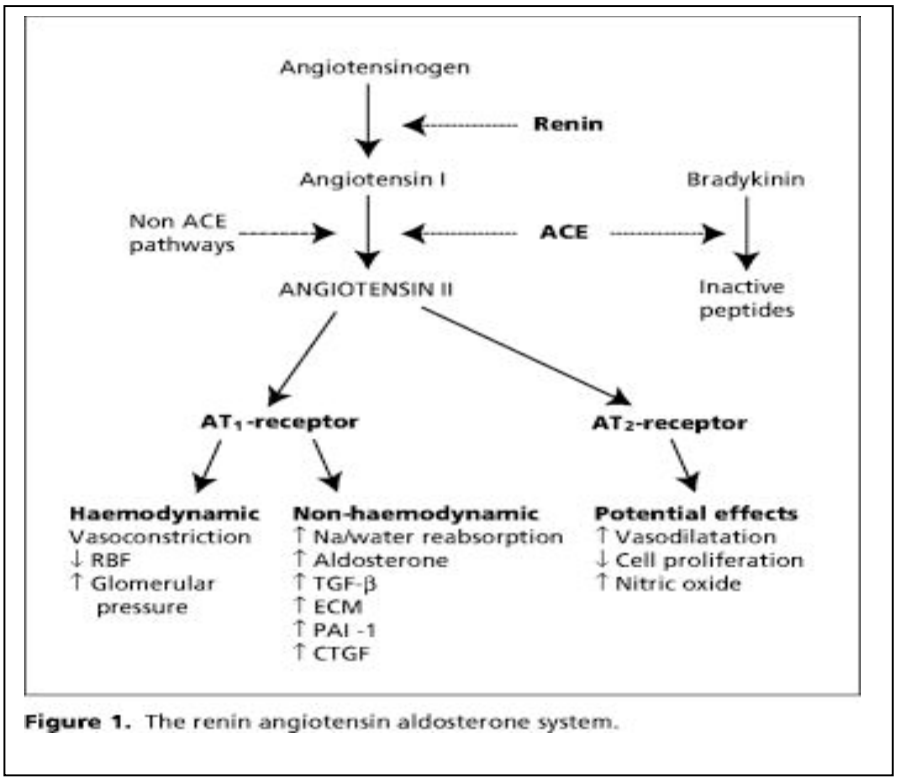

Figure 3. Effects of renin-angiotensin-aldosterone system[16]

   ii. Inhibition of RAAS effective in preventing diabetic nephropathy[17]
   iii. Angiotensin converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB)
      1. Mechanism of action of ACE-I[18]
         a. Prevents the conversion of angiotensin I to angiotensin II
         b. Decreased angiotensin II levels
            i. Decreased vasopressor activity and decreased aldosterone secretion
      2. Mechanism of action of ARB[19]
         a. Reversible angiotensin II receptor antagonist
         b. Deters vasoconstriction and aldosterone secreting effects by binding to the angiotensin II (AT1) receptor
      3. ACE-I and ARB side effects[18,19]
         a. Hyperkalemia, acute kidney injury, cough (seen more with ACE-I), angioedema

iv. Effects on diabetic nephropathy[8,20]

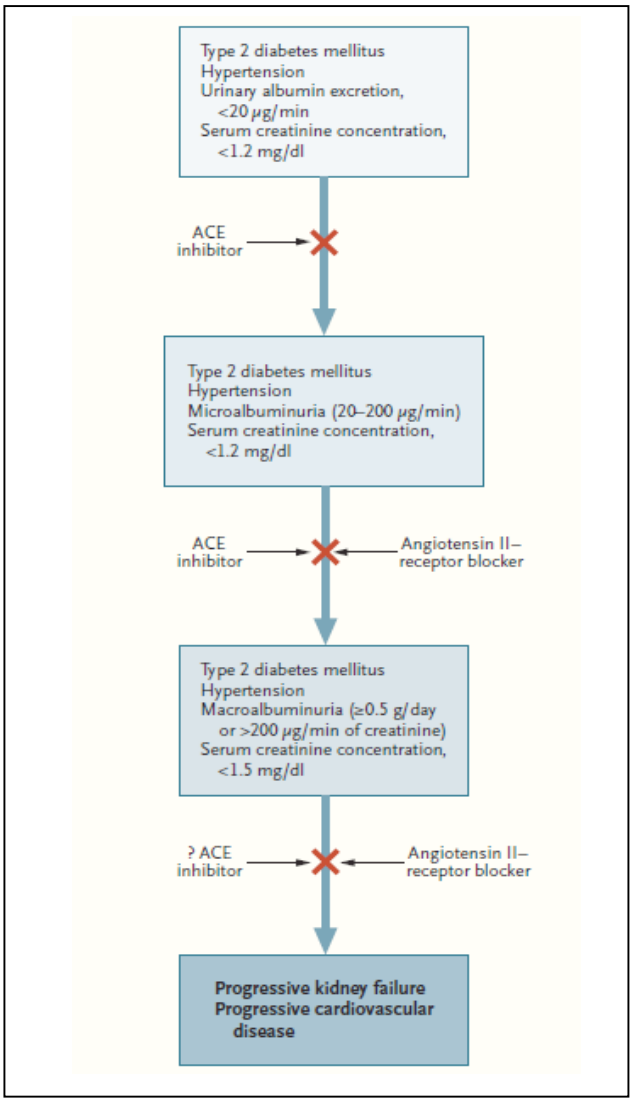

Figure 4. ACE-I vs ARB in progressive nephropathy associated with T2DM[21]

1. ACE-Is have been shown to reduce major cardiovascular disease (CVD) outcomes in patients with DM → supports using in patients with microalbuminuria, a risk factor for CVD
2. ARBs have been shown to reduce rate of progression from microalbuminuria to marcoalbuminuria as well as ESRD
3. Attributed to decrease in BP, dilatation of efferent arterioles, improved endothelial function, reduced inflammation, and vasoprotective effects

v. KDOQI guidelines recommends[5]
   1. ACE-Is and ARBs effective in slowing progression of kidney disease (microalbuminuria) in T1DM or T2DM patients with hypertension

vi. Trials supporting use of ACE-I or ARB in diabetic nephropathy

Table 4. Summary of landmark trials: ACE-I or ARB for diabetic nephropathy

Trial	Population	N	Endpoint	Treatment	Duration	Results
Collaborative Study Group[22]	T1DM with retinopathy and UAE ≥ 500 mg/24 hr*	409	UAE and doubling of SCr	Captopril 25 mg TID vs placebo	3 years	UAE: decrease of 0.3g/24 hr with captopril (p=0.001) Doubling of SCr: 25 vs 43 (p=0.007)
MICRO-HOPE[23]	T2DM with h/o CVD or CV risk factor without or with microalbuminuria	3577	Overt nephropathy	Ramipril 10 mg daily vs placebo	4.5 years	Relative risk of overt nephropathy reduced by 24%; without baseline microalbuminuria, relative risk of developing microalbuminuria reduced by 9%+
ONTARGET[24]	T2DM with atherosclerotic vascular disease or endorgan damage; without micro- or macroalbuminuria	25,620	Progression of proteinuria --> new development of micro- or macroalbuminuria	Ramipril 10 mg daily or telmisartan 80 mg daily or combination of both	56 months	11.7% (R) vs 11.1% (T)+ 11.7% (R) vs 10.4% (C) ++
IDNT[25]	T2DM with HTN or HTN treatment with UAE ≥ 900 mg/24 hr	1715	Reduction in proteinuria	Irbesartan 300 mg daily vs amlodipine 10 mg daily vs placebo	2.6 years	33% vs 6% vs 10%
Parving et al[26]	T2DM with HTN with microalbuminuria	590	Reduction in level of UAE; occurrence of restoration of normoalbuminuria	Irbesartan 150 mg daily vs irbesartan 300 mg daily vs placebo	2 years	24% vs 38% vs 2%; 24% vs 34% vs 21%
RENAAL[27]	T2DM with HTN with macroalbuminuria	1513	Reduction in level of proteinuria (urinary albumin:creatinine)	Losartan 100 mg daily vs placebo	3.4 years	35% with losartan vs increase with placebo

* About 75% of patients in each group were hypertensive
+ Not statistically significant; ++ Statistically significant

1. Majority of these trials included patients who were hypertensive or had CVD risks and already had micro- or marcoalbuminuria
   a. In patients with HTN and/or micro- or macroalbuminuria, ACE-I or ARB are beneficial in reducing proteinuria

IV. Literature reviewing effectiveness of ACE-I or ARB in patients without albuminuria or with microalbuminuria

a. Hypertensive patients or patients with cardiovascular disease without albuminuria[28]

Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in Type 2 Diabetes (BENEDICT). *N Engl J Med* 2004;351:1941-1951.

Design

- Double-blind, placebo-controlled, randomized, multicenter

Objective

- Examine the effects of an ACE-I + a non-dihydropyridine calcium channel blocker (CCB), ACE-I alone, CCB alone, or placebo in preventing microalbuminuria when given to patients with hypertension, T2DM, and normal UAE

Population

- n = 1204; followed for a median of 3.6 years
- Inclusion criteria: > 40 years old, hypertension (untreated with BP $\geq$ 130/85 mmHg or treated with BP < 130/85 mmHg), known history of T2DM < 25 years, UAE < 20 mcg/min, (2 of 3 consecutive, sterile, overnight samples), SCr $\leq$ 1.5 mg/dL
- Exclusion criteria: HgbA1c > 11%, nondiabetic renal disease, specific indication for or contraindication to ACE-I or non-dihydropyridine CCB

Endpoints

- Primary
  - Development of persistent microalbuminuria
- Secondary
  - Follow up systolic and diastolic blood pressure

Protocol

- 6 week washout period where any previous ACE-I was discontinued and 3 week washout period where any previous CCB was discontinued
- Groups
  - Trandolapril 2 mg daily + verapamil 180 mg daily (sustained release)
  - Trandolapril 2 mg daily
  - Verapamil 240 mg daily (sustained release)
  - Placebo
- Target BP 120/80 mmHg
  - Additional antihypertensives were allowed to achieve target BP
  - Use of potassium-sparring diuretics, RAAS inhibitors, non-dihydropyridine CCB not allowed
- Target HgbA1c < 7%
- Magnitude of treatment effect assessed by calculating acceleration factor → quantifies the effect of one treatment relative to another treatment in accelerating or slowing the progression of the disease

Results

- Baseline characteristics similar between groups
- Statistically significant difference in BP in patients receiving ACE-I; no major differences in blood glucose levels and lipid profiles among treatment groups

Outcomes	ACE-I + CCB (n=300)	ACE-I alone (n=301)	CCB alone (n=303)	Placebo (n=300)
Development of persistent microalbuminuria	17 (5.7%)	18 (6%)	36 (11.9%)	30 (10%)
Estimated acceleration factor (95% CI)	0.39 (0.19 to 0.8)	0.47 (0.26 to 0.83)	0.83 (0.45 to 1.51)	
p-value	0.01	0.01	0.54	
Delaying onset of microalbuminuria factor	2.6	2.1	NS	

Outcomes	ACE-I vs no ACE-I onboard	CCB vs no CCB on board
Development of persistent microalbuminuria	35/601 (5.8%) vs 66/603 (10.9%)	53/603 (8.8%) vs 48/601 (8%)
Delaying onset of microalbuminuria factor	2.3	NS

Authors' Conclusions

- Treatment with combo ACE-I + CCB or ACE-I alone significantly reduces incidence of microalbuminuria in patients with T2DM and normal UAE compared to placebo

Comments

- Patients with hypertension (ACE-I or ARB known to be beneficial for BP lowering)
- Average trough BP significantly lower in the groups receiving trandolapril alone or in combination versus placebo group

b. Normotensive without albuminuria or with microalbuminuria[29,30,31]

The EUCLID study group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997;349:1787-1792.	
Design	▪ Double-blind, placebo-controlled, randomized, multicenter
Objective	▪ Assess whether early-stage intervention in patients without hypertension would limit progression of renal disease, and whether this effect differed according to degree of albuminuria
Population	▪ n = 530; followed for 2 years ▪ Inclusion criteria: men and women between 20-59 yr old with insulin-dependent diabetes (IDDM), BP < 155/75-90 mmHg ▪ Exclusion criteria: h/o renal artery stenosis, cardiac-valve obstruction, or accelerated hypertension, recent myocardial infarction, CABG, stroke, congestive cardiac failure, abnormal renal function (SCr > 1.8 mg/dL) in previous 6 months, persistent proteinuira (albumin excretion rate (AER) > 250 mcg/min), persistent haematuria, postural hypotension, medications that affects BP, seropositivity for Hepatitis B or HIV
Endpoints	▪ Primary □ Rate of change in AER
Protocol	▪ One month run in with placebo tablets and made two consecutive timed overnight urine collections just before randomization visit ▪ Randomization stratified by albuminuric status □ Normoalbuminuric group → average of two results indicated that albumin concentration < 15 mg/L □ Microalbuminuric group → higher average concentrations ▪ Groups □ Lisinopril (n = 265) □ Placebo (n = 265) ▪ AER and HgbA1c assessed every 6 months ▪ Starting dose of lisinopril was 10 mg daily → could be increased to 20 mg at 3 months and subsequent visits to achieve a target diastolic BP < 75 mmHg
Results	▪ Baseline characteristics similar between groups ▪ Both groups had similar HgbA1c levels during the trial ▪ Mean diastolic BP = 74 mmHg on active treatment and 77 mmHg on placebo (p=0.0001) – difference carried throughout trial ▪ In the intention-to-treat group, after 2 years (lisinopril n = 244; placebo n = 246) □ AER was 2.2 mcg/min lower in the treatment than in the placebo group □ *Relative treatment difference in AER at 2 years was 24% (p=0.02)* □ Adjustment made for baseline AER and centre, difference persisted → at 2 years, AER was 18.8% lower in the treatment than in the placebo group (2, 32.7; p=0.03) □ Adjustment for diastolic BP at 1 month → reduced percentage difference in AER at 2 years to 17.3% (0.2, 31.5; p=0.05) □ *Normoalbuminuric at baseline → AER at 2 years was 12.7% (-2.9 to 26; p=0.1) lower in the treatment than in the placebo group; absolute difference of 1 mcg/min* □ *Microalbuminurc at baseline → AER at 2 years was 49.7% (-14.5 to 77.9; p=0.1) lower in the treatment than in the placebo group; absolute difference of 34.2 mcg/min* ▪ Separate analysis done to compare actual mean AER at 2 yr visit (only included patients who attended final visit) (lisinopril n = 233; placebo n = 232) □ *Normoalbuminuric at baseline → treatment difference in mean AER was 0.23 mcg/min (p=0.6)* □ *Microalbuminuric at baseline → treatment difference in mean AER was 38.5 mcg/min (p=0.001)*
Authors' Conclusion	▪ Lisinopril slows progression of AER in a mixed population of normoalbuminuric and microalbuminuric normotensive T1DM patients ▪ Greatest effect seen in patients with baseline microalbuminuria (AER ≥ 20 mcg/min)
Comments	▪ Short term study; however, most likely long enough because average duration of diabetes was 13 years ▪ Different results (statistically significant or not) depending on whether ITT is used or including patients who attended final visit ▪ Variations in duration of diabetes and glycemic control → could be applied to a wide variety of patients (duration of diabetes ranged from 9-20 years and HgbA1c ranged from 5.6%-8.4%)

<table>
<tr><td colspan="2">Bilous R, Chaturvedi N, Sjølie A, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes (DIRECT-Renal). Ann Intern Med 2009;151:11-20.</td></tr>
<tr><td>Design</td><td>▪ Three double-blind, placebo-controlled, randomized, multicenter</td></tr>
<tr><td>Objective</td><td>▪ Investigate whether the ARB, candesartan, compared with placebo affects microalbuminuria incidence or rate of change in albuminuria in T1DM and T2DM</td></tr>
<tr><td>Population</td><td>▪ n = 5231 (pooled sample); followed for a median of 4.7 years
▪ Inclusion criteria:
□ DIRECT-Prevent 1: Patients with T1DM and no retinopathy, normoalbuminuria, normotensive
□ DIRECT-Protect 1: Patients with T1DM with evidence of retinopathy, normoalbuminuia, normotensive
□ DIRECT-Protect 2: Patients with T2DM with evidence of retinopathy, normoalbuminuria, normotensive or treated with an antihypertensive (other than a RAAS inhibitor)</td></tr>
<tr><td>Endpoints</td><td>▪ Primary (a priori-determined)
□ Development of microalbuminuria
▪ Secondary (a priori-determined)
□ Rate of change in UAE rate</td></tr>
<tr><td>Protocol</td><td>▪ One month run in with placebo tablets and made two consecutive timed overnight urine collections just before randomization visit
▪ Randomization stratified by hypertensive status in the DIRECT-Protect 2 only
▪ Groups
□ Candesartan 16 mg daily increasing to 32 mg daily after 1 month (n = 2613)
□ Placebo (n = 2618)
▪ UAE rate assessed at baseline and annually thereafter
▪ Lower limit of detection of albumin concentration was 20 mcg/L
▪ In patients who developed microalbuminuira (UAE rate ≥ 20 mcg/min) in 1 or both urine samples at any time to provide 2 more samples → if 3 or 4 of these 4 consecutive samples were positive = microalbuminuria
▪ Patients who were or became hypertensive (BP > 140/85 mmHg) but UAE rate remained normal could be initiated on any non-RAAS blocking antihypertensive agent</td></tr>
<tr><td>Results</td><td>▪ BP was lower in candesartan group than in placebo group by end of study (p<0.001)
▪ Number of patients who developed microalbuminuria did not differ between groups, regardless of previous antihypertensive therapy
<table>
<tr><th>Incidence of microalbuminuria</th><th>Candesartan</th><th>Placebo</th></tr>
<tr><td>T1DM (2 studies)</td><td>5%</td><td>5%</td></tr>
<tr><td>T2DM</td><td>12%</td><td>13%</td></tr>
</table>
▪ For the pooled study population, the unadjusted HR (candesartan vs placebo) was 0.95 (95% CI, 0.78 to 1.16; p =0.60)
▪ A significant reduction of 5.53% in UAE rate occurred in pooled study population; absolute reduction of 0.11 mcg/min</td></tr>
<tr><td>Authors' Conclusion</td><td>▪ Candesartan had no effect on incidence of microalbuminuria over 4.7 years in normoalbuminuric and normotensive patients with T1DM and normoalbuminuric patients with T2DM with or without treated HTN
▪ Adjusted rate of change in UAE rate was statistically significant; however, clinical significance uncertain
▪ Do not recommend use of candesartan or other RAAS blocking agents in primary prevention of diabetic nephropathy in patients with T1DM or T2DM and a low vascular burden</td></tr>
<tr><td>Comments</td><td>▪ Limited generalizability (>50% male and >95% Caucasian)
▪ High proportion of patients in placebo group received open-label RAAS inhibitors – did not change microalbuminuria outcomes
▪ High percent who withdrew consent (9.6%) – patients who withdrew more likely to have had progressive disease and higher event rates → lower event rate in remaining patients
▪ Different results in T2DM patients (compared to HOPE, BENEDICT, ADVANCE) → T2DM patients in DIRECT-Renal had a low burden of vascular damage; therefore, decreased vascular RAAS activity</td></tr>
</table>

Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes (RASS). *N Engl J Med* 2009;361:40-51.

Design

- Double-blind, placebo-controlled, randomized, multicenter

Objective

- Assess the effect of renin-angiotensin blockade with either an ACE-I or ARB on both renal and retinal morphological features in normotensive patients with T1DM and normoalbuminura

Population

- n = 285; followed for 5 years
- Exclusion criteria: hypertension (BP > 135/85 mmHg or receiving an antihypertensive), albumin excretion rate (AER) > 20 mcg/minute, pregnancy, failure to be adherent with placebo tablets during 2 week run-in period, GFR < 90 mL/min

Endpoints

- Primary
  - Change in fraction of glomerular volume occupied by mesangium (the mesangial fractional volume)
- Secondary
  - Changes in other glomerular, vascular, tubular, and interstitial variables and changes in the albumin excretion rate and GFR

Protocol

- Groups
  - Enalapril 10 mg daily
  - Losartan 50 mg daily
  - Placebo
  - During study, doses were doubled (received doubled doses for 2.9±0.9 years)
- BP, albumin excretion rate, and HgbA1c obtained quarterly; GFR assessed yearly
- Target BP < 130/80 mmHg
  - Additional antihypertensives were allowed to achieve target BP if hypertension persisted for 2 weeks
  - Use a medication that does not block renin-angiotensin system
- Microalbuminuria = mean of at least two of three consecutive values between 20 and 200 mcg/min
- Percutaneous biopsy preformed before randomization and 5 years later

Results

- Baseline characteristics similar between groups
- Three groups had similar HgbA1c levels (p=0.54) and insulin doses (p=0.29) during the 5 year period
- Will not report retinopathy results – see article for full results

Outcomes	Enalapril (n=94)	Losartan (n=96)	Placebo (n=95)
Mesangial fractional volume			
Mean at baseline	0.201±0.044	0.189±0.041	0.187±0.045
Mean change at 5 yr	0.005±0.050	0.026±0.054	0.016±0.048
Mean difference	-0.011	0.010	0 (reference)
p-value	0.16	0.17	
Albumin excretion rate (mcg/min)			
Mean at baseline	6.3±4.6	6.5±6.7	6.4±6.2
Mean at 5 yr	6.9±7.8	14±36.1	5.3±3.9
Mean difference	1	8	0 (reference)
p-value	0.74	0.007	
GFR (mL/min)			
Mean at baseline	129±20	131±18	126±22
Mean at 5 yr	123±20	121±21	120±22
Mean difference	0.4	-1.5	0 (reference)
p-value	0.88	0.54	

- Microalbuminuria 5-year cumulative incidence was higher with losartan than with placebo (17% vs 6%, p=0.01) but was not significantly higher with enalapril (4% vs 6%, p=0.96)

Authors' Conclusion

- Did not detect structural or functional benefits on nephropathy from the blockade of the RAAS with an ACE-I or ARB in normotensive patients with T1DM and normoalbuminuria

Comments	▪ Examined AER, GFR, and renal morphological features ▪ Interesting that more patients in the losartan group progressed to microalbuminuria ▪ Results similar to the Collaborative Study Group's captopril trial → benefit with captopril seen in patients with advanced nephropathy, but not seen in patients with SCr < 1.5 mg/dL

V. Summary

a. Glycemic control has been proven to be effective in preventing microvascular complications, including diabetic nephropathy

b. RAAS blockade has been shown to be effective in preventing or slowing progression of micro- or macroalbuminuria in T1DM and T2DM patients with hypertension and/or some evidence of micro- or macroabluminuria

c. RAAS blockade was shown to be effective in preventing nephropathy in T1DM patients with pre-existing microalbuminuria and T2DM patients with hypertension without nephropathy

d. RAAS blockade was not shown to be beneficial in preventing diabetic nephropathy in normotensive and normoalbuminuric T1DM or T2DM patients

Table 5. Summary of recommendations from trials: ACE-I or ARB for diabetic nephropathy?

T1DM or T2DM	HTN	Retinopathy	Diabetic nephropathy	CVD or CVD risk factors	ACE-I or ARB?
T1DM	+	+	+	-	YES
T2DM	-	-	+/-	+	YES*
T2DM	+	-	+	-	YES
T2DM	+	-	+**	-	YES
T2DM	+	-	+^	-	YES
T2DM	+	-	-	-	YES
T2DM	-	-	-/+	+	NO/YES
T1DM	-	-	-/+**	-	NO/YES
T1DM	-	-	-	-	NO
T1DM	-	+/-	-	-	NO
T2DM	-#	+	-	-	NO

* Combination therapy effective in reducing proteinuria, but overall worsens major renal outcomes

** Microalbuminuria ^ Macroalbuminuria # Normotensive or treated with a non-RAAS antihypertensive

VI. Clinical controversy [4]

a. Proteinuria as a surrogate outcome for CKD?
b. National Kidney Foundation (NFK)-KDOQI work group concluded
    i. There is insufficient evidence for acceptance of changes in proteinuria as a surrogate outcome for progression of early diabetic kidney disease
    ii. However, failure to reduce albuminuria does not eliminate a beneficial clinical effect of diabetic kidney disease from a potential intervention
    iii. To be considered efficacious, potential treatments for diabetic nephropathy must show benefits on albuminuria reduction, and also on clinical endpoints (eg. Stage 5 CKD, cardiovascular disease, death)
c. What about all the previous trials with endpoints for proteinuria?

VII. Recommendations

a. Achieve glycemic control (goal HgbA1c < 7%)
b. Would initiate RAAS blockade (ACE-I or ARB) in
    i. T1DM or T2DM patients with evidence of albuminuria with or without hypertension
    ii. T2DM patients without albuminuria with hypertension
c. Would not initiate RAAS blockade (ACE-I or ARB) in
    i. T1DM or T2DM normotensive patients without albuminuria

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