Gout and Hyperuricemia
Prevention of Arthritis, Renal Disease and Adverse CV Outcomes
Kenneth G. Saag, MD MSc
Jane Knight Lowe Professor of Medicine
Division of Clinical Immunology and Rheumatology
Director, UAB CERTs, Center for Outcomes, Effectiveness Research & Education and Center for Research Translation (CORT) in Gout
Overview

- Gout associated comorbidities
- Towards designing a prevention study in hyperuricemia
- Example study design: Preventing hypertension by lowering serum urate
In a study of men with hyperuricemia, 22% with serum urate levels >9 mg/dL developed gouty arthritis over 5 years.  

Comorbidities Associated with Hyperuricemia

- Obesity\(^1,^2\)
- Metabolic syndrome\(^3,^4\)
- Diabetes mellitus\(^5\)
- Heart failure\(^6\)
- Hyperlipidemia\(^1\)
- Hypertension\(^7,^8\)

5. Boyko et al *Diabetes Care* 2000;23:1242
Gout associated with the Metabolic Syndrome

- Insulin resistance promotes increased renal urate reabsorption
- Metabolic Syndrome associated with other factors that increase serum urate (hypertension, obesity)

A Model of Mild Hyperuricemia

Normal rat
sUA (0.5 - 1.4 mg/dL)

Hyperuricemic rat
sUA (1.7 - 3.0 mg/dL)

Uricase inhibitor
Oxonic acid (OA)

Hyperuricemia and Hypertension
A Potential Explanation of Association

- Rats were divided into three groups

<table>
<thead>
<tr>
<th>Control Group</th>
<th>OA/LS Group</th>
<th>OA/LS/AP Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low sodium diet (LS)</td>
<td>Low sodium diet (LS) Oxonic acid (OA)</td>
<td>Low sodium diet (LS) Oxonic acid (OA) Allopurinol (AP)</td>
</tr>
</tbody>
</table>

- 2% oxonic acid induced hyperuricemia
- At week 5, micropuncture procedures were performed

Hyperuricemia and Hypertension
A Potential Explanation of Association (cont’d)

- **Effects on the afferent arteriole after 5 weeks**

  Uncontrolled hyperuricemia: Arteriole thicker, Lumen smaller
  Controlled hyperuricemia: Arteriole thinner, Lumen larger

- **Proposed mechanism**
  - May occur due to a defect in renal uric acid clearance
  - Association to glomerular hypertension may be caused by afferent arteriole thickening
    - Suggestive of hypertrophic vascular remodeling

Development of hypertension in men according to baseline serum urate


*Significantly different from referent group (p<0.05) by log-rank test adjusted for multiple comparisons.

<table>
<thead>
<tr>
<th>Year</th>
<th>HTN (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>2224</td>
</tr>
<tr>
<td>5</td>
<td>5.1</td>
<td>1992</td>
</tr>
<tr>
<td>10</td>
<td>11.7</td>
<td>1717</td>
</tr>
<tr>
<td>15</td>
<td>20.7</td>
<td>1509</td>
</tr>
<tr>
<td>20</td>
<td>28.5</td>
<td>1181</td>
</tr>
</tbody>
</table>

≥ 7.5 mg/dL*
6.1 - 6.79 mg/dL*
6.8 - 7.49 mg/dL*
5.4 - 6.09 mg/dL
< 5.4 mg/dL
Uric Acid–Lowering Treatment Effects Blood Pressure
Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

- 30 asymptomatic adolescents with high SUA levels (≥ 6.0 mg/dL) and newly diagnosed mild essential hypertension
- Allopurinol 200 mg BID for 4 weeks, 2-week washout, and placebo BID for 4 weeks

<table>
<thead>
<tr>
<th>Outcome Measured</th>
<th>Placebo</th>
<th>Allopurinol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP load (%)</td>
<td><strong>48.6</strong> (34.0 to 50.2)</td>
<td><strong>23.3</strong> (15.8 to 30.9)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Diastolic BP load (%)</td>
<td><strong>29.2</strong> (25.6 to 37.1)</td>
<td><strong>18.1</strong> (12.3 to 23.8)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Hypertensive, No./total (%)</td>
<td><strong>29/30</strong> (97)</td>
<td><strong>10/30</strong> (33)</td>
<td><strong>0.001</strong></td>
</tr>
</tbody>
</table>

Blood pressure (BP) load: (as measured by ambulatory BP) is the percentage of time during the study that BP exceeds the 95th percentile

Uric Acid–Lowering Treatment Effects Blood Pressure
Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

• 30 asymptomatic adolescents with high SUA levels (≥ 6.0 mg/dL) and newly diagnosed mild essential hypertension
• Allopurinol 200 mg BID for 4 weeks, 2-week washout, and placebo BID for 4 weeks

Is it possible to prevent/postpone the onset of hypertension by reducing SUA levels?

### Potential Associations with Hyperuricemia

#### Cardiovascular Events and Mortality

<table>
<thead>
<tr>
<th>Finding</th>
<th>Supportive Studies</th>
</tr>
</thead>
</table>
| Hyperuricemia ↑ development of cardiovascular disease, ischemic heart disease, and/or coronary heart disease | ✓ Breckenridge et al.  *(Lancet, 1966)*  
               | ✓ Santos et al  *(Am J Cardiol, 2007)*                   |
| Hyperuricemia ↑ risk of Cardiovascular events              | ✓ SHEP *(J Hypertens, 2000)*                             |
|                                                           | ✓ Worksite Treatment Program *(J Hypertens, 1998)*       |
|                                                           | ✓ PIUMA *(Hypertension, 2000)*                           |
|                                                           | ✓ LIFE 2003 *(Kidney Int, 2000)*                         |
|                                                           | ✓ Darmawan et al. *(J of Rheum, 2003)*                   |
|                                                           | ✓ Lehto et al. *(Stroke, 1998)*                          |
| Hyperuricemia ↑ mortality from coronary heart disease, ischemic heart disease, and overall mortality | ✓ NHANES *(JAMA, 2002)*                                  |
|                                                           | ✓ Bickel et al. *(Am J Cardiol, 2002)*                   |
|                                                           | ✓ Darmawan et al. *(J of Rheum, 2003)*                   |
Hyperuricemia appears to be an independent risk factor for stroke events\textsuperscript{1-3}

\textsuperscript{1}Kim SY, et al. ACR Meeting 2008. Poster 1364.
Renal Disorders Linked to Hyperuricemia

Renal Insufficiency

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in renal function (eg, diminished GFR)</td>
<td>Occur in 30%-60% of gout patients(^1)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>sUA &gt;8.0 mg/dL <strong>independently</strong> increased risk of developing renal insufficiency within 2 years (3-fold in men; 10-fold in women)(^2)</td>
</tr>
</tbody>
</table>
| Renal failure                 | sUA >8.5 mg/dL associated with 8-fold increased risk of renal failure (\(P<.01\))\(^3\)  
                             | ESRD developed in 25% of gout patients prior to the availability of urate-lowering drugs\(^4\) |

~60% of patients with gout are found to have renal dysfunction\(^5\)

Serum Urate Predicts ESRD After 7 Years

Urate independent of proteinuria, age, creatinine, BMI, lipids, and blood pressure

Serum urate mg/dL

Men

<7.0

≥7.0

Women

<6.0

≥6.0

Cumulative incidence of ESRD per 1000 screenees

Number of screenees

15617

7332

21795

3433

Number of ESRD

19

34

19

31

Renal Disorders Linked to Hyperuricemia
Urate (or Gouty) Nephropathy Theory

• Sustained hyperuricemia causes interstitial urate crystal deposition
  - Inflammation, fibrosis, and renal insufficiency follow

• At autopsy, 79%-99% of gout patients had urate nephropathy


Urate nephropathy caused tophaceous deposits in this medulla
What Are the Questions?

What are the Interventions?

• Can reduction in SUA lead to primary or secondary prevention of:
  – Hypertension
  – Atherosclerotic vascular disease
  – Renal disease

• Potential interventions
  – Xanthine oxidase inhibitors
  – Uricosurics
  – Diet and dietary supplements
  – Weight loss
  – Other CVD risk factor modification
What are the Populations of Interest?

• Persons with:
  – Gouty arthritis
  – Hypertension
  – CVD or other CVD risk factors
  – CKD or other CKD risk factors
  – Varying combinations

• General population with hyperuricemia
Effects of Urate Lowering Therapy on Inflammation, Endothelial Function, and Blood Pressure

UAB Center of Research Translation (CORT) in Gout and Hyperuricemia

Grant # P50AR060772

NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases
NATIONAL INSTITUTES OF HEALTH
Urate Lowering Effects on Hypertension

Study Team

UAB Investigators

Kenneth G. Saag, MD, MSc  Principal Investigator
David Calhoun, MD  Co-Principal Investigator
Angelo Gaffo, MD, MSPH  Lead Investigator
Tanja Dudenbostel, MD  Investigator
Suzanne Oparil, MD  Investigator
David Redden, PhD  Investigator, Statistician
Paul Muntner, PhD  Investigator
Dan Feig, MD  Investigator
Jose Leon de la Rocha, MD  Research Associate
Sebastian Sattui, MD  Research Associate
Kerry Renfroe, RN  Study Coordinator
Randall Parks, RN  Program Director
Jeff Foster, MPH  Program Manager
Urate Lowering Effects on Hypertension

Specific Aims

To determine in young adults with pre or stage 1 hypertension whether urate lowering therapy (ULT) with allopurinol will:

- Lower blood pressure (BP)
  - Four weeks of ULT therapy will induce a greater reduction in ambulatory blood pressure levels when compared to four weeks on placebo
  - ULT will induce a greater reduction in ambulatory blood pressure levels in African Americans when compared with other races/ethnicities
Urate Lowering Effects on Hypertension

Specific Aims (cont’d)

- Reduce serum levels of high sensitivity C-reactive protein (hsCRP)
  - Four weeks of ULT will induce a greater reduction in serum levels of high sensitivity C-reactive protein (hsCRP) than placebo
  - ULT will induce a greater reduction in hsCRP in African Americans when compared with other races/ethnicities

- Improve endothelial function
  - ULT will induce a greater reduction in hsCRP in African Americans when compared with other races/ethnicities
  - ULT will induce a greater increase in FMD in African Americans when compared with other races/ethnicities
Urate Lowering Effects on Hypertension

Intervention and Outcomes

- **Intervention:** allopurinol (300mg/d) or placebo in four-week study with crossover
- **Outcomes of interest**
  - Serum urate
  - CRP/hsCRP
  - Endothelial function as measured by flow mediated dilation (FMD)
  - 24 hr Ambulatory BP

**Timeline:**
- **Screening** (wks 0)
  - No intervention
- **Placebo Run-In** (wks 1-2)
  - No intervention
- **First phase of crossover** (wks 3-6)
  - Allopurinol
  - Placebo
- **Washout period** (wks 7-10)
  - No intervention Crossover
  - Placebo -> Allopurinol
- **Second phase of cross-over** (wks 11-14)
  - Placebo
  - Allopurinol
Urate Lowering Effects on Hypertension
Safety Monitoring

• Risk for allopurinol hypersensitivity (.69 per 1000 person years)

• Rate of AHS in younger ambulatory patients with normal kidney function not established

• Screening for HLAB5801 gene in individuals of Han Chinese/Thai descent

and the 'TINECK.  

the COLIC.  

PUNCH CURES THE GOUT.
Acknowledgements

U Nebraska
- Ted Mikuls MD MSPH

UAB
- Jeroan Allison, MD MS
- Jeffrey Curtis, MD MPH
- Mary Elkins
- Angelo Gaffo, MD, MSPH
- Pauline Jolly, PhD, MPH
- Beth Lewis MD, MSPH
- Ryan Outman, MS
- Jeffrey Rosman, PhD
- Jasvinder Singh, MD, MPH
- Gim Gee Teng, MD

U Penn CERTs
- Warren Bilker, PhD
- John Farrar, MD MSPH
- Shawn Fernandez
- Brian Strom, MD, MPH

HMO Research Network CERTs
- Leslie Harrold, MD MPH
- Arnold Chan, PhD
- Richard Platt, MD MPH
- Robert Yood, MD

United States Pharmacopeia
- Rodney Hicks, PhD, ARNP

U Minn
- David Jacobs, PhD

Grant U18 HS 10389