First line treatment of primary hypertension

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No Conflict of Interest

COI Policy
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OUTLINE
First line treatment

- SBP/DBP levels
- Research question
- Goal of Rx - hierarchy of outcomes
- BP lowering versus reduction in clinically relevant outcomes
- First line drug and dose
- Beta-blockers vs. other drug classes
- Evidence versus Guideline recommendations
Importance of BP levels

1. **Diagnosis** of hypertension

3. **Initiation** of therapy

4. Antihypertensive drugs are **approved** based on their BP lowering efficacy as compared to placebo control.

4. Dose **titration** and addition of second drug, third drug ..... is based on an attempt to achieve a **target BP** < 140/90 mmHg
Mean BP

Reduction in resting Mean BP leads to decrease in stroke, MI, and cardiovascular related mortality.

1. Does greater reduction in the magnitude of the mean BP with an antihypertensive drug therapy provide greater benefit?
Mean BP

2. Does similar reduction in the magnitude of mean BP with different antihypertensive drug classes lead to similar benefit?

3. Does reduction in magnitude of the mean BP explain all the benefit in terms of reduction in stroke or CHD?

What about BP variability?
What kind of evidence would you look for?

RCT evidence of antihypertensive drug versus placebo or no treatment

Evidence from a single RCT

OR

Systematic review of all RCTs
Meta-analysis of several RCTs vs. findings from a single RCT

• Combining several RCTs help increase the power to detect a statistically significant difference

• It provides a more accurate estimate of the overall effect with a narrow 95% CI
Meta-analysis of several RCTs vs. findings from a single RCT

• It determines whether **consistent benefit is seen** when the experiment is repeated several times in different clinical settings.

• It **detect differences in outcomes** between different RCTs and helps explore reasons for those differences (heterogeneity).
Published in Cochrane Library

Wright JM, Musini VM. **First-line drugs for hypertension.** *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.:CD001841. DOI: 10.1002/14651858.CD001841.pub2.
Research question - PICOS

**Q** Based on RCTs do first-line antihypertensive drugs as compared to placebo or untreated control provide a mortality and morbidity advantage in adult patients with primary hypertension?

**P** - Adult patients with primary hypertension  
**I** - Antihypertensive drugs  
**C** - Placebo or untreated control  
**O** - All cause mortality, stroke, CHD  
**S** - Randomized controlled trials of at least one year duration
First line treatment of primary hypertension

- Therapy can be started from different classes: Thiazides, Beta-Blockers, ACE inhibitors, Angiotensin Receptor blockers, Renin Inhibitors, Alfa-blockers, Calcium Channel blockers

- First line drug [Most trials (18/24 trials) used stepped care approach - dose titration, addition of supplemental drugs allowed to achieve target BP]
First line treatment of primary hypertension

24 trials; N =58,000

Ambulatory patients recruited from primary care centres (99.7%);

Females: 45% of population

Mean age: 62 years; 6 trials were limited to patients over 60 years (Age range in other trials 21-80 yrs)

Most participants from Western industrialized countries (66% from Europe, 15% from USA)
First line treatment of primary hypertension

All trials excluded patients with angina, CHF

Some trials allowed patients with prior MI or stroke (not recent within previous 3 months)

Conclusions of this review are relevant to primary prevention setting with 73% of total randomized patients

Mean baseline BP – 168/94 mmHg
Hierarchical of health outcomes

Why is it important?

Although we initiate treatment and monitor therapy based on resting BP levels and measure efficacy based on magnitude of reduction of elevated BP in patients with hypertension.

The GOAL of therapy is to:

- Reduction in all cause mortality
- Reduction of total cardiovascular events
  [stroke, MI, heart failure, aortic aneurysm]
Evidence for thiazides

Based on **19 trials in 39,713 patients**

Divided as

**High dose** = starting dose of HCTZ = or > 50mg/day

**Low dose** = starting dose of HCTZ < 50mg/day

Weighted mean dose of thiazide in HCTZ equivalent was **90mg for high dose** and **24 mg for low dose**
Evidence for thiazides

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Stroke</th>
<th>CHD</th>
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<tbody>
<tr>
<td><strong>LD thiazide</strong></td>
<td></td>
<td></td>
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<tr>
<td>8 RCTs in</td>
<td>0.89(0.82, 0.97)</td>
<td>0.68(0.60, 0.77)</td>
<td>0.72(0.61, 0.84)</td>
</tr>
<tr>
<td><strong>19,874 patients</strong></td>
<td></td>
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<tr>
<td><strong>HD thiazide</strong></td>
<td></td>
<td></td>
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<tr>
<td>11 RCTs in</td>
<td>0.90(0.76, 1.05)</td>
<td><strong>0.47(0.37, 0.61)</strong></td>
<td>1.01(0.85, 1.20)</td>
</tr>
<tr>
<td><strong>19,839 patients</strong></td>
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</tbody>
</table>
Evidence for ACEI and low dose thiazides – similar efficacy lower cost

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Stroke</th>
<th>CHD</th>
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<tbody>
<tr>
<td><strong>ACEI</strong></td>
<td></td>
<td></td>
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<tr>
<td>3 trials</td>
<td><strong>0.83(0.72, 0.95)</strong></td>
<td><strong>0.65(0.52, 0.82)</strong></td>
<td><strong>0.81(0.70, 0.94)</strong></td>
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<tr>
<td>in 6002 patients</td>
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<td>in 19,874 patients</td>
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</table>
Evidence for beta-blockers and Calcium channel blockers

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Stroke</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 trials in <strong>19,313</strong> patients</td>
<td>0.96(0.86, 1.07)</td>
<td>0.83(0.72, 0.97)</td>
<td>0.90(0.78, 1.03)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>0.86(0.68, 1.09)</td>
<td>0.58(0.41, 0.84)</td>
<td>0.71(0.45, 1.12)</td>
</tr>
<tr>
<td>1 RCT in <strong>4695</strong> patients</td>
<td></td>
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</table>
Evidence for ARBs and Alpha blockers

No RCT identified that met inclusion criteria.
Magnitude of BP lowering

BP data in this review is heterogeneous

- Because of the number of drugs used in different trials differ
- 16/24 trials were double blind
- BP measurements subjected to bias if observer and patient know what they are receiving

Therefore it was **not possible to assess the BP lowering efficacy of different classes of drugs** or to compare LD and HD thiazides.
Target BP levels

- Target was achieved in 60% of patients

- Target was not achieved in 40% of patients despite dose titration and addition of supplemental drugs

- This also does not mean that patients who do not achieve targets benefit less than those who do, as BP reduction is only partly responsible for the risk reduction of antihypertensive treatment (Boissel 2005)
BP levels – Surrogate outcome

- Lowering of BP is inadequate in predicting health outcomes with antihypertensive therapy.

- Difference in impact of LD and HD thiazide therapy on incidence of CHD despite similar reduction in BP.

- BP lowering with ACEI was greater than LD thiazides but effect on mortality and morbidity was same.
What does evidence show?

CONCLUSIONS

• Start with **LD thiazide - HCTZ 12.5 mg or equivalent**

• **Increase dose if necessary**

• **Do not exceed** 50mg of HCTZ or equivalent

• The fact that **thiazides are similar or more effective** in reducing mortality and morbidity than other drug classes and that evidence is more robust for thiazides is reason itself to prescribe them first in most patients with hypertension

• **Value of this approach** is magnified by the fact that thiazides are **much less expensive** than other classes.
Why BB should not be used in patients with primary hypertension?

Wiysonge et al 2007 CDSR

<table>
<thead>
<tr>
<th></th>
<th>BB vs Diuretics 5RCTs N = 18,241</th>
<th>BB vs. CCB 4RCTs N = 44,825</th>
<th>BB vs ACEI and ARBS 3RCTs N = 10,828</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>1.04 (0.91, 1.19)</td>
<td><strong>1.07 (1.00, 1.14)</strong></td>
<td>1.10 (0.98, 1.24)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>1.17 (0.65, 2.09)</td>
<td><strong>1.24 (1.11, 1.40)</strong></td>
<td>1.30 (1.11, 1.53)</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td>1.12 (0.82, 1.54)</td>
<td>1.05 (0.96, 1.15)</td>
<td>0.90 (0.76, 1.06)</td>
</tr>
</tbody>
</table>
Beta-blocker conclusions
Wiysonge et al 2007

Conclusions
“Thirteen RCTs were found and these trials suggested that first-line beta-blockers for elevated blood pressure were not as good at decreasing mortality and morbidity as other classes of drugs: thiazides, calcium channel blockers, and renin angiotensin system inhibitors”.

Evidence versus Canadian Guidelines

“Initial therapy should be monotherapy with a thiazide diuretic (Grade A); a beta-blocker (in patients younger than 60 years of age, Grade B); an ACE inhibitor (in nonblack patients, Grade B); a long-acting CCB (Grade B) or an ARB (Grade B).”
Evidence versus Guidelines

“The 2007 European Society of Hypertension/Cardiology guidelines on the management of hypertension concluded that the amount of BP reduction is the major determinant of reduction in CVS risk in patients with hypertension, not the choice of antihypertensive drug”.
“In the absence of a specific indication, there are three main classes of drugs that have been used for initial monotherapy: thiazide diuretics, long-acting calcium channel blockers (most often a dihydropyridine), and ACE inhibitors or angiotensin II receptor blockers (ARBs). Each of these classes of drugs have been equally effective in monotherapy trials if the attained blood pressure is similar”.
THANK-YOU
Any Questions??