Cardiovascular Pharmacology

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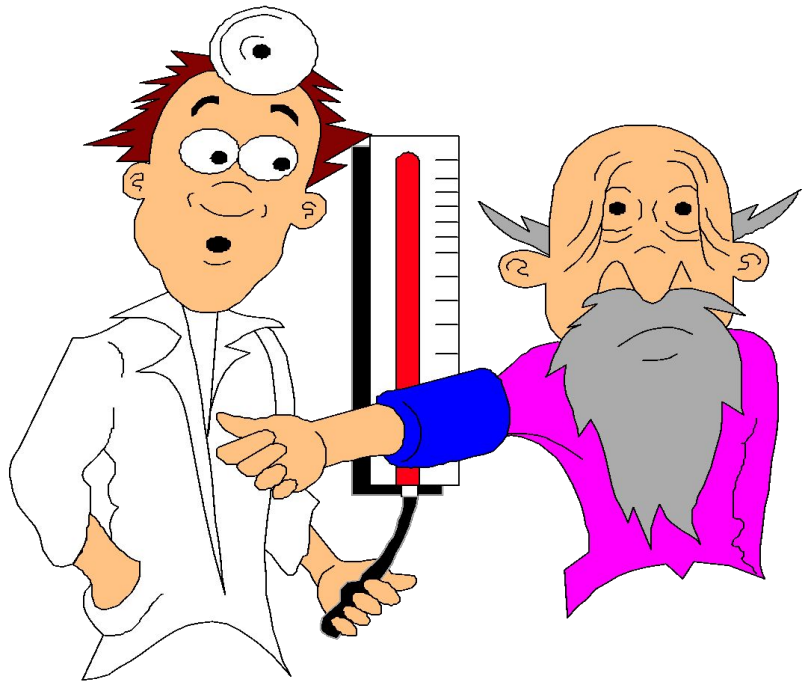
Cardiovascular Pharmacology

- Antihypertensives
- Antianginal
- Drugs for HF
- Antiarrythemics
- Drugs for Hyperlipoproteniemia

Antihypertensives

- Hypertension is defined as elevation in systolic blood pressure (SBP > 130 mm Hg) or diastolic blood pressure (DBP > 80 mm Hg) on at least two occasions.



Hypertension: Key Points

- Hypertension is a common disorder, affecting approximately 30% of adults in USA.
- Although many patients have no symptoms, can leads to heart diseases and stroke, the top two causes of death in the world. Most patients are not even aware they are hypertensive. Therefore, this disease is sometimes called the "silent killer“
- Aetiology:

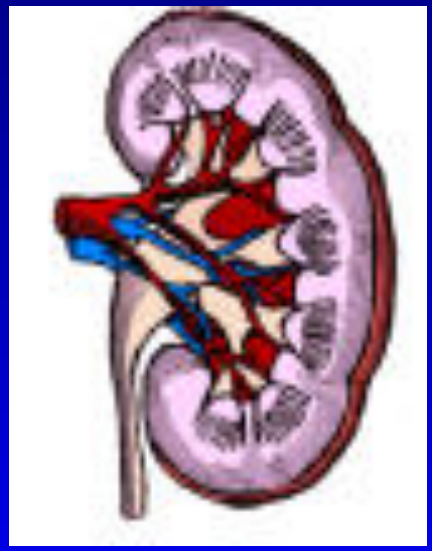
1. *Primary hypertension*: The majority of patients (90-95%) have essential hypertension (no identifiable underlying cause), treated with drugs in addition to lifestyle changes
2. *Secondary hypertension*: A smaller number of patients (5-10%) have secondary hypertension (identifiable underlying condition), treated by removing the underlying disease and antihypertensive drugs

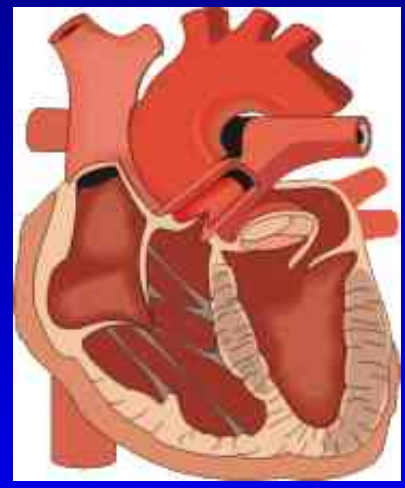
Target Organs

Retinopathy

Stroke

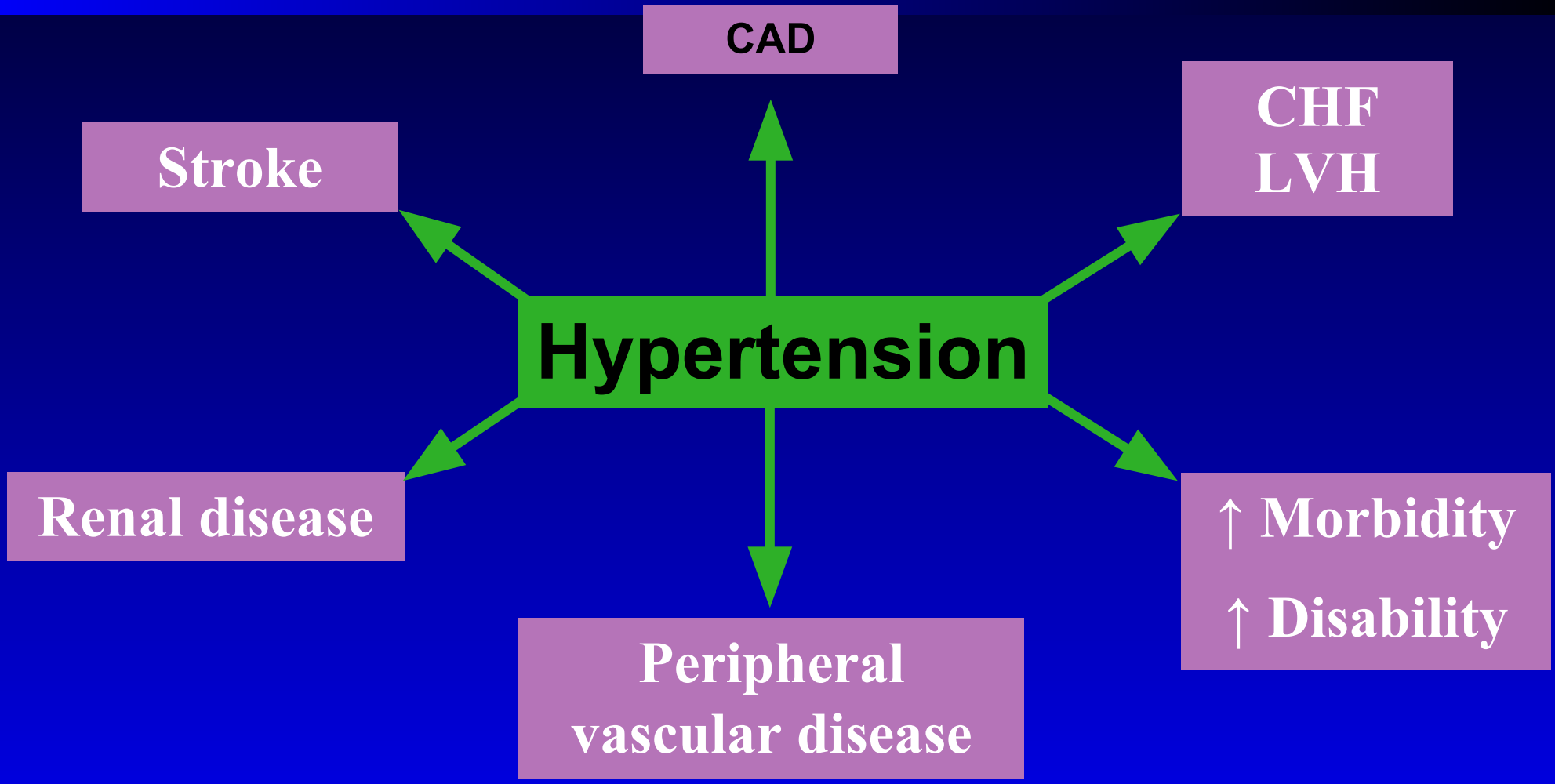
Nephropathy





LVH,
IHD HF

Hypertension: Morbidity and Mortality



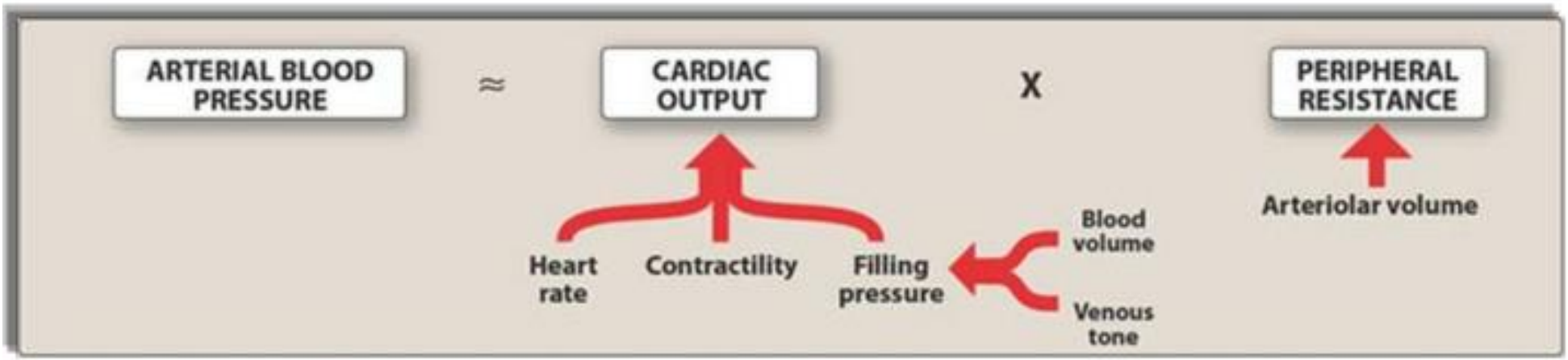
National High Blood Pressure Education Program Working Group. *Arch Intern Med.* 1993;153:186-208.

Antihypertensive Therapy: The Goal

- To control blood pressure
- To prevent complications
- The goal of antihypertensive therapy is to reduce CV and renal morbidity and mortality. For most patients, the goal is to decrease BP (<130/80 mmHg) or even less in high risk patient like DM.
- The benefit of treatment is greatest in those with high risk.

Principles of blood pressure regulation

- Regulated by the following:
  1. Cardiac output
  2. Peripheral vascular resistance
  3. Volume of intravascular fluid (controlled at the kidney)

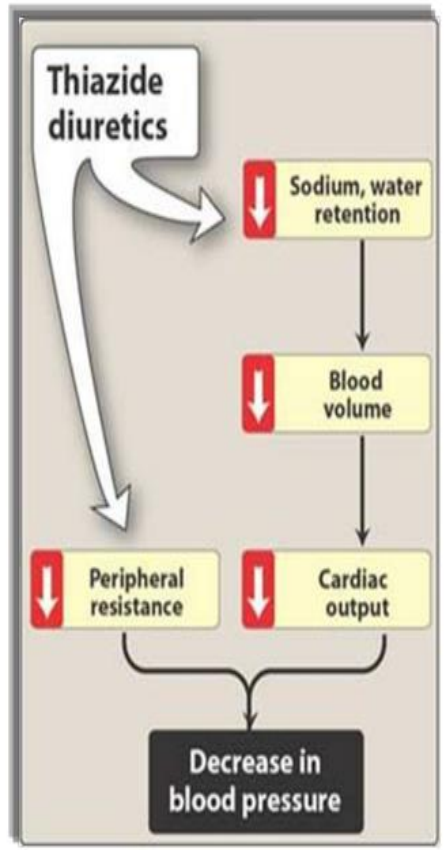


Antihypertensive Agents

1	ACE inhibitors *(Angiotensin converting enzyme inhibitors)*	Enalapril, Lisinopril, Ramipril, Captopril
2	ARBs *(Angiotensin receptor blockers)*	Telmisartan, Olmesartan, Losartan, Candesartan, Valsartan
3	Calcium channel blockers	Amlodipine, Felodipine, Nimodipine, Nifedipine, Isradipine, Verapamil, Diltiazem
4	Beta blockers	Atenolol, Metoprolol, Bisoprolol, Labetolol, Propranolol,
5	Diuretics	Hydrochlorthiazide, Chlorthiazide, Chlorthalidone, Spironolactone, Furosemide
6	Direct Vasodilators	Hydralazine, Minoxidil, Sodium Nitropruside, Diazoxide
7	Alpha blockers	Terazosin, Doxazosin, Prazosin
8	Central Alpha 2 Agonists	Clonidine, Methyldopa

Diuretics -1

- Diuretics: *Initial effects*: basically acting as antihypertensive drugs by increasing Na and H2O renal excretion thereby decreasing the blood volume and COP. *later on* diuretics decrease PVR.



Diuretics

- As a class agents diuretics are effective in treating patients with volume dependant form of HT (black, elderly, obese, renal), HT complicated with HF, Resistant HT and Renal impairment

Diuretics: Thiazide diuretics

- Thiazide diuretics (like hydrochlorthiazide, chlorthalidone…) widely used as initial monotherapy unless there are compelling reasons to choose another agents.
- They are also useful in combination with variety of other antihypertensives (B-Blockers, ACEIs or ARBs).
- With the exception of metolazone, TD are not effective when GFR severely reduced.
- Low dose thiazide diuretics are effective and safe AntiHT agents in mild-moderate HT

Diuretics: Loop diuretics

- Loop diuretics (like frusemide, torsemide, ethacrynic acid..) are not usually used as AntiHT agent (short acting, required multiple daily dosing).
- However they are indicated in HT emergency, renal insufficiency and when multiple drugs with salt retaining properties are used.

B-blockers -2

- Metoprolol, Nebivolol, Atenolol.. they reduce BP primarily by decreasing HR, stroke volume and so COP followed by reduction in PVR.
- Inhibit renin release from the kidney and so decreasing the formation of Ang II and aldosterone secretion.
- Release of vasodilator PGs

B-blockers

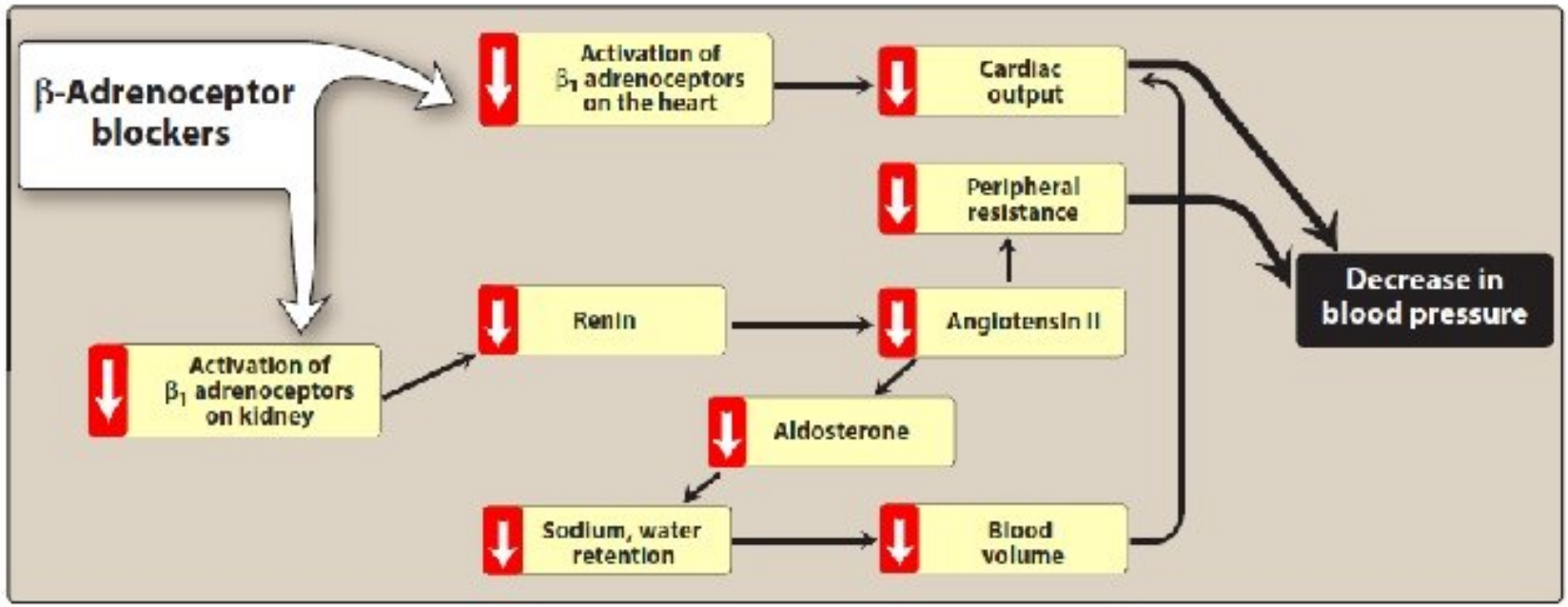


Figure 17.8
Actions of β-adrenoceptor–blocking agents.

Lippincott Illustrated reviews Pharmacology, 6th edition, 2015

B-blockers

- The primary benefit of b-blockers are seen in hypertensive patients with concomitant heart diseases (SV tachyarrhythmia, previous MI, stable IHD, chronic HF)
- B-blockers are commonly used as first line therapy for HT especially for young white patients or as alternative for diuretics.
- B-blockers are suitable antiHT drugs for patients with increase adrenergic drive and those with renin value.

Ideal Profile of AntiHT B-blockers

- Cardioselective
- Long acting (to prevent BP fluctuation)
- Simple Pks profile (good patient compliance)
- Effective in standard dose
- Has added vasolilating effect
- Has neutral effect on lipids

Conditions that discourage use of B-blockers

- Severe COLD
- 2nd and 3rd degree heart block
- Severe occlusive PVDs
- These are commonly found in elderly and diabetic patients

ά1 –blockers -3

- Selective ά1 –blockers (prazocin, doxazosin, terazosin) are competitive blockers of ά 1-adrenoceptors. They decrease PVR and so lower arterial Bp by causing relaxation of both arterial and venus smooth muscles so they reduce preload and after load (balanced vasodilators).
- They have minimal change on COP
- They are free from metabolic side effects.
- They have no or lesser place in initial monotherapy for HT.

ά1 –blockers: uses in HT

- They are usually combined with B-blocker (to prevent reflex tachycardia) and diuretics (to counter salt and water retention).
- Mild-moderate HT especially those patients with metabolic syndrome and those with BPH
- PVDs
- Refractory HF

ά1 –blockers: side effects

- Reflex tachycardia
- First-dose phenomena: brisk sever hypotension after the first or second dose of the drug usually 2 hours after administration. To avoid this phenomenon, we give the dose at bed time or (slow titration) start with small dose and increase it gradually.
- Orthostatic hypotension
- Nasal and conjunctival congestion
- Failure of (or retrograde) ejaculation

Mixed ά and β-blockers -4

- *Labetalol:* used in the treatment of gestational HT and hypertensive emergency.
- *Carvidolol:* is indicated in the treatment of HF (mild-moderate) HF and HT.

Drug acting on RAAS

- Angiotensin Converting Enzyme Inhibitors (ACEIs)
- Angiotensin Receptor Blockers (ARBs)
- Renin Inhibitors

ACE Inhibitors -5

- ACEIs (captopril, lisinopril, fosinopril, enalapril, enalaprilat, zofinopril..)

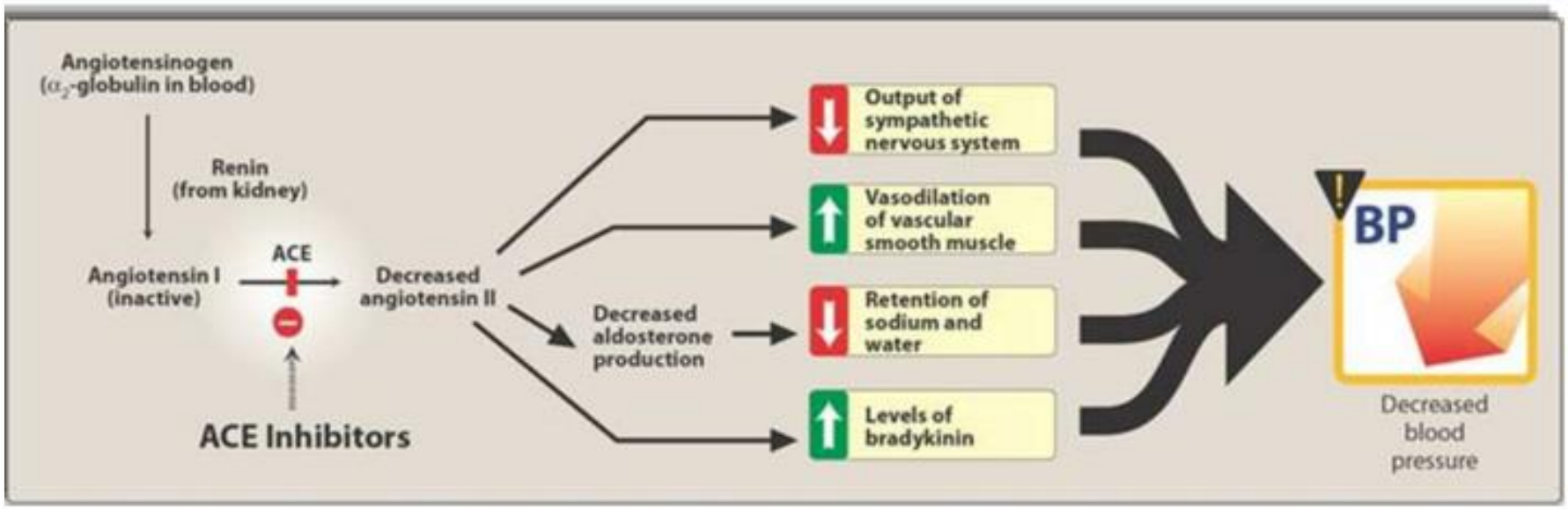
RAAS: Key points

- Renin is produced by the kidney in response to renal *ischemia, hypoxemia and B2-adrenergic* stimulation.
- Renin converts angiotensinogen (circulating protein) into Angiotensin-I (Ang I) which is *inert substance*.
- Later, Ang-I is converted into *Ang-II by the action of ACI.*
- *Ang-II is a potent vasoconstrictor causing increase in PVR and stimulate aldosterone release (Na and H2O retention).*
- ACE is responsible for *breakdown of bradykinin* (that increase production of nirtic oxide and PG, *potent vasodilators*)

ACEIs: Mechanism of action

- ACEIs lower blood pressure by reducing the PVR *without reflexively increasing COP, HR or contractility.*
- They *block the conversion of Ang-I to Ang-II* (vasoconstrictor mediated by AT1 receptor). Further they lead to *accumulation of Bradykinin* (vasodilator).
- They also decrease the secretion of aldosterone thereby *decrease Na and water retention*.
- ACEIs *reduce both cardiac preload and afterload*, so they decrease the workload on the heart.

ACE inhibitor: Mechanism of action



ACEIs: Uses

- Hypertension: as monotherapy or in combination therapy.
- Heart failure
- MI: post MI phase, they prevent cardiac remodelling.
- Asymptomatic LV dysfunction (LV hypertrophy).
- Diabetic nephropathy: decrease albuminuria

ACEIs: PKs

- All ACEIs are orally bioavailable, an exception is *Enalalprilat* is the only drug of this class available IV.
- Most ACEIs are prodrugs which undergo hepatic conversion to an active metabolite. Only *captopril and lisinopril* are given as active drugs, so they preferred in patient with severe hepatic impairment.
- ACEIs are excreted primarily via the kidneys. *Fosinopril* is the only ACEI that is not eliminated primarily by the kidney, it does not required dose adjustment in patient with renal impairment.

ACEIs: Side effects

- Dry cough (occurs in 10% of patients, it is due to accumulation of bradykinin and substance P in the pulmonary tree and resolves with few days of discontinuation of the drug)
- Hypotension
- Rash, Fever, Altered taste
- Hyperkalemia (K level must be monitored)
- Angioedema (is rare but life threatening)
- Teratogenic (so contraindicated in pregnancy)

Angiotensin II receptor blockers (ARBs) -6

- Losratan, irbesartan, telmisartan…
- They act by blocking AT1 receptors, decreasing the activation of these receptors by angiotensin II. Their pharmacologic effect similar to ACEIs (produce arteriolar and venous dilatation and block aldosterone secretion..)
- ARBs do not increase bradykinin level.
- They are alternative to ACEIs, they should not be combined with ACEIs as they have similar mechanism and side effects.
- Similar side effects of ACEIs but risk of cough and angioedema is very low.
- Teratogenic (so contraindicated in pregnancy)

Selective renin inhibitor: Aliskiren -7

- Selective renin inhibitor
- It directly inhibits renin and lower blood pressure as effectively as ACEIs and ARBs
- Aliskiren should not be combined with ACEIs or ARBs
- It is metabolized by CYP 3A4 (so it is subject to drug-drug interaction)
- Diarrhoea is side effect (in higher dose)
- It can also cause cough and angioedema but less than ACEIs .
- Teratogenic (so contraindicated in pregnancy)

Effect of various drug classes on RASS

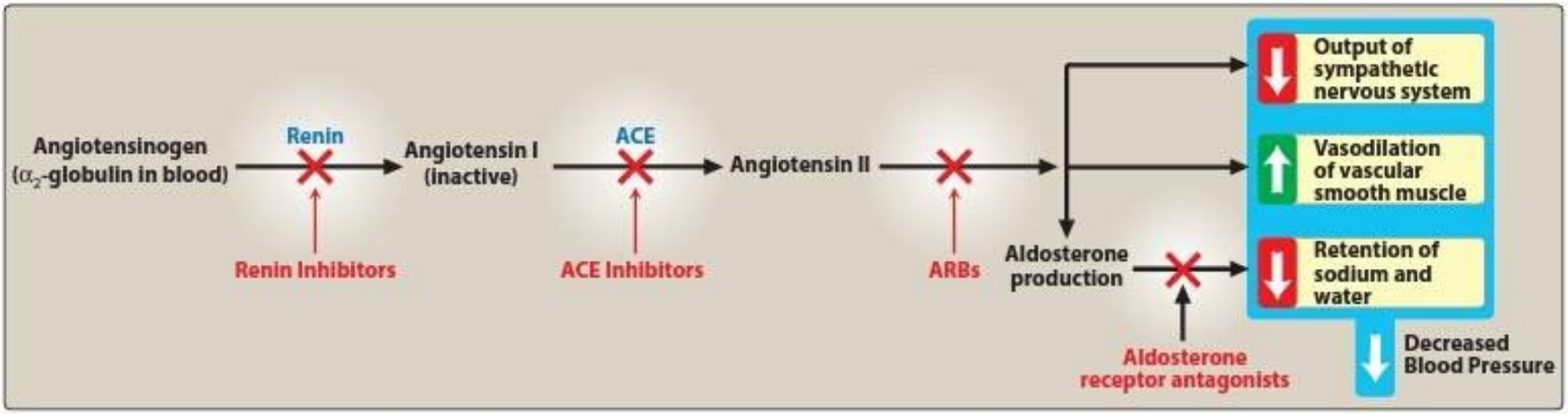


Figure 17.10

Effects of various drug classes on the renin–angiotensin–aldosterone system. Blue = drug target enzymes; red = drug class.

Calcium Channel Blockers (CCBs) -8

1- Dihydropyridines (DHP):

- Nifedipine
- Nimodipine
- Amlodipine
- Felodipine
- Isradipine

2- Non-DHP:

- Diliazem
- Verapamil

CCBs: Mechanism of action

- CCBs block the inward movement of the Ca by binding and blocking the L-type voltage gated Ca channels in the heart and smooth muscles (of peripheral arterioles and coronary arteries) causing dilatation and relaxation mainly of the arterioles. CCBs do not dilate veins.
- All CCBs are therefore vasodilators decreasing arteriolar tone and systemic PVR resulting arterial BP (decrease after load).
- In addition, CCBs decrease myocardial contractility (-ve inotropic) and the conduction in cardiac muscles (-chronotropic).
- Diliazem and verapamil: primary action on heart (cardiac effect while the primary action of Dihydropyridines on arterioles (peripheral effect)

CCBs: PKs

- They are orally active agents. Verapamil and nicardipine are also given by IV route
- Most of them have short half lives (3-8 hours). Amlodipine has very long half life.
- High plasma protein binding and extensive metabolism
- All CCBs are save in pregnancy and renal failure

CCBs: Uses

- Hypertension and HT emergencies: CCBs are alternative first line antihypertensive agents and can be used safely in pregnancy, asthma, DM or renal impairment. Nifidipine (SL) and nicardipine (IV) are used in HT emergencies
- Angina pectoris (stable, unstable and it's the drug of choice in variant type).
- As antiarrhythmic especially verapamil; it is the second choice in treatment or termination of SVT
- PVDs
- Subarrchinoid hemorrhage (nimodipine by cerebral vasodilatation)
- Al though CCBs are contraindicated in HF, amlodipine can be used in the treatment of HF
- Migraine prophylaxis especially verapamil
- Tocolytics

CCBs: Side effects

- Headache, flushing of the face and dizziness
- Hypotension
- Edema
- Constipation (dose dependent side effect of verapamil)
- Gingival hyperplasia (DHP)
- AV block & heart failure (verapamil and diltiazem)
- Fatigue (more frequent with DHP)

Centrally acting drugs: Methyldopa and -9 Clonidine

- *Methyldopa:* it is a prodrug metabolized in brain to methyl norepinephrine, acts an agonist of central presynaptic ά2 receptors to reduce adrenergic (sympathetic) outflow from the CNS.
- PKs: Rapidly absorbed, t½ approximately 2 h (multiple daily dosing). Even after i.v. injection *effects starts after a delay of about 6-8 h probably due to time taken for transportation to brain and conversion to methyl NE.*
- Side effects: sedation, drowsiness, hyperprolactinemia.
- Uses: mainly used in the *treatment of HT in pregnancy (safe).*

Direct Vasodilators -10

- Hydralazine, Minoxidil and diazoxide (direct acting smooth muscle relaxants) act by producing relaxation of vascular smooth muscles in arteries and arterioles, decrease PVS thereby lowering blood pressure.
- Both agent produce *reflex cardiac stimulation*, so increase myocardial contractility, HR and oxygen consumption. This effect my precipitate IHD and HF in predisposed patients.
- Theses agents *increase plasma renin* concentration, resulting in sodium and water retention. *These undesirable effects can be overcome by concomitant use of diuretic (to decrease sodium retention) and b-blocker (to prevent reflex tachycardia).*

Direct Vasodilators

- *Hydralazine* is safely used in treatment of hypertension during pregnancy. Side effects: headache, tachycardia, lupus like syndrome.
- *Minoxidil*: is used topically to treat male pattern baldness. Side effect: hypertrichosis.
- *Diazoxide:* Acts by opening K+ channels in arteriolar smooth muscle cells. Used for short term treatment of hypertensive emergencies. It causes hyperglycemia

Hypertensive emergency

- Hypertensive emergency is a life threatening situation characterized by severe elevation in blood pressure (SPB> 180 mm Hg or DBP > 120 mm Hg) with evidence of impending or progressive target organ damage.
- It require timely (gradual) BP reduction with IV drug to prevent or limit organ damage. Treatment depends on type of organ damage and/or comorbidities.
- Drugs used in hypertensive emergency: Nicardipine, clevidepine, nitroprusside, nitroglycerin, esmolol, labetalol, hydralazine , Diazoxide, fenoldopam.

Fenoldopam

- Fenoldopam is dopamine D1 receptors agonist. It causes dilatation of arterioles, increase renal perfusion and natriuresis.
- PKs: rapid onset of action, t½ approx. 5 min.
- Side effects: reflex tachycardia and increases intraocular pressure so should be avoided in glaucoma

Drugs to be avoided for treatment of hypertension associated with other diseases:

Pregnancy	ACEI, ARBs, Aliskiren, β-blockers, diuretics
Diabetes mellitus	Diuretics, β-blockers
Angina pectoris	Vasodilators
Bronchial asthma	β-blockers
Peripheral vascular disease	β-blockers
CHF	CCBs except amlodipine, α and β-blockers


Thank You