Hypertension

Pharmacological treatment

Sep 12, 2010

吳靜芬

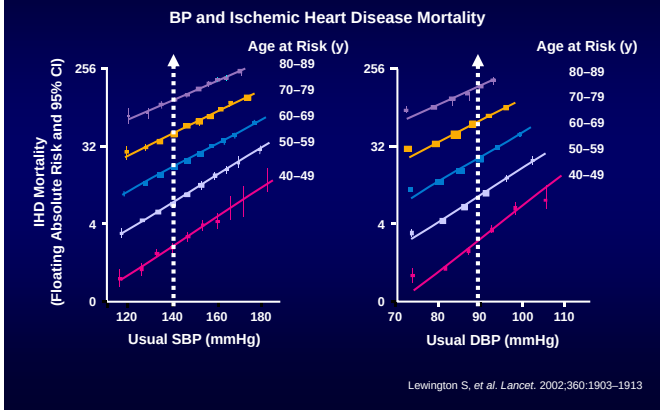
96年國人十大死因排行榜

1. 惡性腫瘤 Malignant neoplasms
2. 心臟疾病 Heart disease
3. 腦血管疾病 Cerebrovascular disease
4. 糖尿病 Diabetes mellitus
5. 事故傷害 Accidents and adverse effects
6. 肺炎 Pneumonia
7. 慢性肝病及肝硬化 Chronic liver disease and cirrhosis
8. 腎炎、腎徵候群及腎性病變 Nephritis, nephritic syndrome and nephrosis
9. 自殺 Suicide
10. 高血壓性疾病 Hypertensive disease

資料來源: 行政院衛生署資料

LIP-DC-0903001

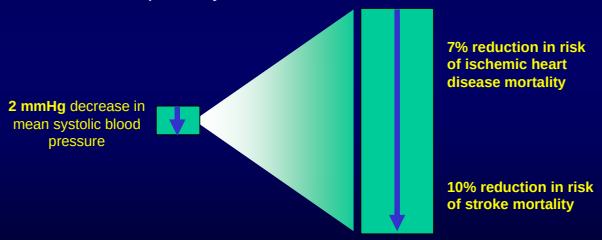
Increases in Mortality Associated with Increased BP at All Ages



Lewington S, *et al. Lancet.* 2002;360:1903–1913

Blood Pressure Reductions as Little as 2 mmHg Reduce the Risk of Cardiovascular Events by up to 10%

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

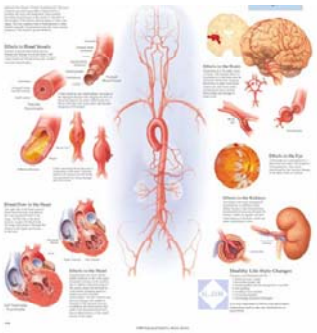


Lewington S, *et al. Lancet.* 2002;360:1903–1913

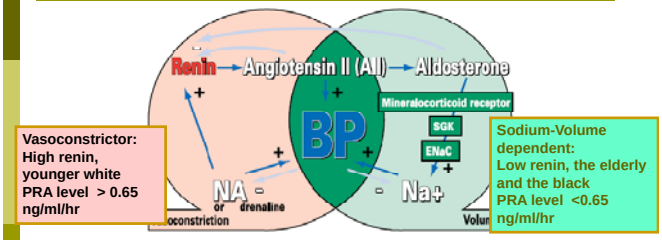
The main purposes of treating hypertension are

- To decrease long-term cardiovascular mortality and morbidity (stroke, CAD, heart failure)
- To protect from target organ damage (cardiac hypertrophy, renal failure, atherosclerosis)
- To avoid acute hypertension related complications (aortic dissection, acute lung edema, intracranial hemorrhage…)

Hypertension is a systemic disease



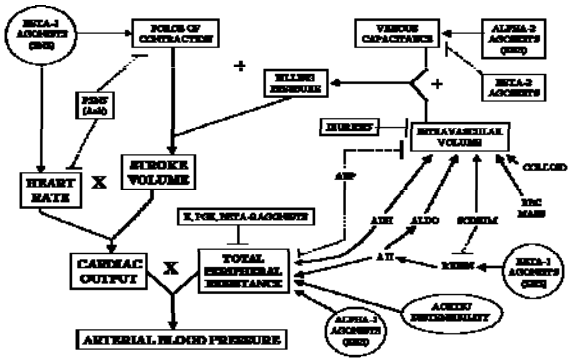
Types of hypertension: mechanism of hypertension



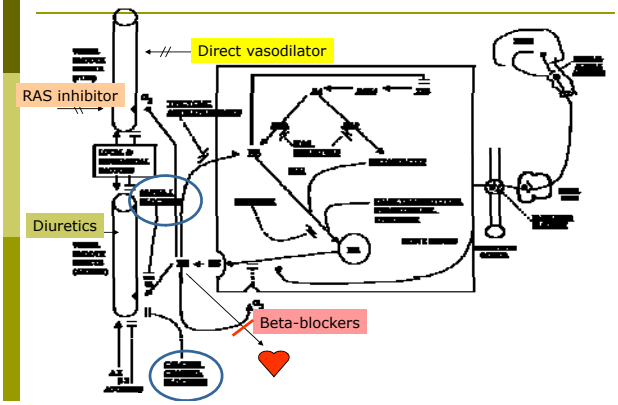
- BP= cardiac output * peripheral resistance
- Salt, volume, renin-angiotensin-aldosterone system, sympathetic activation, aortic stiffness and arteriolar resistence

Heart 2001;86:113-20

The pathophysiology of hypertension



Mechanism of antihypertensive medications



Special antihypertensive agents- Central agents

- Central agents (alpha-2 agonists)- **Clonidine**
  a. Decreases sympathetic outflow to the beta-1 system receptors:
     i. Decreased cardiac output
     ii. Relative reduction in tendency of heart rate to rise
  b. Has little effect on alpha-1 receptor system:
     i. Baroreceptor reflexes are preserved.
     ii. Little change in peripheral resistance
  c. Acts directly on venous alpha-2 receptors to cause venoconstriction.

Special antihypertensive agents- Central agents

- **Methyldopa**
  a. Decreases sympathetic outflow to the alpha-1 receptors of the arterioles, thereby reducing peripheral resistance with little (but some) effect on the heart
  b. Some antinatriuretic effect occurs (probably due to some reduction in renal vascular resistance).

Medications we frequently use

- RAS inhibitor: Angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor inhibitor (ARB), direct renin inhibitor, aldactone
- Beta-blocker
- Calcium channel blocker :benzothiazepines (e.g., diltiazem and clenazem), phenylalkylamines (e.g., verapamil and gallopamil) and dihydropyridines
- Diuretics
- Direct vasodilator
- Alpha-blocker

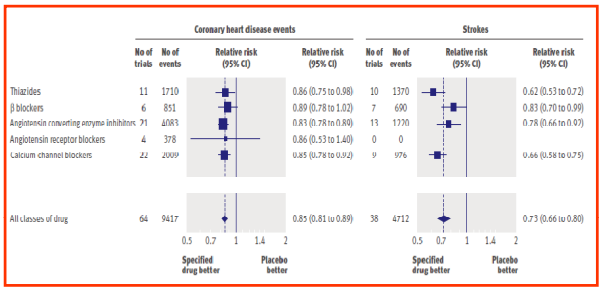
Efficacy among current classes of antihypertensive medications

Drugs	Systolic/Diastolic	Fall in blood pressure (mmHg (95%CI))
Thiazides	Systolic	8.8 (8.3 to 9.4)
	Diastolic	4.4 (4.0 to 4.8)
Beta-blockers	Systolic	9.2 (8.6 to 9.9)
	Diastolic	6.7 (6.2 to 7.1)
ACE inhibitors	Systolic	8.5 (7.9 to 9.0)
	Diastolic	4.7 (4.4 to 5.0)
Angiotensin II receptor antagonists	Systolic	10.3 (9.9 to 10.8)
	Diastolic	5.7 (5.4 to 9.0)
Calcium channel blockers	Systolic	8.8 (8.3 to 9.2)
	Diastolic	5.9 (5.6 to 6.2)

standardized to the average starting blood pressure across all trials of 154 mmHg systolic and 97 mmHg diastolic

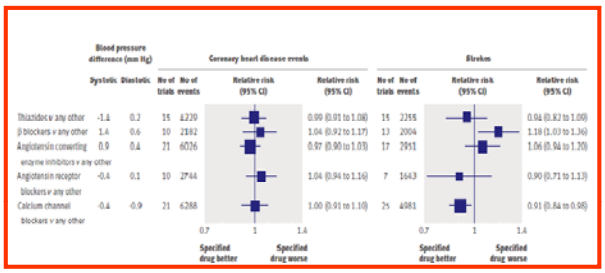
Health Technol Assess 2003, 7(31):1–94

Relative risk estimates of coronary heart disease events and stroke in single drug trials



BMJ 2009;338:b1665

Relative risk estimates of coronary heart disease events and stroke in 46 drug comparison trials



BMJ 2009;338:b1665

Heart Failure

Class of drug	No of trials	No of episodes	Relative risk*(95% CI)
Blood pressure difference trials			
Single drug therapy:			
Calcium channel blockers	13	1519	0.81 (0.69 to 0.94)
Thiazides	5	222	0.59 (0.45 to 0.78)
β blockers	13	2846	0.77 (0.69 to 0.87)
Angiotensin converting enzyme inhibitors	16	3834	0.74 (0.68 to 0.81)
Angiotensin receptor blockers	3	1675	0.82 (0.73 to 0.92)
All drug classes except calcium channel blockers	36†	8553†	0.76 (0.72 to 0.81)
Combination drug therapy	7	144	0.57 (0.36 to 0.92)
Drug comparison trials			
Calcium channel blockers v any other drug class	21	4572	1.22 (1.10 to 1.35)
Drug comparisons not involving calcium channel blockers:			
Thiazides	2	2335	0.91 (0.64 to 1.30)
β blockers	2	335	1.04 (0.84 to 1.29)
Angiotensin converting enzyme inhibitors	9	5063	0.98 (0.91 to 1.06)
Angiotensin receptor blockers	7	2436	1.00 (0.93 to 1.08)

Choice of Antihypertensive Drugs from 2007 ESC/ESH guidelines

- The main benefits of antihypertensive therapy are due to lowering of BP *per se*
- Five major classes of antihypertensive agents – thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β- blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. β-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes
- Because in many patients more than one drug is needed, emphasis on identification of the first class of drugs to be used in often futile. Nevertheless, there are many conditions for which there is evidence in favor of some drugs versus others either as initial treatment or as part of a combination therapy (compelling indications)

Journal of Hypertension 2007;25:1105-1187

To choose appropriate antihypertensive medications

- The contraindications
- The compelling indications
- The pathophysiology of hypertension of each individual hypertensive patient
- The tolerance profile
- Special considerations: pregnancy, lactation, hypertension crisis, erectile dysfunction

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Compelling and possible contraindications to use of antihypertensive drugs

	Compelling	Possible
Thiazide diuretics	Gout	Metabolic syndrome Glucose intolerance Pregnancy
Beta-blockers	Asthma A-V block (grade 2 or 3)	Peripheral artery disease Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease
Calcium antagonists (dihydropiridines)		Tachyarrhythmias Heart failure
Calcium antagonists (verapamil, diltiazem)	A-V block (grade 2 or 3) Heart failure	
ACE inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	
Angiotensin receptor antagonists	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Diuretics (antialdosterone)	Renal failure Hyperkalaemia	

To choose appropriate antihypertensive medications

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- The compelling indications
- The pathophysiology of hypertension of each individual hypertensive patient
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- Special considerations: pregnancy, lactation

Recommended Drug Classes for Specific Compelling Indications

Indication	*Diuretic*	*Beta blocker*	*Angiotensin-converting enzyme inhibitor*	*Angiotensin receptor blocker*	*Calcium channel blocker*	*Aldosterone antagonist*
Chronic kidney disease			X	X		
Diabetes	X	X	X	X	X	
Heart failure	X	X	X	X		X
High coronary disease risk	X	X	X		X	
Postmyocardial infarction		X	X			X
Recurrent stroke prevention	X		X			

To choose appropriate antihypertensive medications

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-
- The pathophysiology of hypertension of each individual hypertensive patient
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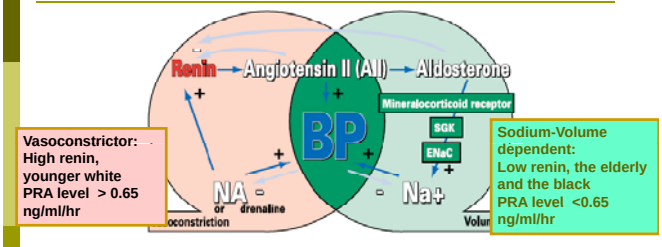
- Special considerations: pregnancy, lactation, hypertension crisis, erectile dysfunction

Types of hypertension



- BP= cardiac output * peripheral resistancne
- Younger hypertensive: 2 fold increase in sympathetic activity and 20% increase of cardiac output

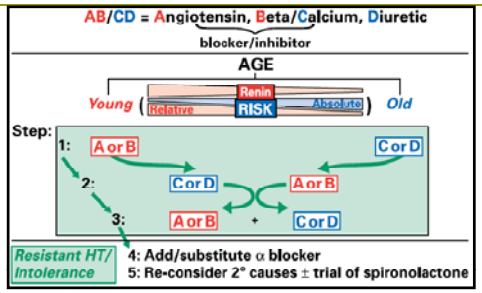
Heart 2001;86:113-20

Proof from the epidemiology: the Framingham Heart Study

Predictors of IDH	Predictors of ISH
Young age	Older age
Male sex	Female sex
High BMI at baseline	Increasing BMI during F/U (but weaker than in young)
Increasing BMI during F/U	De-novo hypertension
Increased peripheral resistance	Increased arterial stiffness

Circulation 2005;111:1121-7

The AB/CD rules



The antihypertensive therapy should be individualized and initiated with the drug class that is most likely to work in each individual patients

Heart 2001;86:113-20

To choose appropriate antihypertensive medications

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- The tolerance profile
- Special considerations: pregnancy, lactation, hypertension crisis, erectile dysfunction

Adverse Effects And Persistence

Adverse Effects

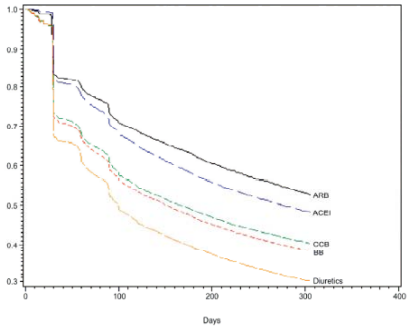
Drug class	No. of trials	Percent (95%CI) with symptoms (treated minus placebo)[1] 1/2 standard dose	Standard dose	Twice standard dose
Thiazides	59	2.0 [-2.2 to 6.3]	9.9 [6.6 to 13.2]	17.8 [11.5 to 24.2]
BBs	62	5.5 [0.3 to 10.7]	7.5 [4.0 to 10.9]	9.4 [3.6 to 15.2]
ACEi	96	3.9 [-3.7 to 11.6]	3.9 [-0.5 to 8.3]	3.9 [-0.2 to 8.0]
ARBs	44	-1.8 [-10.2 to 6.5]	0 [-5.4 to 5.4]	1.9 [-5.6 to 9.3]
CCBs	96	1.6 [-3.5 to 6.7]	8.3 [4.8 to 11.8]	14.9 [9.8 to 20.1]

Persistence

	Duration	ARBs	ACEi	CCBs	BBs	Diuretics
Bloom [15]	12	64%	58%***	50%	43%	38%
Conlin [18]	48	50.9%	46.5%	40.7%**	34.7%**	16.4%**
Hasford [36]	12	51.3%	42.0%	43.6%	49.7%	24.4%
Degli-Esposti [23]	12	41.7%	32.2%	26.7%	36.9%	25.9%
Erkens [37]	12	62.0%	59.7%	34.7%	35.0%	33.0%
Veronesi [19]	24	68.5%	64.5%	51.6%**	44.8%**	34.4%*
Hasford [17]	12	36.4%	38.2%	25.9%	25.8%	21.9%
Patel [16]	12	51.9%	48.0%	38.3%	40.3%	29.9%

Cardiovascular Diabetology 2009, 8:18

Time to therapy discontinuation of antihypertensive monotherpay

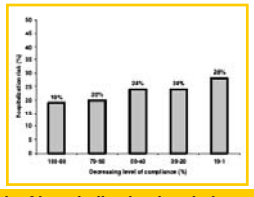


J Clin Hypertens (Greenwich) 2007, 9 (9):692–700

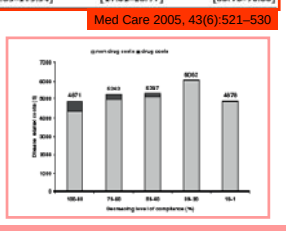
Healthcare cost

Antihypertensive	Continuers [95%CI]	Switchers [95%CI]	Discontinuers 95%CI]	Total [95%CI]
Diuretics	€ 65.09 [58.67–71.52]	€ 153.10 [137.59–168.62]	€ 8.17 [7.60–8.75]	€ 33.45 [30.97–35.93]
Beta-blockers	€ 109.29 [102.46–116.12]	€ 158.73 [139.61–177.84]	€ 22.52 [24.24–22.79]	€ 63.40 [59.94–66.86]
Calcium-channel blockers	€ 234.62 [224.78–244.47]	€ 199.62 [183.45–215.78]	€ 38.24 [36.78–39.70]	€ 104.43 [100.07–108.79]
ACE inhibitors	€ 196.28 [189.69–202.86]	€ 237.53 [222.28–252.79]	€ 34.76 [33.53–35.99]	€ 108.25 [104.43–112.09]
Angiotensin II antagonists	€ 326.16 [313.05–339.27]	€ 268.07 [241.53–294.59]	€ 67.10 [62.89–71.31]	€ 201.53 [191.24–211.81]
Total	€ 171.73 [167.43–176.04]	€ 205.10 [196.85–213.34]	€ 28.29 [27.62–28.97]	€ 88.09 [86.10–90.08]

Med Care 2005, 43(6):521–530



Risk of hospitalization in relation to the level of compliance for hypertension



Disease-related healthcare costs in relation to the level of compliance

To choose appropriate antihypertensive medications

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- Special considerations: pregnancy, lactation, hypertension crisis, erectile dysfunction

Classification of Hypertension in Pregnancy

Chronic hypertension	BP ≥140 mm Hg systolic or 90 mm Hg diastolic prior to pregnancy or before 20 weeks gestation
	Persists >12 weeks postpartum
Preeclampsia	BP ≥140 mm Hg systolic or 90 mm Hg diastolic with proteinuria (>300 mg/24 h) after 20 weeks gestation
	Can progress to eclampsia (seizures)
	More common in nulliparous women, multiple gestation, women with hypertension for ≥4 years, family history of preeclampsia, hypertension in previous pregnancy, renal disease
Chronic hypertension with superimposed preeclampsia	New onset proteinuria after 20 weeks in a woman with hypertension
	In a woman with hypertension and proteinuria prior to 20 weeks gestation:
	Sudden 2- to 3-fold increase in proteinuria
	Sudden increase in BP
	Thrombocytopenia
	Elevated AST or ALT
Gestational hypertension	Hypertension without proteinuria occurring after 20 weeks gestation
	Temporary diagnosis
	May represent preproteinuric phase of preeclampsia or recurrence of chronic hypertension abated in midpregnancy
	May evolve to preeclampsia
	If severe, may result in higher rates of premature delivery and growth retardation than mild preeclampsia
Transient hypertension	Retrospective diagnosis
	BP normal by 12 weeks postpartum
	May recur in subsequent pregnancies
	Predictive of future primary hypertension

Treatment of chronic hypertension in pregnancy

Agent	Comments
Methyldopa	Preferred on the basis of long-term follow-up studies supporting safety
BBs	Reports of intrauterine growth retardation (atenolol)
	Generally safe
Labetalol	Increasingly preferred to methyldopa because of reduced side effects
Clonidine	Limited data
Calcium antagonists	Limited data
	No increase in major teratogenicity with exposure
Diuretics	Not first-line agents
	Probably safe
ACEIs, angiotensin II receptor antagonists	Contraindicated
	Reported fetal toxicity and death

1. treatment should be reinstituted once BP reaches 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic

JNC 7. Hypertension 2003;42;1206-1252

Treatment of Acute Severe Hypertension in Preeclampsia

Hydralazine	5 mg IV bolus, then 10 mg every 20 to 30 minutes to a maximum of 25 mg, repeat in several hours as necessary
Labetalol (second-line)	20 mg IV bolus, then 40 mg 10 minutes later, 80 mg every 10 minutes for 2 additional doses to a maximum of 220 mg
Nifedipine (controversial)	10 mg PO, repeat every 20 minutes to a maximum of 30 mg
	Caution when using nifedipine with magnesium sulfate, can see precipitous BP drop
	Short-acting nifedipine is not approved by US Food and Drug Administration for managing hypertension
Sodium nitroprusside (rarely when others fail)	0.25 μg/kg/min to a maximum of 5 μg/kg/min
	Fetal cyanide poisoning may occur if used for more than 4 hours

- Preeclampsia is more common in women with chronic hypertension, with an incidence of approximately 25%
- Treatment of preeclampsia includes hospitalization for bed rest, control of BP, seizure prophylaxis in the presence of signs of impending eclampsia, and timely delivery
- Preeclampsia rarely remits spontaneously and in most cases worsens with time
- Vaginal delivery is preferable to cesarean delivery to avoid the added stress of surgery
- Selection of antihypertensive agents and route of administration depends on anticipated timing of delivery

Lactations

- all antihypertensive drugs that have been studied are excreted into human breast milk
- in mothers with stage 1 hypertension → withhold medications and close monitor
- No short-term adverse effects have been reported from exposure to methyldopa or hydralazine
- Propanolol and labetalol are preferred if a BB is indicated
- ACEIs and ARBs should be avoided on the basis of reports of adverse fetal and neonatal renal effects

Hypertensive Crises: Emergencies and Urgencies

- Hypertensive emergencies severe elevations in BP (180/120 mm Hg) complicated by evidence of impending or progressive target organ dysfunction (hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, or eclampsia)
- Hypertensive urgencies are those with severe elevations in BP without progressive target organ dysfunction

Treatment of Acute Severe Hypertension in Preeclampsia

Drug	Dose	Onset of Action	Duration of Action	Adverse Effects†	Special Indications
Vasodilators					
Sodium nitroprusside	0.25–10 μg/kg/min as IV infusion‡	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or eclampsia
Nicardipine hydrochloride	5–15 mg/h IV	5–10 min	15–30 min, may exceed 4 h	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 μg/kg per min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100 μg/min as IV infusion‡	2–5 min	5–10 min	Headache, vomiting, methaemoglobinaemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25–5 mg every 6 h IV	15–30 min	6–12 h	Precipitous fall in pressure in high-renin states; variable response	Acute left ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10–20 mg IV	10–20 min IV	1–4 h IV	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
	10–40 mg IM	20–30 min IM	4–6 h IM		
Adrenergic inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 min	5–10 min	3–6 h	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
	0.5–2.0 mg/min IV infusion				
Esmolol hydrochloride	250–500 μg/kg/min IV bolus, then 50–100 μg/kg/min by infusion; may repeat bolus after 5 min or increase infusion to 300 μg/min	1–2 min	10–30 min	Hypotension, nausea, asthma, first-degree heart block, HF	Aortic dissection, perioperative
Phentolamine	5–15 mg IV bolus	1–2 min	10–30 min	Tachycardia, flushing, headache	Catecholamine excess

*These doses may vary from those in the *Physicians' Desk Reference* (51st edition).
†Hypotension may occur with all agents.
‡Requires special delivery system.

Erectile Dysfunction and Hypertension

- Available data regarding individual effects of antihypertensive drug therapy are confounded by age, vascular disease, and hormonal status
- TOMHS study: diuretics most
- VA Cooperative trial: no difference between CCB, ACEI, hydrochlorothiazide, or BB compared with placebo
- Sildenafil or other phosphodiesterase-5 inhibitors: safe without nitrate

Drug class	Age-adjusted relative risk of ED
Angiotensin II antagonists	2.4
Non-selective beta-blockers	2.0
Calcium antagonists	1.6
Diuretics	1.4
ACE-inhibitors	1.2
Selective beta-blockers	1.0
Statins	0.9
Organic nitrates	0.8

The risk of ED appeared to be higher in men using calcium antagonists, angiotensin II antagonists, non-selective beta-blockers, or diuretics, but ED was not associated with organic nitrates, angiotensin converting enzyme (ACE)-inhibitors, selective beta-blockers, or statins. Data from Shiri et al. *Int J Impot Res* 2007;**19**:208–12.

Is it the problems of the drugs??

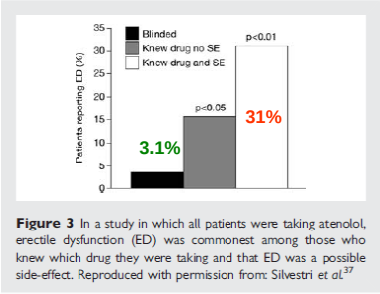

Figure 3 In a study in which all patients were taking atenolol, erectile dysfunction (ED) was commonest among those who knew which drug they were taking and that ED was a possible side-effect. Reproduced with permission from: Silvestri *et al.*[37]

Eur Heart J 2003;24:1928–932

Common Substances Associated With Hypertension in Humans

Prescription Drugs
Cortisone and other steroids (both cortico- and mineralo-), ACTH
Estrogens (usually just oral contraceptive agents with high estrogenic activity)
Nonsteroidal anti-inflammatory drugs
Phenylpropanolamines and analogues
Cyclosporine and tacrolimus
Erythropoietin
Sibutramine
Ketamine
Desflurane
Carbamazepine
Bromocryptine
Metoclopramide
Antidepressants (especially venlafaxine)
Buspirone
Clonidine, BB combination
Pheochromocytoma; BB without α-blocker first; glucagon
Clozapine

Street drugs and other "natural products"
Cocaine and cocaine withdrawal
Ma huang, "herbal ecstasy," and other phenylpropanolamine analogs
Nicotine and withdrawal
Anabolic steroids
Narcotic withdrawal
Methylphenidate
Phencyclidine
Ketamine
Ergotamine and other ergot-containing herbal preparations
St. John's wort
Food substances
Sodium chloride
Ethanol
Licorice
Tyramine-containing foods (with MAO-I)
Chemical elements and other industrial chemicals
Lead
Mercury
Thallium and other heavy metals
Lithium salts, especially the chloride

若諸有情，眾病逼切，
無救無歸，無醫無藥，
無親無家，貧窮多苦，
我之名號，一經其耳，
眾病悉除，身心安樂，
家屬資具，悉皆豐足，
乃至證得，無上菩提