

## Antihypertensive drug

The antihypertensives are a class of drugs that are used to treat hypertension (high blood pressure), Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease, There are many classes of antihypertensives, which lower blood pressure by different means; among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium channel blockers, the beta blockers, and the angiotensin II receptor antagonists or ARBs.

### Main complications of persistent High blood pressure

#### Brain:

- Cerebrovascular accident (*strokes*)
- Hypertensive encephalopathy:
  - confusion*
  - headache*
  - convulsion*

#### Retina of eye:

- Hypertensive retinopathy

#### Heart:

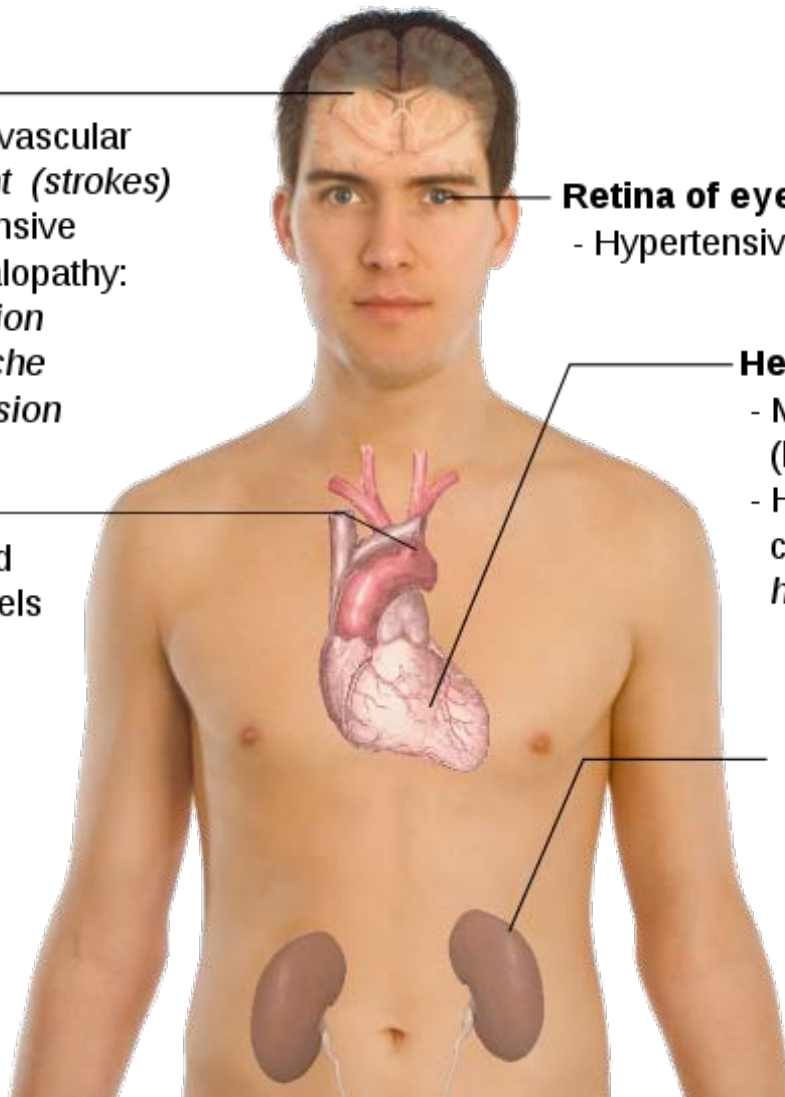
- Myocardial infarction (*heart attack*)
- Hypertensive cardiomyopathy:  
*heart failure*

#### Blood:

- Elevated sugar levels

#### Kidneys:

- Hypertensive nephropathy:  
*chronic renal failure*



## AVAILABLE AGENTS

# 1-Diuretics

Diuretics help the kidneys eliminate excess salt and water from the body's tissues and blood.

In medicine, diuretics are used to treat heart failure, liver cirrhosis, hypertension and certain kidney diseases. Some diuretics, such as acetazolamide, help to make the urine more alkaline and are helpful in increasing excretion of substances such as aspirin in cases of overdose or poisoning. Diuretics are often abused by sufferers of eating disorders, especially bulimics, in attempts at weight loss.

The antihypertensive actions of some diuretics (thiazides and loop diuretics in particular) are independent of their diuretic effect. That is, the reduction in blood pressure is not due to decreased blood volume resulting from increased urine production, but occurs through other mechanisms and at lower doses than that required to produce diuresis. Indapamide\* was specifically designed with this in mind, and has a larger therapeutic window for hypertension (without pronounced diuresis) than most other diuretics.

### **\*\*Indapamide:**

is a non-thiazide sulphonamide diuretic drug marketed by Servier, generally used in the treatment of hypertension, as well as decompensated cardiac failure. The US trade name for indapamide is Lozol. Indapamide is marketed as Natrilix outside of the US. Combination preparations with perindopril (an ACE inhibitor antihypertensive) are also available, It is described as a thiazide-like diuretic.

**Indications:** Hypertension and edema due to congestive heart failure.

**Contraindications:** Indapamide Indapamide is contraindicated in known hypersensitivity to sulfonamides, severe renal failure, hepatic encephalopathy or severe hepatic failure and hypokalemia (low blood potassium levels).

### **Types of Diuretics:**

- 1) High ceiling loop diuretics
- 2) Thiazides
- 3) Carbonic Anhydrase Inhibitors
- 4) Digitalis
- (5) Potassium-sparing diuretics
- (6) Calcium-sparing diuretics
- (7) Osmotic diuretics
- (8) Low ceiling diuretics

**Loop diuretics:**

- 1) bumetanide
- 2) ethacrynic acid
- 3) furosemide
- 4) torsemide

**Thiazide diuretics:**

- 1) epitizide
- 2) hydrochlorothiazide and chlorothiazide
- 3) bendroflumethiazide

**Potassium-sparing diuretics:**

- 1) amiloride
- 2) triamterene
- 3) spironolactone

**Thiazide-like diuretics:**

- 1) indapamide
- 2) chlorthalidone
- 3) metolazone

Only the thiazide and thiazide-like diuretics have good evidence of beneficial effects on important endpoints of hypertension, and hence, should usually be the first choice when selecting a diuretic to treat hypertension. The reason why thiazide-type diuretics are better than the others is (at least in part) thought to be because of their vasodilating properties.

In the United States, the JNC7 (The Seventh Report of the Joint National Committee on Prevention of Detection, Evaluation and Treatment of High Blood Pressure) recommends starting with a thiazide diuretic if single therapy is being initiated and another medication is not indicated.

Despite thiazides being cheap, effective, and recommended as the best first-line drug for hypertension by many experts, they are not prescribed as often as some newer drugs. This is because they have been associated with increased risk of new-onset diabetes and as such are recommended for use in patients over 65 where the risk of new-onset diabetes is outweighed by the benefits of controlling systolic blood pressure.

## 2- Adrenergic receptor antagonists

**Beta blockers**

- atenolol
- metoprolol
- nadolol
- oxprenolol
- pindolol
- propranolol
- timolol

**Alpha blockers:**

- doxazosin
- phentolamine
- indoramin
- phenoxybenzamine
- prazosin
- terazosin
- tolazoline

**Mixed Alpha + Beta blockers:**

- bucindolol
- carvedilol
- labetalol

Although beta blockers lower blood pressure, they do not have a positive benefit on endpoints as some other antihypertensives. In particular, beta-blockers are no longer recommended as first-line treatment due to relative adverse risk of stroke and new-onset diabetes when compared to other medications.

In the United Kingdom, the June 2006 "Hypertension: Management of Hypertension in Adults in Primary Care" guideline of the National Institute for Health and Clinical Excellence, downgraded the role of beta-blockers due to their risk of provoking type 2 diabetes.

# 3- Adrenergic receptor agonists

## Alpha-2 agonists:

- clonidine
- methyldopa
- Guanfacine

Epinephrine has higher affinity for the alpha-2 receptor than has norepinephrine, which, in turn, has much higher affinity than has isoprenaline. Nonselective agonists include clonidine, an antihypertensive. Clonidine is an Alpha 2 Agonist used to reduce blood pressure. It was initially thought to act via presynaptic Alpha 2 receptors, reducing the amount of NE released.

$\alpha$ 2A selective agonists include guanfacine (an antihypertensive) and octopamine, which is also a  $\beta$ 3 agonist, (R)-3-Nitrobiphenylene is an  $\alpha$ 2C selective agonist.

# 4- Calcium channel blockers

Calcium channel blockers block the entry of calcium into muscle cells in artery walls.

## Dihydropyridines:

- amlodipine
- felodipine
- isradipine
- lercanidipine
- nicardipine
- nifedipine
- nimodipine
- nitrendipine

## Non-dihydropyridines:

- diltiazem
- verapamil

# 5-ACE inhibitors

ACE inhibitors inhibit the activity of Angiotensin-converting enzyme (ACE), an enzyme responsible for the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor.

- captopril
- enalapril
- fosinopril
- lisinopril
- perindopril
- quinapril
- ramipril
- trandolapril
- benazepril

# 6-Angiotensin II receptor antagonists

Angiotensin II receptor antagonists work by antagonizing the activation of angiotensin receptors.

- candesartan
- eprosartan
- irbesartan
- losartan
- olmesartan
- telmisartan
- valsartan

# 7-Aldosterone antagonists

**Aldosterone receptor antagonists:**

- eplerenone
- spironolactone

Aldosterone antagonists are not recommended as first-line agents for blood pressure, but spironolactone and eplerenone are both used in the treatment of heart failure.

# 8- Vasodilators

Vasodilators act directly on the smooth muscle of arteries to relax their walls so blood can move more easily through them; they are only used in hypertensive emergencies or when other drugs have failed, and even so are rarely given alone.

**Sodium nitroprusside**, a very potent, short-acting vasodilator, is most commonly used for the quick, temporary reduction of blood pressure in emergencies (such as malignant hypertension or aortic dissection).

**Hydralazine** and its derivatives are also used in the treatment of severe hypertension, although they should be avoided in emergencies. They are no longer indicated as first-line therapy for high blood pressure due to side effects and safety concerns, but hydralazine remains a drug of choice in gestational hypertension.

# 9-Centrally acting adrenergic drugs

Central alpha agonists lower blood pressure by stimulating alpha-receptors in the brain which open peripheral arteries easing blood flow. Central alpha agonists, such as clonidine, are usually prescribed when all other anti-hypertensive medications have failed. For treating hypertension, these drugs are usually administered in combination with a diuretic.

- Clonidine
- Guanabenz
- Methyldopa
- Moxonidine

Adverse effects of this class of drugs include sedation, drying of the nasal mucosa and rebound hypertension.

Some **adrenergic neuron blockers** are used for the most resistant forms of hypertension:

- Guanethidine
- Reserpine

## Future treatment options:

### Blood pressure vaccine

Blood pressure vaccinations are being trialed and may become a treatment option for high blood pressure in the future. Research on the vaccine CYT006-AngQb published in The Lancet on the 8 March 2008 titled, "Vaccination against high blood pressure: a new strategy" showed patients experienced a drop in systolic and diastolic blood pressure after taking the vaccine. Effective blood pressure vaccines would assist those people who forget to take their medication. It would also help those who stop taking their medication due to side effects or falsely believing they don't need them anymore once their blood pressure is lowered.

## Choice of initial medication

For mild blood pressure elevation, consensus guidelines call for medically-supervised lifestyle changes and observation before recommending initiation of drug therapy. However, according to the American Hypertension Association, evidence of sustained damage to the body may be present even prior to observed elevation of blood pressure. Therefore the use of hypertensive medications may be started in individuals with apparent normal blood pressures but who show evidence of hypertension related nephropathy, proteinuria, atherosclerotic vascular disease, as well as other evidence of hypertension related organ damage.

The largest study, **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)**, concluded that thiazide-type diuretics are better and cheaper than other major classes of drugs at preventing cardiovascular disease, and should be preferred as the starting drug.

**Thiazide diuretics** are effective, recommended as the best first-line drug for hypertension by many experts, and are much more affordable than other therapies, Hydrochlorothiazide is perhaps the safest and most inexpensive agent commonly used in this class and is very frequently combined with other agents in a single pill. Doses in excess of 25 milligrams per day of this agent incur an unacceptable risk of low potassium or Hypokalemia. Patients with an exaggerated hypokalemic response to a low dose of a thiazide diuretic should be suspected to have Hyperaldosteronism, a common cause of secondary hypertension.

**Adverse effects of thiazide diuretics** include hypercholesterolemia, and impaired glucose tolerance with increased risk of developing Diabetes mellitus type 2. The thiazide diuretics also deplete circulating potassium unless combined with a potassium-sparing diuretic or supplemental potassium, However as the Merck Manual of Geriatrics notes, "thiazide-type diuretics are especially safe and effective in the elderly."

Current UK guidelines suggest starting patients over the age of 55 years and all those of African/Afrocaribbean ethnicity firstly on calcium channel blockers or thiazide diuretics, whilst younger patients of other ethnic groups should be started on ACE-inhibitors. Subsequently if dual therapy is required to use ACE-inhibitor in combination with either calcium channel blocker or a (thiazide) diuretic. Triple therapy is then of all three groups and should the need arise then to add in a fourth agent, to consider a further diuretic (e.g. spironolactone or furosemide), an alpha-blocker or a beta-blocker. Prior to the demotion of beta-blockers as first line agents, the UK sequence of combination therapy used the first letter of the drug classes and was known as the "ABCD rule".

The choice between the drugs is to a large degree determined by the characteristics of the patient being prescribed for, the drugs' side-effects, and cost. For example, asthmatics have been reported to have worsening symptoms when using beta blockers. Most drugs have other uses; sometimes the presence of other symptoms can warrant the use of one particular antihypertensive (such as beta blockers in case of tremor and nervousness, and alpha blockers in case of benign prostatic hyperplasia). The JNC 7 report outlines compelling reasons to choose one drug over the others for certain individual patients.

## **Non-drug treatment options**

Several studies have found that hibiscus tea (As an infusion) has a substantial antihypertensive effect attributable to the flower's ACE-inhibiting anthocyanin content, and possibly to a diuretic effect. One study found that hibiscus conferred an antihypertensive effect comparable to 50 mg./day of the drug captopril.

Another potential treatment is Coenzyme Q10 (found in almost Meat, Fish, Oils, Nuts, Vegetables, Fruit), which a meta analysis of 12 studies found reductions in systolic pressure of 10-17 points and a reduction in diastolic pressure of 8-10 points with doses of roughly 200mg/day.

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