Essential Hypertension

Ying Shan

Department of cardiology

Huashan Hospital

Outline

- Epidemiology
- Mechanism
- Pathology
- Clinical manifestation
- Diagonsis and differentiation
- Treatment

Objectives

Be able to:

- Make diagnosis of hypertension
- Identifying potential secondary cause of hypertension
- Assessing the overall CV risks and target organ damage of the patients with HTN
- Familiar with the principles of treatment
- Familiar with non-pharmacological strategy and pharmacological treatment of HTN

Hypertension is one of the leading public health problems worldwide, if untreated, often leads to lethal complication.

Epidemiology of Hypertension

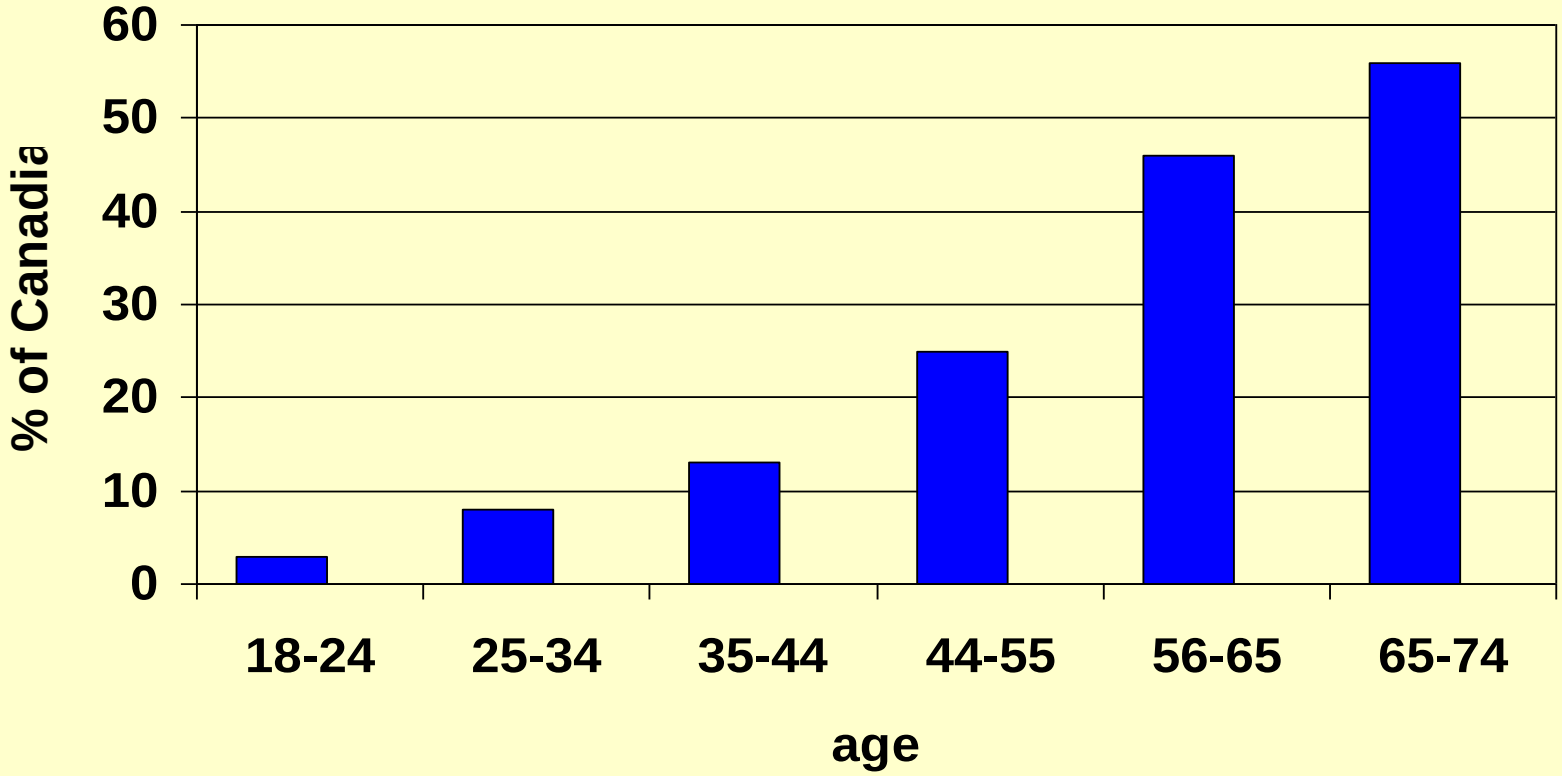
- 50 million individuals in the United States have hypertension[1]

- 277,000 deaths annually in US due to hypertension[2]

[1]American Association of Clinical Endocrinologists Medical Guidelines For Clinical Practice for the Diagnosis and Treatment of Hypertension. Endocrine Practice, Vol 12 No. 2 March/April 2006

[2]National Center for Health Statistics. Health, United States, 2005, with Chartbook on the Health of Americans. Hyattsville, Maryland: 2004. Available at: http://www.cdc.gov/nchs/hus.htm

What percent of Canadians have hypertension?



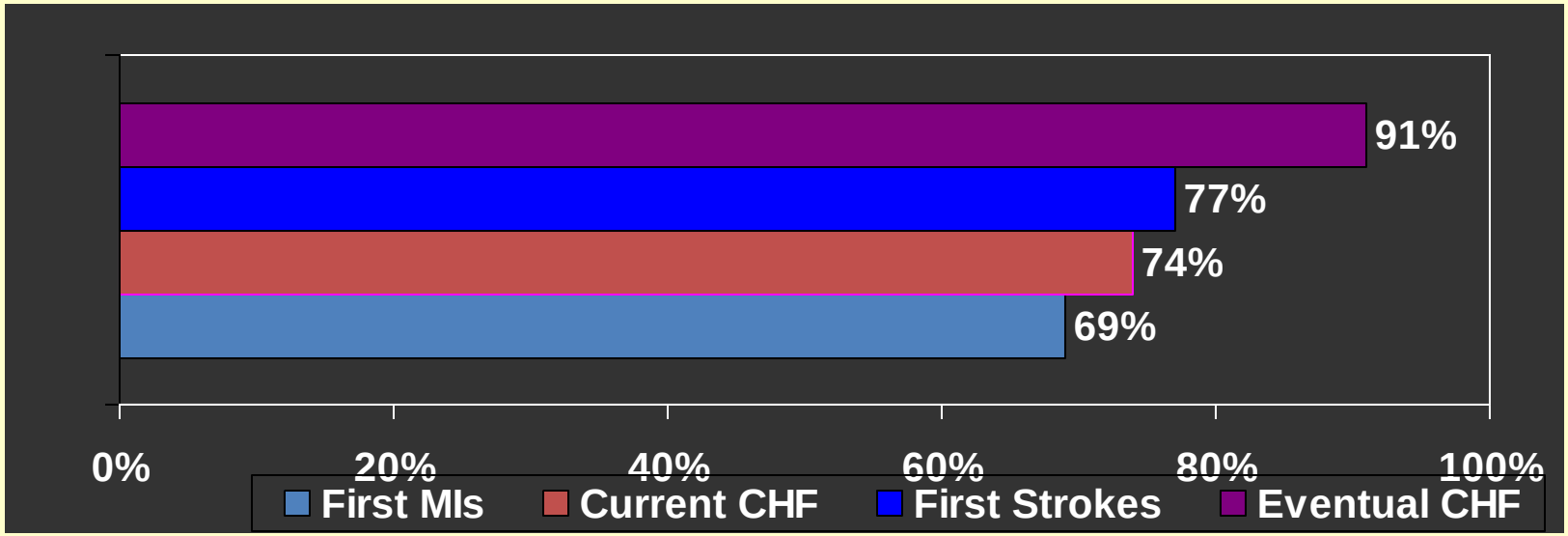
CCHS CMAJ 1992

International Collaborative Study of Cardiovascular Disease in ASIA (InterASIA)

- **27.2% of the Chinese adult population age 35 to 74 years has hypertension**
- **The percentage of those with hypertension who were aware(44.7%), treated(28.2%), and controlled(8.1%) was unacceptably low**

Hypertension Remains One of the Most Important factors of CV Risk

BP >140/90 mm Hg is associated with:



BP, blood pressure; CHF, congestive heart failure; MI, myocardial infarction

Rosamond W et al. *Circulation*. 2007;115:1-103.

MECHANISMS OF ESSENTIAL HYPERTENSION (1)

- **Genetic Predisposition** --one of the most common complex genetic disorder
- Genetic heritability 30%

MECHANISMS OF ESSENTIAL HYPERTENSION (2)

- **Environment –** salt intake, obesity, occupation, alcohol intake, crowding**.**

MECHANISMS OF ESSENTIAL HYPERTENSION (3)

- **Insulin Resistance/ hyperinsulinemia—increase arterial pressure…mechanism unclear**
  - **Hyperinsulinemia produces renal sodium retention and increases sympathetic activity**
  - **Vasular smooth-muscle hypertrophy secondary to the mitogenic action of insulin**
  - **Insulin modifies ion transport across the cell membrance.**

MECHANISMS OF ESSENTIAL HYPERTENSION (4)

- Sympathetic nervous hyperactivity
- Endothelial cell dysfunction
- Deficiencies of various vasodepressor hormones

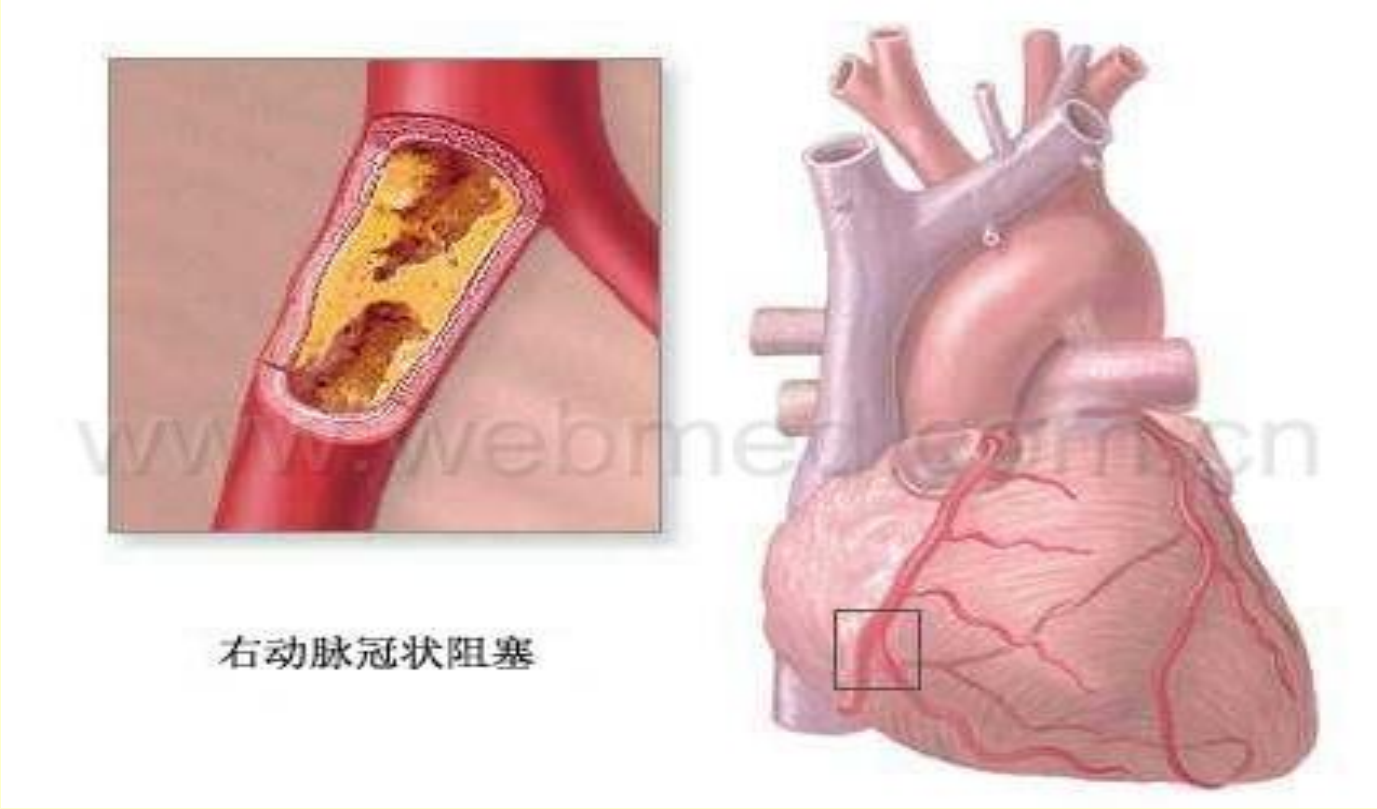
PATHOLOGY

Heart--The hypertension creates a greater pressure load on the heart to induce the **hypertrophy.**

This left ventricle is very thickened (slightly over 2 cm in thickness), but the rest of the heart is not greatly enlarged. This is typical for hypertensive heart disease.

The left ventricle is markedly thickened in this patient with severe hypertension that was untreated for many years. The myocardial fibers have undergone hypertrophy.

Coronary heart disease



Brain

- Vascular occlusion
- Hemorrhage
- encephalopathy

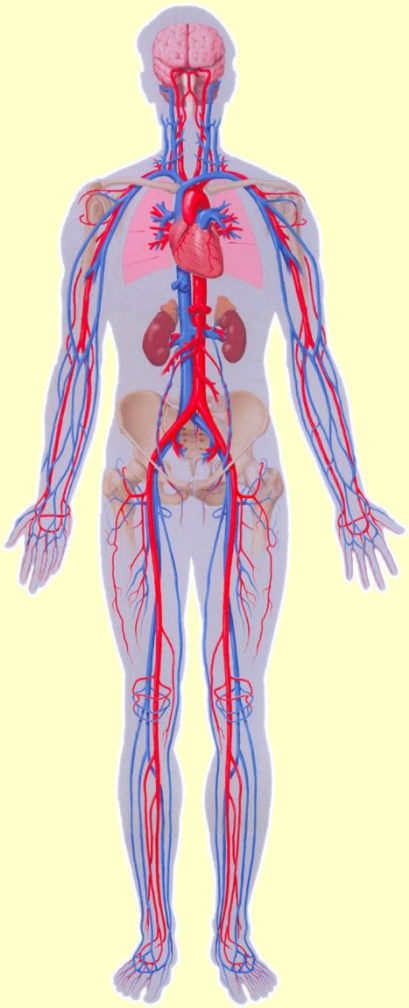
Kidney

- **hypertensive nephropathy**

  (eGFR < 60ml/min/1.73 m^2)

- **microalbuminuria**

Search for target organ damage



Cerebrovascular disease
- transient ischemic attacks
- ischemic or hemorrhagic stroke
- vascular dementia

Hypertensive retinopathy

Left ventricular dysfunction

Left ventricular hypertrophy

Coronary artery disease
- myocardial infarction
- angina pectoris
- congestive heart failure

Chronic kidney disease
- hypertensive nephropathy (eGFR < 60 ml/min/1.73 m^2)
- albuminuria

Peripheral artery disease
- intermittent claudication
- ankle brachial index $\leq$ 0.9

CLINICAL MANIFESTATION

Symptoms

- no specific symptoms referable to their blood pressure elevation
- headache is characteristic of only severe hypertension
- Other complaints that may be related to elevated blood pressure include dizziness, palpitations, easy fatigability, and impotence.

Physical Examination

- General appearance
- blood pressures and pulses in the two upper extremities
- Funduscopic findings
- auscultation for bruits originating in stenotic renal arteries

Laboratory tests

	2010 guideline	changes
Routine tests	•blood glucose and hematocrit; •serum potassium and calcium, •creatinine (eGFR), •lipoprotein profile •EKG	—
Optional tests	•24h ABPM •Echo •Carotid ultrosonic •PBG（when FBG≥6.1mmol/L或110mg/dL) •homocysteine •Microalbumiuria •Proteinuria •Fundus exam •Chest X-ray •PWV •ABI	Add: •24h ABPM •Homocysteine •PWV •ankle/arm blood pressure index<0.9（ABI）

24h ABPM

	2010 guideline
Diagnosis for HTN	•24h>130/80mmHg •Day-time>135/85mmHg •Night-time>120/70mmHg
Nighttime BP related definition	Percentage reduction in nocturnal blood pressure: (Daytime BP_{mean} - nighttime BP_{mean}) / daytime BP_{mean}。 •Dipper BP： reduction in nocturnal blood pressure 10-20%。 •Non-Dipper bp： reduction in nocturnal blood pressure <10%。 •Ultra-dipper BP ： reduction in nocturnal blood pressure >20%。
Morning peak BP	•SBP_{mean}within 2h after getting up -$SBP_{minimum}$ during sleep)， if≥35mmHg, elevated

Diagnosis

- 2 readings; separated apart
- Patient should not ingest caffeine or smoke for 30 minutes before readings
- Patient should sit for 5 minutes with arm at heart level before blood pressure is checked
- BP should be routinely measured in different days

Classification of blood pressure

Classification of blood pressure for adults on 2010 guideline of diagnose and treatment of HTN in China

classification	SBP(mmHg)	DBP(mmHg)
normal	<120	<80
prehypertension	120~139	80~89
hypertension	≥140	≥90
stage 1	140~159	90~99
stage 2	160~179	100~109
stage 3	≥160	≥100
Systolic hypertension	≥140	<90

Classification of blood pressure

Classification of blood pressure for adults on JNC-7

Blood Pressure Classification	SBP mmHg	DBP mmHg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 Hypertension	140–159	or 90–99
Stage 2 Hypertension	≥160	or ≥100

SBP, systolic blood pressure; DBP, diastolic blood pressure

Search for potentially modifiable factors that can induce/aggravate hypertension

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

Risk factors that may affect prognosis in 2010 China guideline

-Cardiovascular risk factors

- hypertension（stage1-3）
- man ＞ 55； women >65
- smoker
- IGT（PBG 7.8-11.0 mmol/L）and/orIFG（6.1-6.9 mmol/L） new in 2010 chinese guideline
- hyperlipidemia：TC≥5.7mmol/L（220mg/dL）or LDL-C>3.3mmol/L（130mg/dL）or HDL-C<1.0mmol/L（40mg/dL）
- family history of early CVD：（first degree relative <50岁） new in 2010 chinese guideline
- abdominal obesity：（waistline:man≥90cm woman≥85cm）或obesity（BMI≥28kg/m^2） new in 2010 chinese guideline
- homocysteine>10μmol/L

微量白蛋白尿：30-300mg/24h或
白蛋白/肌酐比≥
≥30mg/g（3.5mg/mmol）

Risk factors that may affect prognosis in 2010 China guideline

-Target organ damage

- LVH：EKG：Sokolow-Lyons>38mv or Cornell>2440mm·mms，
Echo：LVMI：man>125g/m^2 ，woman>120g/m^2
- carotid ultrosound:IMT>0.9mm,or athersclerosis plague
- carotid-femoral pulse wave velocity >12m/s
- ankle/arm blood pressure index <0.9
- eGFR<60ml/min/1.73m2
or blood Cr slightly elevated：man 115-133 mol/L（1.3-1.5mg/dL），woman 107-124 mol/L（1.2-1.4mg/dL）；microalbuminuria:30-300mg/24h or albumin/cretinine ≥30mg/g（3.5mg/mmol）

new
new
new

•delete：LVH on X-ray

微量白蛋白尿：30-300mg/24h或
白蛋白/肌酐比≥
≥30mg/g（3.5mg/mmol）

Risk factors that may affect prognosis in 2010 China guideline

-Coexist clinical complication

- Cerebral vascular disease: cerebral hemorrhage、ischemic stroke、TIA
- Heart disease: MI, agina,revascularization, congestive heart failure
- Renal disease: diabetic nephropathy, impaired renal function: blood Cr: man >133mol/L(1.5mg/dL);woman >124mol/L(1.4mg/dL)、proteinuria (>300mg/24h)
- Peripheral artery disease
- Retinopathy: bleeding or oozing, pepilledema
- Diabetes: FBG: ≥7.0mmol/L(126mg/dL)、PBG: ≥11.1mmol/L(200mg/dL)、HbA1c: >6.5%

new

Cardiovascular risk stratification of HTN patients

	Other risk factors and history	BP(mmHg) stage 1 SBP 140~159 or DBP 90~99	stage 2 SBP 160~170 or DBP 100~109	stage 3 SBP≥180 or DBP≥110
I	no risk factors	low-risk	moderate-risk	high-risk
II	1~2 risk factor	moderate-risk	moderate-risk	very-high risk
III	≥3 risk factors or target organ damage	high-risk	high-risk	very high risk
IV	coexist clinical complications、DM	very high risk	very high risk	very high risk

Category of Hypertension

- Primary hypertension
  - Also called essential
  - Responsible for 90-95% of all hypertensive population

Secondary Causes of HTN

- Sleep apnea
- Drug-induced or drug related
  - Including OTC medications
- Chronic kidney disease
  - Polycystic kidneys
- Renal artery stenosis
- Primary aldosteronism
- Renovascular disease
- Chronic steroid therapy and Cushing's disease
- Pheochromocytoma
- Coarctation of the Aorta
- Thyroid or parathyroid disease

JAMA. 2003:289:2560-2577.

Renal parenchymal disease

- secretion of vasoactive materials resulting in a systemic change in arterial
- a derangement in the renal handling of sodium and fluids leading to volume expansion
- Diagnosis is based on history and creatinine, urinalysis,urine culture and radionuclide renogram

Renovascular hypertension

Patients presenting with two or more of the following clinical clues listed below suggesting renovascular hypertension should be investigated.

- sudden onset or worsening of hypertension and > age 55 or < age 30
- the presence of an abdominal bruit
- hypertension resistant to 3 or more drugs
- a rise in creatinine of 30% or more associated with use of an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker
- other atherosclerotic vascular disease, particularly in patients who smoke or have dyslipidemia
- recurrent pulmonary edema associated with hypertensive surges

Renovascular hypertension

The following tests are recommended, when available, to screen for renal vascular disease:

- captopril-enhanced radioisotope renal scan*
- doppler sonography
- magnetic resonance angiography
- CT-angiography (for those with normal renal function)

* captopril-enhanced radioisotope renal scan is not recommended for those with glomerular filtration rates <60 mL/min

Pheochromocytoma

patients with the following characteristics:

- Paroxysmal and/or severe sustained hypertension refractory to usual antihypertensive therapy;
- Hypertension and symptoms suggestive of catecholamine excess (two or more of headaches, palpitations, sweating, etc);
- Incidentally discovered adrenal mass;

Screening for Pheochromocytoma

- Screening for pheochromocytoma should include a 24 hour urine for metanephrines and creatinine.
- Assessment of urinary catecholamine (VMA) is inadequate.
- A normal plasma metanephrine level can be used to exclude pheochromocytoma in low risk patients but the test is performed by few laboratories.

Cushing's syndrome

- 24h urine test for cortisol and creatinine
- Consecutive cortisol level

Primary aldosteronism

patients with the following characteristics:

- Spontaneous hypokalemia (<3.5 mmol/L).
- Profound diuretic-induced hypokalemia (<3.0 mmol/L).
- Hypertension refractory to treatment with 3 or more drugs.
- Incidental adrenal adenomas.

Screening for hyperaldosteronism

- Screening for hyperaldosteronism should include plasma aldosterone and renin activity (or renin concentration)
- - measured in morning samples.
- - taken from patients in a sitting position after
- resting at least 15 minutes.

- Aldosterone antagonists, ARBs, beta-blockers and clonidine should be discontinued prior to testing.

- A positive screening test should lead to referral or further testing.

Coartation of the aorta

- Physical examination
- X-ray finding
- Echocardiogram
- CTA or MRA

Treatment of Hypertension

OBJECTIVES

1. Reduce blood pressure
2. Reduce risk of cardiovascular disease
3. Reduce end organ damage
4. Maintain quality of life.

TREATMENT GOALS

- SBP < 140 mm Hg
- DBP < 90 mmHg
- In patients with :
  - Diabetes or renal disease

    BP goal < 130/80 mm Hg.

Controlling other cardiovascular risk factors.

Lifestyle Modifications to Manage Hypertension

	SBP reduction
dietary sodium reduction	2-8mmHg
regular aerobic physical activity	4-9mmHg
a diet rich in fruits, vegetables, and lowfat dairy products	8～-14 mmHg
Weight control	5～-20 mmHg
Quit smoking	---
Limit alcohol intake	2～-4 mmHg

Diuretics

Effect:

- short term-sodium diuresis and volume depletion
- long term- reduction of peripheral vascular resistance
- Usually effective within 3-4 days
- Reduce the mortality and morbidity in the long-term trial

Diuretics

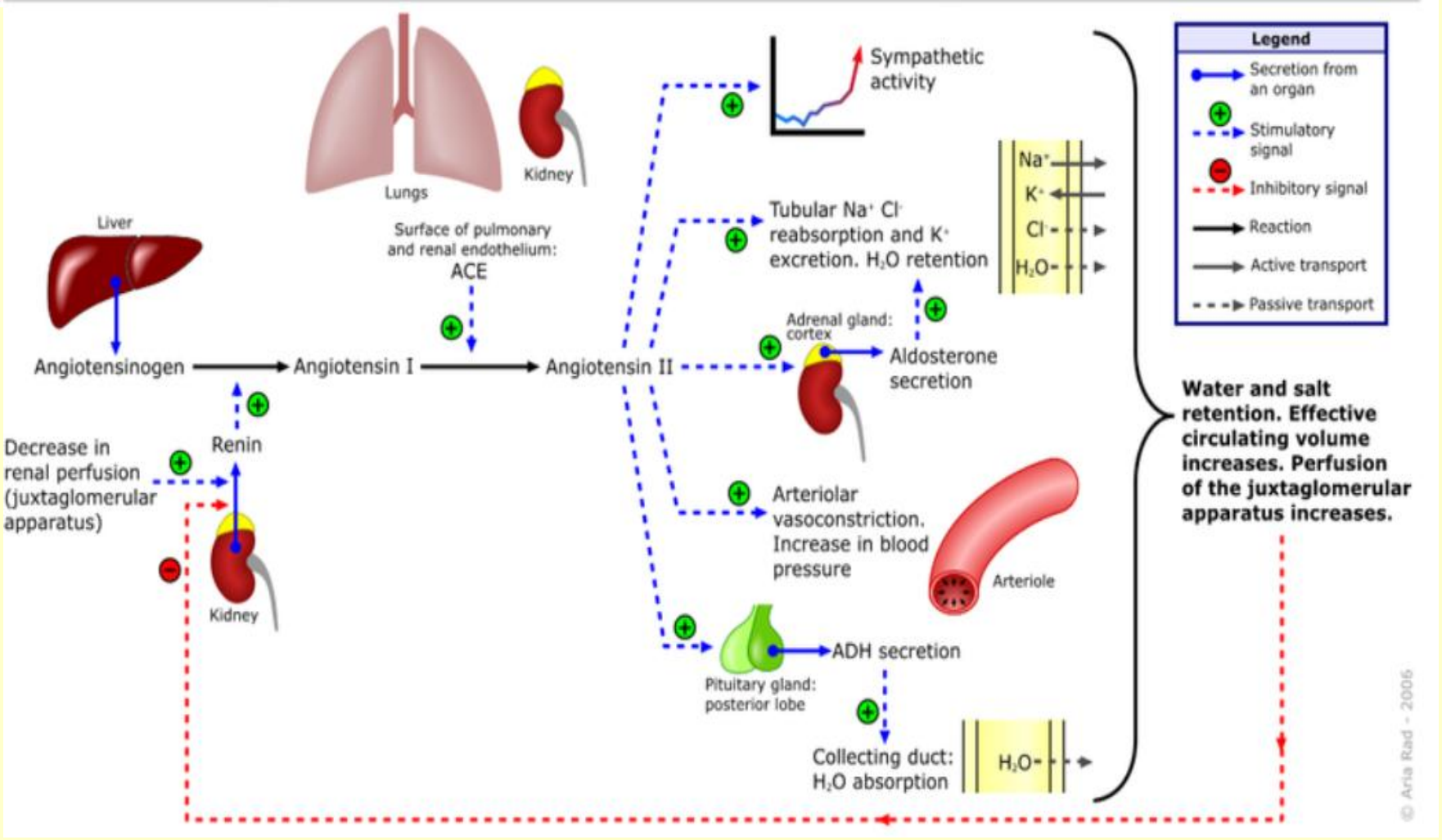
Category:

- thiazide diuretic
- loop diuretic
- Aldosterone antagonists

Diuretic Precautions

- Electrolyte imbalances-hypokalemia
- Hyperuricemia due to uric acid retention
- Carbohydrate intolerance, and hyperlipidemia

Renin angiotensin aldosterone system



Angiotensin Converting Enzyme (ACE) Inhibitors

Effect:

- **Inhibit the generation of a potent vasoconstrictor (angiotensin II)**
- **Retard the degradation of a potent vasodilator (bradykinin), alter prostaglandin production**
- **Modify the activity of the adrenergic nervous system.**
- **Useful in renal or renovascular hypertension and in diabetic patients**

ACEI Inhibitors precaution

- Hyperkalemia
- Increase in creatinine
- Angioedema
- Coughing
- In patients with bilateral renal artery stenosis, rapid deterioration of renal function may occur

Angiotension Receptor Blockers (ARB's)

Effect:

- **Blockade of AT1 receptors directly causes vasodilation and water clearence**
- **The utility, efficacy, and tolerability of ARBs are similar to those of the ACE inhibitors**
- **Appear to cause fewer side effects, Specifically, they do not cause excessive cough or angioedema**

Calcium Channel Blockers

Effect:

- **Modify calcium entry into cells by interacting with specific binding sites on the a_1 subunit of the L-type voltage-dependent calcium channel, leading vasodilation**
- **Useful in angina pectoris**

Calcium Channel Blockers

Category

- **Dihydropyridines:**
  - **Amlodipine**
- **Non-dihydropyridine:**
  - **Verapamil**
  - **Diltiazem**

CCBs precaution

- **Dihydropyridines:**

  reflex tachycardia

- **Non-dihydropyridine:**

  - **slow atrioventricular conduction**
  - **negative inotropic actions, be caution in patients with heart failure**

Antiadrenergic agents

β-Adrenergic receptor blockers

Effect:

- **Block sympathetic effects on the heart - reducing cardiac output; lowering arterial pressure**
- **Block adrenergic nerve-mediated release of renin**

Antiadrenergic agents

β-Adrenergic receptor blockers

Category

- **Cardioselective β-blocking agents**

  Metoprolol Atenolol Bisolol

- **Nonselective b-blockers agents**

  Propranolol Timolol

- **Both α- and β -adrenergic blocking action**

  Labetalol Carvedilol Arotinolol

Antiadrenergic agents

β-Adrenergic receptor blockers precautions

- **Precipitate congestive heart failure**
- **Asthma in susceptible individuals**
- **Slow atrioventricular conduction**

Antiadrenergic agents

α-Adrenergic receptor blockers

Effect:

- **not usually used as first-line therapy**
- **Phentolamine and phenoxybenzamineblock both presynaptic (a_2) and postsynaptic (a_1)**
- **Prazosin, terazosin, and doxazosin selectively block only a_1 receptors**

Antiadrenergic agents

α-Adrenergic receptor blockers precautions

- Phentolamine and phenoxybenzamine develop tolerance
- a_1 receptors blocker (doxazosin) can produce substantial hypotension following the first dose
- The doxazosin arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was terminated prematurely because of a significant increase in the risk of congestive heart failure.

Antiadrenergic agents

Centrally acting blocker

Effect:

- **the drugs and their metabolites stimulate a_2 receptors in the vasomotor centers of the brain, thereby reducing sympathetic outflow and arterial pressure**
- **rebound hypertension may occur rarely when clonidine is stopped**
- **not used as first-line therapy**

Vasodilators

Effect:

- **Hydralazine-cause direct relaxation of vascular smooth muscle , reduce peripheral resistance**
- **antihypertensive effect is partly negated by a reflex increase in sympathetic discharge that raises heart rate and cardiac output**

Principle of drug treatment

- **Low dose**：**initial with low dose and gradually increase the dosage. Safety and tolerance are very important**
- **Long-acting fomulations**：**recommed daily-dose drugs to control 24h BP, especially to control nighttime and morning peak BP.**
- **Combination therapy**：**combination of 2 or more drugs for stage 2-3 patients. Initial with 2 low-dose drugs or fixed conbination preparations.**
- **individualized**：**make drug choice according to the patients' condition, tolerance, wishes, long-term affordability.**

Antihypertensive drugs

category	Drug added	Drug deleted
CCB	L-amlodipine、extend-release felodipine、benidipine、sustained-release verapamil	nisoldipine
ACEI	—	quinapril、trandolapril
ARB	—	—
diuretic	Eplerenone	—
β-blocker	sustained-release metoprolol	

Antihypertensive drugs

- New：direct renin inhibitor: Aliskiren,150-300mg
- New: fixed combination compounds

Compelling indications and contraindictions

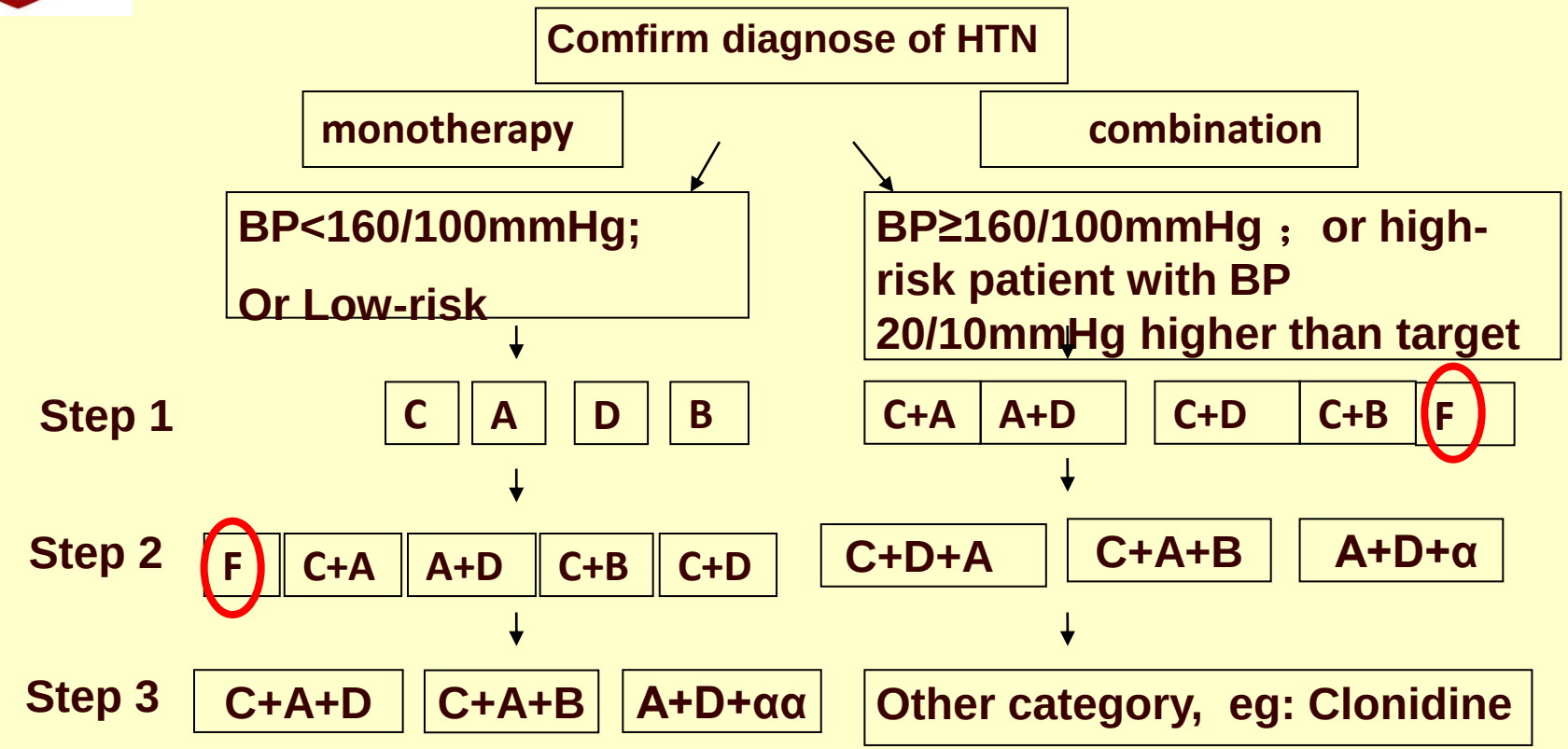
category	indications	contraindication	
		absolutely	relatively
CCB（dihydropyridine)	Eldly HTN、PAD、SBP HTN、stable agina、carotid atherosclerosis、coronary atherosclosis（delete:gestation）	无	tachyarrthymia, HF
CCB（non-dihydropyridine)	agina、carotid atherosclerosis、Supraventricular tachycardia	Ⅱ-ⅢAVB	HF
ACEI	HF、agina、after MI、LVH、LV dysfunction、carotid atherosclerosis、Non-diabetic kidney disease、diabetic nephropathy、proteinuretic/ Microalbuminuria、metabolism syndrome	pregnancy Hyperkalemia Bilateral renal artery stenosis	
ARB	diabetic nephropathy、proteinuretic/ Microalbuminuria、CAD、HF、LVH、AF prevention、ACEI induced coughing、metabolism syndrome	pregnancy Hyperkalemia Bilateral renal artery stenosis	
Thiazide diuretic	HF、eldly HTN、very eldly HTN、SBP HTN	Gout	pregnancy
Loop diuretic	CKD、HF		
Aldosterone antagonists	HF、after MI	Renal failure hyperkalemia	
B-blocker	agina、after MI、tachyarrthymia、stable CHF（delete:gestation）	Ⅱ—Ⅲavb asthma	COPD、PAD、IGT、athlete
α-blocker	Prostatic hyperplasia、hyperlipidemia	Orthostatic hypotension压	HF

Combination of antihypertensive drugs

- Recommedation of optimal combination therapy
- Propose the fix-dose combinations as the new trend of treatment
- Recommedation of 3 drugs combination: A+C+D

Priority recommend	General recommend	Not routinely recommend
D-CCB+ARB	diuretic+βblocker	ACEI+βblocker
D-CCB+ACEI	αblocker+βblocker	ARB+βblocker
ARB + thiazide diuretic	D-CCB+Potassium-sparing diuretics	ACEI+ARB
ACEI + thiazide diuretic	thiazide diuretic + Potassium-sparing diuretics	Drug acting on central nervous system+β-blocker
D-CCB+thiazide diuretic		
D-CCB+-blocker		

Algorithm for treatment of hypertension



Note：A：ACEI or ARB；B：β-blocker；C：dihydropyridime；D：thiazide diuretic； α: α-blocker。 F：fixed low-dose combination。