Practical Points in Hypertension Management

นครินทร์ ศันสนยุทธ
แผนกโรคหัวใจและหลอดเลือด
โรงพยาบาลพระมงกุฎเกล้า
๑๙ กรกฎาคม ๒๕๕๕
Overview

• Definition, classification of hypertension (HTN)
• Etiology
• Office BP, 24h ambulatory BP, Home BP
• Patient assessment
• Treatment
• Guidelines
What is the estimated prevalence of hypertension in Thailand?

a) 2-3%

b) 5%

c) 10%

d) 20%

e) 50%
Epidemiology: Hypertension in Asia

Hypertension affects approximately 1 billion people worldwide

- **China**: 27.2%
- **Malaysia**: 33%
- **Thailand**: 21% (>160/95)
- **Taiwan**: 25%
- **Korea**: 33.7%
- **Philippines**: 17.4%
- **Hong Kong**: 20%
- **Malaysia**: 33%

Refs:
What is the estimated prevalence of hypertension in Thailand?

a) 2-3%
b) 5%
c) 10%
d) 20%
e) 50%
Persons who are normotensive at age 55 have a .....% lifetime risk for developing HTN.

a) 10%

b) 20%

c) 40%

d) 60%

e) 90%
Residual Lifetime Risk of Hypertension in Women and Men Aged 65 Years

Adapted with permission from Vasan RS, et al. JAMA. 2002;287:1003-1010.
**Persons who are normotensive at age 55 have a ......% lifetime risk for developing HTN.**

a) 10%
b) 20%
c) 40%
d) 60%
e) 90%
### Definition and Classification of BP in European and US Adults: ESH–ESC and JNC 7 Guidelines

<table>
<thead>
<tr>
<th>BP category</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
<th>BP category</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESH–ESC</strong>¹</td>
<td></td>
<td></td>
<td><strong>JNC 7</strong>²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>&lt;120 &amp;</td>
<td>&lt;80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>120–129 &amp;/or</td>
<td>80–84</td>
<td>Normal</td>
<td>&lt;120 &amp;</td>
<td>&lt;80</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139 &amp;/or</td>
<td>85–89</td>
<td>Pre-HTN</td>
<td>120–139 or</td>
<td>80–89</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>140–159 &amp;/or</td>
<td>90–99</td>
<td>Stage 1</td>
<td>140–159 or</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>160–179 &amp;/or</td>
<td>100–109</td>
<td>Stage 2</td>
<td>≥160 or</td>
<td>≥100</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>≥180 &amp;/or</td>
<td>≥110</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated systolic HTN</td>
<td>≥140 &amp;</td>
<td>&lt;90</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

²Chobanian et al. JAMA 2003;289:2560–72
normal blood pressure in other age groups

a. neonates - 1 year = 60/40
b. 3-4 years of age = 70/50
c. 7 years of age = 100/70
d. teens to adult = 120/80
Magnitude of the hypertension

- 62% of strokes and 49% of CHD events attributed to elevated BP*
- 26% of adults worldwide (972 million) have hypertension**
- Estimated lifetime risk of developing hypertension is 90%***
- Most patients are asymptomatic!!

Rule of halves

- Only 1/2 have been diagnosed
- Only 1/2 of those diagnosed have been treated
- Only 1/2 of those treated are adequately controlled
- Thus, only 12.5% overall are adequately controlled
Why should hypertension be treated?

- ischaemia
- myocardial infarction
- cardiac hypertrophy
- congestive heart failure
- stroke
- TIA (transient ischaemic attack)
- PRIND (prolonged, reversible, ischaemic, neurological deficit)
- nephrosclerosis
- atrophy of nephrons
- renal failure
- retinopathy
- lesions
- swelling of optic disc
- blindness
Hypertension and Cardiovascular Risk

• Lowering BP has been associated with reductions in the incidence of
  – Stroke by 30–35%
  – MI by 20–25%
  – Heart failure by >50%

Ogden L et al. Hypertension 2000;35:539–43
Etiology of HT

- **Essential hypertension:**
  - > 90% of cases
  - hereditary component

- **Secondary hypertension:**
  - < 10% of cases
  - common causes: chronic kidney disease, renovascular disease
  - other causes: endocrine disorders, Takayasu, Coartation of aorta, medication/substance, OSA
Causes of 2° Hypertension

- **Prescription drugs:**
  - prednisone, fludrocortisone, triamcinolone
  - amphetamines/anorexiant: phendimetrazine, phentermine, sibutramine
  - antivascular endothelin growth factor agents
  - estrogens: usually oral contraceptives
  - calcineurin inhibitors: cyclosporine, tacrolimus
  - decongestants: phenylpropanolamine & analogs
  - erythropoiesis stimulating agents: erythropoietin, darbepoietin
Causes of 2° Hypertension

- Prescription drugs:
  - NSAIDs, COX-2 inhibitors
  - venlafaxine
  - bupropion
  - bromocriptine
  - buspirone
  - carbamazepine
  - clozapine
  - ketamine
  - metoclopramide
When to work up 2° HT

- Age < 35, (> 50 year)
- Severe HT, sudden onset
- Poorly controlled with multiple drug combination
- Increased BP in well controlled HT
- Specific features; cushing, hyperthyroidism
What is the most common cause of hypertension in a 33 years old man?

a) Essential hypertension

b) Co-arctation of aorta

c) Renovascular disease

d) drugs and substances abuse

e) Pheochromocytoma
The vast majority of cases of hypertension are of essential or idiopathic origin. Coarctation of the aorta, endocrine disorders and renal disease account for approximately 5 per cent of causes.
What is the most common cause of hypertension in a 33 years old man?

a) Essential hypertension
b) Co-arctation of aorta
c) Renovascular disease
d) drugs and substances abuse
e) Pheochromocytoma
Evaluate hypertensive patients

- Level of BP
- Target organ damage
- Other CV risk factors
CV Mortality Risk Doubles with Each 20/10 mm Hg BP Increment*

*Individuals aged 40-69 years, starting at BP 115/75 mm Hg.
CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure
JNC VII. JAMA. 2003.
SBP Reductions as Little as 2 mm Hg Reduce the Risk of CV Events by Up to 10%

- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years

Measurement of BP
Arterial Blood Pressure

- **Sphygmomanometer**

- **MAP** = \( \frac{(SBP) + 2 \ (DBP)}{3} \) = DBP + 1/3(PP)

- **BP** = CO x TPR
# BP Measurement Techniques

<table>
<thead>
<tr>
<th>Method</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-office</strong></td>
<td>Two readings, 5 minutes apart, sitting in chair. Confirm elevated reading in contralateral arm.</td>
</tr>
<tr>
<td><strong>Ambulatory BP monitoring</strong></td>
<td>Indicated for evaluation of “white-coat” HTN. Absence of 10–20% BP decrease during sleep may indicate increased CVD risk.</td>
</tr>
<tr>
<td><strong>Self-measurement</strong></td>
<td>Provides information on response to therapy. May help improve adherence to therapy and evaluate “white-coat” HTN.</td>
</tr>
</tbody>
</table>
Office BP Measurement

- Use auscultatory method with a properly calibrated and validated instrument.

- Patient should be seated quietly for 5 minutes in a chair (not on an exam table), feet on the floor, and arm supported at heart level.

- Appropriate-sized cuff should be used to ensure accuracy.

- At least two measurements should be made.

- Clinicians should provide to patients, verbally and in writing, specific BP numbers and BP goals.
Which arm should be used to measure BP?

a) Left arm
b) Right arm
c) Arm with higher BP
d) Arm with lower BP
e) Dominant arm
f) Non-dominant arm
Which arm should be used to measure BP?

a) Left arm
b) Right arm
c) Arm with higher BP
d) Arm with lower BP
e) Dominant arm
f) Non-dominant arm
If we use too big small for the patient’s arm, what kind of error will we get?

a) The measured BP will be lower than true BP
b) The measured BP will be higher than true BP
If we use too big small for the patient’s arm, what kind of error will we get?

a) The measured BP will be lower than true BP

b) The measured BP will be higher than true BP
# Self measurement of BP

<table>
<thead>
<tr>
<th>Date</th>
<th>Hours</th>
<th>Tension artérielle</th>
<th>Freq. card.</th>
<th>Médic.</th>
<th>Mélasse</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Août</td>
<td>18h00</td>
<td>192 / 72</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Août</td>
<td>19h00</td>
<td>145 / 74</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Août</td>
<td>20h00</td>
<td>145 / 74</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Août</td>
<td>10h00</td>
<td>140 / 72</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Août</td>
<td>11h00</td>
<td>142 / 74</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Août</td>
<td>12h00</td>
<td>142 / 74</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Août</td>
<td>13h00</td>
<td>142 / 74</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Août</td>
<td>14h00</td>
<td>142 / 74</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Août</td>
<td>15h00</td>
<td>142 / 74</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

And®
UA-767

Omron® HEM-747
Self-Measurement of BP

- Provides information on:
  1. Response to antihypertensive therapy
  2. Improving adherence with therapy
  3. Evaluating white-coat HTN

- Home measurement of $>135/85$ mmHg is generally considered to be hypertensive.

- Home measurement devices should be checked regularly.
Home BP measurement

- Self measurement of BP
  - Avg BP > 135/85 at home = HTN
  - Wrist and finger manometers are not recommended

http://www.familymedshop.com/prod_img/p...
Home BP

- Self-measurement of BP at home is of clinical value and its prognostic significance is now demonstrated. These measurements should be encouraged in order to:
  - provide more information on the BP lowering effect of treatment at trough, and thus on therapeutic coverage throughout the dose-to-dose time interval
  - improve patient's adherence to treatment regimens
  - there are doubts on technical reliability/environmental conditions of ambulatory BP data
- Self-measurement of BP at home should be discouraged whenever:
  - it causes anxiety to the patient
  - it induces self-modification of the treatment regimen
- Normal values are different for office and home BP (Table 5)
Ambulatory BP Monitoring

- ABPM is warranted for evaluation of “white-coat” HTN in the absence of target organ injury.

- Ambulatory BP values are usually lower than clinic readings.

- Awake, individuals with hypertension have an average BP of >135/85 mmHg and during sleep >120/75 mmHg.

- BP drops by 10 to 20% during the night; if not, signals possible increased risk for cardiovascular events.
24-hour BP Profile in Hypertensive Patients: The Morning BP ‘Surge’ and “dipper”

Millar-Craig M et al. Lancet 1978;795–797
Ambulatory BP

- Although office BP should be used as reference, ambulatory BP may improve prediction of cardiovascular risk in untreated and treated patients
- Normal values are different for office and ambulatory BP (Table 5)
- 24-h ambulatory BP monitoring should be considered, in particular, when
  - considerable variability of office BP is found over the same or different visits
  - high office BP is measured in subjects otherwise at low total cardiovascular risk
  - there is a marked discrepancy between BP values measured in the office and at home
  - resistance to drug treatment is suspected
  - hypotensive episodes are suspected, particularly in elderly and diabetic patients
  - office BP is elevated in pregnant women and pre-eclampsia is suspected
Table 5  Blood pressure thresholds (mmHg) for definition of hypertension with different types of measurement

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office or clinic</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td>24-hour</td>
<td>125–130</td>
<td>80</td>
</tr>
<tr>
<td>Day</td>
<td>130–135</td>
<td>85</td>
</tr>
<tr>
<td>Night</td>
<td>120</td>
<td>70</td>
</tr>
<tr>
<td>Home</td>
<td>130–135</td>
<td>85</td>
</tr>
</tbody>
</table>
Who is the highest risk person?

A. A 65-year-old diabetic man with BP 140/90 mmHg

B. A 50-year-old woman with BP 190/120 mmHg

C. A 65-year-old man with metabolic syndrome, smoking, and BP of 170/80 mmHg

D. A 65-year-old man with previous MI and BP of 130/80 mmHg
Target-Organ Damage

- **Brain**: stroke, transient ischemic attack, dementia
- **Eyes**: retinopathy
- **Heart**: LVH, angina, CHF
- **Kidney**: chronic kidney disease
- **Vascular**: Aortic dissection, AAA, peripheral arterial disease
<table>
<thead>
<tr>
<th>Other risk factors</th>
<th>Normal SBP 120–129 or DBP 80–84</th>
<th>High normal SBP 130–139 or DBP 85–89</th>
<th>Grade 1 HT SBP 140–159 or DBP 90–99</th>
<th>Grade 2 HT SBP 160–179 or DBP 100–109</th>
<th>Grade 3 HT SBP ≥180 or DBP ≥110</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other risk factors</td>
<td>No BP intervention</td>
<td>No BP intervention</td>
<td>Lifestyle changes for several months then drug treatment if BP uncontrolled</td>
<td>Lifestyle changes for several weeks then drug treatment if BP uncontrolled</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
<tr>
<td>1–2 risk factors</td>
<td>Lifestyle changes</td>
<td>Lifestyle changes</td>
<td>Lifestyle changes for several weeks then drug treatment if BP uncontrolled</td>
<td>Lifestyle changes for several weeks then drug treatment if BP uncontrolled</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
<tr>
<td>≥3 risk factors, MS or OD</td>
<td>Lifestyle changes and consider drug treatment</td>
<td>Lifestyle changes and Drug treatment</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Lifestyle changes</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
<tr>
<td>Established CV or renal disease</td>
<td>Lifestyle changes + Immediate drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
</tbody>
</table>
Who is the highest risk person?

A. A 65-year-old diabetic man with BP 140/90 mmHg

B. A 50-year-old woman with BP 190/120 mmHg

C. A 65-year-old man with metabolic syndrome, smoking, and BP of 170/80 mmHg

D. A 65-year-old man with previous MI and BP of 130/80 mmHg
Evaluate hypertensive patients

- Level of BP
- Target organ damage
- Other CV risk factors
Levels of Risk Associated with Smoking, Hypertension and Hypercholesterolaemia

Hypertension (SBP 195 mmHg)

Smoking

Serum cholesterol level (8.5 mmol/L, 330 mg/dL)

Adapted from Poulter N et al., 1993
Investigations
Which of the followings is not the routine investigation recommended by ESC 2007 guidelines?

a) Serum uric acid
b) Serum $K^+$
c) Fasting blood glucose
d) CXR
e) EKG
Routine investigation recommended by ESC 2007 guidelines

- Total cholesterol
- Triglyceride
- HDL
- Direct LDL
- Hct, Hb
- UA
- EKG

- FBG
- Uric acid
- K
- Cr
- Estimated CrCl, GFR
Which of the followings is not the routine investigation recommended by ESC 2007 guidelines?

a) Serum uric acid
b) Serum $K^+$
c) Fasting blood glucose
d) CXR
e) EKG
Treatment of Hypertension

- Lifestyle modification
- Medical therapy
<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate Systolic Blood Pressure Reduction (mm Hg)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Maintain normal body weight (body mass index 18.5–24.9 kg/m²)</td>
<td>5–20 per 10-kg weight loss</td>
</tr>
<tr>
<td>DASH-type dietary patterns</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat</td>
<td>8–14</td>
</tr>
<tr>
<td>Reduced salt intake</td>
<td>Reduce daily dietary sodium intake as much as possible, ideally to 65 mmol/day (1.5 g/day sodium, or 3.8 g/day sodium chloride)</td>
<td>2–8</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Regular aerobic physical activity (at least 30 min/day, most days of the week)</td>
<td>4–9</td>
</tr>
<tr>
<td>Moderation of alcohol intake</td>
<td>Limit consumption to 2 drinks/day in men and 1 drink/day in women and lighter-weight persons</td>
<td>2–4</td>
</tr>
</tbody>
</table>

Sodium Recommendations from IOM Report

- **Upper Limit (UL):**
  
  2.3 g (100 mmol)/day for adults

- **Adequate Intake (AI):**
  
  1.5 g (65 mmol)/day for adults
Sodium Dose Response Trials: DASH-Sodium Trial*

1.5 (65)    2.4 (106)     3.3 (143)
Sodium Level: gm/d (mmol) per day

+2.1
+1.3
+1.7
+4.6
+6.7
+3.0

Systolic Blood Pressure

Control Diet

DASH Diet

*p<.0001

P<.0001

*Sacks, 2001 (412 prehypertensive and hypertensive adults)
SODIUM RECOMMENDATIONS

• *For general population:*
  – consume less than 2,300 mg (approximately 1 teaspoon of salt) of sodium per day

• *For individuals with hypertension, blacks, and middle-aged and older adults:*
  – consume no more than 1,500 mg of sodium per day
## Effects of Reduced Na on CVD Events: Results from 3 Randomized Trials

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>OUTCOME</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>TONE (2001) 639 Elderly</td>
<td>↓ Na</td>
<td>21% ↓ CVD events</td>
</tr>
<tr>
<td>Taiwan Veterans (2006) 1,981 Elderly</td>
<td>↓ Na /↑ K Salt</td>
<td>41%* ↓ CVD Mortality</td>
</tr>
<tr>
<td>TOHP Follow-up (2007) 3,126 Prehypertensives</td>
<td>↓ Na</td>
<td>30%* ↓ CVD events</td>
</tr>
</tbody>
</table>

*p<0.05
Sources of Dietary Sodium

- Food Processing 77%
- Inherent 12%
- At the Table 6%
- During Cooking 5%

Mattes and Donnelly, JACN, 1991; 10: 383
Antihypertensive medications
Antihypertensive drugs


Direct vasodilators
Thiazide diuretics
Central α₂ agonists
Calcium antagonists-
non-DHPs
Beta-blockers
Calcium antagonists-
DHPs
ACE inhibitors
ARBs
Vaccine
Renin inhibitor
Polypills

Effectiveness and general tolerability

Peripheral sympatholytics
Ganglion blockers
Veratrum alkaloids

DHP, dihydropyridine;
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker
Diuretics

• Exact hypotensive mechanism unknown

• Initial BP drop caused by diuresis
  – reduced plasma & stroke volume decreases CO and BP
  – causes compensatory increase in peripheral vascular resistance

• Extracellular & plasma volume return to near pretreatment levels with chronic use
  – peripheral vascular resistance becomes lower than pretreatment values
  • results in chronic antihypertensive effects
Diuretics

- **Thiazide**
  - chlorthalidone, hydrochlorothiazide (HCTZ), indapamide, metolazone
- **Loop**
  - bumetanide, furosemide, torsemide
- **Potassium-sparing**
  - amiloride, triamterene
- **Aldosterone antagonists**
  - eplerenone, spironolactone
Thiazide Diuretics

- Dose in morning to avoid nocturnal diuresis
- **Adverse effects:**
  - hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperuricemia, hyperglycemia, hyperlipidemia, sexual dysfunction
  - lithium toxicity with concurrent administration
- More effective antihypertensives than loop diuretics unless CrCl < 30 mL/min
- Chlorthalidone 1.5 to 2 times as potent as HCTZ
Loop Diuretics

- Dose in AM or afternoon to avoid nocturnal diuresis
- Higher doses may be needed for patients with severely decreased glomerular filtration rate or heart failure
- **Adverse effects:**
  - hypokalemia, hypomagnesemia, hypocalcemia, hyperuricemia, hearing loss, rash, pancreatitis
Side effects of diuretics

- Hyponatremia
- Dyskalemia
- Hyperuricemia
- Hyperglycemia
- Hyper or hypocalcemia
- Dyslipidaemia
- Hearing loss
- Rash
- Thrombocytopenia
- Volume contraction
- Impotence
Potassium-sparing Diuretics

- Dose in AM or afternoon to avoid nocturnal diuresis
- Generally reserved for diuretic-induced hypokalemia patients
- Weak diuretics, generally used in combination with thiazide diuretics to minimize hypokalemia

**Adverse effects:**
- may cause hyperkalemia especially in combination with an ACE inhibitor, angiotensin-receptor blocker or potassium supplements
- avoid in patients with CKD or diabetes
Aldosterone antagonists

- Dose in AM or afternoon to avoid nocturnal diuresis
- Due to increased risk of hyperkalemia, eplerenone contraindicated in CrCl < 50 mL/min & patients with type 2 diabetes & proteinuria
- **Adverse effects:**
  - may cause hyperkalemia especially in combination with ACE inhibitor, angiotensin-receptor blocker or potassium supplements
  - avoid in CKD or DM patients
  - Gynecomastia: up to 10% of patients taking spironolactone
Compelling indications

Thiazide diuretics

- Isolated systolic hypertension (elderly)
- Heart failure
- Hypertension in blacks
**Renin - Angiotensin Cascade**

- **Prorenin** → Renin (Kidney)
- ACE (vascular endothelium)
- **Angiotensinogen** → **Angiotensin I** → **Angiotensin II**

**Renin inhibitor**

**ACEI**

**ARB**

- **Thirst**
- **Pressure effect**
- **Sympathetic stimulation**
- **Renal actions**
- **Aldosterone secretion**
- **ADH release**
- **Cellular growth**
- **Vasoconstriction**
ACEI Pharmacology

• Differences:
  – Active Moieties
    • sulfhydryl - Captopril
    • phosphinyl - Fosinopril
    • carboxyl - Enalapril, lisinopril, Benzapril, Quinapril, Ramapril, Trandilopril, Moexipril
  – Potency & Plasma half life
  – Distribution and affinity for tissue bound ACE
  – Cardiac affinity
    • quinapril > lisinopril > fosinopril > captopril
  – Excretion - all renal (fosinopril and trandolapril also metab by liver)
## Adverse Effects of ACEI

<table>
<thead>
<tr>
<th>Class effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></td>
</tr>
<tr>
<td>Increased frequency in renin-dependent states, eg.</td>
</tr>
<tr>
<td>Low Na intake and concomitant diuretic use</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
</tr>
<tr>
<td>Incidence $10\text{-}40%$, Dose-dependent, mechanism unknown but possibly related to bradykinin or substance P; often necessitates cessation of therapy</td>
</tr>
<tr>
<td><strong>Hyperkalemia</strong></td>
</tr>
<tr>
<td>Frequent and usually minor, stabilizes after the $1^{st}$ wk</td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
</tr>
<tr>
<td>Most often due to decreased renal perfusion, eg. RAS or low output state</td>
</tr>
</tbody>
</table>
## Adverse Effects of ACEI

<table>
<thead>
<tr>
<th>Class effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Teratogenic effect:</strong></td>
</tr>
<tr>
<td>ACEI must be discontinued <strong>immediately</strong> if pregnancy is confirmed or suspected</td>
</tr>
<tr>
<td><strong>Angioedema</strong></td>
</tr>
<tr>
<td><strong>usually occurs 1st month</strong></td>
</tr>
<tr>
<td><strong>Dysgeusia</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sulfhydryl-related effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutropenia:</strong> Rare (&lt;0.05%), high incidence in patients with collagen vascular diseases</td>
</tr>
<tr>
<td><strong>Rash:</strong> 1%, usually maculopapular, pruritic; rarely exfoliative dermatitis</td>
</tr>
<tr>
<td><strong>Oral lesions:</strong> Rare, scalded mouth syndrome</td>
</tr>
<tr>
<td><strong>Proteinuria:</strong> 1% of patients receiving captopril, but paradoxically captopril will decrease proteinuria in diabetic nephropathy</td>
</tr>
</tbody>
</table>
Contraindications of ACEI

- Pregnancy
- Renal insufficiency
- Hyperkalemia requires caution
- Bilateral renal artery stenosis or equivalent lesions
- Preexisting hypotension
Compelling indications

ACE inhibitors
- Heart failure
- LV dysfunction
- Post-myocardial infarction
- Diabetic nephropathy
- Non-diabetic nephropathy
- LV hypertrophy
- Carotid atherosclerosis
- Proteinuria/
  - Microalbuminuria
- Atrial fibrillation
- Metabolic syndrome
ARBs

- Angiotensin Receptor Blockers
- Do not block bradykinin breakdown
  - less cough than ACE Inhibitors
- Adverse effects:
  - orthostatic hypotension
  - renal insufficiency
  - hyperkalemia
Chemical structures of Angiotensin II Receptor Blockers

Eprosartan

Losartan

Valsartan

Irbesartan

Candesartan

Telmisartan

HOOC
## ARBs – Comparison of pharmacological properties

<table>
<thead>
<tr>
<th></th>
<th>Olmesartan</th>
<th>Losartan</th>
<th>Candesartan</th>
<th>Irbesartan</th>
<th>Telmisartan</th>
<th>Eprosartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Receptor antagonism</td>
<td>Non-competitive</td>
<td>Competitive (active metabolite is non-competitive)</td>
<td>Non-competitive</td>
<td>Non-competitive</td>
<td>Non-competitive</td>
<td>Competitive</td>
<td>Non-competitive</td>
</tr>
<tr>
<td>AT$_1$:AT$_2$ affinity</td>
<td>12,500</td>
<td>1,000</td>
<td>&gt;10,000</td>
<td>8,500</td>
<td>&gt;3,000</td>
<td>1,000</td>
<td>20,000</td>
</tr>
<tr>
<td>t$_{1/2}$ (hours)</td>
<td>10-15</td>
<td>6-9</td>
<td>9</td>
<td>11-15</td>
<td>&gt;20</td>
<td>5-9</td>
<td>9</td>
</tr>
<tr>
<td>T$_{max}$ (hours)</td>
<td>1-2</td>
<td>3-4</td>
<td>3-4</td>
<td>1.5-2</td>
<td>0.5-1</td>
<td>1-2</td>
<td>2-4</td>
</tr>
<tr>
<td>V$_d$ (L)</td>
<td>16-29</td>
<td>34</td>
<td>0.1 L/kg</td>
<td>53-93</td>
<td>500</td>
<td>~13</td>
<td>~23</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>25.6</td>
<td>~33</td>
<td>14</td>
<td>60-80</td>
<td>50</td>
<td>13</td>
<td>23</td>
</tr>
</tbody>
</table>
## ARBs – Comparison of pharmacological properties (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Olmesartan</th>
<th>Losartan</th>
<th>Candesartan</th>
<th>Irbesartan</th>
<th>Telmisartan</th>
<th>Eprosartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal elimination (%)</td>
<td>50-65</td>
<td>60</td>
<td>67</td>
<td>80</td>
<td>98</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>Urinary elimination (%)</td>
<td>35-50</td>
<td>35</td>
<td>33</td>
<td>20</td>
<td>&lt;1</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>CYP450 metabolism</td>
<td>No</td>
<td>Yes CYP 3A4</td>
<td>No</td>
<td>Yes CYP 2C9</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>No</td>
<td>Rifampin, fluconazole</td>
<td>No</td>
<td>No</td>
<td>Digoxin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Effect of food (↓ AUC%)</td>
<td>None</td>
<td>10</td>
<td>None</td>
<td>None</td>
<td>6-20</td>
<td>25</td>
<td>40-50</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>od</td>
<td>od/bid</td>
<td>od/bid</td>
<td>od</td>
<td>od</td>
<td>od/bid</td>
<td>od</td>
</tr>
</tbody>
</table>
Compelling indications

Angiotensin receptor antagonists
- Heart failure
- Post-myocardial infarction
- Diabetic nephropathy
- Proteinuria/Microalbuminuria
- LV hypertrophy
- Atrial fibrillation
- Metabolic syndrome
- ACEI-induced cough
Compliance at 1 year with antihypertensive treatment

ACE, angiotensin-converting enzyme; CCB, calcium-channel blocker; ARB, angiotensin II receptor blocker

Direct Renin Inhibitor

• 1\textsuperscript{st} agent FDA approved in 2007: aliskiren
• Inhibits angiotensinogen to angiotensin I conversion
• FDA approved as monotherapy & combination therapy with other antihypertensives
• Efficacy demonstrated with other antihypertensives including amlodipine, HCTZ, ACEIs/ARBs
• Does not block bradykinin breakdown
  – less cough than ACE Inhibitors
• Adverse effects: orthostatic hypotension, hyperkalemia
β-Blockers

• Inhibit renin release
  – weak association with antihypertensive effect

• Negative chronotropic & inotropic cardiac effects reduce CO
  – β-blockers with intrinsic sympathomimetic activity (ISA)
    • do not reduce CO
    • lower BP
    • decrease peripheral resistance
  – Membrane-stabilizing action on cardiac cells at high enough doses
β-Blockers

- **Adverse effects:**
  - bradycardia, AVB
  - acute heart failure
  - hyperuricemia, dyslipidaemia, hyperglycemia
  - fatigue, impotence
  - abrupt discontinuation may cause rebound effects
  - bronchospastic pulmonary disease exacerbation
  - may aggravate intermittent claudication, Raynaud’s phenomenon
β-Blockers

• Cardioselective
  – atenolol, betaxolol, bisoprolol, metoprolol, nebivolol
• Nonselective
  – nadolol, propranolol, timolol
• Intrinsic sympathomimetic activity
  – acebutolol, carteolol, penbutolol, pindolol
• Mixed α- and β-blockers
  – carvedilol, labetolol
β-Blockers

• Metabolized primarily by the liver
  – Carvedilol
  – Propanolol
  – Metoprolol
  – Labetalol
Some comments on Betablockers

- Meta-analyses suggest β-blocker based therapy may not reduce CV events as well as other agents.
- Findings may only apply to atenolol.
- Atenolol t½: 6 to 7 hrs yet it is often dosed once daily.
  - IR forms of carvedilolol & metoprolol tartrate have 6- to 10- & 3- to 7-hour half-lives respectively: always dosed at least BID.
Compelling indications

Beta-blockers

- Angina pectoris
- Post-myocardial infarction
- Heart failure
- Tachyarrhythmias
- Glaucoma
- Pregnancy
CCBs

- **Calcium Channel Blockers**
- Inhibit influx of $\text{Ca}^{2+}$ across cardiac & smooth muscle cell membranes
  - muscle contraction requires increased free intracellular $\text{Ca}^{2+}$ concentration
  - CCBs block high-voltage (L-type) $\text{Ca}^{2+}$ channels resulting in coronary & peripheral vasodilation
- dihydropyridines vs non-dihydropyridines
  - different pharmacologically
  - similar antihypertensive efficacy
CCBs

• **Dihydropyridines:**
  - amlodipine, felodipine, isradipine, nicardipine, nifedipine, lercanidipine, manidipine

• **Non-dihydropyridines:**
  - diltiazem, verapamil
CCBs

- **Dihydropyridines:**
  - baroreceptor-mediated reflex tachycardia due to potent vasodilating effects
  - do not alter conduction through atrioventricular node
    - not effective in supraventricular tachyarrhythmias

- **Non-dihydropyridines:**
  - decrease HR, slow atrioventricular nodal conduction
  - may treat supraventricular tachyarrhythmias
<table>
<thead>
<tr>
<th>Generation</th>
<th>Type</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td>conventional (multiple dosing)</td>
<td>Verapamil, Diltiazem, Nifedipine, Felodipine, Isradipine, Nicardepine, Nitrendipine</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td>modified release (once/twice daily)</td>
<td>Verapamil SR, Nifedipine XL/GITS, Felodipine ER, Diltizem CD, Isradipine CR</td>
</tr>
<tr>
<td><strong>Third generation</strong></td>
<td>intrinsically long-acting</td>
<td>Amlodipine, Manidipine, Lercanidipine</td>
</tr>
</tbody>
</table>

1. Long **plasma** half-life
2. Long **tissue / membrane** half-life

Messerli FH. *Am J Hypertens* 2002; 15: S94-S97
Compelling indications

**Calcium antagonists (dihydropyridines)**
- Isolated systolic hypertension (elderly)
- Angina pectoris
- LV hypertrophy
- Carotid/Coronary Atherosclerosis
- Pregnancy
- Hypertension in blacks
Compelling indications

Calcium antagonists (verapamil/diltiazem)
- Angina pectoris
- Carotid atherosclerosis
- Supraventricular tachycardia
ESH–ESC Recommendations for Combining BP-lowering Drugs

Preferred combination

Less frequently used/combo used as necessary

Copyright © 2007, with permission from Lippincott Williams and Wilkins
α₁-Blockers

- Not recommended as 1\textsuperscript{st} line therapy
- Inhibit smooth muscle catecholamine uptake in peripheral vasculature: vasodilation & BP lowering
- \textbf{Adverse effects:}
  - orthostatic hypotension
  - 1\textsuperscript{st} dose phenomenon: transient dizziness, faintness, palpitations, syncope within 1 to 3 hours of 1\textsuperscript{st} dose
  - lassitude, vivid dreams, depression
  - priapism
  - $\text{Na}^+/\text{H}_2\text{O}$ retention
Central $\alpha_2$-Agonists

• Stimulate $\alpha_2$-adrenergic receptors in the brain
  – reduces sympathetic outflow from the brain's vasomotor center
    • increases vagal tone
  – peripheral stimulation of presynaptic $\alpha_2$-receptors may further reduce sympathetic tone
  – decrease HR, CO, TPR, plasma renin activity, baroreceptor activity
Central $\alpha_2$-Agonists

- **Adverse effects:**
  - sodium/water retention
  - abrupt discontinuation may cause rebound HTN
  - depression
  - orthostatic hypotension
  - dizziness

- **Clonidine:** anticholinergic side effects

- **Methyldopa:** can cause hepatitis, hemolytic anemia (rare)
Central $\alpha_2$-Agonists

- Most effective if used with a diuretic
  - minimizes fluid retention
- Use caution in elderly patients
Direct Arterial Vasodilators

- Direct arterial smooth muscle relaxation causes antihypertensive effect (little or no venous vasodilation)
  - reduce impedance to myocardial contractility
  - potent reductions in perfusion pressure activate baroreceptor reflexes
  - baroreceptor activation: compensatory increase in sympathetic outflow; tachyphylaxis can cause loss of antihypertensive effect
    - counteract with concurrent β-blocker
    - clonidine if β-blocker contraindicated
Direct Arterial Vasodilators

• **Adverse effects:**
  – sodium/water retention
  – angina

• **Hydralazine** can cause lupus-like syndrome

• **Minoxidil** can cause hypertrichosis
Which agents for which patients??

- One man’s meat is another man’s poison

De Rerum Natura

Lucretius 1st century B.C.
Guidelines
Lifestyle modifications

Not at goal BP*

Hypertension without compelling indications

Stage 1
Thiazide-type diuretics for most. May consider ACE inhibitor, ARB, β-blocker, CCB, or combination

Stage 2
Two-drug combination for most (usually including thiazide-type diuretic)

Hypertension with compelling indications

Drug(s) for the compelling indications
Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed

If not at goal, optimize dosages or add additional drugs until goal BP is achieved.
Consider consultation with hypertension specialist

*BP goal <140/90 mmHg or <130/80 mmHg for those with diabetes or chronic kidney disease

Chobanian et al. JAMA 2003;289:2560–72
Copyright © 2003 American Medical Association. All rights reserved
## Compelling Indications for Individual Drug Classes

<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Initial Therapy Options</th>
<th>Clinical Trial Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>THIAZ, BB, ACEI, ARB, ALDO ANT</td>
<td>ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES</td>
</tr>
<tr>
<td>Postmyocardial infarction</td>
<td>BB, ACEI, ALDO ANT</td>
<td>ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS</td>
</tr>
<tr>
<td>High CAD risk</td>
<td>THIAZ, BB, ACE, CCB</td>
<td>ALLHAT, HOPE, ANBP2, LIFE, CONVINCE</td>
</tr>
</tbody>
</table>
## Compelling Indications for Individual Drug Classes

<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Initial Therapy Options</th>
<th>Clinical Trial Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>THIAZ, BB, ACE, ARB, CCB</td>
<td>NKF-ADA Guideline, UKPDS, ALLHAT</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>ACEI, ARB</td>
<td>NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>THIAZ, ACEI</td>
<td>PROGRESS</td>
</tr>
</tbody>
</table>
Consider: BP level before treatment
Absence or presence of TOD and risk factors

Choose between

Single agent at low dose

Previous agent at full dose
Switch to different agent at low dose

If goal BP not achieved

2-drug combination at low dose

Previous combination at full dose
Add a third drug at low dose

If goal BP not achieved

2–3 drug combination at full dose
Full-dose monotherapy

2–3-drug combination at full doses

Mild BP elevation
Low/moderate CV risk
Conventional BP target

Marked BP elevation
High/very high CV risk
Lower BP target

TOD = target organ damage

Copyright © 2007, with permission from Lippincott Williams and Wilkins
Updated UK NICE Guidelines for the Treatment of Newly Diagnosed Hypertension

- **Step 1**
  - <55 years
  - ACEI (or ARB*)
  - ≥55 years or black patients at any age
  - CCB or thiazide-type diuretic

- **Step 2**
  - ACEI (or ARB*) + CCB or ACEI (or ARB*) + thiazide diuretic

- **Step 3**
  - ACEI (or ARB*) + CCB + diuretic

- **Step 4**
  - Add further diuretic therapy, α-blocker, or β-blocker.
  - Consider seeking specialist advice

*If ACE inhibitor (ACEI) not tolerated

---

Aged under 55 years

Step 1

A

Aged over 55 years or black person of African or Caribbean family origin of any age

Step 1

C

Key

A – ACE inhibitor or angiotensin II receptor blocker (ARB) ¹³
C – Calcium-channel blocker (CCB) ¹³
D – Thiazide-like diuretic

Step 2

A + C

Step 3

A + C + D

Step 4

Resistant hypertension

A + C + D + consider further diuretic ¹⁴, ¹⁵ or alpha- or beta-blocker ¹⁶

Consider seeking expert advice

¹² Choose a low-cost ARB.
¹³ A CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure.
¹⁴ Consider a low dose of spironolactone ¹⁵ or higher doses of a thiazide-like diuretic.
¹⁵ At the time of publication (August 2011), spironolactone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.
¹⁶ Consider an alpha- or beta-blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective.
How low should we go?
# Target BP

## Summary of guidelines

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>140/90</td>
<td>140/90</td>
<td>140/95</td>
<td>140/90</td>
<td>140/90</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DM, renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CVD, DM, renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CVD, DM, renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DM, MI, Stroke, renal, proteinuria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CAD, CAD equi (DM,CKD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>130/80</td>
</tr>
</tbody>
</table>
## Target BP
### Summary of guidelines

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>140/90</td>
<td>140/90</td>
<td>140/95</td>
<td>140/90</td>
<td>140/90</td>
<td></td>
<td></td>
<td>140/90 (&lt;80 y) 150/100 (&gt;80 y)</td>
</tr>
<tr>
<td><strong>DM, renal</strong></td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
<td></td>
<td>DM</td>
</tr>
</tbody>
</table>
Take home messages

- Hypertension is the most important risk factor that contributes to highest number of morbidity and mortality

- Hypertension is very common

- Current standard of treatment for hypertension still need to be improved
Take home messages

- **Approach:**
  - Level of BP
  - Target organ damage
  - Other risk factors

- **Treatment guidelines:**
  - Lifestyle modification
  - Medication