Tight Blood Glucose and Blood Pressure (BP) Control for Prevention and Management of Diabetic Nephropathy

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Presentation Outline

- Impact of diabetic nephropathy
- Screening, assessment, and referral guidelines
- Strategies for reducing development and slowing progression
- Evidence supporting tight blood glucose and BP control as effective strategies
  - Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC)
  - Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) study
- Roundtable discussion
Diabetes is the Most Common Primary Diagnosis in Patients With Kidney Failure

Patient Primary Diagnosis

- Diabetes: 45%
- Glomerulonephritis: 20%
- Hypertension: 30%
- Other: 5%

Incidence Rates: Major Causes of End-Stage Renal Disease (ESRD) in the US*

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate per Million Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>'81</td>
<td>160</td>
</tr>
<tr>
<td>'83</td>
<td>140</td>
</tr>
<tr>
<td>'85</td>
<td>120</td>
</tr>
<tr>
<td>'87</td>
<td>100</td>
</tr>
<tr>
<td>'89</td>
<td>80</td>
</tr>
<tr>
<td>'91</td>
<td>60</td>
</tr>
<tr>
<td>'93</td>
<td>40</td>
</tr>
<tr>
<td>'95</td>
<td>20</td>
</tr>
<tr>
<td>'97</td>
<td>0</td>
</tr>
<tr>
<td>'99</td>
<td>0</td>
</tr>
<tr>
<td>'01</td>
<td>0</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race.

Natural History of Diabetic Nephropathy

*GFR = glomerular filtration rate.

Molitch ME. Diabetes Care. 1994;17:756-760.
### Screening for Nephropathy in Primary Care Practices

<table>
<thead>
<tr>
<th>Microalbuminuria</th>
<th>Clinical albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random urine albumin/creatinine ratio (µg/mg or mg/g)</td>
<td>30-299</td>
</tr>
<tr>
<td>24-hr urine albumin (mg)</td>
<td>30-299</td>
</tr>
</tbody>
</table>

- **Annual screening**
  - Begin after 5 yrs duration for type 1 diabetes patients
  - Begin at time of diagnosis for type 2 diabetes patients
- **In absence of infection, strenuous exercise, or hematuria**
- **Confirm elevated value before starting drug therapy**
  - 2 of 3 tests positive over 3-6 months

Albuminuria and Retinopathy Relative to GFR in Type 2 Diabetes Patients

The Third National Health and Nutrition Examination Survey (NHANES III)

<table>
<thead>
<tr>
<th></th>
<th>GFR ≥60*</th>
<th>GFR &lt;60*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria</td>
<td>32%</td>
<td>45%</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>5%</td>
<td>19%</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>15%</td>
<td>28%</td>
</tr>
<tr>
<td>No retinopathy or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuminuria</td>
<td></td>
<td>30%</td>
</tr>
</tbody>
</table>

*mL/min/1.73 m².

Assessment of Kidney Function

- Urine albumin excretion (UAE) annually
- Serum creatinine annually
- Estimate GFR from serum creatinine
- Calculator for estimated GFR
  - Google: type MDRD into search space

ADA. *Diabetes Care*. 2005;28(suppl 1):S4-S33.
Institute for Clinical Systems Improvement (ICSI). Available at:
Diabetic Nephropathy Referral Guidelines

• Consider referral to physician experienced in the care of diabetic renal disease for any of the following:
  – GFR <60 mL/min/1.73 m²
  – Hyperkalemia or hypertension that are difficult to manage
  – Rapidly increasing UAE
  – Rapidly decreasing GFR
  – Levels of urinary albumin or GFR inappropriate for diabetes duration

• When GFR <30 mL/min/1.73 m², nephrology consult is recommended

ADA. Diabetes Care. 2005;28(suppl 1):S4-S33.
# Stages in Chronic Kidney Disease Progression Are Defined by GFR

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

Annual Transition Rates in Type 2 Diabetes Patients
UK Prospective Diabetes Study 64 (UKPDS 64)

- No Nephropathy: 1.4%
- Microalbuminuria: 2.0% → 3.0%
- Albuminuria: 2.8% → 4.6%
- Elevated Creatinine or Renal Replacement Rx: 2.3% → 19.2%

Strategies to Reduce the Development and Progression of Diabetic Nephropathy

• Near normoglycemia
  – Prevents development and retards progression

• BP control
  – Goal of <130/80 mm Hg

• Use of agents active in the renin-angiotensin system
  – Angiotensin converting enzyme (ACE) inhibitors
  – Angiotensin II receptor blockers (ARBs)

• Low protein intake
Epidemiology of Diabetes Interventions and Complications (EDIC) Study
The EDIC Study: Nephropathy Findings


- Study objective: Determine long-term effects of intensive vs conventional diabetes treatment on kidney function.

- Observational follow-up of the DCCT*

*More information on the DCCT is provided in Module 1: Hyperglycemia and DMC.*
EDIC Background: DCCT Objective and Study Design

• Objective: Determine whether maintaining blood glucose levels near normal range decreases severity and frequency of DMC in type 1 diabetes patients

• Study design
  – N = 1,441 type 1 diabetes patients
  – Randomized, controlled trial
  – Mean duration: 6.5 yrs
  – Primary and secondary prevention cohorts
  – Conventional and intensive therapy regimens
  – Regular assessment of DMC

EDIC Background: DCCT Nephropathy Outcomes

Primary Prevention

- Microalbuminuria ≥40 mg/24 h: Conventional, P < 0.04
- Albuminuria ≥3000 mg/24 h: Conventional, P = 0.4

Secondary Intervention

- Microalbuminuria ≥40 mg/24 h: Intensive, P = 0.01
- Albuminuria ≥3000 mg/24 h: Intensive, P = 0.001

Median A1C
- Conventional: 9.1%
- Intensive: 7.3%

EDIC Study Design

• 96% (1,375) of DCCT patients agreed to participate

• Encouraged intensive diabetes management (IDM)
  – Conventional treatment group received IDM instruction
  – Goal: near normal A1C levels

• Routine diabetes and other medical care through primary care providers, only some of whom were DCCT physicians/nurses

• Annual assessments of retinopathy, nephropathy, neuropathy, and macrovascular disease
EDIC Study Design

• Major nephropathic outcomes
  – Microalbuminurina (28 µg/min ≤ AER* < 208 µg/min)
  – Albuminurina (AER ≥ 208 µg/min)
  – Hypertension (BP ≥ 140/90 mm Hg OR treatment with antihypertensive medication)
  – Doubling of baseline (obtained during DCCT) serum creatinine concentration
  – Serum creatinine concentration ≥ 2.0 mg/dL
  – Dialysis and/or renal transplantation

*AER = albumin excretion rate.

EDIC Study Results—Nephropathy: A1C Levels

At DCCT closeout, cumulative incidences of microalbuminuria were 22% and 34% in the intensive and conventional cohorts, respectively.

At DCCT closeout, cumulative incidences of albuminuria were 3.8% and 6.3% in intensive and conventional cohorts, respectively.
EDIC Study Results–Nephropathy: Other Kidney Outcomes

• Number of participants reaching a serum creatinine concentration $\geq 2.0$ mg/dL was significantly lower in intensive group ($P = 0.004$)

• No significant difference between groups for doubling of baseline serum creatinine concentration or dialysis and/or renal transplantation

EDIC Study Results–Nephropathy: Hypertension

- Hypertension defined as BP >140/90 mm Hg
- More participants from former conventional group developed hypertension
- Lower systolic and mean arterial BP among former intensive group participants ($P = 0.003$ and $P = 0.02$, respectively)

Clinical Translation

- Better glycemic control delays the onset of albuminuria and its progression
  - Early data suggest prevention/delay in progression to fall in GFR

- The earlier the onset of improved glycemic control, the better

- Even with relaxation of control, a prolonged period of near-normoglycemia has long-lasting benefits, including improved BP
**Relation Between Achieved BP and GFR**

- **MAP (mm Hg)**
  - 95, 98, 101, 104, 107, 110, 113, 116, 119

- **GFR (mL/min/year)**
  - -14, -12, -10, -8, -6, -4, -2, 0

- **r = 0.69; P < 0.05**

- **Untreated Hypertension**
  - 130/80
  - 140/90

- **Data Sources**
  - Parving et al, 1989
  - Viberti et al, 1993
  - Klahr et al, 1993
  - Hebert et al, 1994
  - Lebovitz et al, 1994
  - Moschino et al, 1996
  - Bakris et al, 1996
  - Bakris et al, 1997
  - GISEN Group, 1997

- **MAP formula**
  \[ \text{MAP} = \frac{\text{SBP} + 2 \times \text{DBP}}{3} \]

- **References**
Changes in Glomular Structure With Increased Glomerular Pressure

Initial Hypothesis of Brenner et al

Increased Systemic Blood Pressure

Increased angiotensin II action causes relaxation of efferent arteriole and reduction in intraglomerular pressure

Decrease in angiotensin II action causes relaxation of efferent arteriole and reduction in intraglomerular pressure
Renin-angiotensin System

Angiotensinogen (liver) \rightarrow \text{Renin (juxtaglomerular)} \rightarrow \text{Angiotensin I} \rightarrow \text{Angiotensin II} \rightarrow \text{ATR1}

\text{ACEI} \rightarrow \text{ACE} \rightarrow \text{ARB}

\text{ATR1} = \text{Type 1 angiotensin II receptor}

\text{Vasoconstriction} \rightarrow \text{Volume retention}

RENAAL Study


- Study objective: assess the role of an angiotensin II receptor antagonist in patients with type 2 diabetes and nephropathy
RENAAL Study Design

• Prospective, multicenter trial
  – 1,513 hypertensive patients with type 2 diabetes
  – Inclusion criteria:
    • Age: 31-70 yrs
    • Urinary albumin/creatinine >300 mg/g
    • Serum creatinine 1.3-3.0
  – Randomized to placebo or 50 mg losartan, increased to 100 mg if BP not controlled after 4 wks
  – BP controlled (<140/90) with other non-ACEI and non-ARB

• Endpoints: doubling serum creatinine, ESRD, death

• Mean follow-up duration was 3.4 yrs

# RENAAL Study: BP Comparison

<table>
<thead>
<tr>
<th></th>
<th>Losartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>152/82</td>
<td>153/82</td>
</tr>
<tr>
<td>Year 1</td>
<td>146/78</td>
<td>150/80</td>
</tr>
<tr>
<td>Year 2</td>
<td>143/77</td>
<td>144/77</td>
</tr>
<tr>
<td>Year 3</td>
<td>140/74</td>
<td>142/74</td>
</tr>
</tbody>
</table>

RENAAL Study Patients Reaching the Primary Composite Endpoint*

Risk reduction = 16%

$P = 0.02$

Placebo†
(n = 762)

Losartan†
(n = 751)

*Doubling of SCr, ESRD, death.
†In combination with open-label diuretic, calcium channel blocker, β-blocker, α-blocker, and/or centrally acting agent.

### RENAAL Study: Primary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Losartan (%)</th>
<th>Placebo (%)</th>
<th>RR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint</td>
<td>43.5</td>
<td>47.1</td>
<td>16%</td>
<td>≤0.02</td>
</tr>
<tr>
<td>Doubling of creatinine</td>
<td>21.6</td>
<td>26.0</td>
<td>25%</td>
<td>≤0.02</td>
</tr>
<tr>
<td>ESRD</td>
<td>19.6</td>
<td>25.5</td>
<td>28%</td>
<td>≤0.02</td>
</tr>
<tr>
<td>Death</td>
<td>21.0</td>
<td>20.3</td>
<td>-2%</td>
<td></td>
</tr>
<tr>
<td>Rate of change of Ccr (mL/min/1.73 m^2/yr)</td>
<td>-4.4*</td>
<td>-5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary albumin/creatinine</td>
<td>-35%</td>
<td>0</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinue for high K+</td>
<td>1.1%</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>140/74</td>
<td>142/74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR = Risk reduction

*15% reduction.

Average Number of Antihypertensive Agents per Patient to Achieve Target Systolic BP (SBP)

TRIAL (SBP Achieved)

- ALLHAT (138 mm Hg)
- IDNT (138 mm Hg)
- RENAAL (141 mm Hg)
- UKPDS (144 mm Hg)
- ABCD (132 mm Hg)
- MDRD (132 mm Hg)
- HOT (138 mm Hg)
- AASK (128 mm Hg)

Number of Antihypertensive Medications

Systematic Review: Renal Outcomes of ACE Inhibitors and ARBs in Diabetic Nephropathy

- **ACE Inhibitors** compared with placebo: 9 trials with 1,907 patients
  - ESRD: RR 0.64 (0.40-1.03)
  - Doubling of creatinine: RR 0.60 (0.34-1.05)
  - Progression micro- to macroalbuminuria: RR 0.45 (0.28-0.71)

- **ARBs** compared with placebo: 3 trials with 3,251 patients
  - ESRD: RR 0.78 (0.67-0.91)
  - Doubling of creatinine: RR 0.79 (0.67-0.93)
  - Progression micro- to macroalbuminuria: RR 0.49 (0.32-0.75)
  - No data in type 1 diabetes

Clinical Translation

• BP goal of 130/80 is important
• Agents that block the renin-angiotensin-aldosterone system can decrease the progression of diabetic nephropathy and are the preferred initial agents
• Usually 2 or more drugs are necessary to control BP as nephropathy progresses
Summary

• DCCT/EDIC demonstrated the benefits of glycemic control to near-normal glucose levels
  – Delays onset and progression of albuminuria, fall in GFR
  – Prolonged period of glycemic control has long-lasting benefits
• BP control is also important in improving kidney function
  – Several agents may be required to achieve target BP
  – RENAAL supports the use of agents that target the renin-angiotensin-aldosterone system as first-line agents