How to optimise the use of thiazide type diuretics: lessons from JNC VII

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India
What does JNC VII recommend?

Key messages

“Thiazide type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from the other classes.”

“If BP is more than 20/10 mm Hg above goal BP, consideration should be given to initiating therapy with 2 agents, 1 of which usually should be a thiazide-type diuretic.”
So, very clearly…

Whether as

In monotherapy

or

In combination

Thiazide type diuretic is almost always indicated
Because of...

Increasing evidence showing better/comparative BP control with these drugs and also excellent cardiovascular protection

Why is this important?
The goal in hypertension management

Not only

Reducing high blood pressure

But also

Reduction of morbidity & mortality from cardiovascular disease

What is this evidence?
Evidence from

JNC VI

...to JNC VII

STOP 2
PROGRESS
ALLHAT
STOP-2 shows…

- Blood pressure decreased similarly in all treatment groups

- Old and new antihypertensive drugs were similar in prevention of cardiovascular mortality or major events

PROGRESS shows…

Addition of a thiazide type diuretic to perindopril caused a 43% reduction in recurrent stroke occurrence.

Progress, Lancet 2001; 358 : 1033-1041
ALLHAT shows…

- **Thiazide type diuretics should be preferred for first step antihypertensive therapy**

- **Striking findings** –
  - **Diuretics are unsurpassed in lowering BP, reducing clinical events & tolerability.**
  - **Since a large no. of patients require more than one drug to control their BP, it is reasonable to infer that a diuretic be included in all multiple drug regimens if possible.**

*JAMA* 2002;288:2981-2997

*JAMA* 2002;288:3039-3041
To summarise...

1993 JNC V
Thiazide diuretics 1st line

1997 JNC VI
Thiazide diuretics 1st line

TOMHS

2003 JNC VII
STOP-2 PROGRESS ALLHAT

Logically diuretics will remain 1st choice
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Usual dose, range, mg/d</th>
<th>Daily frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Chlorothiazide</td>
<td>125-500</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td>12.5-25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>12.5-50</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Polythiazide</td>
<td>2-4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Indapamide</td>
<td>1.25-2.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Metolazone</td>
<td>0.5-1.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
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</table>
Which criteria would define an ideal thiazide type diuretic?

- Effective, importantly at low doses
- Additional cardiovascular benefits
- True once-daily
- Good safety profile
Ideal thiazide type diuretic

Efficacy
# Efficacy in Hypertensive Patients

## Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Indapamide SR 1.5 mg</th>
<th>Hydrochlorothiazide 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in SBP</td>
<td>-22.7 ± 15.4</td>
<td>-19.4 ± 15.5</td>
</tr>
<tr>
<td>Mean change in DBP</td>
<td>-11.8 ± 9.7</td>
<td>-10.8 ± 8.5</td>
</tr>
<tr>
<td>Patients with BP control (%)</td>
<td>75</td>
<td>67</td>
</tr>
</tbody>
</table>

*J of Hypertension 2001; 19:343-350*
## Efficacy in reducing systolic blood pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Indapamide SR 1.5 mg</th>
<th>Hydrochlorothiazide 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in SBP</td>
<td>-24.7 ± 12.3</td>
<td>-18.5 ± 11.2</td>
</tr>
<tr>
<td>Mean change in DBP</td>
<td>-6.1 ± 5.9</td>
<td>-3.1 ± 7.3</td>
</tr>
<tr>
<td>Patients with BP control (%)</td>
<td>84</td>
<td>71</td>
</tr>
</tbody>
</table>

*J of Hypertension 2001; 19:343-350*
The paradigm has shifted to systolic blood pressure.

**JNC VII recommends**

“In persons older than 50 years, systolic blood pressure of more than 140 mm Hg is a much more important cardiovascular risk factor than diastolic BP.”

“In the majority of patients controlling systolic hypertension has been considerably more difficult than controlling diastolic hypertension.”
Better than amlodipine in systolic blood pressure reduction

Mean decrease in SBP (mm Hg)

-12  -10  -6  0  5

Indapamide SR: -12
Amlodipine: -5

P=0.05

London G.J Hypertens. In press release
Better than enalapril in systolic blood pressure reduction

Mean decrease in SBP (mm Hg)

Indapamide SR

-23.8

Enalapril

-21

P=0.02

Ideal thiazide type diuretic

Additional cardiovascular benefits

Heart

LVH regression
LVH regression - why is it important?

LVH is common in hypertensive patients

LVH is an independent risk factor of cardiovascular mortality and morbidity

Regression of LVH with treatment improves cardiovascular prognosis
Prevalence of LVH
in different population groups

No hypertension | Hypertension | Hypertension + Diabetes
5% | 50% | 80%

The risk of CV events is 4 times greater with LVH.

5-year rate of total CV events (%)

- Normal LV mass: 6%
- LV hypertrophy: 24% (x4)

Casale PN, Devereux RB, Milner M et al, Ann Intern Med 1986;105:173-178
Evidence for thiazide type diuretics

Chlorthalidone

-40
-32
-24
-16
-8
0

Diuretic  Beta blocker  ACEI  Ca antagonist  alpha antagonist

Diuretic  Beta blocker  ACEI  Ca antagonist  alpha antagonist

Change in LVM (g) at 1 year

ACEI and diuretic similar

Hydrochlorothiazide

-40
-32
-24
-16
-8
0

Diuretic  Beta blocker  ACEI  Ca antagonist  alpha antagonist  Centrally acting agents

Diuretic  Beta blocker  ACEI  Ca antagonist  alpha antagonist

Change in LVM (g) at 1 year

Evidence for thiazide type diuretics-Indapamide SR

This is one of the most methodologically rigorous studies

Reduction of LVMI (g/m^2) was significantly greater with Indapamide SR as compared to enalapril

BP reduction (mmHg)

Indapamide SR

-8.4

Enalapril

-1.9

J Hypertens 2000;18:1465-1475
Why is indapamide SR superior in LVH regression?

…. because indapamide SR has a specific action on cardiac myocytes…. 

<table>
<thead>
<tr>
<th>Cardiomyocytes</th>
<th>Extracellular matrix proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Width: -16.3%</td>
<td>Collagen: -44.5%</td>
</tr>
<tr>
<td>Volume: -29.9%</td>
<td>Fibronectin: -49.6%</td>
</tr>
<tr>
<td></td>
<td>Laminin: -19.5%</td>
</tr>
</tbody>
</table>

Before treatment: 

After treatment: 

…. independent of its blood pressure lowering effect

Whereas the other thiazide diuretics

- Decrease LVH by reducing left ventricular volume
- No effect on thickness of the wall/septum

**Important because**

1 mm increase in thickness of posterior wall

7 fold increase in risk of death

Dahlof B. Am J Hypertension 1992;5:95-110
Cooper RS Am J Cardiol 1990; 65:440-445
Additional cardiovascular benefits

Kidney

Reducing microalbuminuria
Type 2 diabetic patients with microalbuminuria

- Evidence with hydrochlorothiazide vs enalapril
  - No reduction in microalbuminuria seen with hydrochlorothiazide

- Evidence with indapamide SR vs enalapril
  - Equivalent reduction in microalbuminuria with both drugs

BMJ 1993; 306: 175-182;
J of Hypertension 2004, 22: 1613-1622
Ideal thiazide type diuretic

Additional cardiovascular benefits

Brain

Stroke prevention
Secondary stroke prevention

As per JNC VII

Indapamide SR is the only evidence based thiazide type diuretic to have shown reduction in recurrent stroke
# Secondary stroke prevention

## PROGRESS study

<table>
<thead>
<tr>
<th>ACEI + indapamide</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent stroke</td>
<td>43%</td>
</tr>
<tr>
<td>Major vascular events</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Progress, Lancet 2001; 358: 1033-1041*
Ideal thiazide type diuretic

True once-daily
True once-daily

- Better compliance
- Control of hypertension is persistent and smooth
- Protection against the early morning surge in BP
## Trough to peak ratio

<table>
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<tr>
<th>Thiazide type diuretics</th>
<th>Trough to peak ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>71</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>41</td>
</tr>
<tr>
<td>Indapamide SR</td>
<td>89</td>
</tr>
</tbody>
</table>

*www.pharmacol-fr.org*
*Arch Mal Coeur Vaiss 1996:2-12*
Indapamide SR 1.5mg – unique patented hydrophilic matrix

Powerful antihypertensive efficacy over 24 hours

Improved kinetic profile

Improved efficacy-acceptability ratio
Ideal thiazide type diuretic

Safety
Safety

- **Hypokalemia**
  - Incidence 4 times higher with hydrochlorothiazide as compared to indapamide SR\(^1\)

- **Creatinine clearance**
  - Improved with indapamide SR whereas fell in all patients on hydrochlorothiazide\(^2\)

- **Sexual dysfunction**
  - No impairment with indapamide SR\(^3\) whereas 17.1% with chlorthalidone\(^4\)

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In conclusion…

JNC VII recommends

Thiazide type diuretic as first line drugs

In monotherapy

In combination
In conclusion…

Amongst the thiazide type diuretics, indapamide SR could be the drug of choice

◆ Is as effective- even more in reducing SBP
◆ Additional cardiovascular benefits
  ✷ Heart, Kidney and Brain
◆ Is a true once daily
◆ Excellent safety profile
Thank You