Antihypertensive Agents Part-2

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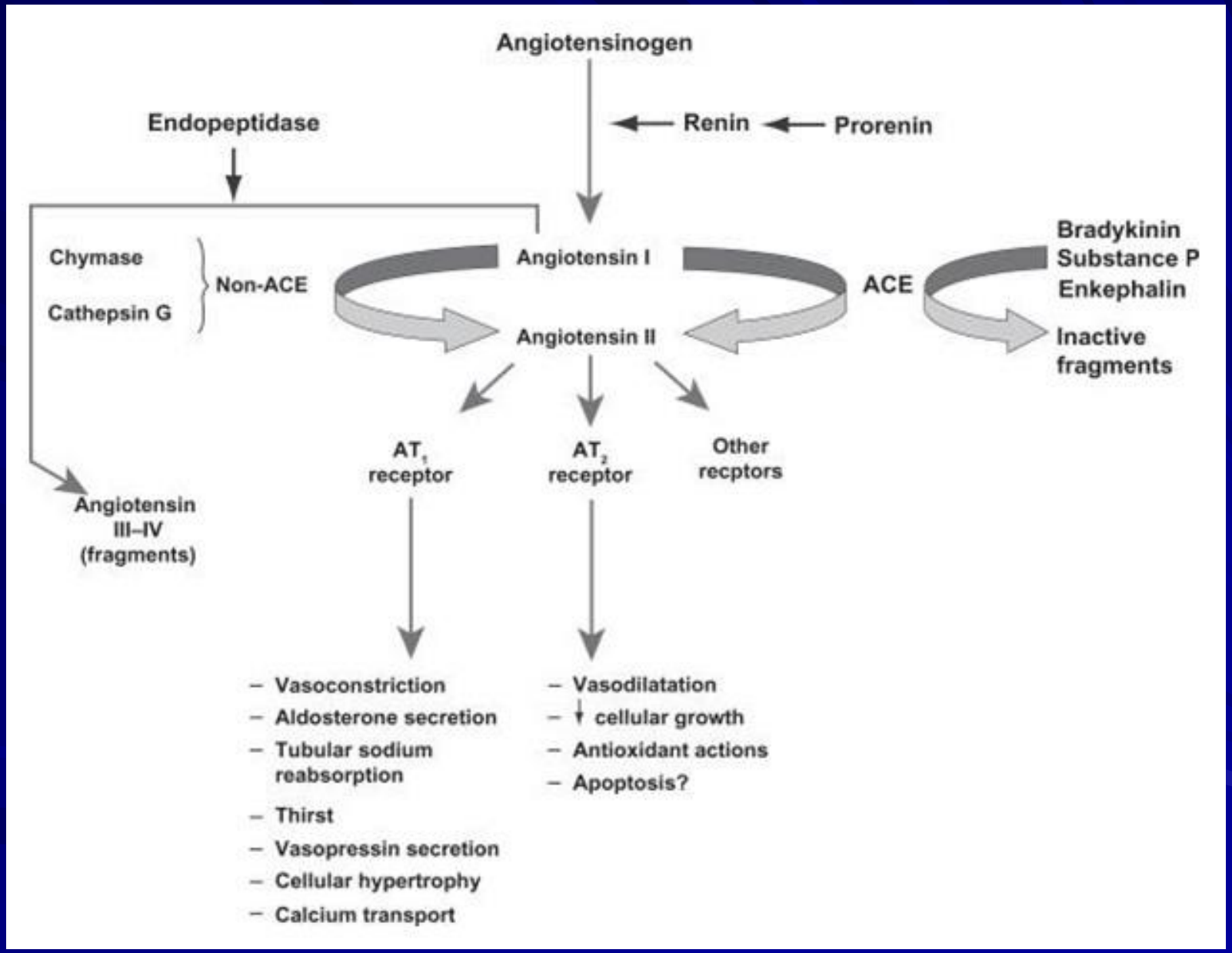
Agents that block production or action of angiotensin

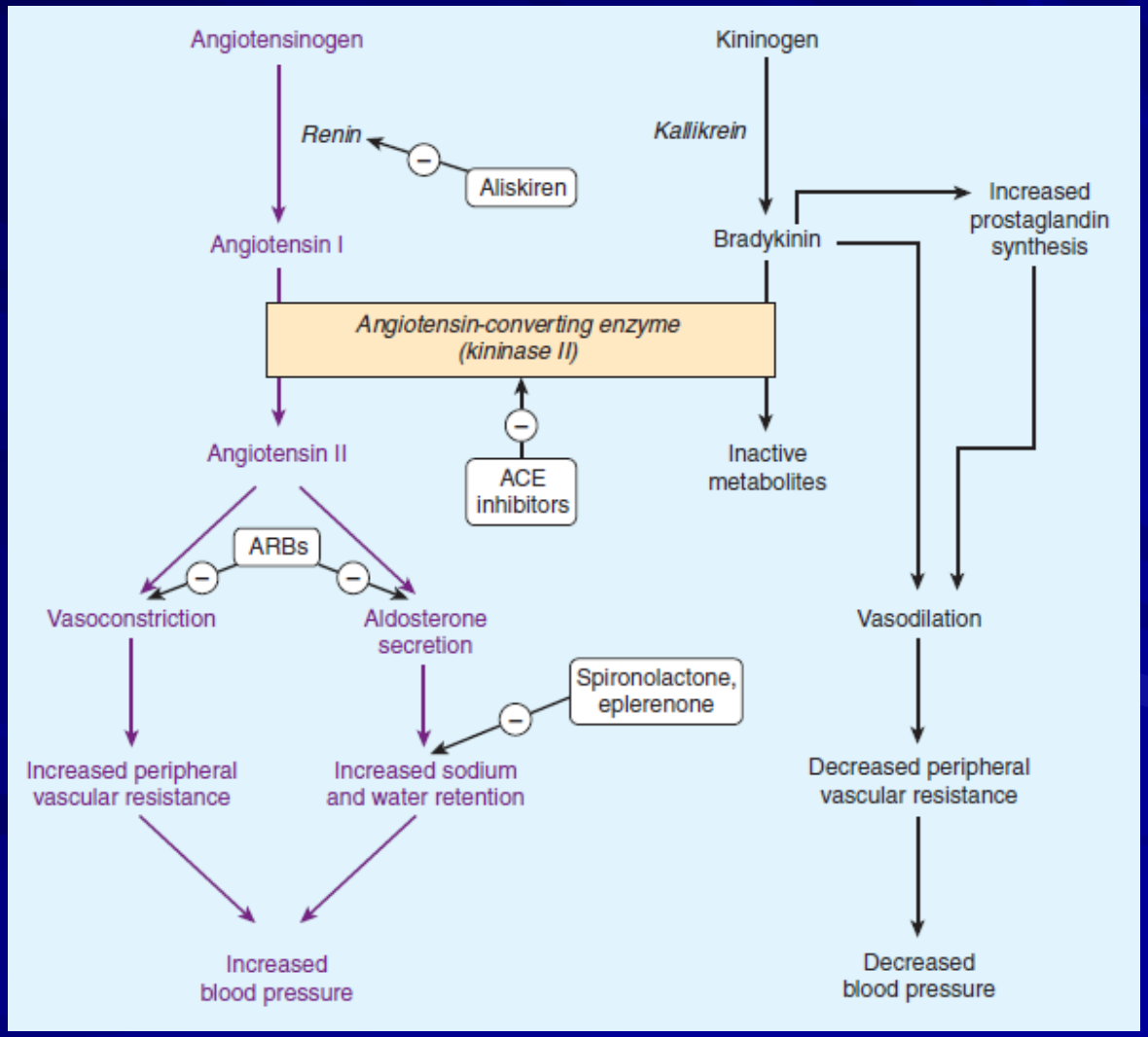
Angiotensin-converting enzyme inhibitors (ACE inhibitors)

(Captopril, Enalpril, Lisinopril, Quinapril, Ramipril, Benazepril and Fosinopril)

The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, rate, or contractility. These drugs block the ACE that cleaves AngI to form the potent vasoconstrictor AngII


Angiotensinogen
Endopeptidase
Renin
Prorenin
Chymase
Cathepsin G
Non-ACE
Angiotensin I
ACE
Bradykinin
Substance P
Enkephalin
Angiotensin II
Inactive fragments
AT1 receptor
AT2 receptor
Other recptors
Angiotensin III–IV (fragments)
– Vasoconstriction
– Aldosterone secretion
– Tubular sodium reabsorption
– Thirst
– Vasopressin secretion
– Cellular hypertrophy
– Calcium transport
– Vasodilatation
– ↓ cellular growth
– Antioxidant actions
– Apoptosis?

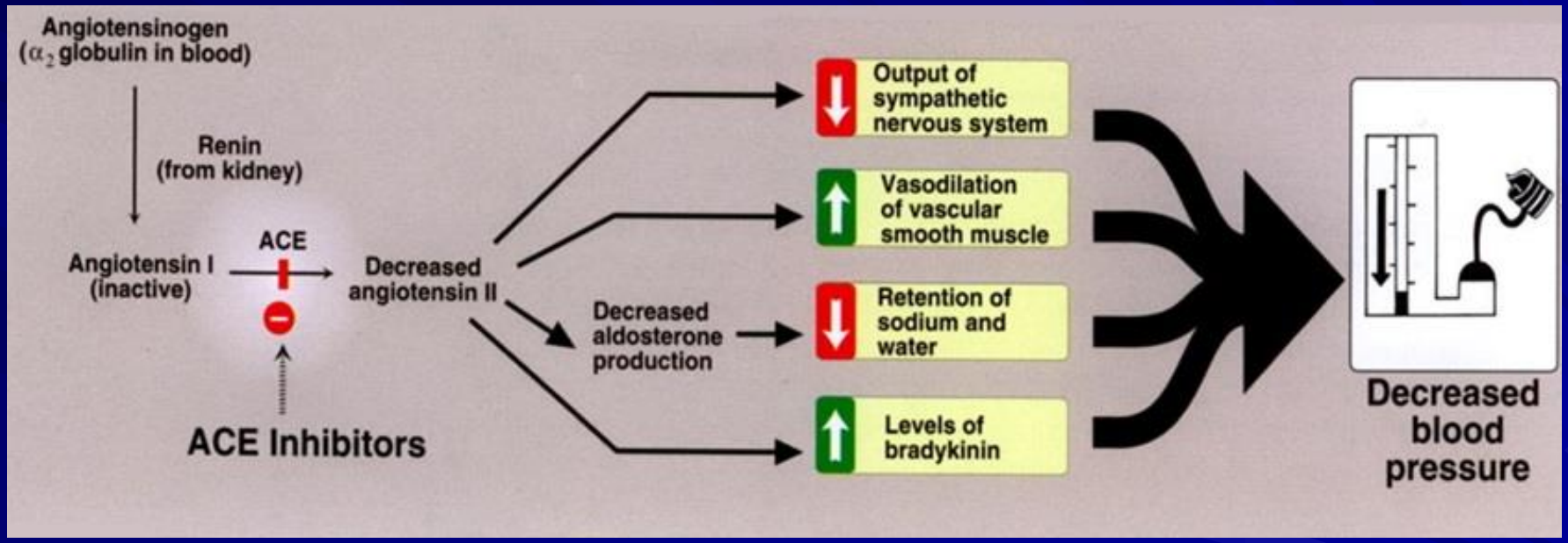
Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers



ACE inhibitors

Vasodilation occurs as a result of the combined effects of lower vasoconstriction caused by:

- Decrease levels of angiotensin II also decrease the secretion of aldosterone, resulting in decreased sodium and water retention
- Increase levels of bradykinin which is the potent vasodilator.


Angiotensinogen
(α_2 globulin in blood)
Renin
(from kidney)
Angiotensin I
(inactive)
ACE
Decreased
angiotensin II
ACE Inhibitors
Decreased
aldosterone
production
Output of
sympathetic
nervous system
Vasodilation
of vascular
smooth muscle
Retention of
sodium and
water
Levels of
bradykinin
Decreased
blood
pressure

Adverse Effects of ACE Inhibitors

- Dry cough (due to increased levels of bradykinin in the pulmonary tree), rash, fever, altered taste, hypotension (in hypovolemic states) and hyperkalemia.
- Potassium levels must be monitored, and potassium supplements or spironolactone are contraindicated.
- Angioedema is a rare but potentially life-threatening reaction and may also be due to increased levels of bradykinin
- Reversible renal failure can occur in patients with severe renal artery stenosis
- Feto-toxic and should not be used by women who are pregnant.

Therapeutic Uses of ACE Inhibitors

- Slow the progression of diabetic nephropathy and decrease albuminuria.
- Chronic heart failure. patient following a myocardial infarction.

Angiotensin II Receptor Antagonists (ARBS) (Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan and Eprosartan).

- They produce vasodilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention.

Angiotensin II Receptor Antagonists

- ARBs decrease the nephrotoxicity of diabetes, making them an attractive therapy in hypertensive diabetics
- Cough and angioedema are significantly decreased.
- Feto-toxic.

Vasodilators

- Direct vasodilators
  - Oral asodilators (hydralazine,minoxidil)
  - Parentral vasodilators (nitroprusside,diazoxide)
- Calcium channel blockers

Direct Vasodilators

- Arterial (Hydralazine, Minoxidil, Diazoxide and Fenoldopam).
- Arterial and venous (nitroprusside).

Direct Vasodilators

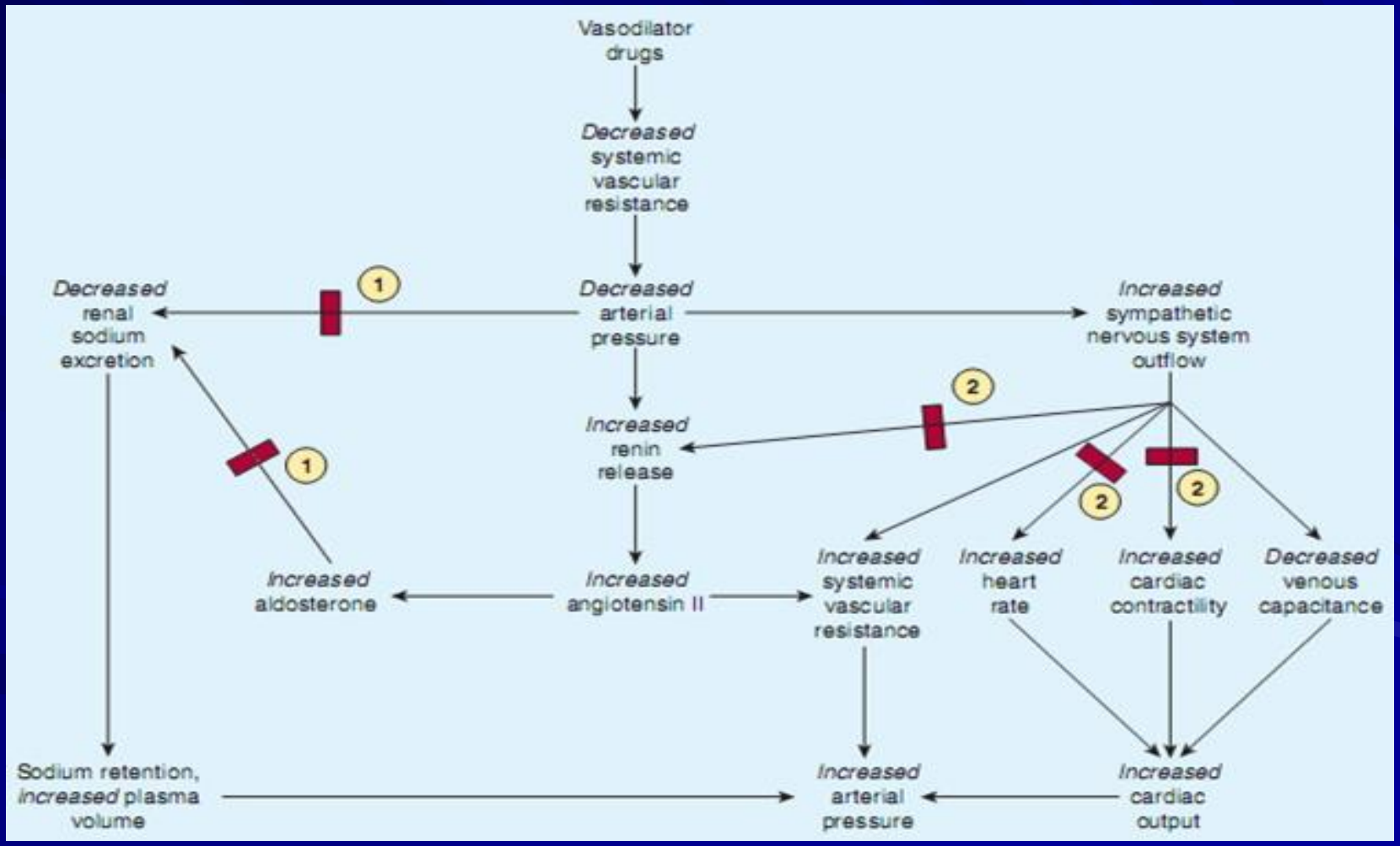
Hydralazine , Minoxidil

Vasodilators produce relaxation of vascular smooth muscle, which decreases resistance and therefore decreases blood pressure.

These agents produce reflex stimulation of the heart, resulting in the competing symptoms of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals.

Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be blocked by concomitant use of a diuretic and a beta-blocker.

Compensatory responses to vasodilators; basis for combination therapy with a blockers and diuretics. **1** Effect blocked by diuretics. **2** Effect blocked by a blockers.



Fenoldopam

It is a peripheral dopamine-1 receptor agonist that is given as an intravenous infusion. Unlike other parenteral antihypertensive agents, fenoldopam maintains or increases renal perfusion while it lowers blood pressure. Fenoldopam can be safely used in all hypertensive emergencies and may be particularly beneficial in patients with renal insufficiency.

Hydralazine

- It is used to treat moderately severe hypertension .
- It is used in combination with a beta-blocker such as propranolol (to balance the reflex tachycardia) and with a diuretic (to decrease sodium retention). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance.
- A lupus-like syndrome can occur with high dosage, but it is reversible on discontinuation of the drug.

Minoxidil

- It causes dilation of resistance vessels (arterioles) but not of capacitance vessels (venules).
- It is used for treatment of severe to malignant hypertension
- Minoxidil causes sodium and water retention, edema and congestive heart failure.
- Minoxidil treatment also causes hypertrichosis

Sodium Nitroprusside

- It is administered intravenously, and causes prompt vasodilation with reflex tachycardia
- Acting equally on arterial and venous smooth muscle
- It is used in treating hypertensive emergencies as well as heart failure

Calcium Channel Blockers

1. Verapamil
2. Diltiazem
3. Dihydropyridines (nifedipine, amlodipine, felodipine, isradipine, nicardipine and nisoldipine)

Calcium Channel Blockers (CCBs)

They are effective in treating hypertension in patients with angina or diabetes.

High doses of short-acting CCBs should be avoided because of increased risk of myocardial infarction.

Verapamil

- It effects on both cardiac and vascular smoothmuscle cells.
- It is used to treat angina, supraventricular tachyarrhythmias, and migraine headache.
- It should be avoided in patients with congestive heart failure due to its negative inotropic effects.

Diltiazem

- It effects both cardiac and vascular smoothmuscle cells; however
- It has a less pronounced negative inotropic effect on heart compared to that of verapamil.

Mechanism of Action of (CCBs)

Block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles.

Therapeutic uses of (CCBs)

hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease .

Dihydropyridines (Nifedipine, Amlodipine and Felodipine)

They have a much greater affinity for vascular calcium channels than for calcium channels in the heart, therefore particularly attractive in treating hypertension.

Nicardipine, a calcium channel blocker, can be given as an intravenous infusion

Amlodipine and nicardipine, have the advantage that they show little interaction with other cardiovascular drugs, such as digoxin or warfarin, which are often used concomitantly with calcium channel blockers.

Pharmacokinetics of (CCBs)

Have short half-lives (3-8 hours).

Sustained-release preparations permit less frequent dosing.

Adverse Effects of (CCBs)

Constipation, dizziness, headache and a feeling of fatigue caused by a decrease in blood pressure, edema

Hypertensive Emergency

- It is life-threatening situation in which the DBP is either >150 mm Hg with SBP >210 mm Hg or a DBP of 130 mm Hg in an individual with preexisting complications
- (nitroprusside, fenoldopam or diazoxide) are combined with diuretics (furosemide) and β blockers to lower blood pressure