

## Pharmacology and Prescribing in Hypertension

### Abstract

In this article in the series of 'bite sized' pharmacology, we will look at the pharmacological actions of drugs used in the management of hypertension. This article will outline the issues and areas of intervention required in hypertension with reference to current guidelines and formulary. It will illustrate the common therapeutic interventions in patients with Stage 1, Stage 2 and Severe Hypertension taking into account a stepwise approach incorporating inter individual variations affecting drug choice.

It will then go on to examine the main types of drug used and their pharmacodynamic actions. The management will be considered within the NICE guidance and evidence base. Exercises will be provided to help you apply this knowledge to your prescribing practice.

### Hypertension



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Hypertension can be broken down into two distinct categories;

Essential hypertension- This is where there is no direct attributable cause to explain the persistently elevated blood pressure.

Secondary hypertension- This is where the raised blood pressure can be attributed, wholly or partly to another primary condition

- Diabetes
- Renal Disease

- Thyroid Disease
- Cushings Syndrome- steroids used to treat
- Pheochromocytoma
- Obesity
- Pregnancy

The National Institute for Health & Care Excellence have produced guidelines for the diagnosis and management of hypertension in adults (NICE CG127- <https://www.nice.org.uk/guidance/cg127> ).

It defines hypertension in the following way

- **Stage 1 hypertension** Clinic blood pressure is 140/90 mmHg or higher **and** subsequent ambulatory blood pressure monitoring (ABPM) daytime average or home blood pressure monitoring (HBPM) average blood pressure is 135/85 mmHg or higher.
- **Stage 2 hypertension** Clinic blood pressure is 160/100 mmHg or higher **and** subsequent ABPM daytime average or HBPM average blood pressure is 150/95 mmHg or higher.
- **Severe hypertension** Clinic systolic blood pressure is 180 mmHg or higher **or** clinic diastolic blood pressure is 110 mmHg or higher.

Exercise

With reference to your own area of practice, explore the categories of hypertensive patients you deal with and establish the diagnosis of the condition within recognised guidelines and parameters.

The primary goal of drug therapy is to improve cardiovascular function and reduce the clinical symptoms as well as preventing secondary conditions or major events.

Table 1: Drugs Commonly Used in the Management of Hypertension

Action of Drug	Class Examples
Cardio-inhibitory	Beta-adrenoceptor Blockers Calcium Channel Blockers
Vasodilators	Angiotensin Converting Enzyme Inhibitors Angiotensin receptor Blockers
Diuretics	Thiazide Diuretics Loop Diuretics Potassium Sparing Diuretics

### Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, explore the range of anti-hypertensive drugs available.

Reconcile this with your local policy on prescribing in hypertension and NICE Guidance.

### Pharmacology of Individual Classes of Drugs

#### Diuretics

Diuretic drugs increase urine output by the kidney (i.e. promote diuresis). This is accomplished by altering how the kidney handles sodium and water (Rang et al 2015). If the kidney excretes more sodium, then water excretion will also increase. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system (see figure 1). Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect).

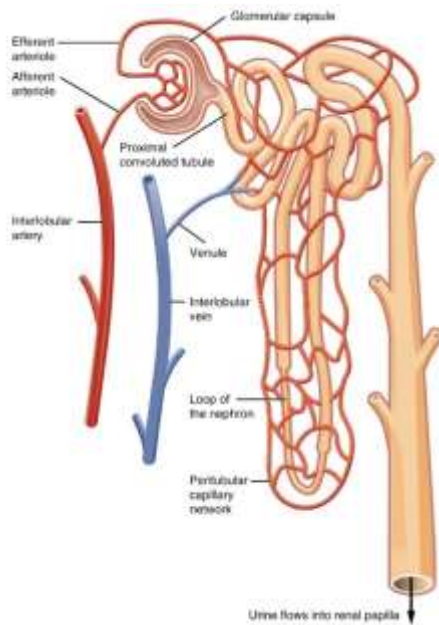


Figure 1- The renal Tubular System from Wikimedia Commons

*Loop diuretics* have their effect by a profound inhibition of the sodium-potassium-chloride co-transporter located in the thicker ascending portion of the loop part of the nephron. This efficient transporter is responsible for 25% of the sodium reabsorption that occurs. Blockade of this normal mechanism gives rise to an increase in the concentration of sodium found in the distal tubule, and as a result there is less water reabsorption into the collecting duct, as the water stays with the higher sodium level. This promotes diuresis (water excretion) and natriuresis (sodium excretion). Loop diuretics are very strong diuretics (Neal 2016). These drugs also promote production of prostaglandins by the kidney itself. These are needed to maintain normal kidney function and increase the efficacy of these drugs by contributing to renal blood flow efficiency.

They are useful if added to other antihypertensive treatment to improve control in those with resistant hypertension or impaired renal function (BNF2018).

Examples- furosemide and bumetanide.

*Thiazide and related diuretics*, have their action by inhibition of the sodium-chloride transporter mechanism found in the distal tubule of the nephron. This system is responsible for around 5% reabsorption of sodium, meaning that these drugs are classed as weaker than loop diuretics (Barber and Robertson 2015).

They are however often adequately strong enough to produce the necessary diuretic effect.

Examples- Bendroflumethiazide, Indapamide.

*Potassium sparing diuretics*, antagonize the actions of aldosterone in the distal part of the distal tubule. This allows more sodium and the water that naturally follows, to move to the collecting duct for excretion in the urine. They do not produce hypokalaemia to the same extent as the loop and thiazide diuretics. This is because inhibition of aldosterone-sensitive sodium reabsorption, means that there is a reduction in the amount of potassium and hydrogen exchanged for sodium by this transport mechanism.

Other diuretics in this class can have their effects by directly inhibiting sodium channels collocated with the aldosterone-sensitive sodium pump, and have similar effects (Neal 2016). This class of diuretic is categorised as a weak diuretic, and as such they are often used in combination with thiazide or loop diuretics to reduce the potential hypokalaemia associated with those drugs (BNF 2018).

Examples – Amiloride, Spironolactone

### Vasodilators

As the name implies, vasodilator drugs relax the smooth muscle in blood vessels, which causes the vessels to dilate. Dilation of arterial (resistance) vessels leads to a reduction in systemic vascular resistance, which leads to a fall in arterial blood pressure. Dilation of venous (capacitance) vessels decreases venous blood pressure.

The Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARB's) are examples of vasodilatory drugs used in hypertension. Their actions are on the Renin-Angiotensin-Aldosterone System (see figure 2) where vasoconstriction is part of the normal mechanism.

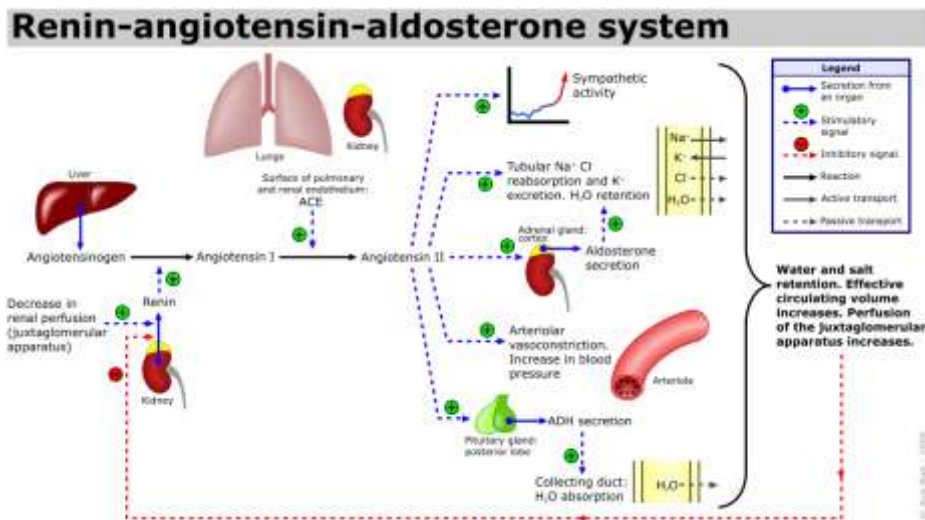


Figure 2 Renin-Angiotensin-Aldosterone System from Wikimedia Commons

### *ACE inhibitors*

These cause vasodilation by blocking angiotensin II production and inhibiting the metabolism of bradykinin. This in turn reduces arterial pressure, and the work of the heart.

They also reduce sympathetic activity produced by adrenaline by blocking the effects of angiotensin II on sympathetic nerve modulation of noradrenaline. This blocks the normal vasoconstrictive mechanisms.

In addition they promote the excretion of sodium and water by the kidney through a process where the action of angiotensin II in the kidney is inhibited as is aldosterone secretion. This reduces circulating volume, and in turn reduces blood pressure.

Examples- Enalapril, Ramapril, Perindopril

### *ARBs*

These drugs are receptor antagonists that block angiotensin II receptors on blood vessels and in the heart. These receptors stimulate vascular smooth muscle contraction. Blocking this contraction produces relaxation and dilation. They do not inhibit ACE, and therefore do not increase bradykinin metabolism, which contributes to the side effects of ACE inhibitors such as persistent dry cough and angioedema.

Examples- Candesartan, Irbesartan

### Cardio Inhibitory Drugs

#### *Beta Adrenoceptor Blockers*

Beta-blockers are drugs that bind to beta-adrenoceptors and thereby block the binding of noradrenaline and adrenaline to these receptors. This inhibits normal sympathetic effects that act through these g-protein coupled receptors. These g protein receptors are linked to cyclic adenosine monophosphate (cAMP). The heart contains  $\beta_1$  and  $\beta_2$  subtypes, but  $\beta_1$  outnumbers  $\beta_2$ . The smooth muscle of the rest of the vascular system has  $\beta_2$ -adrenoceptors. Beta blockers have relatively little vascular effects and the majority effect is produced through cardiac modulation. They lead to a reduction in cardiac output and can decrease heart rate and may have an effect on renin production from the kidney. An additional effect is altered baroreceptor reflex sensitivity which is a parasympathetic activity (BNF 2018).

Examples- Propranolol, Bisoprolol, Metoprolol.

### *Calcium Channel Blockers (CCBs)*

Many CCBs bind to L-type calcium channels which are found in vascular smooth muscle.

The channels regulate the movement of calcium ions into muscle cells. This movement is the precursor to smooth muscle contraction. The inhibition of this normal mechanism causes vascular smooth muscle relaxation. The dihydropyridine class of CCBs is commonly used as they have a high affinity for vascular tissue. Non-dihydropyridine drugs have a relatively high affinity but are not as selective as the dihydropyridine class.

Examples- Amlodipine (dihydropyridine), Diltiazem, Verapamil (non-dihydropyridine).

### Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, look up the specific class and modes of action of drugs you regularly expect to prescribe. Use this information to augment your personal formulary knowledge.



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NICE Guidelines give a good overview of which antihypertensive is most appropriate depending on the stage of hypertension and the individual characteristics of the patient, including age, sex and family origin, but it is important that we consider how to apply the



guidelines within the context of the actual patient in front of us and ensure that we do not blindly and rigorously apply the guidelines, but rather use them to tailor a patient specific plan for the people we are prescribing for.

#### Reflective Exercise

Access the NICE guidance and choose, for a typical patient from your area of practice, the most appropriate first line treatment based on evidence.

<https://www.nice.org.uk/guidance/cg127>)

#### References & Further Reading

Barber and Robertson (2015) *Essentials of Pharmacology for Nurses* 3rd Edition McGraw Hill London

BNF Online via NICE2018 <https://bnf.nice.org.uk/>

Electronic Medicines Compendium <https://www.medicines.org.uk/emc>

Neal, M.J. (2016) *Medical Pharmacology at a Glance* 8<sup>th</sup> Edition, Wiley Blackwell, Oxford

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Rang, H.P., Ritter. J.M., Flower. R.J. and Henderson, G. (2015) *Rang and Dales*

*Pharmacology* 8<sup>th</sup> ed. Churchill Livingstone. London.