Diuretics, Potassium, Glucose Intolerance, and CVD Risk
What are the implications of differences in “new diabetes”?

• Keep in perspective in context of CVD differences observed in ALLHAT.

• Determine long-term morbidity/mortality consequences of thiazide-associated diabetes: observational studies/ALLHAT follow-up.

• Determine preventability/reversibility:
  --Weight control, increased physical activity
  --Maintain potassium balance

• Test combined regimens for reducing risk of DM.
ALLHAT Diabetics & Nondiabetics
Lisinopril/Chlorthalidone

Relative Risk and 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diabetics</th>
<th>Nondiabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.00 (0.87, 1.14)</td>
<td>0.99 (0.88, 1.11)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.02 (0.91, 1.13)</td>
<td>1.00 (0.91, 1.09)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07 (0.90, 1.28)</td>
<td>1.23 (1.05, 1.44)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.22 (1.05, 1.42)</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.08 (1.00, 1.17)</td>
<td>1.12 (1.05, 1.19)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.17 (0.87, 1.57)</td>
<td>1.05 (0.74, 1.48)</td>
</tr>
</tbody>
</table>

There is no difference in treatment group effect by baseline history of diabetes.
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- Keep in perspective in context of CVD differences observed in ALLHAT.
- **Determine long-term morbidity/mortality consequences of thiazide-associated diabetes:** observational studies (+ ALLHAT follow-up*).
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*Forthcoming data.
Diabetes on AHT & CHD risk: Samuelsson 1996

- 686 HT men treated with thiazide &/or β blocker, followed 15 yrs for RF’s, up to 22 yrs for NFMI or CHD death (133 events).
- Diabetes at baseline signif. associatd with CHD--RR 2.1 (1.1, 4.1), but incident diabetes was not—RR 1.5 (0.4, 6.0).
- No results reported separately by drug class. (At 10 yrs only 10% on thiazide but not β blocker.)

Glucose change on AHT and risk of MI: Dunder 2003

- 291 treated HT on thiazide &/or β blocker (66 on thiazide without β blocker) versus 1358 untreated men (mean BP 128/80).
- From age 50 to 60, FBG↑ 0.44 mmol/l more in HTs. (↑BMI 0.66 vs 0.46, p=0.07)
- MI incidence (253 events) after age 60—23.0% (HT) vs 13.5% (NHT) (p<0.001)

ΔFBG & MI (Dunder 2003), continued

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Treated HT Unadjusted RR per 1 S.D. (95% CI)</th>
<th>Non-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL FBG</td>
<td>1.04 (0.83, 1.28)</td>
<td>1.16 (1.01, 1.31)</td>
</tr>
<tr>
<td>Δ FBG</td>
<td>1.37 (1.16, 1.59)</td>
<td>1.14 (0.98, 1.32)</td>
</tr>
<tr>
<td>BL SBP</td>
<td>0.99 (0.75, 1.30)</td>
<td>1.27 (1.06, 1.50)</td>
</tr>
<tr>
<td>Δ SBP</td>
<td>0.96 (0.75, 1.22)</td>
<td>1.25 (1.07, 1.46)</td>
</tr>
</tbody>
</table>

Adjusted RR per 1 S.D. (95% CI)

| Δ FBG       | 1.50 (1.25, 1.78)*                          | 1.04 (0.86, 1.24)# |

*Δ SBP NOT INCLUDED  #Δ SBP INCLUDED
New diabetes and CVD risk: Verdecchia 2004

- 795 treated HTs, median FU 6 yrs.
- Diuretic rx (low-mod dose HCTZ or CLTD) independently predictive of new diabetes.
- Adjusted* RR (95% CI) of CVD-renal event (n=63)
  --BL DM, 3.57 (1.65, 7.73)
  --New DM, 2.92 (1.33, 6.41)
- Results for specific regimens not given, & only 11% on diuretic/β blocker alone.

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**DPP: Incidence of Diabetes**

- **Placebo (n=1082)**
- **Metformin (n=1073, p<0.001 vs. Placebo)**
- **Lifestyle (n=1079, p<0.001 vs. Metformin, p<0.001 vs. Placebo)**

**Risk reduction**
- **31% by metformin**
- **58% by lifestyle**
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Hypotheses

• Glucose intolerance/hyperglycemia ("dysglycemia") with thiazide use largely attributable to potassium depletion.
• Dysglycemia correctable/preventable by K+ repletion/maintenance.
• Any ↑ CVD risk with thiazide-associated dysglycemia attenuated by K+ repletion.
Potassium and glucose: Types of evidence

- 5 small (total N=42) depletion studies
  -- Normal human subjects
  -- K+ ↓ by diet, diuretic, or cation exchange
  -- Short-term follow-up (10 d – 6 wk)
- Long-term observational studies in treated hypertensive patients.
- Secondary analyses of clinical trials.
- Missing: specifically designed RCTs.
First clinical study: Saglid, 1961

• 3-period sequential design (11-14 days).
• 5 healthy young men on prepared diet.
• Combined glucose tolerance (GT)/insulin responsiveness test before potassium depletion via K+ exchange resin, right afterward, and following recovery.
• Results: reduced GT followed by recovery.
• No insulin resistance (IR).

Other clinical studies (I)

• Rapoport 1964
  --16 subjects with + family history or IFG
  --In 7, CTZ rx→↓GT in week 1, normalized with K+ repletion during week 2.

• Gordon 1973
  --In 5/5 healthy MF, 2 wks K+ depletion→↓GT; 2 wks K+ repletion normalized 4/5.
  --Mechanism: delayed INS release, no IR.

Other clinical studies (II)

• Rowe 1980
  -- 7 healthy M, low K+ intake + resin, for 1 week.
  -- Mild (mean 5%) depletion of total K+ $\rightarrow$ ↓GT proportional to ↓INS release; no IR.

• Helderman 1983
  -- 9 healthy men, 100 mg HCTZ for 10 days.
  -- In 7, also KCl (80 meq then adjusted for losses) $\rightarrow$ no changes in GT, INS sensitivity, etc.
  -- In 2, no KCl $\rightarrow$ sig. hypokalemia, ↓GT, ↓β cell rsp

HCTZ, potassium, & insulin sensitivity: Pollare 1989

- RCT of HCTZ, 25-50 mg, vs captopril, 50-100 mg, in XO design of 4-mo periods.
- FBG & INS levels ↑ in HCTZ gp compared with placebo period, & with captopril.
- INS Sensitivity by euglycemic clamp ↓ 15% with HCTZ, ↑ 19% with captopril.
- Correlation with change in serum K+ (r = -0.24) ns; total body K+ not measured.

Long-term study of treated hypertensives: Murphy 1982

- 34/137 (1-yr cohort) patients on high-dose thiazides with 4 GTTs over 14 years.
- 6→diabetes (3 with initial IGT), 7→IGT.
- No weight gain; no diff. by β blocker use.
- Persistently low K+ assoc. with IGT
  --<3.6 mm/l x 3→↑ 2h gluc by 2.7 mm/l
  --3.6+ mm/l x 3→↑ 2h gluc by 0.1 mm/l
- 7 mo post-thiazide, FG↓10%, 2h gluc ↓25%

Long-term study of treated hypertensives: Andersson 1991*

- 53 pts randomized to 2.5-5 mg BFMZ, with 8-16 meq KCl.
- In exams at 1 (n=53), 6 (n=49), and 10 years (n=45):
  --Mean serum K+ 4.0-4.2 meq/l at each visit, no ↓ total body K+.
  --No deterioration on OGTTT overall, only one patient developed DM.

*1 arm of RCT described in Bergland 1986.

EWPHE Sub-study: Amery 1978

- Placebo-controlled RCT in pts 60 and over
  - HCTZ, 25-50 mg/triamterene, 50-100 mg
  - FBG@1 (n=119), 2 (48), 3 (24) yrs, +/-GTT
- Effects on glucose clearest @ 2 years
  - Net FBG↑ of 12.7 mg/dl, ↑GTT “AOC”
  - Δglucose/ΔK+ correlation: ≈ - 0.4
  - No effects @ 1 yr, ↑FBG only @ 3 yrs
- Only 2 pts treated for new DM in each group

## EWPHE Substudy, contin.

<table>
<thead>
<tr>
<th>Range of ( \Delta K^+ ) @ 2 yrs</th>
<th>( \Delta FBG ) (n) @ 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.5 to -0.4</td>
<td>Diuretic: +14.1 (9), Placebo: +5.4 (5)</td>
</tr>
<tr>
<td>-0.3 to +0.2</td>
<td>Diuretic: +6.4 (9), Placebo: -3.1 (14)</td>
</tr>
<tr>
<td>+0.3 to +2.5</td>
<td>Diuretic: +5.3 (3), Placebo: -8.0 (7)</td>
</tr>
</tbody>
</table>
Potassium depletion appears to be a major intervening factor between thiazide treatment and dysglycemia.

• Evidence is incomplete; no RCT tested dysglycemia prevention by adequate K+ management.

• Both reduced insulin release and decreased insulin sensitivity have been demonstrated; findings not consistent.
Evidence conflicting re thiazide-associated dysglycemia increasing CVD risk.

- Positive studies do not distinguish diuretics from other drugs in regimen.
- Most DM occurring during thiazide rx is not caused by thiazide.
- RR may be attenuated by fluctuating K+ status; further analyses needed.
More attention than is often given to preventing or reversing hypokalemia is warranted, especially in patients at risk of diabetes.
Diuretics, Potassium, Glucose
Implications for Research

Well-designed randomized trials comparing various thiazide-based regimens for effects on potassium balance and glucose tolerance are needed.