Hypertension Update 2008

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Definition of Hypertension

- Continuous variable
- At some point the risk becomes high enough to justify treatment
- Treatment decisions based on overall risk
- The higher the risk the lower the threshold for treatment
- Office BP taken in sitting position with arm at the level of the heart is long standing standard
Is Systolic or Diastolic BP more important

• Younger patients – diastolic BP is more important
• After the age of 50 diastolic BP gradually falls and systolic BP becomes more important
24 hour Ambulatory BP

- Better correlation with end organ damage
- Better correlation with cardiovascular events
- Impractical to do in everyone
Blood pressure Treatment thresholds and Targets

• Depends on risk profile of the patient
• 140/90 recommended by most guideline groups
• The lower the better down to 110/70
• Lower has been proven to be better for high risk groups, cardiovascular disease, renal disease
24hr BP measurement

<table>
<thead>
<tr>
<th></th>
<th>24 h</th>
<th>Daytime</th>
<th>Nighttime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal BP</td>
<td>&lt;115/75</td>
<td>&lt;120/80</td>
<td>&lt;100/65</td>
</tr>
<tr>
<td>Normal BP</td>
<td>&lt;125/75</td>
<td>&lt;130/85</td>
<td>&lt;110/70</td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td>&gt;130/80</td>
<td>&gt;140/85</td>
<td>&lt;120/70</td>
</tr>
</tbody>
</table>

Main uses of 24 Hr BP are, suspected white coat hypertension, resistant hypertension, end organ damage with “normal BP”

Other uses ? Borderline BP, labile hypertension
Role of home BP measurements?

- Increasing use in most western countries
- Devices cheaper and more reliable (avoid in AF and frequent ectopics)
- 2 BP’s at 5 min intervals morning and night for 7 days
- Often show BP is better than office BP
- May stop additional medication and over-treatment
Masked hypertension

• abnormal 24hr or home BP with normal office pressure
• suspect in patients with evidence of end organ damage and normal office BP
• Said to occur in 10% of patients in large population studies using 24Hr BP monitoring
Significance of intermittent BP elevations

- White coat hypertension
- Sporadic spikes in BP – labile hypertension
- Prognosis not quite normal
- Higher risk of more sustained BP later in life
- Lifetime risk of cardiovascular complications increased
Obesity and Hypertension

- Bogalusa heart study tracked children over many years into adulthood and showed a strong correlation between BMI and hypertension in middle age.
- Weight loss often difficult to achieve and effects on BP are variable.
Salt and Hypertension

- Reduced salt intake over many years reduces cardiovascular risk independent of initial BP.
- Salt restriction in hypertensive patients with normal renal function has very modest effect on BP.
- Very low salt diets relatively ineffective at reducing BP in most patients.
Obstructive Sleep Apnea

- Sleep apnea a common cause of HT
- CPAP reduces BP
- Reductions may be dramatic
- Common cause of resistant hypertension
Non Steroidal Anti-inflammatory drugs

• In some patients make BP much more difficult to control
• Also applies to Cox2 inhibitors
• Careful evaluation of the need for these drugs in hypertensive patients with difficult control
Alcohol and BP

- Intake of up to 2 drinks per day has no effect on BP
- Increased BP at greater levels especially in men
Etiology of Hypertension

- “Primary” in vast majority of cases
- Genetic basis has proved elusive
- Even in animal models of hypertension candidate genes not easily identified
- Human genome study found no significant gene association for hypertension
Secondary Hypertension

- Suspect in young patients with severe hypertension, older patient with resistant hypertension
- Renal Artery stenosis, FMD versus atherosclerosis
- Coarctation of Aorta
- Pheochromocytoma
- Conn's syndrome
Drug Therapy of Hypertension

Diuretics

• Differences between thiazides (longer acting chorthalidone more effective in some studies than hydrochclorthiazide)
• May cause gout and abnormal glucose metabolism
• Spironolactone – impressive BP drop when added to 3 drugs in ASCOT study – average 22/11
• Often good effect at 25mg
• Need to monitor K
• Gynecomastia a problem in some (dose related)
# B Blockers

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Weak to none</th>
<th>Some evidence</th>
<th>Strong evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (uncomplicated)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post MI</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Stable angina without MI</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative (noncardiac surgery)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOCM</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HOCM = hypertrophic obstructive cardiomyopathy; MI = myocardial infarction.

Source: Cardiosource © 2008 American College of Cardiology
### B Blockers in Hypertension

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Parameter</th>
<th>No. of Trials</th>
<th>Mortality</th>
<th>Myocardial Infarction</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane (2007)</td>
<td>Overall</td>
<td>4</td>
<td>0.99 (0.88-1.11)</td>
<td>0.93 (0.81-1.07)</td>
<td>0.80 (0.66-0.96)</td>
</tr>
<tr>
<td>Bradley et al. (2006)</td>
<td>Overall</td>
<td>4</td>
<td>0.99 (0.88-1.11)</td>
<td>0.93 (0.81-1.07)</td>
<td>0.80 (0.66-0.96)</td>
</tr>
<tr>
<td>Khan et al. (2006)</td>
<td>Younger</td>
<td>2</td>
<td>0.94 (0.79-1.10)</td>
<td>0.85 (0.71-1.03)</td>
<td>0.84 (0.65-1.10)</td>
</tr>
<tr>
<td>Khan et al. (2006)</td>
<td>Elderly</td>
<td>5</td>
<td>0.91 (0.74-1.12)</td>
<td>0.98 (0.83-1.16)</td>
<td>0.78 (0.63-0.98)</td>
</tr>
<tr>
<td>Lindholm et al. (2005)</td>
<td>Overall</td>
<td>7</td>
<td>0.95 (0.86-1.04)</td>
<td>0.93 (0.83-1.05)</td>
<td>0.81 (0.71-0.93)</td>
</tr>
<tr>
<td>Carlberg et al. (2004)</td>
<td>Overall</td>
<td>4</td>
<td>1.01 (0.89-1.15)</td>
<td>0.99 (0.83-1.19)</td>
<td>0.85 (0.72-1.01)</td>
</tr>
</tbody>
</table>

Numbers represent hazard ratio (95% confidence interval). Source: Cardiosource © 2008 American College of Cardiology
B Blockers - summary

- Reduce stroke but about half as well as other drugs
- Do not reduce cardiac or total mortality – especially atenolol
- Less effective at reducing central BP than other drugs
- Higher discontinuance rate in drug trials and associated with a small weight gain
- Increase insulin resistance, may not apply to newer vasodilating B Blockers
Renin Angiotensin system

- Renin released by kidney, converts the peptide angiotensinogen to angiotensin1.
- Angiotensin 1 is converted by angiotensin converting enzyme to angiotensin 2
- Angiotensin 2 is bioactive and acts on receptors to cause a number of different actions
  - vasoconstriction increasing BP
  - Releases aldosterone from the adrenal gland and vasopressin from pituitary (water and salt retention increasing BP)
- Has specific tissue effects that promote release of many mediations involved in metabolic processes
Blocking the renin angiotensin system RAS

- Angiotensin converting inhibitors ACE
- Angiotensin receptor blockers ARB
- Direct renin inhibitors DRI

- May be a benefit of using more than 1 agent to more completely block the RAS
- Particularly important in high risk patients
Angiotensin Receptor Blockers

• In NZ used primarily in patients with side effects from ACE inhibitors
• Overseas, primary treatment for the majority of patients because they have less side effects and are as, or more effective
• Relaxation for Losartan – cough on 1 ACE. Can be added to ACE for BP and CHF
ACCOMPLISH: A Novel Hypertension Trial

• Traditional approach to hypertension management:
  – Initiate monotherapy then sequentially add medications to achieve target BP

• ACCOMPLISH:
  – Initiate single tablet combination therapy in high-risk hypertension
  – Specific combinations may confer target organ protection in addition to their BP-lowering effects
ACCOMPLISH: Design

Screening
Amlodipine 5 mg + benazepril 20 mg

Randomization
Benazepril 20 mg + HCTZ 12.5 mg

Amlodipine 5 mg + benazepril 40 mg

Month 1
Benazepril 40 mg + HCTZ 12.5 mg

Amlodipine 5 mg + benazepril 40 mg

Month 2
Benazepril 40 mg + HCTZ 25 mg

Free add-on antihypertensive agents*

Month 3

Free add-on antihypertensive agents*

Month 4

Titrated to achieve BP < 140/90 mmHg; < 130/80 mmHg in patients with diabetes or renal insufficiency

*Beta blockers; alpha blockers; clonidine; (loop diuretics).

Jamerson KA et al. Am J Hypertens. 2003;16(part2)193A
Kaplan Meier for Primary Endpoint

- Cumulative event rate
- HR (95% CI): 0.80 (0.72, 0.90)
- 20% Risk Reduction
- Time to 1st CV morbidity/mortality (days)
- $p = 0.0002$
- ACEI / HCTZ
- CCB / ACEI
- INTERIM RESULTS Mar 08
Primary Endpoint and Components

- Composite CV mortality/morbidity
- Cardiovascular mortality
- Non-fatal MI
- Non-fatal stroke
- Hospitalization for unstable angina
- Coronary revascularization procedure
- Resuscitated sudden death

Risk Ratio (95%)

- Composite CV mortality/morbidity: 0.80 (0.72–0.90)
- Cardiovascular mortality: 0.81 (0.62–1.06)
- Non-fatal MI: 0.81 (0.63–1.05)
- Non-fatal stroke: 0.87 (0.67–1.13)
- Hospitalization for unstable angina: 0.74 (0.49–1.11)
- Coronary revascularization procedure: 0.85 (0.74–0.99)
- Resuscitated sudden death: 1.75 (0.73–4.17)

INTERIM RESULTS Mar 08
Summary

• Single tablet combination therapy was initiated in 11,462 high risk hypertensive patients

• After mean follow-up of 39 months,
  – The combination of ACEI / CCB was superior to ACEI / diuretic
  – CV morbidity / mortality was reduced by 20% (p=0.0002)
  – Hard CV Endpoint (CV death, stroke and MI) was reduced by 20% (p=0.007)
Approach to treatment

- Different national organizations have different recommendations
- Most controversial are NICE (UK) - excludes B Blockers
- Cost of drugs less of an issue with generics now available and much reduced prices for ACE inhibitors
Younger Patients

• Longer acting ACE inhibitor
• Followed by Calcium channel blocker
• Followed by diuretic/ACE combination
• Followed by B Blocker
• Followed by spironolactone

• Use ARB if intolerant of ACE
• Use B Blocker earlier if have IHD
Older patients

- Diuretic or CCB first
- Followed by ACE/diuretic combination
- Followed by spironolactone
- Followed by B Blocker

- Start with ACE in diabetics
- B Blockers earlier in IHD patients