Guideline 1
Screening and diagnosis of DKD

1.1 All patients with diabetes should be screened annually
   Type 1 diabetes 5 years after diagnosis;(A)
   From diagnosis of type 2 diabetes. (B)

Screening should include:
   Urine Albumin-Creatinine ratio (ACR); (B)
   Serum creatinine and eGFR. (B)
1.2 Confirm elevated ACR in the absence of UTI with 2 additional tests over the next 3 to 6 months.

- Microalbuminuria: ACR 30 to 300 mg/g
- Macroalbuminuria: ACR >300 mg/g

Two of the three samples should fall within the micro or macroalbuminuric range to confirm classification.
Causes of ESRD in the U.S.

- Diabetes: 43%
- Hypertension: 19%
- Glomerulonephritis: 23%
- Cystic Kidney: 12%
- Other Causes: 3%
CKD in Diabetes

- 30 to 40% of Type 1 and Type 2 develop CKD

- Most of them have Diabetic Nephropathy (DKD)

- 1 in 5 (mostly Type 2) have Ischemic Nephropathy (Nephrosclerosis)
DKD (Diabetic Nephropathy)
DKD (Diabetic nephropathy)
Kimmelstiel-Wilson's "Lesion"
NKF-KDOQI guidelines

(Kidney Disease Outcomes Quality Initiatives)

KIDNEY.ORG/PROFESSIONALS/KDOKI
Albuminuria

Normal < 30 mg/24h
Microalbuminuria 30 to 300 mg
Macroalbuminuria > 300 mg

Usual 24 h urine creatinine = 1 g

Albumin-Creatinine ratio (ACR)
Normal < 30 mg/g
Microalbuminuria 30 mg/g
Macroalbuminuria > 300 mg/g
Guideline 1
Screening and diagnosis of DKD

1.3 CKD should be attributable to diabetes if:

Macroalbuminuria is present ($\text{ACR} > 300 \text{ mg/g}$); (B) or

Microalbuminuria is present and:

- The patient has Retinopathy
- The patient has had Type 1 Diabetes for > 10 years (A)
Guideline 1
Screening and diagnosis of DKD

1.4 Consider other causes of CKD (B)

- Absence of Retinopathy
- Rapid loss of GFR
- Rapid increase in Proteinuria
- Refractory Hypertension
- Active Urine Sediment
- Suspicion of systemic Disease
- >30% GFR reduction after therapy with ACEI/ARB
DKD, clinical features

- Retinopathy, always
- Microalbuminuria and then Macroalbuminuria.

In CKD 3 and 4, always with macroproteinuria, often in the nephrotic range.
20% of the patients with diabetes and CKD have Ischemic Nephropathy (Arteriolar nephrosclerosis)
Ischemic Nephropathy, clinical features

Arterial HTN, always.

Microalbuminuria.

In CKD stages 3 and 4, they continue to have Microalbuminuria (ACR<300 mg/g).
Case # 1
Normotensive Normoalbuminuric Type 1 Diabetic

- 32 y.o. male with T1DM since age 22, referred for primary prevention of Diabetic Nephropathy. Very compliant. On an insulin pump
- BP: 106/68
  A1c: 6.6%
- S. Creatinine: 0.9 mg/dL
- Urine Albumin/Creatinine: 12 mcg/g. (normal<30)
- Would ACE-I Rx would help preventing Diabetic Nephropathy?
- Your recommendation?
Renal and Retinal Effects of Losartan and Enalapril in T1 Diabetics

M. Mauer MD, NEJM July 2009

5 year Followup, with Renal Biopsies

Normotensive Normoalbuminuric

- Treatment:
  - Placebo,
  - Losartan, 100 mg/d
  - Enalapril, 20 mg/d

- Conclusions:
  - Early blockade of the RAS did not slow progression of the nephropathy in Type 1 diabetics, but it did slow progression of the retinopathy
Guideline 6: Management of Albuminuria in Normotensive patients with diabetes

6.1. We recommend not using ACE-Is or ARBs for the primary prevention of DKD in normotensive, normoalbuminuric patients (1A)
DKD
Primary Prevention

- Optimal Glycemic control
A1c and Microvascular Complications (DCCT)
Case # 2
Normotensive Microalbuminuric Type 1 Diabetic

- 28 y.o. woman with T1DM since age 23, with Microalbuminuria.
  Compliant. Insulin pump

- BP: 95/60
- A1c: 6.4%.
- S. Creatinine: 0.6 mg/dL
- Urine Albumin/Creatinine : 40 mcg/g
  Repeat studies: 38 and 36 mcg/g, 6 and 12 m. later

- Referred regarding possible ACE-I therapy.

- Your recommendation: Treat?
  Observe?
Case # 2: 12 years later, 2 children
Normotensive Microalbuminuric Type 1 Diabetic

- 40 y.o. woman with T1DM since age 23.
  Insulin pump
- BP: 102/60
- A1c: 6.7%.
- S. Creatinine: 0.7 mg/dL
- ACR: 33 to 52 mcg/g

- Never treated with ACE-Is.
Guideline 6: Management of Albuminuria in Normotensive patients with diabetes

6.2. We suggest using an ACE-I or an ARB in patients with diabetes and an ACR>30mg/g who are at high risk of DKD or its progression (2C)

- High risk patients:
  - Macroalbuminuria
  - Poor Diabetes control
  - Rising Blood Pressure
  - Retinopathy
  - Family Hx of DKD, Hypertension
## ACE-I on Diabetic Nephropathy

**Edmund J. Lewis NEJM 1993;1456-1642**

### Captopril v. Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Captopril (N = 207)</th>
<th>Placebo (N = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35±7</td>
<td>34±8</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>Black</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>22±7</td>
<td>22±7</td>
</tr>
<tr>
<td>Hypertension (%)†</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Antihypertensive therapy (%)</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)§</td>
<td>137±19</td>
<td>140±20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)§</td>
<td>85±11</td>
<td>86±12</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)§</td>
<td>102±12</td>
<td>104±13</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)¶</td>
<td>1.3±0.4</td>
<td>1.3±0.4</td>
</tr>
<tr>
<td>24-Hour urinary protein excretion (mg/day)</td>
<td>2500±2500</td>
<td>3000±2600</td>
</tr>
<tr>
<td>24-Hour urinary urea nitrogen (g/day)¶</td>
<td>11±5</td>
<td>10±5</td>
</tr>
<tr>
<td>24-Hour creatinine clearance (ml/min)</td>
<td>84±46</td>
<td>79±35</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>11.8±2.8</td>
<td>11.6±2.8</td>
</tr>
</tbody>
</table>

### A: Doubling S. Creatinine

#### B: Death, Dialysis, Transplant

![Graph A](chartA.png)

- Percentage who doubled baseline creatinine
- P = 0.007

![Graph B](chartB.png)

- Percentage who died or needed dialysis or transplant
- P = 0.006
Effects of Losartan in Renal and CV outcomes in patients with type 2 Diabetes and Nephropathy

Barry Brenner MD et al, NEJM, Sept 2001
N = 250.
Combination Treatment of ARBs and ACEIs in Nondiabetic Nephropathy

*Time to doubling of SCr or ESRD.
Dual RAS Blockade

Based on the ONTARGET Trial outcomes
( Ongoing Telmisartan alone and in combination with Ramipril Global Endpoint Trial)

and the ALTITUDE trial outcomes
(Aleskiren and ACE-I)

Dual blockade cannot be recommended
HTN and DKD

- Type 1 diabetes patients with DKD
- BP untreated for 2 years
- After 2 years of observation the BP was treated with conventional meds, BBs, Apresoline and Furosemide.
  
  (No CCBs/ACE-Is/ARBs)

Parving H H et al. BMJ, volume 294, June 6 1987
Proteinuria Is a Risk factor in T2DM

Survival (all-cause mortality)

Follow-Up (y)

Normoalbuminuria (n = 191)
Microalbuminuria (n = 86)
Macroalbuminuria (n = 51)

$P < 0.01$ normo- vs microalbuminuria; $P < 0.001$ normo- vs macroalbuminuria; $P < 0.05$ micro- vs macroalbuminuria.

Ibersartan Diabetic Nephropathy Trial
Proteinuria and Renal Outcome
Ibersartan Diabetic Nephropathy Trial
Average Proteinuria Reduction
Irbesartan Diabetic Nephropathy Trial
Reduction of Proteinuria and Renal Outcome
Reduction of Proteinuria

BP control

RAAS Blockade

ACE-Is
ARBs
Direct Renin Inhibitors (Aliskerin)
Spironolactone, Eplerenone
DKD, Rx with Spironolactone

- Spironolactone reduced the proteinuria in DKD patients treated with ACE-Is or ARBs
Additive Effect of ACE Inhibition and ARB Blockade in Patients With Diabetic Nephropathy

**Graphs:**
- **Albuminuria (mg/24 h):**
  - Placebo
  - Benazepril
  - Valsartan
  - Dual blockade

- **Blood Pressure (mm Hg):**
  - Placebo
  - Benazepril
  - Valsartan
  - Dual blockade

**Legend:**
- Systolic
- Diastolic

**Note:**
ARB = angiotensin receptor blocker.
Reduction of Proteinuria

BP control

RAAS Blockade
ACE-Is
ARBs
Direct Renin Inhibitors (Aliskerin)
Spironolactone, Eplerenone

Non DHP CCB
Verapamil
Diltiazem

Low Salt Diet
Diuretics
Proteinuria Reduction in CKD

Goals:

- < 500 mg/d (Protein-creatinine ratio < 0.5), or
- 50% reduction over baseline

Protein-creatinine ratio (mg/mg), urine spot sample.

- 0.2 < 150 mg/24h
- 1.0 = 1 gm
- 3.5 = 3.5 gm (nephrotic range proteinuria)
Case # 3
Type 2 Diabetic with HTN, CKD 3, Microalbuminuria

- 67 y.o with T2DM for 16 years, on insulin therapy (Glargine and short acting analog). A1c 8%.
- ACR: 180 mg/g
- Serum creatinine 1.8 mg/dL, eGFR 36 ml/m.
- BP: 138/80 (Amlodipine, Metoprolol, Furosemide)
- ARB added for renal protection had to be held twice b/o substantial hyperkalemia. Low K diet, and ARB dose reduction failed

Options:

a) Switch to ACE-I
b) Chronic Kayexalate
c) Combined very low doses of ACE-I/ARB
d) No ACE-I, no ARB
UK Prospective Diabetes Study

- A1c of 7% v. 7.9% reduced the risk of:
  - any diabetes endpoint: 12%
  - microvascular endpoints: 25%
  - M.I.: 16%
Guideline 2:
Management of Hyperglycemia and General Diabetes Care in CKD

- **2.1** We recommend a target A1c of 7% or lower, to prevent or delay progression of the microvascular complications including DKD. (1A)

- **2.2** We recommend not treating to an A1c target of <7% in patients at risk of hypoglycemia. (1B)

- **2.3** We suggest that target A1c be extended above 7% in individuals with comorbidities or limited life expectancy and risk of hypoglycemia (2C)
DKD; Secondary Prevention

- Blood Pressure Control
- Glycemic Control
- Treat with ACE-Is, ARBs...
- Treat Proteinuria
- Treat Hyperlipidemia
UK Prospective Diabetes Study

- A1c of 7% v. 7.9% reduced the risk of:
  - any diabetes endpoint 12%
  - microvascular endpoints 25%
  - M.I. 16%

- Tight BP control 144/82 v. 154/87 reduced the risk of:
  - any diabetes endpoint 24%
  - microvascular endpoints 37%
  - stroke 44%

- “THE BENEFIT FROM TIGHT GLYCEMIC CONTROL IS LOWER THAN THE BENEFIT FROM INADEQUATE BLOOD PRESSURE CONTROL...”
Don’t worry about the glucometer get the BP under control
DKD; Secondary Prevention

- Blood Pressure Control
- Glycemic Control
- Treat with ACE-Is, ARBs...
- Reduce Proteinuria
- Treat Hyperlipidemia
ACE-Is v. Conventional Therapy in Type 1 Diabetes

Baseline creatinine ≥1.5 mg/dL

Patients With Doubling of SCr (%)

Follow-Up (y)

Placebo (n = 49)  
P < 0.001

Captopril (n = 53)

Guideline 3: Management of Hypertension in Diabetes and CKD

- 3.1 Patients with diabetes and CKD 1-4, should be treated with an ACE-I or ARB usually in combination with a diuretic. (A)

- 3.2 Target BP should be 130/80 mm Hg. (B)
Control of Arterial Hypertension

ACCORD Hypertension subgroup

Patients treated to lower the systolic blood pressure to 120 mm/Hg did no better than those whose systolic pressure was 140.
DKD; Secondary Prevention

- Blood Pressure Control
- Glycemic Control
- Treat with ACE-Is, ARBs...
- Treat Proteinuria
- Treat Hyperlipidemia
Proteinuric CKD

- RAS inhibitors have preferential benefits in patients with Proteinuric Kidney Disease

- Protein excretion > 500 mg/d identifies those who will benefit most from antihypertensive therapy with RAS inhibitors
DKD; Secondary Prevention

- Blood Pressure Control
- Glycemic Control
- Treat with ACE-Is, ARBs...
- Treat Proteinuria
- Treat Hyperlipidemia
Guideline 4: Dyslipidemia in Diabetes and CKD

4.1 We recommend LDL-C lowering medicines (statins) to reduce the risk of CV disease in patients with CKD including in patients with Diabetes including those who received a renal transplant. (1B)

4.2 We recommend not initiating statin therapy in patients on dialysis. (1B)
Non Proteinuric CKD

- There is no preferential benefit of RAS inhibitors in patients with CKD and proteinuria < 500mg/d

- No “Renal Protection” of RAS inhibitors in patients with minimal to modest proteinuria
DKD, cumulative death rate
WHO LET THE AMERICANS ON BOARD?
Watch out!

Diabetes can appear right under your nose