Risk factor modification
Blood pressure/cholesterol etc

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Objectives
To be able to design an effective, safe and cost-effective therapeutic plan for the treatment of patients with high blood pressure/cholesterol

Non-drug measures
Activity
Nutrition
Lose weight
Smoking?
Salt?
Potassium

Drug-Induced
Prescription Drugs:
NSAIDs, including coxibs
Corticosteroids and anabolic steroids
Oral contraceptive and sex hormones
Vasoconstricting/sympathomimetic decongestants
Calcineurin inhibitors (cyclosporin, tacrolimus)
Erythropoietin and analogues
Monoamine oxidase inhibitors (MAOIs)
Midodrine
Other substances: Licorice root. Stimulants including cocaine, Salt, Excessive alcohol use

High Blood Pressure
Measurement
must be determined under relaxed conditions and should be done on at least 3 separate occasions (3 sets of 3 readings with an interval of at least 2 weeks between readings unless the initial level is very high >120 mmHg or target organ damage is present)
patient should sit or lie down quietly for at least five minutes before blood pressure measurement
avoid smoking or eating within the 30 minutes prior to measurement

Smoking and risk

From CHEP 2006
BMI and risk

Lancet 2006;368:666–78

BMI and risk
Age 70-75


Quality of life comparisons

<table>
<thead>
<tr>
<th>Condition</th>
<th>QOL utilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild stroke</td>
<td>0.70</td>
</tr>
<tr>
<td>Angina</td>
<td>0.64</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>0.66</td>
</tr>
<tr>
<td>Comprehensive diabetes care</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Diabetes Care 2007;30:2478-83

Patient values and risk assessment

“As in previous years, it needs to be reiterated that the CHEP hypertension management recommendations are based solely on efficacy data. Considerations relating to individual patient/physician preferences and cost-effectiveness of different drug classes have not been a component of this process and need to be considered by the physician and patient when individualizing therapy”

Describing Benefits

The chance
WITH NO TREATMENT

The chance
WITH TREATMENT

Risk of what and over how long
Definitions

WHAT
CVD is cardiovascular disease
Typically = CHD + cerebrovascular
CHD = coronary heart disease = fatal and non-fatal MIs and sometimes angina
Cerebrovascular disease = fatal and non-fatal strokes - and sometimes TIs
CVD sometimes includes other conditions - heart failure, peripheral vascular disease

HOW LONG - 5 or 10 years
How accurately can we predict risk?


How good is the Framingham risk estimate?

UK - overestimates mortality from CHD by 47% and non-fatal CHD by 57%

Germany, Italy, and Denmark - overestimates risk by 50%

BMJ 2003;327:1-6
What do you REALLY need to know to make a reasonable estimate of CVD risk???

Similar findings

CHOLESTEROL OR CRP really not needed

**Factors to consider when choosing a drug**

1. Efficacy at lowering risk of cardiovascular disease
2. Tolerability/allergies
3. Frequency of dosing
4. "2-fers" - for blood pressure
5. Cost

**Lipid-lowering drugs**

<table>
<thead>
<tr>
<th>Table 4: Lipid-lowering Agents</th>
<th>Effect on Lipoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>LDL</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>iii</td>
</tr>
<tr>
<td>Nicotinic</td>
<td>ii</td>
</tr>
<tr>
<td>Fibrate</td>
<td>++</td>
</tr>
<tr>
<td>Rosuvatil</td>
<td>++</td>
</tr>
</tbody>
</table>
Evidence for CVD benefit - typically over 5 years

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Total stroke</th>
<th>Total CHD</th>
<th>Total CVD</th>
<th>Withdrawal due to adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE (%)</td>
<td>7</td>
<td>3-4</td>
<td>3-4</td>
<td>8-9</td>
<td>3</td>
</tr>
<tr>
<td>Thiazide</td>
<td>0.89</td>
<td>0.63</td>
<td>0.84</td>
<td>0.70</td>
<td>3.22 (2.90, 3.57)</td>
</tr>
<tr>
<td>BB</td>
<td>0.96</td>
<td>0.83</td>
<td>0.90</td>
<td>0.89</td>
<td>4.59 (4.15, 5.13)</td>
</tr>
<tr>
<td>CCB</td>
<td>0.86</td>
<td>0.58</td>
<td>0.77</td>
<td>0.71</td>
<td>NR</td>
</tr>
<tr>
<td>ACEI</td>
<td>0.83</td>
<td>0.65</td>
<td>0.81</td>
<td>0.76</td>
<td>0.67 (0.85)</td>
</tr>
</tbody>
</table>

Treatment of Hypertension in the Elderly typically over 5 years - 2-3 years for the over 80

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>CV mortality and morbidity</th>
<th>Withdrawal due to adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE (%)</td>
<td>12</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>60 years or older</td>
<td>0.9</td>
<td>0.72</td>
<td>1.71 (1.45, 2.00)</td>
</tr>
<tr>
<td>BASELINE (%)</td>
<td>14</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>80 years or older</td>
<td>0.98</td>
<td>0.75</td>
<td>0.65 (0.87)</td>
</tr>
</tbody>
</table>

Cochrane Library

Treatment blood pressure targets for hypertension (Review)

Arguedas JA, Perez MI, Wright JM

Objective:
To determine if lower BP targets (135/85 mmHg) are associated with reduction in mortality and morbidity as compared with standard BP targets (140-160/90-100 mmHg)


7 RCTs, N=22,089

Despite a -4/-3 mmHg greater achieved reduction in systolic/diastolic BP, p< 0.001, attempting to achieve “lower targets” instead of “standard targets” did not change

total mortality (RR 0.92, 95% CI 0.86-1.15)
myocardial infarction (RR 0.90, 95% CI 0.74-1.09)
stroke (RR 0.99, 95% CI 0.79-1.25)
heart failure (RR 0.88, 95% CI 0.59-1.32)
major cardiovascular events(RR 0.94, 95% CI 0.83-1.07)
end-stage renal disease (RR 1.01, 95% CI 0.81-1.27)

“Antihypertensive drugs used in the treatment of adults (primary prevention) with mild hypertension (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) have not been shown to reduce mortality or morbidity in RCTs.”

“Treatment caused 9% of patients to discontinue treatment due to adverse effects.”

August 2012

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**6 year data**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Fatal CHD or non-fatal MI (%)</th>
<th>Mortality (%)</th>
<th>Combined CHD (%)</th>
<th>Stroke (%)</th>
<th>Combined CVD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>11.5</td>
<td>17.3</td>
<td>19.9</td>
<td>5.6</td>
<td>30.9</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>11.3</td>
<td>16.8</td>
<td>19.9</td>
<td>5.4</td>
<td>32.0</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>11.4</td>
<td>17.2</td>
<td>20.8</td>
<td>6.3</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Relative risk reduction: NSS

Absolute risk reduction: 11* 7*

NNT: 143 42

* p <0.05 lisinopril vs. chlorthalidone

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**Meta-analysis of 4 HTN trials**

6,825 patients - atenolol versus placebo/no treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All deaths (%)</th>
<th>CVD death (%)</th>
<th>MIs (%)</th>
<th>Strokes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>13.0</td>
<td>7.8</td>
<td>7.2</td>
<td>8.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.3</td>
<td>8.0</td>
<td>7.3</td>
<td>8.2</td>
</tr>
</tbody>
</table>

RR: NSS

ARR: 0.9

NNT: 111 143

Lancet 2004;364:1684–9

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**ALLHAT - high-risk hypertensive patients randomized to ACE inhibitor or calcium channel blocker vs. diuretic**

Patients

33,357 patients with hypertension and 1 or more risk factors - mean age 67, 47% women, diabetics (36%), history of heart disease (25%), smoker (22%), HDL < 0.9 mmol/L (12%)

Treatment

chlorthalidone, amlopidine or lisinopril – 2nd line therapy allowed was atenolol, clonidine or reserpine

Duration

4.9 years

Results

Blood pressure differences at 5 years compared with chlorthalidone group

Systolic – amlodipine 0.8 mmHg higher, lisinopril 2.0 mmHg higher

Diastolic – amlodipine 0.8 mmHg lower, lisinopril no difference

**Meta-analysis of 5 HTN trials**

17,671 patients - atenolol versus other agents (thiazides,ACEI CCB)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All deaths (%)</th>
<th>CVD death (%)</th>
<th>MIs (%)</th>
<th>Strokes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>8.0</td>
<td>5.1</td>
<td>4.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Other</td>
<td>7.1</td>
<td>4.4</td>
<td>4.5</td>
<td>4.2</td>
</tr>
</tbody>
</table>

RR: 11 14

ARR: 0.9 0.7

NNT: 111 143

Lancet 2004;364:1684–9
13 beta-blocker vs other anti-HTN trials
105,951 patients
No difference for MI or mortality, 16% more strokes in BB group
7 beta-blocker versus placebo or no treatment trials
27,433 patients
No reduction for MI or mortality, 19% decrease in stroke
(approx. 0.2% ARR?)
No change in any endpoint in either the atenolol or non-atenolol sub-group
Lancet Oct 18 2005

Levels and break points

**CHOLESTEROL**
There are NO studies that have looked at getting patients to different cholesterol levels

**BLOOD PRESSURE**
Less than 135/85 "Despite a -4/-3 mmHg greater achieved reduction in systolic/diastolic BP, attempting to achieve "lower targets" instead of "standard targets" did not change total mortality, MI, stroke, CHF, major CV events or ESRD" Cochrane Review 2009;Issue 3:CD004349

**DIABETES**
three end points - Overall CHD - Strokes, Overall Mortality
5 years - lower HbA1c by 1% - compared to "standard" treatment
CHD - they state there was a 1.5% ↓ in CHD one table ↓ from
Strokes - NSS, Mortality - NSS
Hypoglycemic events
↑ from 28.6% to 38.1% - Severe -1.2% to 2.3%
Participants gained 2.5 kg more in the intensive group Lancet 2009;373:1765–72

After initial change only measure every 3-5 years

Within-person coefficient of variation is ~7%
Single measurement
95% CI
Total chol ~ -0.80 to 0.80 mmol/L
LDL chol ~ -0.5 to 0.5 mmol/L

Ezetimibe

**Statins in secondary prevention**
10-20 mg - 5-6% ARR in MIs and strokes
Inc. dose 4-8X you get an additional 1-2% ARR

short-term variability - a combination of analytic variability and week-to-week biological fluctuation around a stable average

Baseline LDL
33% dec (10-20mg)
Add 10% dec (40-80mg)
95% CI +/-0.5
Arbitrary threshold
Tolerability

almost all high blood pressure medications produce a similar incidence of side effects and are equally well tolerated however, the types of side effects are different

Examples of “2-fers”
Ischemic heart disease (BB, CCB)
Previous MI (BB, ACEI)
CHF (DIUR, ACEI, BB, A2B)
COPD and asthma (avoid BB for asthma)
Type-2 diabetes (ACEI?, ARB? – avoid CCB?)
Type-1 diabetes (ACEI?)
Hyperlipidemia (avoid anything that would worsen lipids enough to require drug therapy)
Atrial fibrillation (BB, CB)
Migraine (BB, ACEI?)

Remember issue of betablockers

Key point
Start with a LOW!!!!!!! dose

Thiazides
TOXICITY (thiazides)
Hypokalemia
Gout
Hypomagnesemia
Hypercalcemia
Hyperlipidemia
Blood dyscrasias
Photosensitivity
Gynecomastia (spironolactone)

Betablockers
acebutolol (Sectral, Monitan)
atenolol (Tenormin, generics)
bisoprolol (Monocor)
carvedilol (Coreg)
nadolol (Corgard, generics)
metoprolol (Lopressor, Betaloc, generics)
oxprenolol (Trasicor, Slow-Trasicor)
propranolol (Inderal, Inderal LA, generics)
sotalol (Sotacor)
pindolol (Visken, generics)

Betablockers
CONTRAINDICATIONS
Asthma or chronic bronchitis with bronchospasm
Raynauds
Intermittent claudication?
Bradycardia, atrio–ventricular conduction defects
TOXICITY
Fatigue
Bradycardia
Asthma
CNS effects
Cold extremities
ACE Inhibitors

CONTRAINDICATIONS
Intolerance or allergic reaction to ACE inhibitors
Pregnancy
Rapidly worsening renal failure
Severe hypotension
Bilateral renal artery stenosis, unilateral renal artery stenosis in a patient with one kidney

TOXICITY
Acute renal failure - esp if volume depleted
Hyperkalemia
Hypotension
Dry cough
Rash, mucosal ulcerations
Angioedema

Angiotensin II receptor antagonists

CONTRAINDICATIONS
Intolerance or allergic reaction to ARBs
Pregnancy
Rapidly worsening renal failure
Severe hypotension
Bilateral renal artery stenosis, unilateral renal artery stenosis in a patient with one kidney

TOXICITY
Acute renal failure - esp if volume depleted
Hyperkalemia
Hypotension
Angioedema - reported

Calcium channel blockers

amlopidine (Norvasc)
diltiazem (Cardizem SR, Cardizem CD, generics)
felodipine SR (Plendil, Renedil)
nicardipine (Cardene)
nifedipine (Adalat, Adalat PA, Adalat XL, generics)
verapamil (Isoptin, Isoptin SR, generics)
### Calcium channel blockers

**CONTRAINDICATIONS**
- Severe left ventricular dysfunction (EF < 20-30%)
- Second- or third-degree AV block or sick sinus syndrome (unless a functioning ventricular pacemaker is in place)
- Wolff-Parkinson-White syndrome
- Wide-complex ventricular tachycardia

**TOXICITY**
- Hypotension
- Headache
- Bradycardia (verapamil)
- Dizziness or lightheadedness
- Exacerbation of congestive heart failure (verapamil)
- Constipation
- Peripheral edema
- Heart burn

### Alpha blockers

- prazosin (Minipress, generics)
- doxazosin (Cardura, generics)
- terazosin (Hytrin, generics)

### Centrally acting agents

- clonidine (Catapres, generics)
- methyldopa (Aldomet, generics)
- reserpine (Serpasil)

### When to stop

Stepped-down therapy should be considered in patients whose blood pressures during the previous few visits have been well controlled approximately 50% of patients with well-controlled blood pressures successfully undergo either a reduction in dosage or number of drugs and remain normotensive for a time

### How to stop

Very gradual dosage and drug discontinuation
- a precise discussion of why drug reduction is being done
- dosage should be reduced by 50%, with reassessment of blood pressure at 2 weeks
- if the patient is still normotensive, reduce the dosage by another 50% (i.e., to 25% of the initial dose) and recheck the blood pressure in another 2 weeks

### Lipid-lowering drugs

**Resins**
- cholestyramine
- colestipol (Colestid)

**Cholesterol Absorption Inhibitor**
- ezetimibe (Ezetrol)

**HMG CoA Reductase Inhibitors**
- atorvastatin
- fluvastatin (Lescol)
- lovastatin (Mevacor, generics)
- pravastatin (Pravachol, generics)
- rosuvastatin (Crestor)
- simvastatin (Zocor, generics)
### Lipid-lowering drugs

**Niacin (Nicotinic Acid) derivatives**
- niacin, immediate release
- niacin, slow release (SR)
- niacin, extended release (ER)

**Fibrates**
- bezafibrate (Bezalip)
- fenofibrate (Generics)
- fenofibrate microcoated (Lipidil Supra, generic)
- fenofibrate micronized (Lipidil Micro, generics)
- fenofibrate nanocrystals (Lipidil EZ, generics)
- gemfibrozil (Lopid, generics)

### Lipid-lowering drugs

**Resins**
- Common: Constipation (>10%), bloating, abdominal fullness, flatulence, ↑ triglycerides, ↑ transaminases (reversible).
- Rare: hyperchloremic acidosis, cholecystitis, cholelithiasis, pancreatitis, malabsorption syndrome, GI bleeding, peptic ulceration.

**Cholesterol Absorption Inhibitor**
- Common: back pain, arthralgia, diarrhea, abdominal pain, fatigue, dizziness, headache.
- Rare: myopathy, rhabdomyolysis, hepatitis, acute pancreatitis, thrombocytopenia.

**HMG CoA Reductase Inhibitors**
- Common: ↑ CPK, ↑ transaminases (reversible), mild upper GI disturbances, myalgias (with and without CPK elevation), sleep disturbances, headache, rash.

### Lipid-lowering drugs

**Niacin (Nicotinic Acid) derivatives**
- Common: hot flushes and pruritus, dry skin, acanthosis nigricans (reversible), reactivation of peptic ulcer, GI disturbances, ↑ blood glucose, glucose intolerance, uric acid and transaminases.
- Rare: torsades de pointes, severe hepatotoxicity (more frequent with slow-release formulation), ↑ blood glucose, uric acid, transaminases.

**Fibrates**
- Upper GI disturbances (nausea, abdominal pain, flatulence), myalgias, ↑ bile lithogenicity, ↑ CK, ↑ creatinine (not representative of renal function deterioration).