Structure and Function of the Kidney

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Nephrology & Hypertension
Board Certified Clinical Pharmacotherapist
Division of Nephrology & Hypertension
Laboratory Tests of Renal Function
Role of Biochemical Testing

• Role of biochemistry:
  • Rarely establishes the cause
  • Screening for damage
  • Monitoring progression

• Presentation of patients: -
  • Symptom or physical sign
  • Systemic disease with known renal component

• Effective management of renal disease depends upon establishing a definitive diagnosis:
  • Detailed clinical history
  • Diagnostic imaging and biopsy
Renal Function Tests - Urine volumes

- 750 - 2000 mL/24 h typical in health
- oliguria < 400
- anuria < 100
- polyuria > 3000
Biochemical Tests of Renal Function

- Measurement or estimate of GFR
- Urinalysis
Plasma creatinine

- 0.6-1.2 mg/dl (50 - 140 umol/L)

- Increases in concentration as GFR decreases

- *NOT proportional to renal damage*
Relationship between Serum Creatinine Concentration and Creatinine Clearance

![Graph showing the relationship between serum creatinine concentration and creatinine clearance. The graph includes a line indicating the relationship and horizontal lines representing different ranges or limits, possibly indicating upper limit of normal (ULN).]
Plasma Creatinine

Change within an individual patient is usually more important than the absolute value

[pCreat]

0 mL/min 140 mL/min

GFR
Plasma Creatinine Concentration

Difficulties: -

• Concentration depends on balance between input and output
• Production determined by muscle mass which is related to age, sex and weight
• Concentration inversely related to GFR
  – Small changes in creatinine within and around the reference limits = large changes in GFR
• Reference limits can be misleading
Effect of Muscle Mass on Serum Creatinine

- Normal Muscle Mass
- Increased Muscle Mass
- Reduced Muscle Mass

Creatinine Input
 Plasma Pool Content
 Output Kidney

Normal Kidneys
Diseased Kidneys
Normal Kidneys
Diseased Kidneys
24-hour Collections

Time consuming inconvenient and accurate?
Plasma Creatinine in Chronic Renal Disease

- Plot of reciprocal of plasma creatinine concentration predicts when intervention is required in end stage renal failure
Early Treatment Makes a Difference

![Graph showing the impact of different treatments on GFR over time. Early Treatment delays the onset of Kidney Failure compared to No Treatment or Current Treatment.]
Blood Urea Nitrogen (BUN)

- Useful test but must be interpreted with great care
- Always consider input, output and patient’s fluid volume
- Quick, simple measurement
- Wide reference range 10-20 mg/dl (3-8 mmol/L)
- Sensitive but non-specific index of illness

- GI bleed
- Trauma
- Renal hypoperfusion
  - Decreased RBF
  - Decreased ECFV

- Acute renal impairment
- Chronic renal disease
- Post-renal obstruction
  - Calculus
  - Tumour
Estimated Ccr (mL/min)

- \((140 - \text{age})(\text{body weight in kg})\)
  \[72 \times \text{serum creatinine in mg/dL}\]

- Example:
- For man, age 70 years, weight 58 kg, serum creatinine 1.3 mg/dL, estimated Ccr = 43 mL/min;
- For woman with similar values, estimated rate would be 37 mL/min.
Estimated Ccr (mL/min)

- Simplified 4-variable MDRD study formula
  \[ GFR = 186.3 \times (SCR)^{-1.154} \times (\text{age in years})^{-0.203} \times 1.212 \times 0.742 \]  
  (if patient is black) x 0.742 (if female)

- Early statistical analysis shows very promising results. May represent the most accurate choice of this group.

- This may be especially true in chronic kidney disease.
Scr Does Not Accurately Reflect Kidney Function

<table>
<thead>
<tr>
<th></th>
<th>70-Year-Old, 60-kg White Woman</th>
<th>25-Year-Old, 70-kg Black Man</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scr</td>
<td>1.2 mg/dL</td>
<td>1.2 mg/dL</td>
</tr>
<tr>
<td>CrCl as estimated by Cockcroft-Gault formula</td>
<td>41.3 mL/min</td>
<td>93.2 mL/min</td>
</tr>
<tr>
<td>GFR as estimated by MDRD equation</td>
<td>47.2 mL/min/1.73 m²</td>
<td>95.0 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

CrCl=creatinine clearance.
Relationship Between SCr and Drugs

- Tubular secretion of creatinine:
  - Cimetidine (Tagamet)
  - Trimethoprim (SMZ/TMP)

A rise in serum creatinine concentration and a decline in the calculated creatinine clearance
Nephrotoxicity

- The majority of drugs commonly used in clinical practice have a low incidence of renal toxicity

- The exact frequency of nephrotoxicity is difficult to determine

- Discrepancies between animal and clinical studies

- Lack of uniformity in defining the criteria for renal dysfunction
Cystatin C

- Cystatin C is a 13 KD protein produced by all cells at a constant rate
- Freely filtered
- Re-absorbed and catabolized by the kidney and does not appear in the urine
Diagnostic Performance Of A Cystatin C-based GFR Prediction Equation

Percent error

Age (years)
Diagnostic Performance Of A Creatinine-based GFR Prediction Equation (MDRD)
Urinalysis

• Fresh sample = Valid sample.

• Appearance: -
  – Blood
  – Color (hemoglobin, myoglobin,)
  – Turbidity (infection, nephrotic syndrome)

• Specific gravity: -
  – sticks measure ionic species only (not glucose)

• pH: -
  – Normal = acidic, except after meal
Normal Urine Colors
Abnormal Urine Colors
Turbid Urine
Urinalysis

• Urine sediments
  – Microscopic examination of sediment from freshly passed urine.
    • Looking for cells, casts (proteins), fat droplets
    • Red Cell casts - hematuria - glomerular disease
    • White cell cast + polymorphs + bacteriuria = pylonephrites
    • Lower UTI polymorphs no casts
    • Acute glomerulnephritis = hematuria, cells, casts
    • Chronic glomerulonephritis = less sediment
Urine Microscopy:

• Cells, Casts and Crystals.
• Casts are formed within nephron.
• Casts suggest kidney pathology.
• Casts can be made up of Protein, lipid, cells or mixed.
• Crystals suggest high concentration or altered solubility.
RBC in Urine:
WBC in Urine:
RBC Casts:
Epithelial Casts in Urine:
WBC Cast Urine:
Urine Oxalate Crystals:
Urinalysis

Eosinophiluria: Acute allergic interstitial nephritis, atheroembolism

Crystalluria: Acyclovir, sulfonamides, methotrexate, ethylene glycol toxicity, radiocontrast agents

Granular casts: ATN, glomerulonephritis, interstitial nephritis

RBC casts: Glomerulonephritis, malignant HTN

WBC casts: Acute interstitial nephritis, pyelonephritis
Complete Blood Count

- Leukocytosis: Common in ARF
- Leukopenia and thrombocytopenia: SLE or TTP
- Anemia and rouleaux formation: multiple myeloma
<table>
<thead>
<tr>
<th>Blood Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine phosphokinase (CPK) elevations</td>
</tr>
<tr>
<td>Elevations in liver transaminases</td>
</tr>
<tr>
<td>Hypocalcemia (moderate)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Urine specific gravity</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg H₂O)</td>
</tr>
<tr>
<td>Urine sodium (mEq/L)</td>
</tr>
<tr>
<td>Plasma BUN/creatinine ratio</td>
</tr>
<tr>
<td>Urine/plasma creatinine ratio</td>
</tr>
</tbody>
</table>
FeNa

- Calculation of fractional excretion of sodium (FeNa)
  - FeNa = (urine Na/plasma Na)/(urine creatinine/plasma creatinine)

- FeNa <1 % = prerenal ARF

- FeNa >1% = ATN
Lab interpretation

• Remember, we are clinicians and the lab values must be interpreted within clinical context

• So, on to clinical context…
Urinalysis

• Glucose
  – Increased blood glucose
  – Low renal threshold or other tubular disorders

• Proteinuria
  – Normal < 200 mg/24h. Urine sticks = >300mg/L
  – Causes: -
    • overflow (raised plasma Low MW Proteins, myoglobin)
    • glomerular leak
    • protein renal origin
Proteinuria

- Proteinuria
  - Urine protein excretion > 150mg/day
  - About 15-20 mg of the normal urine protein is albumin

- Microalbuminuria
  - Urine [albumin] > 30mg/day but not detectable by urine dipstick

- Nephrotic syndrome
  - Urine protein excretion > 3.5g/day (with hypoalbuminaemia, oedema and hyperlipidaemia)
## Defining Proteinuria

<table>
<thead>
<tr>
<th>Degree of Proteinuria</th>
<th>24 Hour Urine</th>
<th>Urine Dipstick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;30 mg albumin/day</td>
<td>None</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30 – 300 mg/day</td>
<td>None</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>300 – 3500 mg/day</td>
<td>&gt;15 mg/dl (trace)</td>
</tr>
<tr>
<td>Nephrotic Range</td>
<td>&gt;3.5 g /day</td>
<td>&gt;300 mg/dl (3+)</td>
</tr>
</tbody>
</table>
Microalbuminuria

- **Timed Urine (24 hour urine)**  
  (30 – 300 mg/day  
  or 20-200 ug/min)

- **Urine albumin/creatinine ratio** (>30 ug/mg creatinine)

- **Spot microalbumin tests** (detects >2 ug/ml)
<table>
<thead>
<tr>
<th>Level</th>
<th>Concentration (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trace</td>
<td>15</td>
</tr>
<tr>
<td>1+</td>
<td>30</td>
</tr>
<tr>
<td>2+</td>
<td>100</td>
</tr>
<tr>
<td>3+</td>
<td>300</td>
</tr>
<tr>
<td>4+</td>
<td>2000</td>
</tr>
</tbody>
</table>
# Progression of Chronic Renal Disease

<table>
<thead>
<tr>
<th>Creatinine clearance $mL/min$</th>
<th>Plasma change</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 - 120</td>
<td>none</td>
</tr>
<tr>
<td>30 - 60</td>
<td>Increased creatinine,</td>
</tr>
<tr>
<td></td>
<td>Increased urea</td>
</tr>
<tr>
<td>20 - 30</td>
<td>Increased potassium,</td>
</tr>
<tr>
<td></td>
<td>Decreased bicarbonate</td>
</tr>
<tr>
<td>10 - 20</td>
<td>Increased phosphate,</td>
</tr>
<tr>
<td></td>
<td>Increased uric acid</td>
</tr>
</tbody>
</table>
# Pre-renal vs Renal

<table>
<thead>
<tr>
<th>Inciting factors</th>
<th>Prerenal azotemia</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low volume</td>
<td></td>
<td>Toxins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>medication</td>
</tr>
<tr>
<td>BUN/creatinine</td>
<td>&gt;20/1</td>
<td>&lt;20/1</td>
</tr>
<tr>
<td>Urinary Na</td>
<td>&lt;20mEq/l</td>
<td>&gt;40</td>
</tr>
<tr>
<td>FeNa</td>
<td>&lt;1</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>&gt;500</td>
<td>&lt;350</td>
</tr>
<tr>
<td>Urine cells and casts</td>
<td>bland</td>
<td>Lots of cells, muddy granular, dirty brown casts</td>
</tr>
</tbody>
</table>
Acute Nephritic Syndrome

- Syndrome characterised in typical cases by:
  - Haematuria
  - Oliguria
  - Edema
  - Hypertension
  - Reduced GFR
  - Proteinuria
  - Fluid overload
The Nephrotic Syndrome

• Is not a disease but a group of signs and symptoms seen in patients with heavy proteinuria
• presents with oedema
• proteinuria usually > 3.5g / 24hrs (>0.05g / kg / 24hrs in children)
• serum albumin < 30g/l
• other features: hyperlipidaemia, and hypercoaguable state
### Clinical Presentation of Glomerular Disease

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Nephritic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria 150 mg to 3 g</td>
<td>Oliguria</td>
</tr>
<tr>
<td>Hematuria &gt; 5 RBC/ hpf</td>
<td>Hematuria; RBC casts</td>
</tr>
<tr>
<td></td>
<td>Non Nephrotic proteinuria</td>
</tr>
<tr>
<td></td>
<td>Edema, Hypertension</td>
</tr>
<tr>
<td></td>
<td>Acute renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroscopic Hematuria</td>
<td>Nephrotic Syndrome</td>
</tr>
<tr>
<td>Brown/red urine, painless</td>
<td>Proteinuria &gt; 3.5 g/1.73 m²</td>
</tr>
<tr>
<td>Synpharyngitic, or post infectious</td>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td>Asymptomatic hematuria ± proteinuria between episodes</td>
<td>Edema; Lipuria</td>
</tr>
<tr>
<td></td>
<td>Hypercholesterolemia</td>
</tr>
</tbody>
</table>
Laboratory tests of renal function

- glomerular filtration rate impractical
- creatinine clearance unreliable
- plasma creatinine specific but insensitive
- plasma urea subject to problems
- urine volume often forgotten!
Epidemiology of Renal Disease

Richard Bright, M.D.F.R.S.
1789-1858
Father of Nephrology
WHAT IS DIABETIC NEPHROPATHY?
Diabetic Kidney Disease Screening

• WHEN
  – Type 1: after 5 years, then annually
  – Type 2: at diagnosis, then annually

• HOW
  – Albumin-to-Creatinine ratio in random urine
    • Microalbuminuria = 30-300 mg/g
    • Macroproteinuria
  – Estimate GFR (eGFR) from serum creatinine using formulas
  – Retinopathy: useful clue
What is the Natural History of Diabetic Nephropathy?
Definition of Diabetic Nephropathy

• Clinical diagnosis based on Hx, Exam and urine albumin/creatinine ratio in most cases
• Longstanding History of diabetes ± retinopathy
• Macroalbuminuria (a.k.a “overt nephropathy”) defined as random urine albumin/creatinine ratio $\geq 300\ mg/g$
• Hypertension (> 90%)
• Renal Biopsy confirmation is rare
Natural History of Diabetic Nephropathy

- **Albuminuria**
  - Albumin-rich filtrate
  - Podocytes
  - Foot process
  - Glomerular Basement Membrane
  - Damaged Endothelium
  - Albumin Leak

- **Hypertension**
  - BP
  - Time
  - Declining GFR

- **Cardiovascular Death Risk**
  - CV Risk (fold ↑)

- **Declining GFR**
  - ESRD
  - Time

- Graph showing the relationship between GFR and CV Risk over time.
Development of Macroalbuminuria Heralds Rapid Decline in Glomerular Filtration in Type II Diabetes

Nelson RG. et al *NEJM*, 1996
Diabetics with Nephropathy (DM/CKD) are More Likely to Die than to Progress to ESRD

5% Medicare sample, 1996-1997 cohort, 2 year follow-up

<table>
<thead>
<tr>
<th>Status in the entry period</th>
<th>Event Free</th>
<th>ESRD</th>
<th>All Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDM/Non-CKD</td>
<td>90.53</td>
<td>0.07</td>
<td>9.40</td>
</tr>
<tr>
<td>DM/Non-CKD</td>
<td>85.04</td>
<td>0.31</td>
<td>14.65</td>
</tr>
<tr>
<td>NDM/CKD</td>
<td>73.18</td>
<td>2.25</td>
<td>24.57</td>
</tr>
<tr>
<td>DM/CKD</td>
<td>65.12</td>
<td>5.85</td>
<td>29.04</td>
</tr>
</tbody>
</table>

N=1,045,263
Diabetics with Macroalbuminuria are More Likely to Die than Develop ESRD

The United Kingdom Prospective Diabetes Study (approx. 5000 Type 2 Diabetics)
Newly diagnosed, predominantly white, medically treated

No albuminuria → 1.4%

Microalbuminuria → 2.8%
→ 2.0%

Macroalbuminuria → 4.6%
→ 3.0%

Elevated Serum Creatinine → 19%

Adler et al. Kid Int, 2003
What are Diabetics with Nephropathy Dying From?

- Stroke
- Myocardial Infarction
- Heart Failure
- Sudden Death
Diabetic Nephropathy

Improving Outcomes in Diabetic Nephropathy

Prevention of Cardiovascular Events

Prevention of End-Stage Renal Disease
What is the Proper Therapy of Kidney Disease in patients with Diabetes?
### Definition of Abnormal Albuminuria in Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria (Nephropathy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected by dipstick</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Urine Albumin / Cr</td>
<td>30 - 299 mg Alb / g Cr</td>
<td>≥ 300 mg Alb / g Cr</td>
</tr>
<tr>
<td>Renal Risk</td>
<td>Marker of future nephropathy in some</td>
<td>Marker progressive renal disease</td>
</tr>
<tr>
<td>Cardiovascular Risk</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

* Random (Spot) urine preferably A.M. recommended
Diabetic nephropathy affects all renal compartments

- Mesangial
- Arterial
- Glomerular capillaries
- Tubulointerstitium
Hyperfiltration

–Basement membrane thickening and retinopathy

Mesangial expansion; Progressive Microalbuminuria; Hypertension

Nodular glomerulosclerosis

ESRD
Five Stages of Kidney Disease

Stage 1: Hyperfiltration, or an increase in glomerular filtration rate (GFR) occurs. Kidneys increase in size.

Stage 2: Glomeruli begin to show damage and microalbuminuria occurs.

Stage 3: Albumin excretion rate (AER) exceeds 200 micrograms/minute, and blood levels of creatinine and urea-nitrogen rise. Blood pressure may rise during this stage.
Five Stages of Kidney Disease (con’t.)

**Stage 4:** GFR decreases to less than 75 ml/min, large amounts of protein pass into the urine, and high blood pressure almost always occurs. Levels of creatinine and urea-nitrogen in the blood rise further.

**Stage 5:** Kidney failure, or end stage renal disease (ESRD). GFR is less than 10 ml/min. The average length of time to progress from Stage 1 to Stage 4 kidney disease is 17 years for a person with type 1 diabetes. The average length of time to progress to Stage 5, kidney failure, is 23 years.
24Hr BP Profile in Hypertension  
(Dipper vs non-dipper)

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00</td>
<td>175</td>
</tr>
<tr>
<td>11:00</td>
<td>155</td>
</tr>
<tr>
<td>15:00</td>
<td>135</td>
</tr>
<tr>
<td>19:00</td>
<td>115</td>
</tr>
<tr>
<td>23:00</td>
<td>95</td>
</tr>
<tr>
<td>3:00</td>
<td>75</td>
</tr>
<tr>
<td>7:00</td>
<td>55</td>
</tr>
</tbody>
</table>

Sleep
DM Complications; Kidney Disease

- Progression in Type 1 DM
- End Stage Renal Disease
  - Type 1 - 30-40% pts. after 20-30 years.
    - 2003: 20% over 20 years
  - Onset within 2-3 years after nephrotic syndrome.
Pathogenesis

- Advanced Glycosylation End Products
- Non-enzymatic glycosylation of proteins
  - e.g. Hb (HbA\textsubscript{1C})
- Glycosylation of BM proteins
- Stimulation of adhesion molecule expression
Prevention & Treatment - Overview

- Prevention Strategies:
  - Normalize Blood Pressure
    - Goal 125/75
    - ACE inhibitors particularly beneficial
  - Dietary Protein Restriction
    - 0.6-0.8 gm/kg/day in established macroalbuminuria or falling GFR
  - Glycemic Control
  - Regular Monitoring for Nephropathy
  - Avoid Nephrotoxins (NSAIDs, some abx)
Major Therapeutic Maneuvers to Slow Loss of GFR in Diabetic Nephropathy

- Hyperglycemia
- ACEi, ARB
- Weight loss, exercise, smoking cessation
- Normotension
- Euglycemia
- Protein restriction
- Lipid Management
- Glomerulosclerosis
The Renal Injury Triad

- Angiotensin II
- Hypertension
- Proteinuria
ACE Inhibition and Diabetic Nephropathy

409 patients overt proteinuria SCr < 220 equal BP control

ACE inhibitor slows progression of diabetic nephropathy  The effect of the administration of placebo or captopril to patients with type 1 diabetes with overt proteinuria and a plasma creatinine concentration equal to or greater than 1.5 mg/dL (132 μmol/L). The likelihood of a doubling of the plasma creatinine concentration (Pcr) was reduced by more than 50 percent in the captopril group. (Data from Lewis, EJ, Hunsicker, LG, Bain, RP, Rohde, RD, N Engl J Med 1993; 329:1456.)
# Angiotensin II Receptor Blockers in Type 2 Diabetics With Nephropathy

## Progression of Renal Insufficiency

### Primary Endpoint:
Composite of doubling of serum creatinine, end stage renal disease, or death

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Effect</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAAL (n=1,514)</td>
<td>Losartan 50-100 mg vs placebo*</td>
<td>↓ 16% (p=0.02)</td>
<td>3.4 yrs</td>
</tr>
<tr>
<td>IDNT (n=1,715)</td>
<td>Irbesartan 150-300mg vs placebo*</td>
<td>↓ 20% (p=0.02)</td>
<td>2.6 yrs</td>
</tr>
<tr>
<td>IDNT (n=1,715)</td>
<td>Irbesartan 150-300 mg vs Amlodipine*</td>
<td>↓ 23% (p=0.006)</td>
<td>2.6 yrs</td>
</tr>
</tbody>
</table>

*In combination with conventional antihypertensive therapy (excluding ACE inhibitors)

RENAAL=The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study
IDNT=The Irbesartan in Diabetic Nephropathy Trial

## Angiotensin II Receptor Blockers in Type 2 Diabetics

### Progression of Microalbuminuria†

<table>
<thead>
<tr>
<th>IRMA II (n=590)</th>
<th>Primary Outcome: Development of clinical proteinuria‡</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irbesartan 150mg vs placebo</strong>*</td>
<td>↓ 39% (P=0.080)</td>
<td>2 yrs</td>
</tr>
<tr>
<td><strong>Irbesartan 300mg vs placebo</strong>*</td>
<td>↓ 70% (P&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

†Albumin excretion rate of 20 to 200 μg per minute in 2 of 3 consecutive, sterile, overnight urine samples

‡Urinary albumin excretion rate >200 μg per minute and at least 30% higher than baseline in at least 2 consecutive measurements

*In combination with conventional antihypertensive therapy (excluding ACE inhibitors)

IRMA II=The Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients Study

Achieved BP Control and GFR Decline
Clinical Trials of Diabetic and Non-diabetic Renal Disease

- Viberti GC et al. *JAMA* 1993
- Klaur S et al. *NEJM* 1993
- Moschino G et al. *NEJM* 1996
- Bakris GL et al. *Hypertension* 1996
- GISEN Group *Lancet* 1997
Number of Antihypertensives Needed to Achieve Target Blood Pressure

AASK (< 92 mm MAP)
HOT (< 80 mm diastolic)
MDRD (< 92 mm MAP)
ABCD (< 75 mm diastolic)
UKPDS (< 85 mm diastolic)

Bakris et al. AJKD 2000
HOT Study: Significant benefit from intensive treatment in the diabetic subgroup


Major cardiovascular events/1,000 patient-years

Target diastolic blood pressure (mm Hg)

\[ p = 0.005 \text{ for trend} \]
Progression of Renal Disease

- Microalbuminuria
- Proteinuria
- Doubling of Serum Creatinine Levels
- End-Stage Renal Disease

CV Events Death
Microalbuminuria → Proteinuria → ESRD
Proteinuria predicts stroke and CHD events in type II diabetes

7-year follow-up, 1056 patients

U-Prot = Urinary protein concentration.

Is Combination Therapy With An ACE Inhibitor And An ARB Safe And Effective For Patients With Diabetic Renal Disease?
Combination ACEI and ARB in Humans
Antiproteinuric Effect

Proteinuria (g/d)

Baseline | ACEI | ACEI + ARB | ARB | ARB + ACEI
---|---|---|---|---

*P < 0.05 vs baseline.
†P < 0.05 vs other study periods.
COOPERATE: Primary Endpoint

Doubling of Serum Creatinine or Progression to ESRD

Proportion Reaching Endpoint, %

Number at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>5</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>89</td>
<td>88</td>
<td>84</td>
<td>79</td>
<td>65</td>
<td>59</td>
<td>47</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>86</td>
<td>85</td>
<td>83</td>
<td>75</td>
<td>72</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>Combination</td>
<td>88</td>
<td>87</td>
<td>86</td>
<td>83</td>
<td>76</td>
<td>73</td>
<td>67</td>
</tr>
</tbody>
</table>

COOPERATE: UAER

Aliskiren:
A Novel, Orally-Available Renin Inhibitor

- High solubility in water and biological fluids
- Non-peptide drug suitable for oral administration
## Baseline Renal Parameters at Randomization AVOID

<table>
<thead>
<tr>
<th>Renal Parameters</th>
<th>Usual Rx</th>
<th>Aliskiren added</th>
</tr>
</thead>
<tbody>
<tr>
<td>UACR mg/g</td>
<td>778±676</td>
<td>750±687</td>
</tr>
<tr>
<td>eGFR ml/min/1.73m²</td>
<td>67±25</td>
<td>69±26</td>
</tr>
<tr>
<td>mBP mmHg</td>
<td>134/77±12/9</td>
<td>135/78±12/8</td>
</tr>
</tbody>
</table>

AVOID Results

- After 6 months of Aliskiren:
  - UACR ↓20% (95%CL 9-30) p≤.0009
  - UAER ↓18% (95%CL 5-30) p≤.009
- 25% of Aliskiren Rx pts UACR≥50%↓UACR vs. 13% of usual Rx pts. P<.0002
- No changes in eGFR.
- Non-significant ↓mBP in Aliskiren Rx group.
- 4.7% of Aliskiren pts S\textsubscript{K}>6.0 mmol/l vs. 1.7% in usual Rx pts. (ns).
ACEi- or ARB-Based Regimens for Diabetic Nephropathy Do Not Go Far Enough!

ACEi or ARB
ΔGFR = - 6 ml/min/yr
Time to ESRD 6.6 yrs

ACEi + ARB
ΔGFR = - ? ml/min/yr
Time to ESRD ?

No ACEi/ARB or BP control
ΔGFR = - 10 ml/min/yr
Time to ESRD 4 yrs

RAAS blockade + Other?
Slowing the Progression of Kidney Disease:
Benefits of BP Control and RAS Blockade in Patients with Diabetes
Cardiovascular Risk Reduction
Tight Glucose vs Tight BP Control

Stroke  Any DM Endpoint  DM Death  Microvascular Complications

-10 -20 -30 -40 -50

* * * * * P < 0.05

Tight glucose control  Tight BP control

UKPDS. BMJ 1998
## Risk Factors for Progression of Renal Disease

<table>
<thead>
<tr>
<th>Can be modified</th>
<th>Cannot be modified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Age</td>
</tr>
<tr>
<td>Albuminuria/Proteinuria</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Gender</td>
</tr>
<tr>
<td>Hemoglobin A\textsubscript{1C}</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Anemia/Nephrotoxins</td>
<td></td>
</tr>
<tr>
<td>Ca\cdot P\textsubscript{0}4</td>
<td></td>
</tr>
</tbody>
</table>
Risk of Ischemic Heart Disease Related to SBP and Microalbuminuria

N=2,085; 10 year follow-up

Hypertensive Nephropathy
Age-adjusted Stroke Mortality Among Men by State:
United States

*Deaths per 100,000 population

Age-adjusted Stroke Mortality Among Women by State: United States

* Deaths per 100,000 population
Hypertension

• Hypertension is not a disease

Hypertension is perceived to be necessary for adequate perfusion of allograft

• It is an arbitrarily defined disorder to which both environmental and genetic factors contribute

• Major risk factor for so many complications
Benefits of Lowering BP

In stage 1 HTN and additional CVD risk factors, achieving a sustained 12 mmHg-reduction in SBP over 10 years will prevent 1 death for every 11 patients treated.

JNC BP Classifications: SBP

JNC II. Arch Intern Med. 1980;140:1280-1285.
JNC III. Arch Intern Med. 1984;144:1045-1057.
JNC BP Classifications: DBP

JNC II. Arch Intern Med. 1980;140:1280-1285.
JNC III. Arch Intern Med. 1984;144:1045-1057.

Framingham Heart Study

“High-normal” BP Is Not Benign

*CV death, MI, stroke, CHF
†Adjusted for concomitant CV risk factors
Optimal = <120/<80 mmHg
Normal = 120–129/80–84 mmHg
High normal = 130–139/84–89 mmHg

## Blood Pressure Classification

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/ESRD</td>
<td>&lt;120</td>
<td>and &lt;75-80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>or 80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>or 90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>or ≥100</td>
</tr>
</tbody>
</table>

# Treating Blood Pressure to Goal

**JNC VII recommendations:**

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Goal BP (mm Hg)</th>
<th>% of US adults at goal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>&lt;140/90</td>
<td>27%</td>
</tr>
<tr>
<td>African American</td>
<td>&lt;140/90</td>
<td>25%</td>
</tr>
<tr>
<td>Elderly</td>
<td>&lt;140/90</td>
<td>20%</td>
</tr>
<tr>
<td>Diabetic</td>
<td>&lt;130/80</td>
<td>13%</td>
</tr>
<tr>
<td>CAD</td>
<td>&lt;140/90 (lower if angina continues)</td>
<td>33%</td>
</tr>
</tbody>
</table>

* Includes those aged 17+ years with both diagnosed and undiagnosed hypertension.

“Any reduction in blood pressure appears to confer benefit— the closer to normal, the greater the benefit.”

—JNC VII
Reducing blood pressure can lower a patient’s chance of developing CAD.

**Reducing BP Impacts CAD**

-5 mm Hg*: 21%

-7.5 mm Hg*: 29%

-10 mm Hg*: 37%

*Reduction in DBP

Raw, unadjusted incidence rates for men and women aged 25 to 84 years (most were men 40 to 68) from 9 prospective studies.
Hypertension and Chronic Renal Disease: Hemodynamic Abnormalities

Mean BP = Cardiac Output \times \text{Total Systemic Vascular Resistance}
Mechanisms of Renal Damage in HTN

**Normal Kidney**

**Mechanisms**
- Glomerular hypertension
  - Hyperfiltration
- Glomerular barrier dysfunction
  - Proteinuria
- Mesangial cell hyperplasia
- Intrarenal inflammatory processes
- Endothelial dysfunction
- VSMC proliferation

**Blood Pressure**
Renin-Angiotensin Cascade

**Angiotensinogen**

- Non-renin (eg tPA)

**↑ Angiotensin I**

- Non-ACE (eg chymase)

**↑ Angiotensin II**

**Renin**

**ACE**

**Bradykinin**

**Inactive peptides**

**AT₁**

**AT₂**

**ATₙ**
TGF-β plays a key role in extracellular matrix formation in mesangium and interstitium that leads to fibrosis and loss of nephron units.

www.hypertensiononline.org
JNC-7 Algorithm for Treatment of Hypertension

Lifestyle Modifications

Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for those with diabetes or chronic kidney disease)

Initial Drug Choices

Without Compelling Indications

Stage 1 Hypertension
(SBP 140–159 or DBP 90–99 mmHg)
Thiazide-type diuretics for most.
May consider ACEI, ARB, BB, CCB, or combination.

Stage 2 Hypertension
(SBP ≥160 or DBP ≥100 mmHg)
2-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB)

With Compelling Indications

Drug(s) for the compelling indications
Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

Optimize dosages or add additional drugs until goal blood pressure is achieved.
Consider consultation with hypertension specialist.
## Physiological characteristics

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Carrier or channel inhibited</th>
<th>% filtered Na Excreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>Various</td>
<td>Up to 60-65%</td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>Na(^+) –K(^+) –2Cl(^-) carrier</td>
<td>Up to 25%</td>
</tr>
<tr>
<td>Distal Tubule &amp; connecting segment</td>
<td>Na(^+)-Cl(^-) carrier</td>
<td>Up to 3-5%</td>
</tr>
<tr>
<td>Cortical collecting tubule</td>
<td>Na(^+) channel</td>
<td>Up to 1-2%</td>
</tr>
</tbody>
</table>
Loop Diuretics

- Bumetanide (Bumex)
- Ethacrynic acid (Edecrin)
- Furosemide (Lasix)
- Torsemide
## Loop Diuretics

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Bioavailability(%)</th>
<th>IV to PO</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>75</td>
<td>1:1</td>
<td>1</td>
</tr>
<tr>
<td>Torsemide</td>
<td>80</td>
<td>1:1</td>
<td>20</td>
</tr>
<tr>
<td>Furosemide</td>
<td>50</td>
<td>1:2</td>
<td>40</td>
</tr>
<tr>
<td>Ethacrynic Acid</td>
<td>100</td>
<td>1:1</td>
<td>50</td>
</tr>
</tbody>
</table>

Loop Diuretics:  
Mechanism of Action

• Act directly on the ascending limb of the loop of Henle to inhibit sodium and chloride resorption.

• Increase renal prostaglandins, resulting in the dilation of blood vessels and reduced peripheral vascular resistance.
Loop Diuretics:
Therapeutic Uses

- Edema associated with HF or hepatic or renal disease

- Control of hypertension
Thiazide and Thiazide-Like Diuretics

- Hydrochlorothiazide (Esidrix, HydroDIURIL)
- Chlorothiazide (Diaril)
- Trichlormethiazide (Metahydrin)
- Thiazide-like
- Chlorthalidone (Hygroton)
- Metolazone (Mykrox, Zaroxolyn)
Schematic drawing of temporal changes in mean arterial pressure (MAP), total peripheral vascular resistance (TPR), cardiac output (CO) and plasma volume (PV) during thiazide treatment of a hypertensive subject

# Efficacy and Safety of Low Doses of Thiazides

## Dose of Bendroflumethiazide

<table>
<thead>
<tr>
<th>(mg/day)</th>
<th>0</th>
<th>1.25</th>
<th>2.5</th>
<th>5.0</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from 0 to 10 weeks</td>
<td>0</td>
<td>1.25</td>
<td>2.5</td>
<td>5.0</td>
<td>10</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>-3/3</td>
<td>-13/10</td>
<td>-14/11</td>
<td>-13/10</td>
<td>-17/11</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>+0.09</td>
<td>-0.16</td>
<td>-0.2</td>
<td>-0.33</td>
<td>-0.45</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>-1.4</td>
<td>-3.4</td>
<td>+2.5</td>
<td>+0.7</td>
<td>+4.9</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>-2.2</td>
<td>-1.1</td>
<td>0</td>
<td>+4.6</td>
<td>+9.5</td>
</tr>
</tbody>
</table>

# Thiazides and Related Diuretics

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Dose (mg)</th>
<th>Frequency</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>12.5-50</td>
<td>1/day</td>
<td>24-72</td>
</tr>
<tr>
<td>HCTZ</td>
<td>12.5-50</td>
<td>1-2/day</td>
<td>12-18</td>
</tr>
<tr>
<td>Metolazone</td>
<td>0.5-5</td>
<td>1/day</td>
<td>18-24</td>
</tr>
<tr>
<td>Indapamide</td>
<td>1.25-5</td>
<td>1/day</td>
<td>18-24</td>
</tr>
</tbody>
</table>
Mean Office BSP and Change During the First 8-week Study Period

Mean Change From Week 0 To Week 8 In Average Hourly Ambulatory Systolic BP

Potassium-Sparing Diuretics

- Amiloride (Midamor)
- Spironolactone (Aldactone)
- Triamterene (Dyrenium)
- Eplerenone (Inspira)
Potassium-Sparing Diuretics: Mechanism of Action

- Work in collecting ducts and distal convoluted tubules
- Interfere with sodium-potassium exchange
- Competitively bind to aldosterone receptors
- Block the resorption of sodium and water usually induced by aldosterone
Potassium-Sparing Diuretics: Therapeutic Uses

spironolactone *(Aldactone)* and triamterene

- Hyperaldosteronism
- Hypertension
- Reversing the potassium loss caused by potassium-losing drugs
- Ascites
Chemical Structures of Spironolactone and Eplerenone

Spironolactone
SC-09420
C_{24}H_{32}O_4S
(416.58)

Eplerenone
SC-66110
C_{24}H_{30}O_6
(414.50)
Eplerenone is an Aldosterone Blocker with Improved Selectivity

AGONIST
Progesterone Receptor

ANTAGONIST
Androgen Receptor
Glucocorticoid Receptor

% of Full Agonist Response

- Spironolactone (10 μM)
- Eplerenone (10 μM)

Rafestin-Oblin E, data on file
HF with Edema

- Abnormal condition that reflects impaired cardiac pumping
  - Volume overload, ventricular dilation, elevated intracardiac pressure
  - Increased pressure
    - Left side-pulmonary congestion
    - Right side-peripheral edema
HF with Edema

• Diuretics used for fluid management
  – Initiate a loop diuretics
    • Furosemide
  – Refractory congestion
    • Add thiazide/thiazide related
      – Metolazone
  – Spironolactone
    • Prevent hypokalemia
FE Na (%) 

$0 + 0 = 0$

40 mg In AM

40 mg in PM

=0

HF with edema

- **Volume overload (mild to moderate)**- 3 to 5 lbs wt. gain

  **Furosemide**

  - $<120\text{ mg/d}$  
    - Double oral AM dose and add $K^+$ supplement x 1d
  
  - $\geq 200\text{ mg/d}$  
    - Add metolazone 2.5 mg daily and add $K^+$ supplement
  
  - $\geq 200\text{ mg/d} \&$  
    - Add metolazone 5 mg BID and Add $K^+$ supplement
  
  - $>200\text{ mg/d}$  
    - Same as above but admin. IV furosemide equal to AM oral dose x 2d. (take metolazone 30 min. prior to IV furosemide)
    - Consider furosemide gtt.
HF with Edema

• May substitute metolazone with chlorothiazide in previous diuretic regimens

• Adding low-dose spironolactone (12.5-25mg qd)
  – Reduces hypertrophy
  – Prevents hypokalemia
Loop Diuretics

- Furosemide- used for fluid management
- Torsemide- used in patients who have problems with absorption
- Ethacrynic acid- ototoxicity limits use; may use as alternative for patients with a sulfa allergy
<table>
<thead>
<tr>
<th>Interacting Drugs</th>
<th>Potential Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors / K+ - Sparing Diuretics</td>
<td>Increased Hyperkalemia Þ Cardiac Problems</td>
</tr>
<tr>
<td></td>
<td>(Monitor Serum K+ Closely)</td>
</tr>
<tr>
<td>Aminoglycosides / Loop Diuretics</td>
<td>Ototoxicity And Nephrotoxicity.</td>
</tr>
<tr>
<td></td>
<td>(Monitor Hearing And Serum Creatinine Closely)</td>
</tr>
<tr>
<td>Digoxin / Thiazide &amp; Loop D.</td>
<td>Hypokalemia Þ Increased Digoxin Binding &amp; Toxicity</td>
</tr>
<tr>
<td></td>
<td>(Monitor K+ And Cardiac Function)</td>
</tr>
<tr>
<td>ß- Blockers / Thiazide Diuretics</td>
<td>Hyperglycemia, Hyperlipidemia, Hyperuricemia.</td>
</tr>
<tr>
<td>Steroids / Thiazide &amp; Loop D.</td>
<td>Increased Risk Of Hypokalemia</td>
</tr>
<tr>
<td></td>
<td>(Monitor K+ Closely)</td>
</tr>
<tr>
<td>Carbamazepine or Chlorpropamide / Thiazide Diuretics</td>
<td>Increased Risk Of Hyponatremia (Monitor Na+)</td>
</tr>
</tbody>
</table>