Both Amiloride and Nebivolol Have a More Favourable Effect on Glucose Tolerance Than Hydrochlorothiazide in the Treatment of Essential Hypertension


Department of Clinical Pharmacology, Addenbrookes’ Hospital, Cambridge
Disclosures

• This study is an investigator-led study supported by an unrestricted grant from Menarini
Evidence to support thiazide use

- Thiazide and thiazide-like diuretics have been used for treatment of essential hypertension since the 1950’s
- Evidence for their inclusion in clinical guidelines is based on 4 decades of cardiovascular outcome trials
- Chlorthalidone was as beneficial as the comparator drugs in lowering blood pressure and preventing cardiovascular and renal outcomes
- Chlorthalidone was superior in preventing heart failure


Thiazides and new onset diabetes

- **ALLHAT**
  - 9.3% chlorthalidone
  - 7.2% amlodipine
  - 5.6% lisinopril

- **ASCOT**
  - 11.4% atenolol ± thiazide
  - 8.0% amlodipine ± perindopril

- **INSIGHT**
  - 5.6% co-amilozide
  - 4.3% nifedipine

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**Figure 6: Kaplan-Meier curves of cumulative incidence of new-onset diabetes mellitus**

New onset diabetes in ASCOT

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3Bjorn Dahlof et al; Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), Lancet 2005; 366: 895–906

4Morris J Brown et al; Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT), Lancet • Vol 356 • July 29, 2000
Mechanism: thiazides and diabetes

- Mechanism underlying the association of thiazides with diabetes is not understood.
- Not known if the principal defect is impaired insulin secretion or increased insulin resistance\(^5\).
- Changes in plasma potassium concentration may affect glucose tolerance\(^6\).

\(^5\)Barry L. Carter et al; Thiazide-Induced Dysglycemia, Call for Research From a Working Group From the National Heart, Lung, and Blood Institute, Hypertension 2008;52;30-36

Potassium sparing diuretics

- Few studies of glucose metabolism\(^7\)
- BP lowering efficacy of amiloride similar to thiazide in SALT\(^8,9\)
- Cardiovascular outcome studies not available


β₁-selective beta blockade

- Studies investigating metabolic effects of newer β₁-selective selective β-blockers have found them to be neutral or beneficial\(^\text{10}\)
- Outcome studies showing metabolic effects of atenolol used relatively high mean doses
- Our previous study showed no change in 2-hour glucose from baseline during an oral glucose tolerance test (OGTT) after 4 weeks treatment with atenolol\(^\text{11}\)

\(^{10}\text{Basile JN; One size does not fit all: the role of vasodilating beta-blockers in controlling hypertension as a means of reducing cardiovascular and stroke risk. }\text{Am J Med.}123(7\text{ Suppl 1}):\text{S9-15.}\)

\(^{11}\text{Stears AJ et al; Early Metabolic Changes with Thiazide or Beta Blocker Therapy for Essential Hypertension; , Poster Presentation BHS 2008}\)
Study objectives

• Primary objective
  – What are the changes from baseline in an OGTT after 4 weeks treatment with hydrocholorothiazide (HCTZ) compared with amiloride and nebivolol monotherapy and combination therapy with HCTZ/nebivolol?

• Secondary objective
  – What is the effect of each drug/drug combination on blood pressure?
Inclusion/exclusion criteria

Inclusion criteria

• 18-75 years
• BP untreated >140/90 and <170/110mmHg
• BP treated with drugs other than beta blockers or diuretics and BP>140/85mmHg

Exclusion criteria

• Previous intolerance of study drugs
• Diabetes
• Gout, asthma
• Heart failure, liver failure, renal failure, terminal illness
• Women of child bearing potential
• Inability to give informed consent
Study design

Randomised, double blind, placebo controlled, cross-over study

BP, 75g OGTT, and electrolytes measured at 0, 2 and 4 weeks for each phase of study

HCTZ - hydrochlorothiazide
Neb - nebivolol
Amil - amiloride
Baseline characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>17/20</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (41-75)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6 (4.2)</td>
</tr>
<tr>
<td>Baseline SBP (mmHg)</td>
<td>144.3 (13.7)</td>
</tr>
<tr>
<td>Baseline DBP (mmHg)</td>
<td>85.4 (9.9)</td>
</tr>
</tbody>
</table>

Results are mean (sd), except for age which is median (range)
OGTT at baseline and 4 weeks
Amiloride vs HCTZ

Mean 2-hour glucose 6.70 mmol/l on amiloride vs 7.49 mmol/l on HCTZ
OGTT at baseline and 4 weeks

Mean 2-hour glucose  6.77 mmol/l on nebivolol vs 7.49 mmol/l on HCTZ
BP at baseline, 2 and 4 weeks

Systolic BP

Diastolic BP
### Insulin and potassium at baseline and 4 weeks

<table>
<thead>
<tr>
<th></th>
<th>Amiloride</th>
<th>Nebivolol</th>
<th>HCTZ</th>
<th>Combination</th>
<th>Placebo</th>
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<tbody>
<tr>
<td><strong>30 min insulin</strong></td>
<td></td>
<td></td>
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<tr>
<td>(units)</td>
<td>0 wks</td>
<td>4 wks</td>
<td>0 wks</td>
<td>4 wks</td>
<td>0 wks</td>
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<tr>
<td></td>
<td>391.2</td>
<td>467.8†</td>
<td>373.3</td>
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<td>381.2</td>
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<tr>
<td>(297.4)</td>
<td>(267.6)</td>
<td>(250.6)</td>
<td>(257.8)</td>
<td>(223.6)</td>
<td>(253.5)</td>
</tr>
<tr>
<td><strong>K+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>0 wks</td>
<td>4 wks</td>
<td>0 wks</td>
<td>4 wks</td>
<td>0 wks</td>
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<tr>
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<td>4.1</td>
<td>4.5†</td>
<td>4.2</td>
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<tr>
<td>(0.3)</td>
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</table>

*p<0.05, †p<0.001
Negative correlation between change in 2-hour glucose and change in potassium between baseline and 4 weeks

\[ r = -0.28, \ p < 0.0001 \]
Results summary

• Glucose tolerance significantly impaired with HCTZ compared with amiloride or nebivolol
• Similar BP lowering with HCTZ, nebivolol and amiloride
• Combination therapy with HCTZ/nebivolol has better BP lowering efficacy
• Combination therapy has similar metabolic effects to HCTZ monotherapy
• Negative correlation between change in 2-hour glucose and change in plasma potassium
Conclusions

• Should amiloride or an amiloride/thiazide combination replace thiazides as the diuretic of choice?
  – BHF funded ‘Pathway 3’ study - Does a combination of HCTZ/amiloride have a metabolic advantage over HCTZ alone?

• β1-selective beta blockers appear to lack the deleterious effect on glucose tolerance previously reported for atenolol
Acknowledgments

• Study volunteers
• Prof MJ Brown
• Sarah Woods
• Michaela Watts
• Dr Johann Graggaber
• Dr Swe Myint
• Dr Fraz Mir
• Dr Tim Burton
• Staff on Clinical Investigation Ward
Questions?
## Result (mean±sd)

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>0 wks</td>
<td>4 wks</td>
<td>0 wks</td>
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<td>0 wks</td>
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<tr>
<td>(mmol/l)</td>
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<td>5.23</td>
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<td>(0.55)</td>
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<td>(0.59)</td>
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<td>(2.09)</td>
<td>(2.21)</td>
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<tr>
<td>(units)</td>
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<tr>
<td><strong>30 min insulin</strong></td>
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<td></td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>4.1</td>
<td><strong>4.5†</strong></td>
<td>4.2</td>
<td>4.3</td>
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<tr>
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<td>142.3</td>
<td><strong>131.2†</strong></td>
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<td>(15.0)</td>
<td>(14.7)</td>
<td>(16.2)</td>
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<tr>
<td><strong>DBP</strong></td>
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<td><strong>77.4†</strong></td>
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<td>(8.4)</td>
<td>(7.8)</td>
<td>(11.5)</td>
<td>(10.4)</td>
<td>(8.7)</td>
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</tbody>
</table>
Management of hypertension in adults in primary care
NICE guideline 34, June 2006

Choosing drugs for patients newly diagnosed with hypertension

**Abbreviations:**
A = ACE inhibitor
C = calcium-channel blocker
D = thiazide-type diuretic

Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients

**Step 1**
Younger than 55 years
- A

**Step 2**
A + C or A + D

**Step 3**
A + C + D

**Step 4**
Add
- further diuretic therapy
- alpha-blocker
- beta-blocker

Consider seeking specialist advice

**Beta-blockers**
- Beta-blockers are no longer preferred as a routine initial therapy for hypertension.
Clinical management of hypertension in adults
NICE clinical guideline 127, August 2011

[Flowchart showing decision-making process for hypertension management]
### Oral glucose tolerance test

<table>
<thead>
<tr>
<th></th>
<th>Fasting glucose (mmol/l)</th>
<th>2 hour glucose (mmol/l)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt; 6.0</td>
<td>&lt; 7.8</td>
</tr>
<tr>
<td>Impaired</td>
<td>6.1 - 7.0</td>
<td>7.8 - 11.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt; 7.0</td>
<td>&gt; 11.1</td>
</tr>
</tbody>
</table>
Diuretics for hypertension

- Diuretics inhibit sodium reabsorption from different parts of the nephron
- Thiazides - early distal tubule, inhibit sodium-chloride co-transporter (NCT)
- Amiloride - late distal tubule, inhibits epithelial sodium channel (ENaC)
Study Design

• Double-blind, placebo controlled, cross-over study

• Inclusion criteria: essential hypertension, BP >140/85mmHg, <170/110mmHg, no diabetes

• 5 active treatment phases, each phase separated by a 4-week placebo washout

• Patients supplied with home blood pressure monitor for duration of study