Antihypertensive agents

By Robert Pórszász

AHA criteria for hypertension in adults

CLASSIFICATION	BLOOD PRESSURE (mmHg)	
	SYSTOLIC	DIASTOLIC
Normal	<120	and < 80
Prehypertension	120–139	or 80–89
Hypertension, stage 1	140–159	or 90–99
Hypertension, stage 2	≥160	or ≥ 100
Hypertensive crisis	>180	or > 110

General treatment strategy of hypertension

Diagnosis- 3- 6 independent measurements.

Determination of primary vs. secondary hypertension.

If secondary, treat underlying pathology.

If primary, initiate lifestyle changes

- smoking cessation
- weight loss
- diet
- stress reduction
- less alcohol
- etc.

Pharmacological treatment

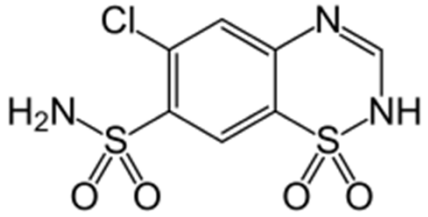
Aim: To reduce blood pressure to the normal range. Two mmHg decrease in BP reduces CV mortality with 7% and stroke incidence with 10%.

Classes of antihypertensive drugs

- First line therapies
  - Diuretics
  - ß-blockers
  - CCB
  - ACEI
  - ARB
- Second line therapies
  - Central sympatholytics (α2 agonists)
  - Peripheral α1 adrenergic receptor antagonists
  - DRI (Direct Renin Inhibitors)
  - Vasodilators

Diuretics

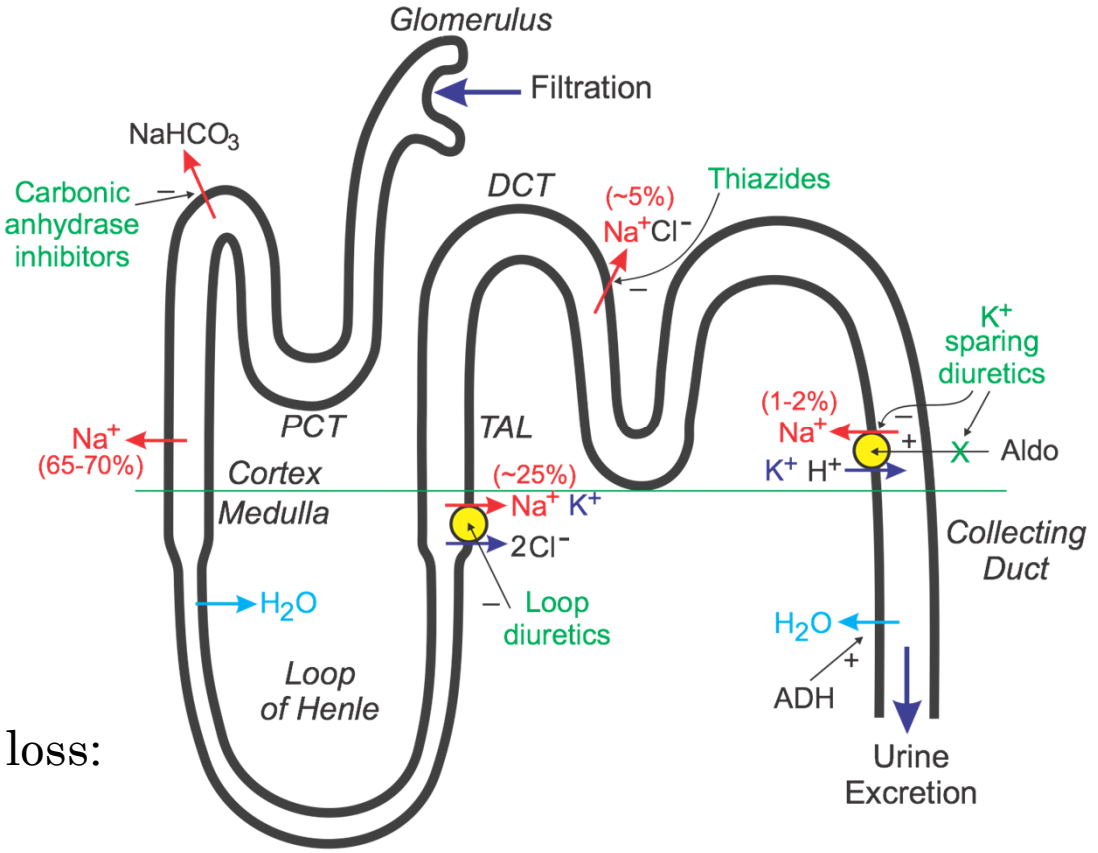
- First choice of drug in the treatment.
- Mainly three groups are used:
  - Thiazides
  - Potassium sparing diuretics
  - Loop diuretics



Chlorothiazide

Thiazides (benzothiadiazines)

Mechanism of K^+ loss:



Because loop and thiazide diuretics increase sodium delivery to the distal segment of the distal tubule, this increases potassium loss (potentially causing *hypokalemia*) because the increase in distal tubular sodium concentration stimulates the aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium and hydrogen ion, which are lost to the urine. The increased hydrogen ion loss can lead to *metabolic alkalosis*. Part of the loss of potassium and hydrogen ion by loop and thiazide diuretics results from activation of the RAAS that occurs because of reduced blood volume and arterial pressure. Increased aldosterone stimulates sodium reabsorption and increases potassium and hydrogen ion excretion into the urine.

Hemodynamic actions of thiazides

PHASES	Blood pressure	Heart rate	Cardiac output	Peripheral resistance
Acute phase (appr. First 1 month)	↓	↑	↓	↑
Chronic phase	↓	↔	↔	↓

Through their effects on sodium and water balance, diuretics decrease blood volume and venous pressure. This decreases cardiac filling (preload) and, by the Frank-Starling mechanism, decreases ventricular stroke volume and cardiac output, which leads to a fall in arterial pressure. The decrease in venous pressure reduces capillary hydrostatic pressure, which decreases capillary fluid filtration and promotes capillary fluid reabsorption, thereby reducing edema if present. There is some evidence that loop diuretics cause venodilation, which can contribute to the lowering of venous pressure. Long-term use of diuretics results in a fall in systemic vascular resistance (by unknown mechanisms) that helps to sustain the reduction in arterial pressure.

Summary of thiazides beneficial effects in the treatment of hypertension

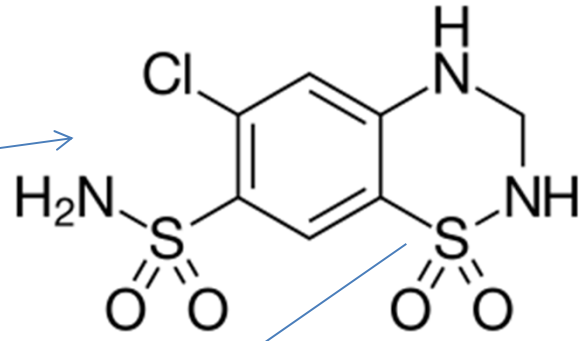
1. Decrease preload
2. Decrease stroke volume and CO
3. Reduces capillary hydrostatic pressure, reduces edema formation
4. Reduces TPR
5. Induce venodilation
6. Decrease of sensitivity of vessels against vasoconstrictors
7. Increased kallikrein production (kininogen-kallikrein-bradykinin pathway)

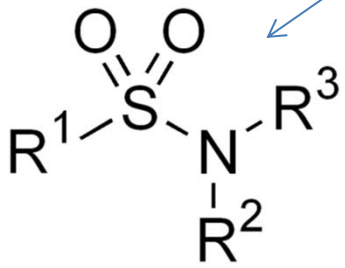
Side effects of thiazides

- Hypokalemia
- Metabolic alkalosis
- Increase of blood glucose (hyperglycemia)
- Temporary hyperlipidemia
- Increase of uric acid level (hyperuricemia, gout risk!)
- Hypercalcemia
- Hyponatremia
- Hypomagnesemia
- Hypocalciuria

Thiazide compounds

Altizide
Bendroflumethiazide
Chlorothiazide
Cyclopenthiazide
Cyclothiazide
Epitizide
Hydrochlorothiazide
Hydroflumethiazide
Mebutizide
Methyclothiazide
Polythiazide
Trichlormethiazide





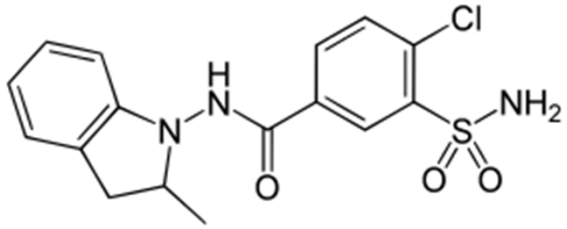
Sulfonamide structure:
Can induce allergy and cross sensitivity with sulfonamide antibiotics!

Thiazide-like compounds

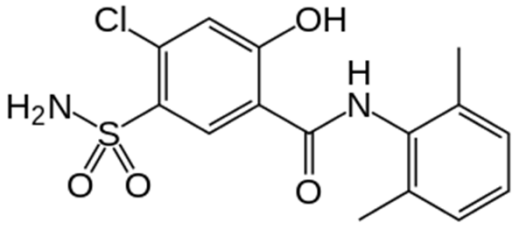
Chlortalidone
Clofenamide
Clopamide
Clorexolone
Fenquizone
Indapamide
Mefruside
Metolazone
Meticrane
Quinethazone
Xipamide

Advantages of indapamide:

1. Lower incidence of hypokalemia
2. Vasodilator:
2.1. Increment of PG synthesis
2.2. Intracellular Ca^{2+} antagonist (calmodulin complex)
2.3 Blockade of slow Ca^{2+} channels
3. Lower incidence of insulin resistance
4. Does not alter glucose and lipid metabolism
5. Only sligh increment in uric acid level
6. 1.25-5.0 mg one daily dose in the morning
7. Fix combination with perindopril (4 mg) (CO-PRENESSA, CO-DALNESSA)



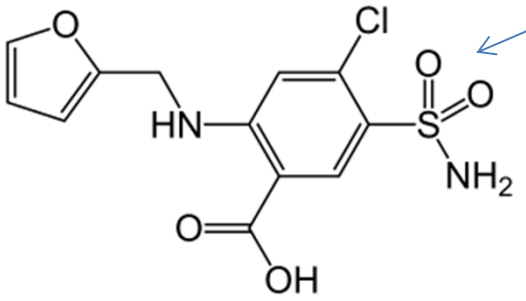
Indapamide



Xipamide

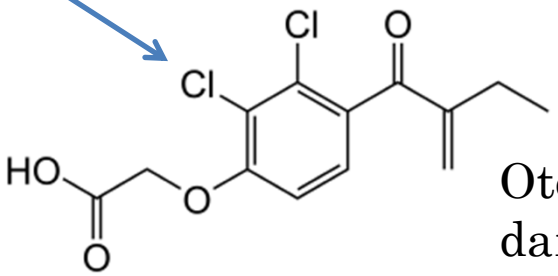
Loop diuretics

Furosemide
Azosemide
Bumetanide
Etacrynic acid
Etozolin
Muzolimine
Ozolinone
Piretanide
Tienilic acid
Torasemide

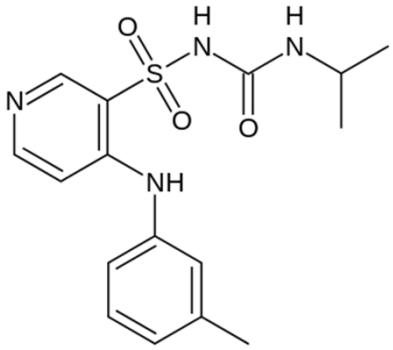


Sulfonamide structure!

- Starts to work in 5 min if i.v. administered
- Tinnitus
- Photosensibilization
- Hyperglycemia
- Gout



Ototoxicity and liver damage in high dose



Potassium sparing diuretics

- Epithelial sodium channel (ESC) blockers
  - Amiloride, triamteren, benzamil
- Aldosterone antagonists
  - Spironolactone, Eplerenone, Canrenone, Finerenone

Beta blockers

- 1st generation (non-selective)

Drug	Membr. stab. effect	ISA	Lipid sol.
Pindolol	+	+ + +	+
Timolol	-	+ -	+
Sotalol	-	-	+
Propranolol	+ +	-	+ +
Oxprenolol	+	+	+ +

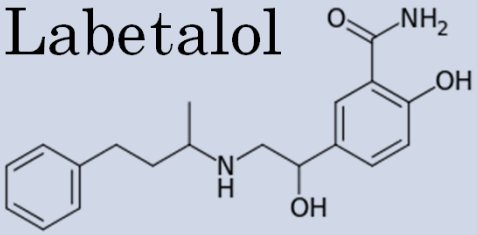
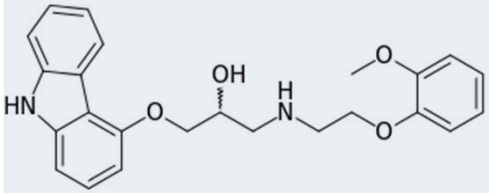
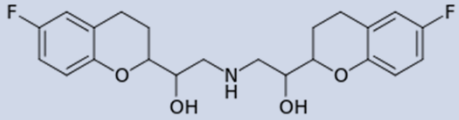
Beta blockers

- 2nd generation (beta1 selective drugs)

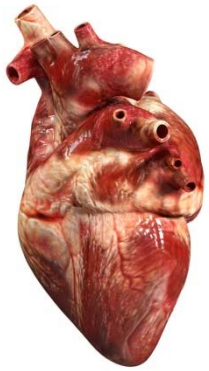
Drug	Membr. stab. effect	ISA	Lipid solubility
Metoprolol	+ -	-	+ +
Atenolol	-	-	-
Esmolol	-	-	+ -
Bisoprolol	-	-	+ -

Beta blockers

- 3rd generation (vasodilatory beta blockers)

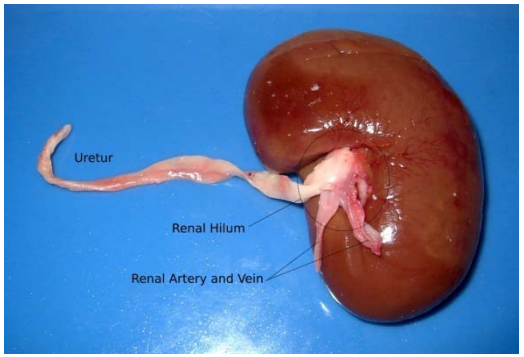
Drug	Lipid solubility	Mechanism of vasodilation
Labetalol 	+ + +	Alpha-receptor blockade
Carvedilol 	+	Alpha-receptor blockade
Nebivolol 	+ -	NO potentiating effect

Antihypertensive MOA of beta blockers



Heart

β1



Kidney

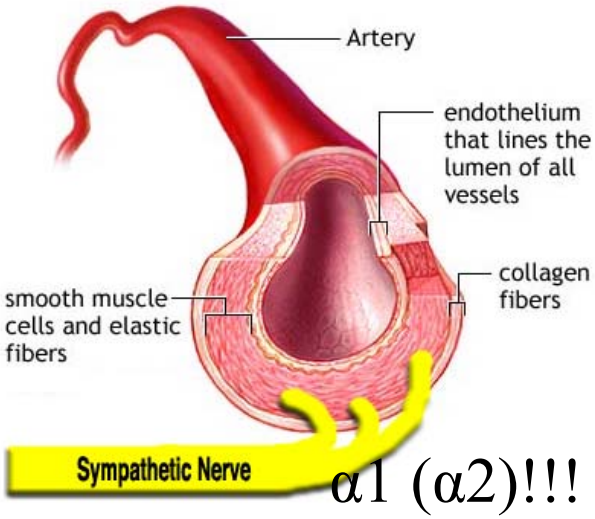
β1

Beta1:Beta2=80:20
Cardioselective beta blockers

β2

Blood vessels

Circulating epinephrine excites beta2 receptors (vasodilation). Beta blockers thus can cause a little vasoconstriction at the beginning.



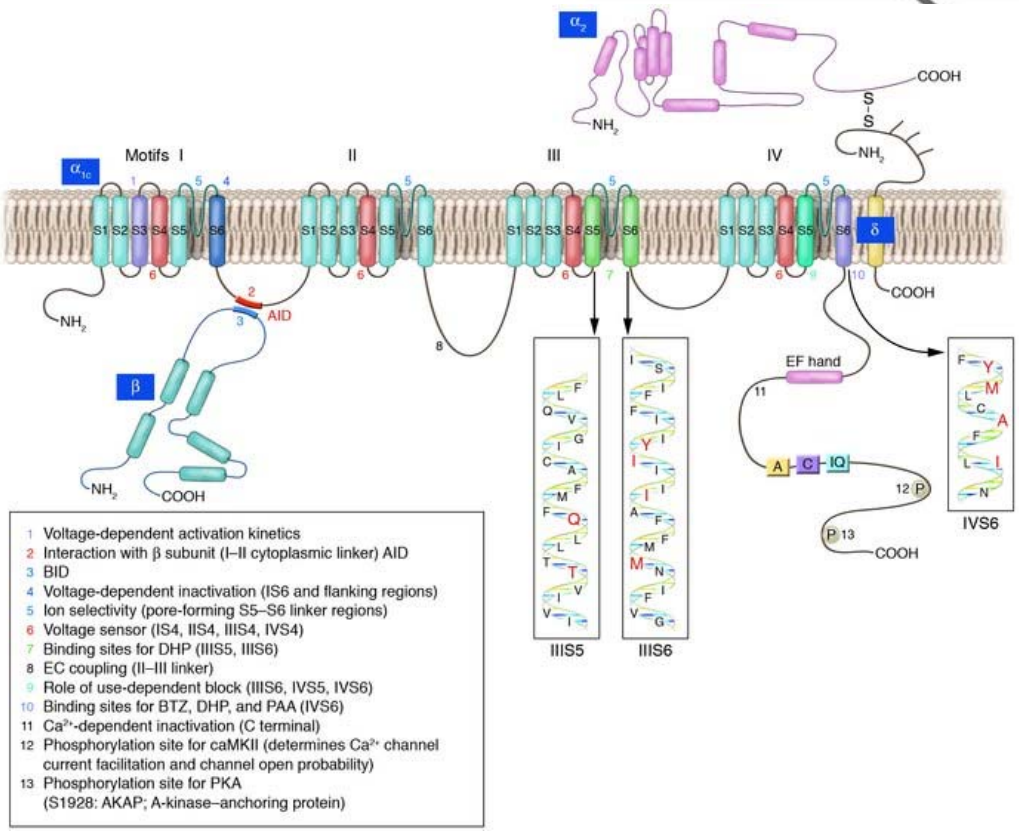
α1 (α2)!!!

Juxtaglomerular apparatus. Beta 1 receptors – renin production (renin-ANG I – ANG II)
After beta receptor blockade, renin-induced ANG I (ANG II) production decreases

CCBs

L-type

- Calcium channel blockers
  - Phenilalkylamines
    - Verapamil
  - Benzothiazepines
    - Diltiazem
  - Dihydropyridines
    - 1st generation
      - Nifedipine
    - 2nd generation
      - Isradipine
      - Nicardipine
      - Felodipine
    - 3rd generation
      - Amlodipine



1 Voltage-dependent activation kinetics
2 Interaction with β subunit (I–II cytoplasmic linker) AID
3 BID
4 Voltage-dependent inactivation (IS6 and flanking regions)
5 Ion selectivity (pore-forming S5–S6 linker regions)
6 Voltage sensor (IS4, IIS4, IIIS4, IVS4)
7 Binding sites for DHP (IIIS5, IIIS6)
8 EC coupling (II–III linker)
9 Role of use-dependent block (IIIS6, IVS5, IVS6)
10 Binding sites for BTZ, DHP, and PAA (IVS6)
11 Ca^{2+}-dependent inactivation (C terminal)
12 Phosphorylation site for caMKII (determines Ca^{2+} channel current facilitation and channel open probability)
13 Phosphorylation site for PKA (S1928: AKAP; A-kinase–anchoring protein)

- Calcium channel blocker

A
- AH-1058
- Amlodipine
- Amlodipine/valsartan
- Anipamil
- Aranidipine
- Arbaclofen placarbil
- Atagabalin
- Azelnidipine

B
- Baclofen
- Barbiturate
- Barnidipine
- Bencyclane
- Benidipine
- Bepridil
- Berbamine
- Bupropion/zonisamide

C
- Calcium channel blocker toxicity
- Canadine
- Carboxyamidotriazole
- Cilnidipine
- Clentiazem
- Clevidipine
- Cycleanine

D
- Darodipine
- Dauricine
- Devapamil
- Dihydropyridine
- Diltiazem
- Dimeditiapramine
- Diproteverine
- Dotarizine

E
- Efonidipine
- Emopamil
- Enpiperate

F
- Falipamil
- Fantofarone
- Felodipine
- Fendiline
- Flunarizine

G
- Gabapentin
- Gabapentin enacarbil
- Gabapentinoid
- Gallopamil

I
- Imagabalin
- Imepitoin
- Isradipine

J
- JTV-519

K
- Kava
- Kavain
- Ketamine

L
- Leconotide
- Lercanidipine
- Levamlodipine
- Lidoflazine
- Lomerizine

M
- Manidipine
- Manoalide
- 4-Methylpregabalin
- Methysticin
- Mibefradil
- Mirogabalin
- Monatepil

N
- Naftopidil
- Nicardipine
- Nifedipine
- Niflumic acid
- Niguldipine
- Niludipine
- Nilvadipine
- Nimodipine
- Nisoldipine
- Nitrendipine
- Norverapamil

O
- Olmesartan/amlodipine
- Oxodipine

P
- PD-217,014
- Phenibut
- Pinaverium bromide
- Pranidipine
- Pregabalin
- Prenylamine

R
- Racemorphan
- Ralfinamide
- Rhynchophylline
- Riodipine

S
- Safinamide
- Sesamodil

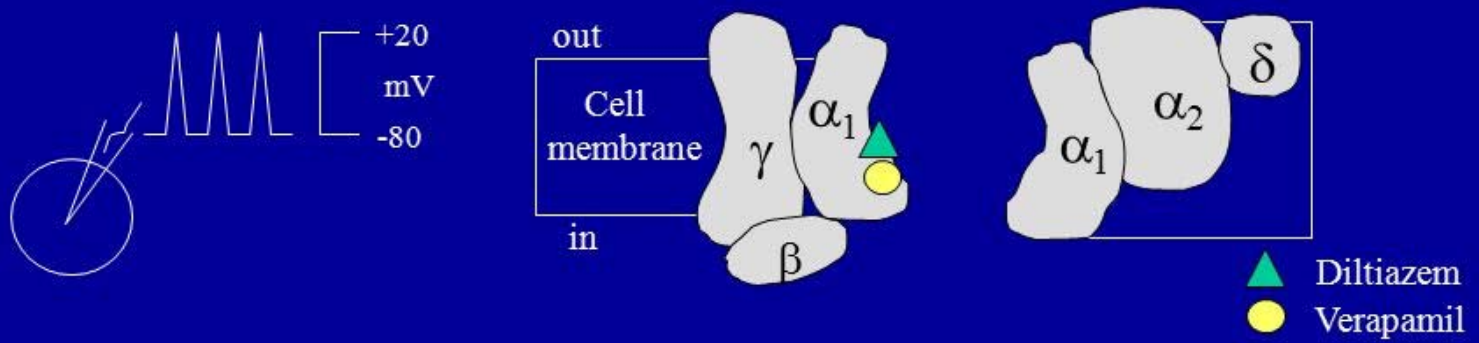
T
- Tetrandrine
- Tolperisone
- TROX-1

V
- Verapamil

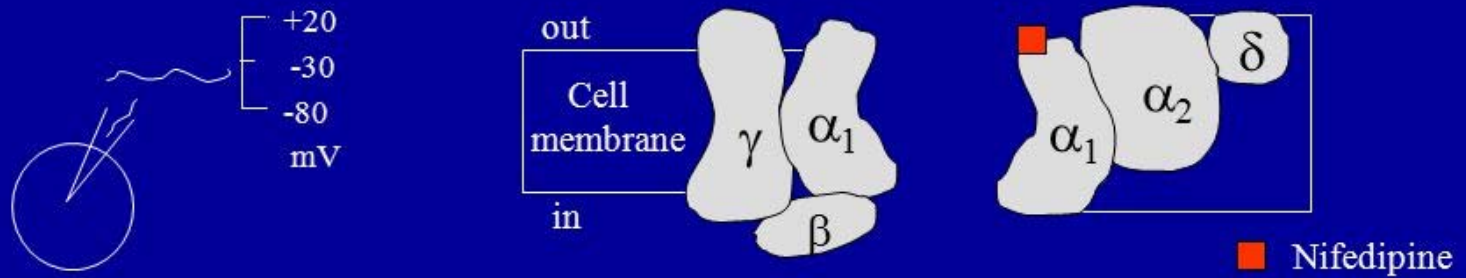
Z
- Ziconotide
- Zonisamide

The different binding sites of CCBs result in differing pharmacological effects

Use-dependent binding (targets cardiac cells)



Voltage-dependent binding (targets smooth muscle)



CCBs

- First generation
  - Verapamil (phenylalkylamine)
  - Diltiazem (benzothiazepine)
  - Nifedipin (dihydropiridine, DHP)
- Second generation
  - Nisoldipine
  - Nitrendipine
  - Isradipine
  - Felodipine
  - Nimodipine
- Third generation
  - Amlodipine
  - Lacidipine
  - Lercanidipine

1st generation agents: short action
Verapamil and diltiazem: specific drugs for sinuatrial and AV node. Antiarrhythmic agents
Nifedipin: specific for smooth muscle. Antianginal and antihypertensive drugs.
2nd generation drugs: long acting, tissue specificity (e.g. nimodipin: specificity for brain vessels)
3rd generation agents: highly lipophylic drugs, long-lasting vasodilation, antiatherosclerotic effect

CCBs

- Advantages:
  - Unlike diuretics no adverse metabolic effects but mild adverse effects like – dizziness, fatigue etc.
  - Do not compromise haemodynamics – no impairment of work capacity
  - No sedation or CNS effect
  - Can be given to asthma, angina and PVD patients
  - No renal and male sexual function impairment
  - No adverse fetal effects and can be given in pregnancy
  - Minimal effect on quality of life

CCBs

- Contraindications:
  - Unstable angina
  - Heart failure
  - Hypotension
  - Post infarct cases
  - Severe aortic stenosis

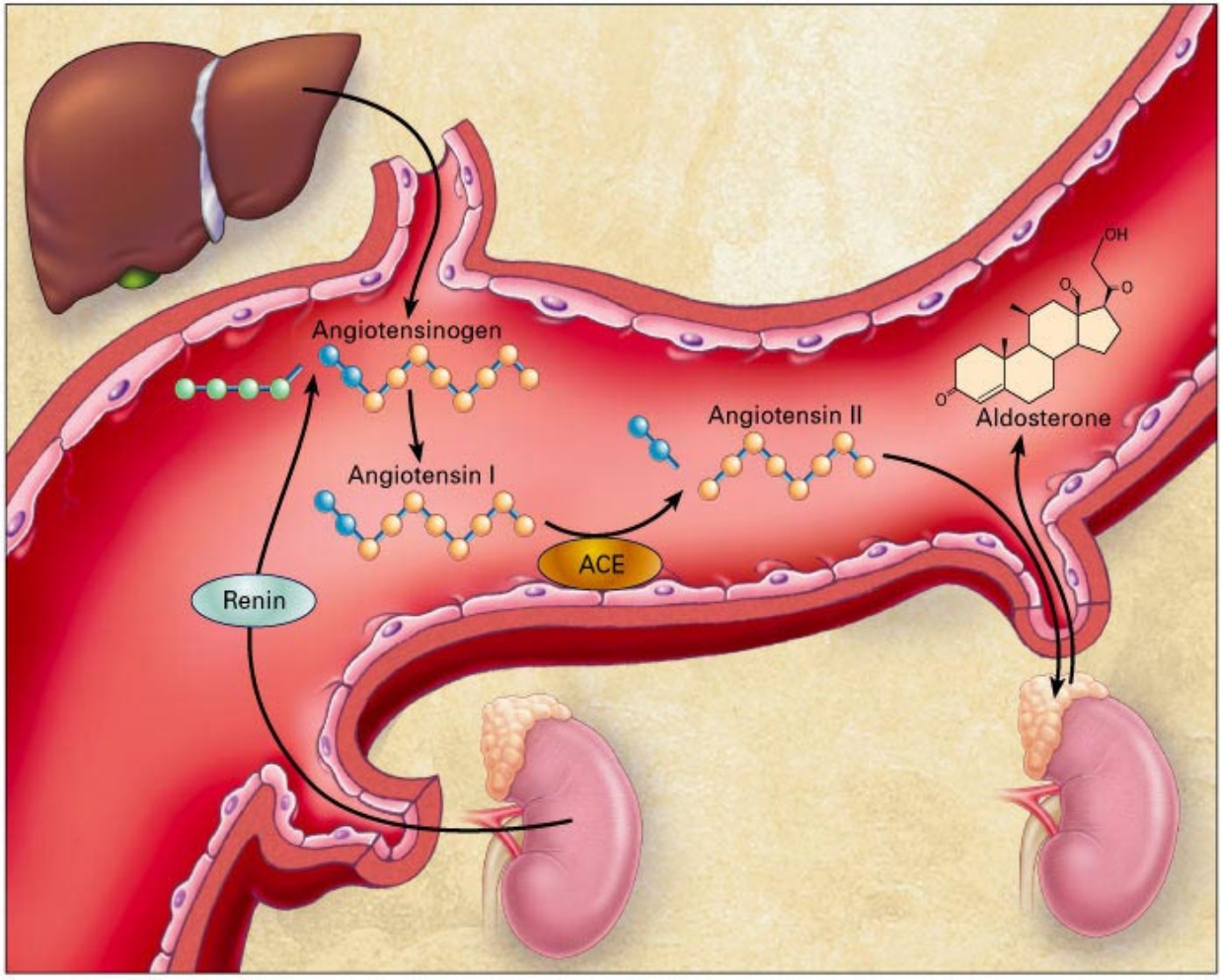
Side effects:
Ankle edema (N)
Tachycardia, palpitation (N)
Constipation (V and D)
Bradycardia (V and D)
AV block (V and D)
60% increase in AMI (short acting nifedipine)

- Preparation and dosage:
  - Amlodipine – 2.5, 5 and 10 mg tablets (5-10 mg OD)
    – Stamlo, Amlopres, Amlopin etc.
  - Nimodipine – 30 mg tab and 10 mg/50 ml injection
    – Vasotop, Nimodip, Nimotide etc.

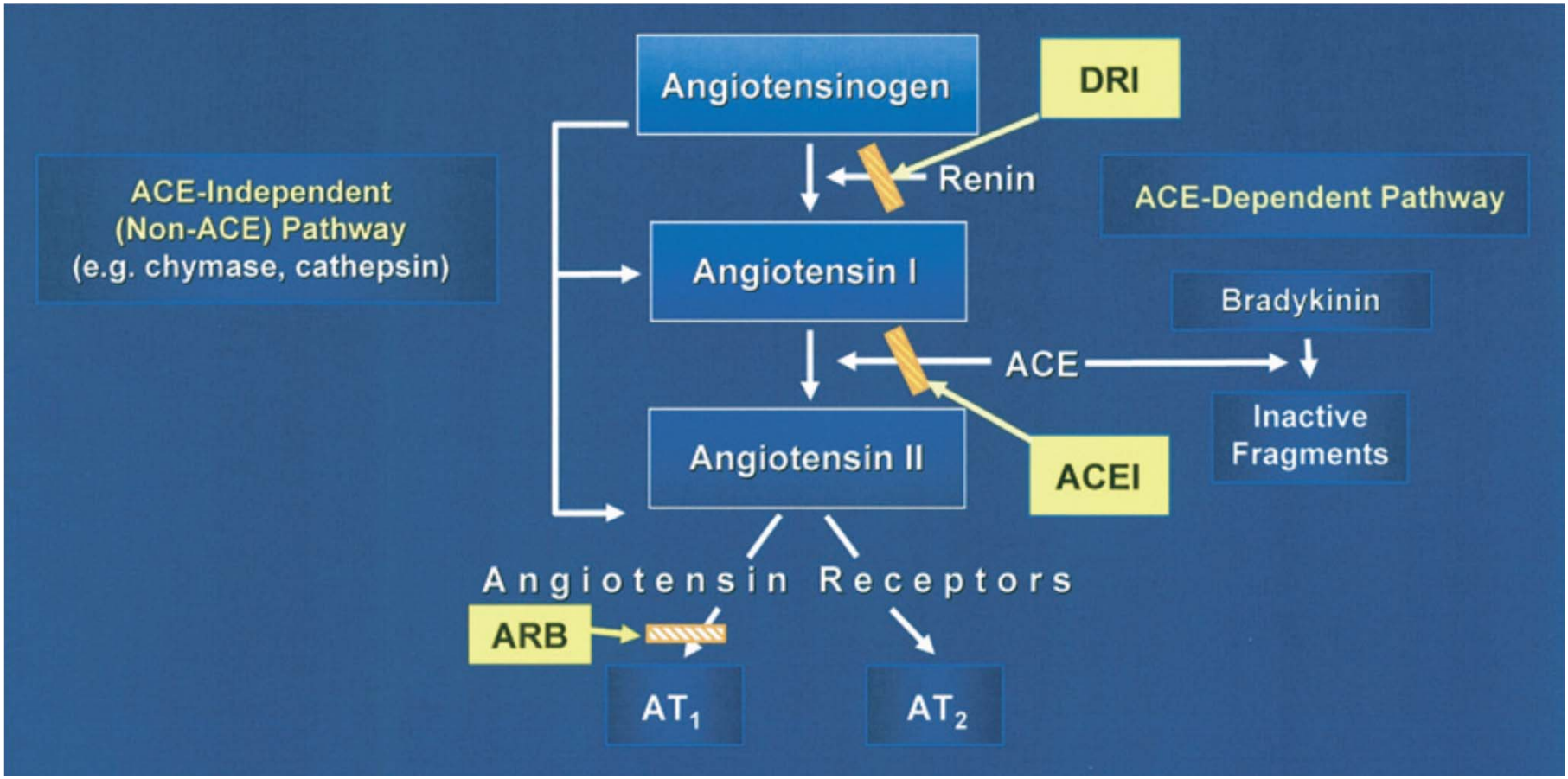
Clevidipine (CLEVIPREX)

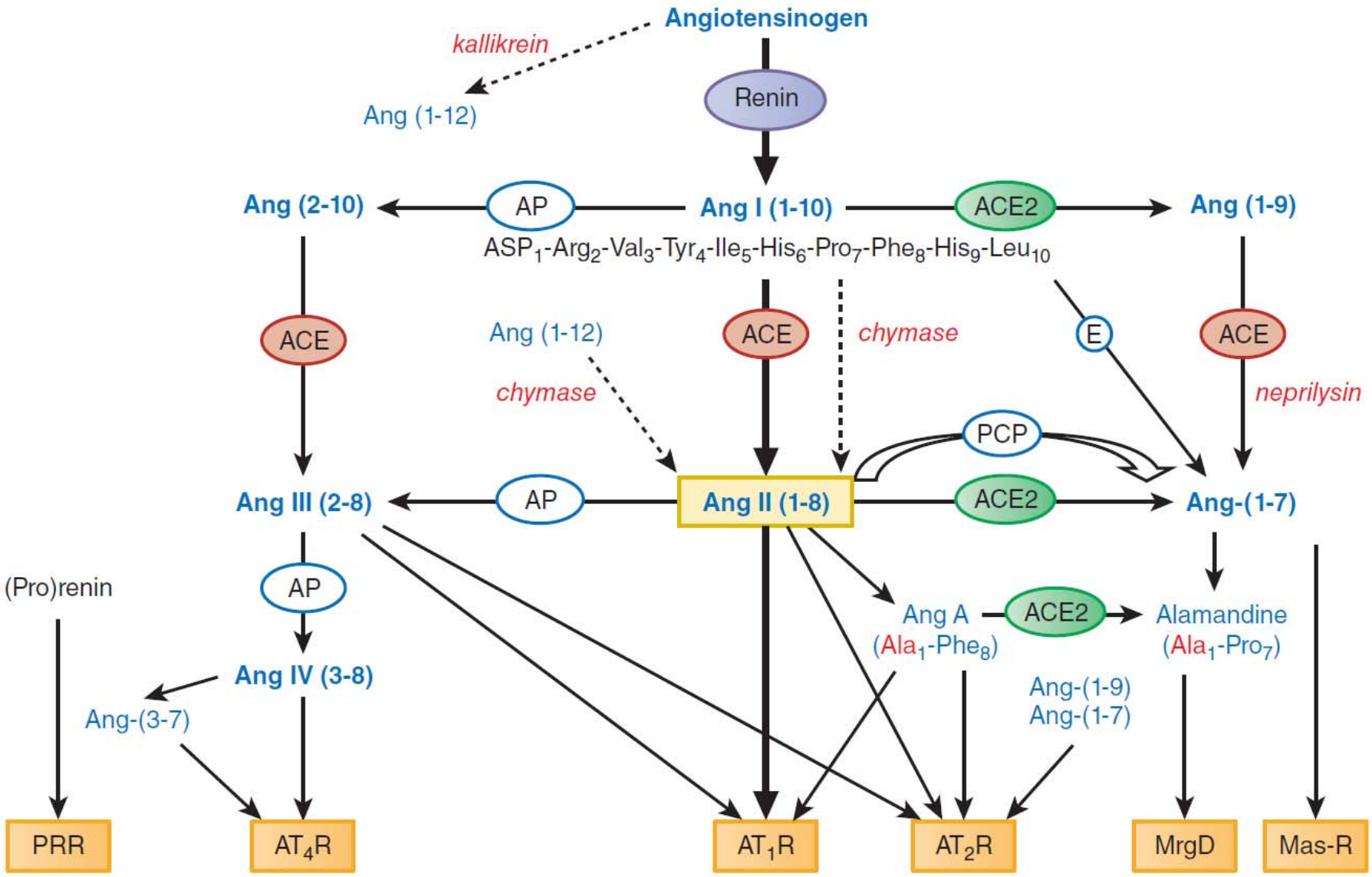
- Highly selective vascular L-type CCB
- No effect on venous capacitance vessels → no effect on pre-load
- Blood and extravascular esterases metabolize it (good in liver and kidney damage), but no change in metabolization in patients pseudocholinesterase deficiency
- Half life: 10-15 min
- Produces a 4-5% reduction in systolic blood pressure within 2–4 minutes after starting a 1–2 mg/hour infusion.
- No evidence of tolerance development even after long infusions.
- Formulated as a lipid emulsion in 20% soybean oil (Intralipid) and contains approximately 0.2 g of fat per mL (2.0 kcal/ml). (TG level can be changed!)
- Contains
  - glycerin (22.5 mg/mL)
  - purified egg yolk phospholipids (12 mg/mL)
  - sodium hydroxide to adjust pH (6.0-8.0).

RAAS


Angiotensinogen
Angiotensin I
Angiotensin II
ACE
Renin
Aldosterone
OH
O
O
O

Pharmacological targets in RAAS

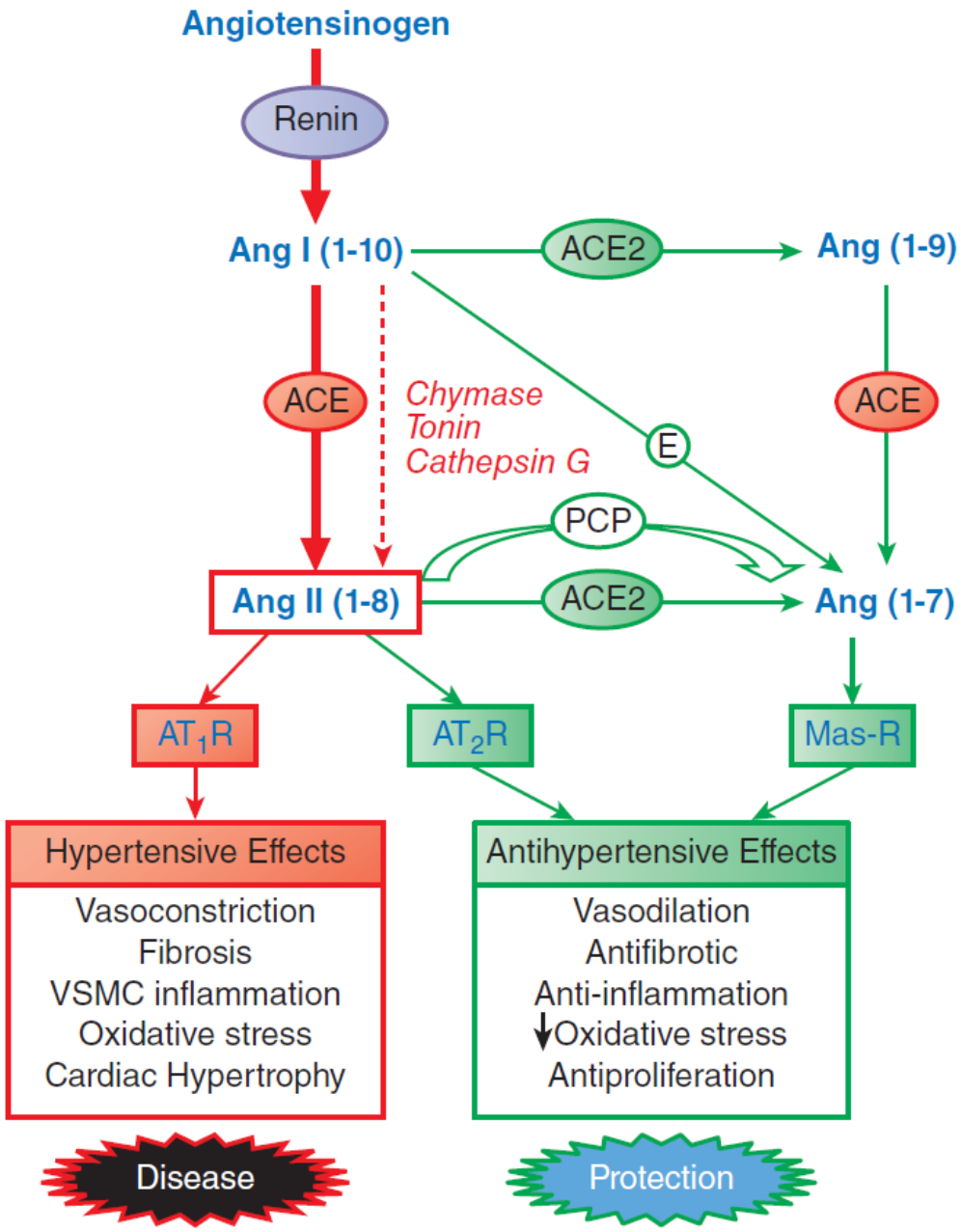




Components of the RAS. The heavy arrows show the classical pathway, and the light arrows indicate alternative pathways. Receptors involved: AT1, AT2, AT4, Mas, MrgD, and PRR. AP, aminopeptidase; E, endopeptidases; PCP, prolylcarboxylpeptidase.

ACE2

- A carboxypeptidase, ACE2, cleaves one amino acid from the carboxyl terminal to convert AngII to Ang(1–7). ACE2 may also convert AngI to Ang(1–9), which is then converted to Ang(1–7) by ACE, neprilysin, and endopeptidases. ACE2 contains a single catalytic domain that is 42% identical to the two catalytic domains of ACE. AngII is the preferred substrate for ACE2, with 400-fold higher affinity than AngI.
- The counterregulation of the actions of AngII by ACE2 occur in at least two ways:
  - 1. It decreases AngII levels and limits its effects by metabolizing it to Ang(1–7).
  - 2. It increases levels of Ang(1–7), which acts on Mas receptors to oppose AngII actions.
- Angiotensin-converting enzyme 2 is not inhibited by the standard ACE inhibitors and has no effect on bradykinin. Reduced expression or deletion of ACE2 is associated with hypertension, defects in cardiac contractility, and elevated levels of AngII. Inhibition of AT1 receptors by ARBs increases the expression of ACE2. Overexpression of the ACE2 gene decreases blood pressure and prevents AngII-induced cardiac hypertrophy in hypertensive rats. ACE2 is protective against diabetic nephropathy through the Ang(1–7)/Mas receptor pathway.

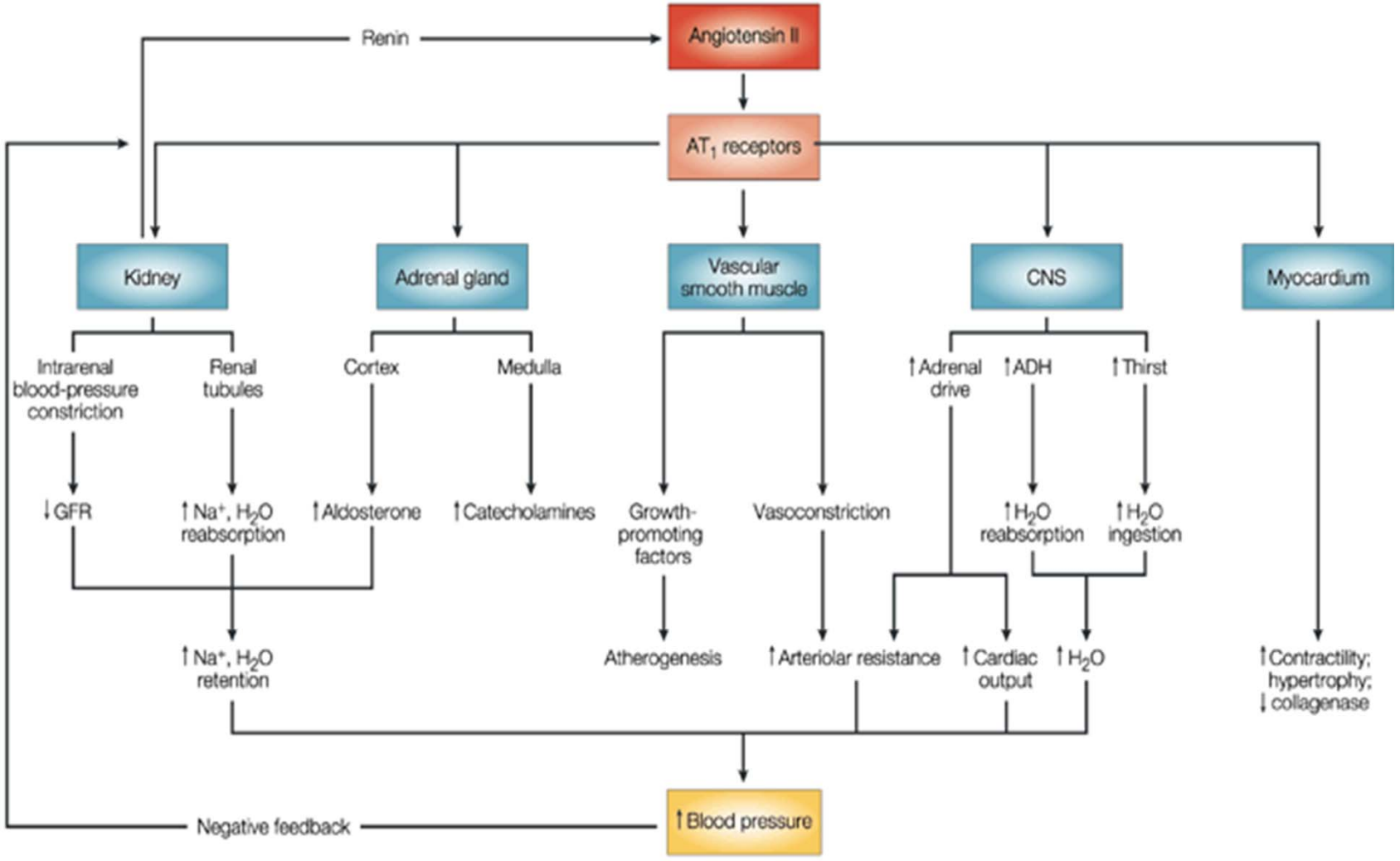


Schematic diagram of opposing arms in the RAS. Therapeutic interventions aim to inhibit the ACE/AngII/AT1 receptor axis (red) and enhance ACE2/Ang(1–7)/Mas receptor axis (green). VSMC: vascular smooth muscle cells.

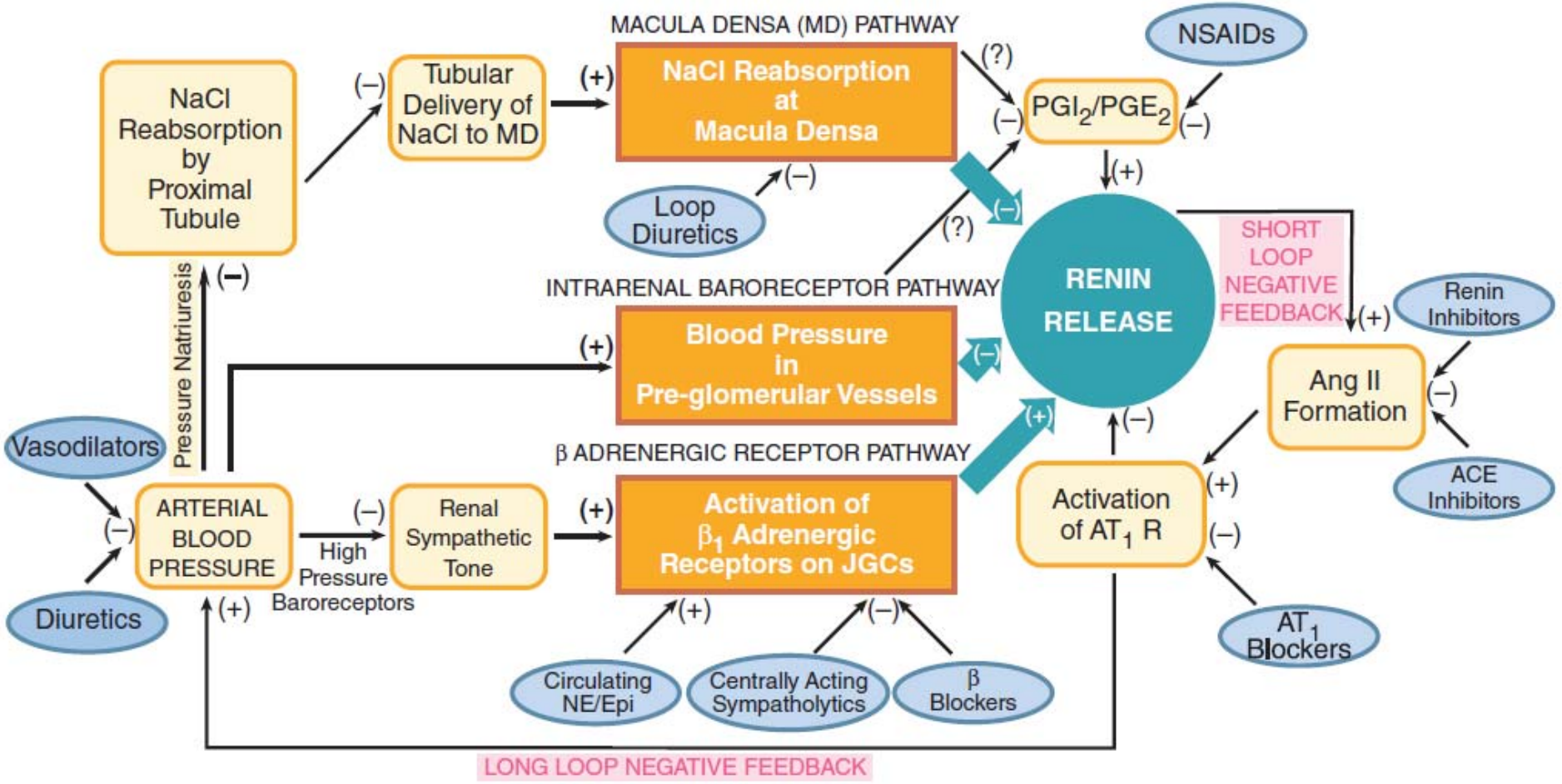
RAS peptides and their identified receptors

RECEPTOR	RAS PEPTIDE	EFFECT
AT_1	AngII, AngIII, AngA, Ang(1–12)	Vasoconstriction hypertrophy Fibrosis, nephropathy
AT_2	AngII, AngIII, Ang(1–7), Ang(1–9), AngA	Vasodilation, antihypertrophy, antifibrosis Natriuresis
Mas	Ang(1–7)	Vasodilation, antihypertrophy, antifibrosis Natriuresis
MrgD	Alamandine	Vasodilation, antihypertrophy, antifibrosis
AT_4	AngIV, Ang(3–7)	Neuroprotection Cognition Renal vasodilation Natriuresis
PRR	Prorenin, renin	Hypertrophy, fibrosis Apoptosis

Major effects of RAAS



Three major physiological pathway of renin release activation



The active site of ACE

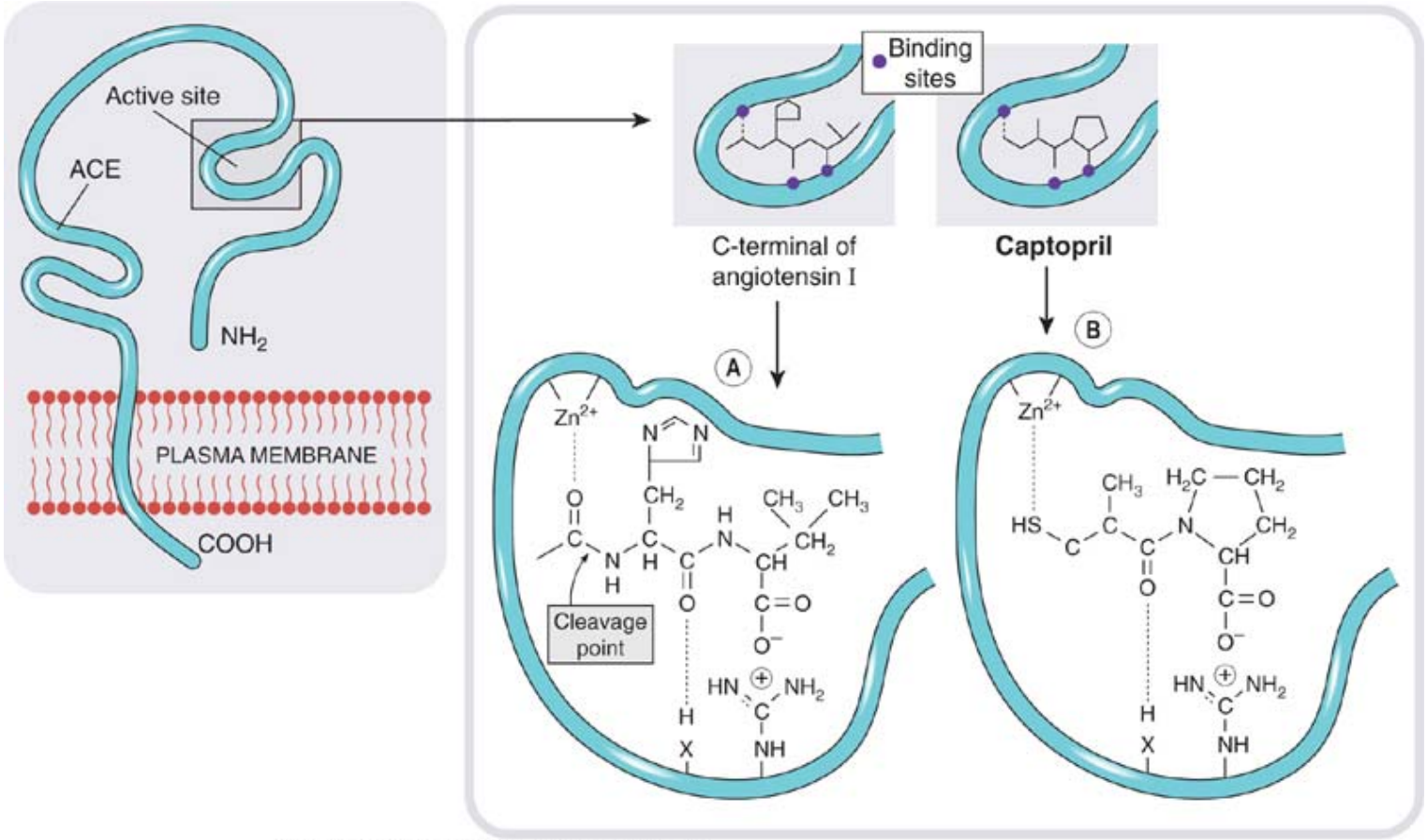
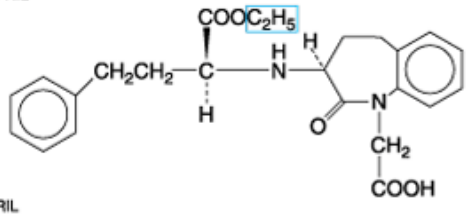


Table 9.1 — Peptide substrates of ACE.

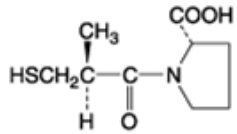
Peptide	Amino acid sequence
Angiotensin I	Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-↑His-Leu
Bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-Pro-↑Phe-Arg
des-Arg^9-bradykinin	Arg-Pro-Pro-Gly-Phe-↑Ser-Pro-Phe
Enkephalins:	
Pentapeptide	Tyr-Gly-Gly-↑Phe-Met
Heptapeptide	Tyr-Gly-Gly-↑Phe-Met-↑Arg-Phe
Octapeptide	Tyr-Gly-Gly-↑Phe-Met-↑Arg-Gly-Leu
β-Neo-endorphin	Tyr-Gly-Gly-↑Phe-Leu-↑Arg-Lys-↑Tyr-Pro
Dynorphin$_{1-8}$	Tyr-Gly-Gly-↑Phe-Leu-↑Arg-Arg-Ile
Dynorphin$_{1-6}$	Tyr-Gly-Gly-↑Phe-Leu-Arg
Neutrotensin	<Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-↑Tyr-Ile-Leu
Substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-↑Gly-↑Leu-Met-NH_2 (4 : 1)
LH-RH	<Glu-His-Trp-↑Ser-Tyr-Gly-Leu-↑Arg-Pro-Gly-NH_2

Arrows denote primary (↑) and secondary (↑) sites of cleavage by ACE.

BENAZEPRIL



CAPTOPRIL



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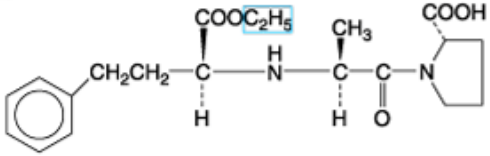
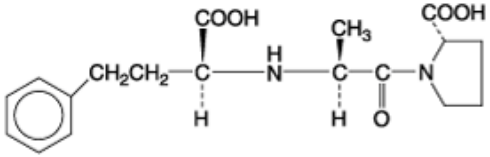
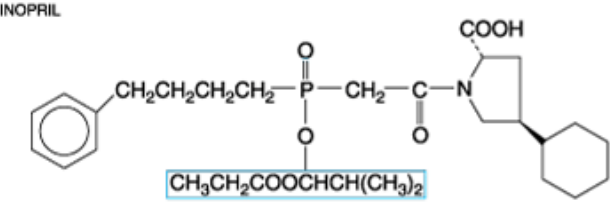


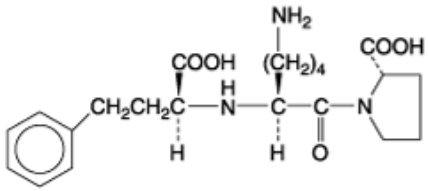
ENALAPRILAT



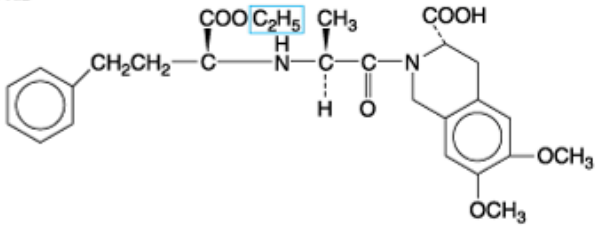
FOSINOPRIL



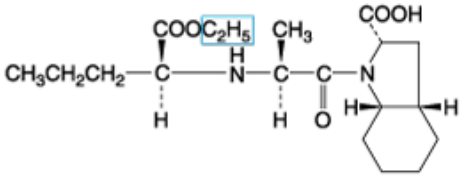
LISINOPRIL



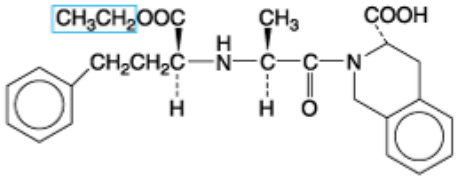
MOEXIPRIL



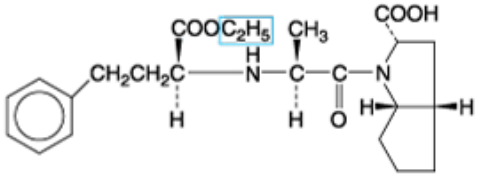
PERINDOPRIL



QUINAPRIL



RAMIPRIL



TRANDOLAPRIL

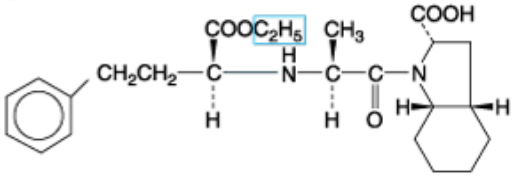


TABLE C136.2

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS: DOSAGE STRENGTHS AND TREATMENT GUIDELINES

Drug	Trade name	Usual total daily dose in hypertension (mg) (frequency/d)[a]	Usual total daily dose in heart failure (mg) (frequency/d)[a]	Comment	Fixed-dose combinations[b]
Benazepril	Lotensin	20–40 (1)	Not FDA approved for heart failure		Benazepril and hydrochlorothiazide (Lotensin HCT)
Captopril	Capoten	75–300 (2–3)	18.75–150.00 (3)	Generically available	Captopril and hydrochlorothiazide (Capozide[c])
Enalapril	Vasotec	5–40 (1–2)	5–40 (2)	Generic and intravenous	Enalapril and hydrochlorothiazide (Vaseretic)
Fosinopril	Monopril	10–40 (1)	10–40 (1)	Renal and hepatic elimination	Fosinopril and hydrochlorothiazide (Monopril-HCT)
Lisinopril	Prinivil, Zestril	10–40 (1)	5–20 (1)	Generically available	Lisinopril and hydrochlorothiazide (Prinzide, Zestoretic)
Moexipril	Univasc	7.5–30.0 (1)	Not FDA approved for heart failure		Moexipril and hydrochlorothiazide (Uniretic)
Perindopril	Aceon	4–16 (1)	Not FDA approved for heart failure	Indicated in high-risk vascular patients	
Quinapril	Accupril	20–80 (1)	10–40 (1–2)		Quinapril and hydrochlorothiazide (Accuretic)
Ramipril	Altace	5–20 (1)	10 (2)	Indicated in high-risk vascular patients	
Trandolapril	Mavik	2–8 (1)	2–4 (1)	Renal and hepatic elimination	

FDA, U.S. Food and Drug Administration; HCT, hydrochlorothiazide.
[a]Lower doses are often recommended to initiate therapy. Higher doses are recommended for chronic therapy to provide full 24-hour coverage.
[b]Fixed-dose combinations in this class all contain a thiazide-type diuretic.
[c]Capozide is indicated for first-step treatment of hypertension.

TABLE C136.1

U.S. FOOD AND DRUG ADMINISTRATION–APPROVED INDICATIONS FOR ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Drug	Hypertension	Heart failure	Diabetic nephropathy	High-risk cardiovascular disease
Captopril	•	• (Post-MI)[a]	•	
Benazepril	•			
Enalapril	•	•[b]		
Fosinopril	•	•		
Lisinopril	•	• (Post-MI)[a]		
Moexipril	•			
Perindopril	•			•[c]
Quinapril	•	•		
Ramipril	•	• (Post-MI)		•[c]
Trandolapril	•	• (Post-MI)		

MI, myocardial infarction.
[a]Captopril and lisinopril are indicated for heart failure treatment post–myocardial infarction and as adjunctive therapy for heart failure.
[b]Enalapril is indicated for high-risk individuals and for asymptomatic and symptomatic patients.
[c]On the basis of results of the Heart Outcomes Prevention Evaluation (HOPE) study and The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA).

Table 22-4. Summary of drugs that inhibit the renin-angiotensin-aldosterone system

Class	Drug[a]	Pharmacokinetics	Adverse effects[b]	Uses	Notes
ACE inhibitors	Captopril	Short acting $t_{1/2}$ ~2 h Dose 2-3 times daily	Cough Hypotension Proteinuria Taste disturbance	Hypertension Heart failure After MI	ACEIs are cleared mainly by renal excretion
	Enalapril	Pro-drug-active metabolite enalaprilat $t_{1/2}$ ~11 h Dose 1-2 times daily	Cough Hypotension Reversible renal impairment (in patients with renal artery stenosis)	As captopril	Lisinopril, perindopril, ramipril, trandalopril are similar Some are licensed for different uses (e.g. stroke, left ventricular hypertrophy)
Angiotensin receptor blockers (ARBs)	Valsartan	$t_{1/2}$ ~6 h	Hypotension Reversible renal impairment (in patients with renal artery stenosis)	Hypertension Heart failure	ARBs are cleared by hepatic metabolism
	Losartan	Long-acting metabolite $t_{1/2}$ ~8 h	As valsartan	As valsartan Diabetic nephropathy	Irbesartan is similar, with $t_{1/2}$ ~10-15 h
	Candesartan	$t_{1/2}$ 5-10 h Long acting because receptor complex is stable	As valsartan	As valsartan	Given as prodrug ester (candesartan cilexetil)
Renin inhibitor	Aliskiren	Low oral bioavailability $t_{1/2}$ 24 h	As valsartan, also diarrhoea	Essential hypertension	Licensed in 2007, the first drug of this type
Aldosterone antagonists	Eplerenone	$t_{1/2}$ 3-5 h	As valsartan, especially hyperkalemia Nausea, diarrhoea	Heart failure after MI	
	Spironolactone	Prodrug converted to canrenone, which has $t_{1/2}$ ~24 h	As eplerenone Also oestrogenic effects (gynaecomastia, menstrual irregularity, erectile dysfunction)	Primary hyperaldosteronism Heart failure Oedema and ascites (e.g. in hepatic cirrhosis)	

[a] All drugs listed are orally active.
[b] Adverse effects common to all drugs listed include hyperkalemia (especially in patients with impaired renal function) and teratogenesis.
ACEI, angiotensin-converting enzyme inhibitor; MI, myocardial infarction.

Examples for ACEI:

enalapril (Vasotec);
quinapril (Accupril);
fosinopril (Monopril);
moexipril (Univasc);
lisinopril (Zestril, Prinivil);
benazepril (Lotensin);
captopril (Capoten)

Clinical use of ACEI

- Antihypertensive
  - ~ 50% response (~90% with diuretic)
  - ↓Systemic Vascular Resistance
  - ↓Stress or Relfex induced sympathetic stimulation
  - → Heart rate
  - ↑ Sodium excretion, ↓ Blood volume
- Congestive Heart Failure
  - ↓Vascular Resistance, Blood volume, Heart rate
  - ↑ C.O. (no change in myocardial O_2 consumption)
- Diabetic Nephropathy
  - Dilates afferent and efferent renal arterioles
  - ↓Glomerular capillary pressure
  - ↓Growth of mesangial cells/matrix due to Ang II?

Side effects of ACEI

- Common
  - Dry Cough
    - 5 – 20% of patients
    - Not dose-related; occurs within 1 wk. – 6 mo.
    - Women > men
    - May Require cessation of therapy
  - Fetopathic Potential
    - Not teratogenic in 1st trimester
    - Developmental defects in 2nd or 3rd trimester
- Rare
  - Angioneurotic Edema (or Angioedema)
    - ~0.1 - 0.5% of patients
    - Not dose-related; occurs within 1st week
    - Severe swelling of mouth, tongue, lips, airway
    - may be life-threatening

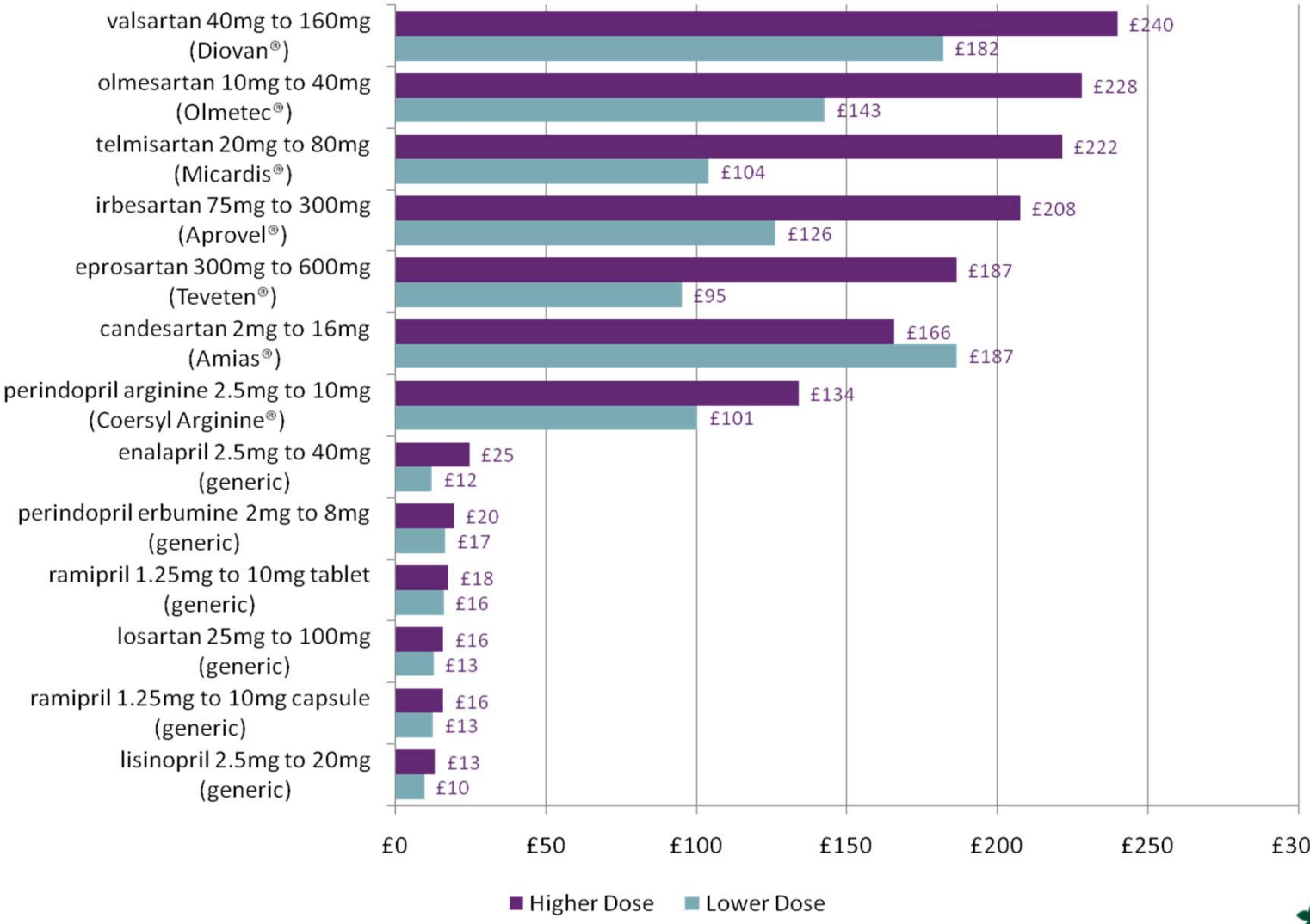
Side effects and contraindications of ACEI

- Rare
  - Hypotension
    - First dose effect in patients with elevated PRA, salt depletion, CHF
  - Hyperkalemia
    - In patients with renal insufficiency, diabetic nephropathy
  - Acute Renal Failure
    - Patients with renal stenosis, heart failure, volume depleted
  - Skin Rash
- Extremely Rare (reversible)
  - Alteration/loss of taste
  - Neutropenia
  - Glycosuria
  - Hepatotoxicity

Additional benefits of ACEI

- Cardioprotective
- Reduce incidence of second heart attack
- Reduce cardiovascular complications in patients with risk factors
- Reduce incidence of diabetes in high risk patients
- Reduce complications in diabetic patients

Annual cost of treatment of ACEIs and ARBs



Patent expiry dates for sartans

- Valsartan — November 2011
- Eprosartan — April 2012
- Candesartan — April 2012
- Azilsartan — June 2012
- Irbesartan — October 2013
- Telmisartan — December 2013
- Olmesartan — February 2017

Target Doses for ACEIs and ARBs in Trials Investigating the Addition of an ACEI or an ARB to Standard Medical Therapy for Stable Ischemic Heart Disease and Preserved Left Ventricular Systolic Function

Clinical Trial	Group	Drug	Trial Target Dose (mg/day)
HOPE	ACEI	Ramipril	10
PART-2	ACEI	Ramipril	5–10
SCAT	ACEI	Enalapril	20
CAMELOT	ACEI	Enalapril	20
EUROPA	ACEI	Perindopril	4–8
PEACE	ACEI	Trandolapril	4
SMILE-ISCHEMIA	ACEI	Zofenopril	60
TRANSCEND	ARB	Telmisartan	80
Kondo J, et al.	ARB	Candesartan	4

Overall Summary of the Evidence-Based Benefits of Adding an ACEI or an ARB to Standard Medical Therapy for Stable Ischemic Heart Disease With Preserved Left Ventricular Systolic Function

Outcome	ACEI		ARB	
	Risk	Level of Evidence	Risk	Level of Evidence
Total Mortality	Decreased	High	No effect	Moderate
CV Mortality	Decreased	Moderate	No effect	Moderate
Nonfatal MI	Decreased	High	No evidence	--
Stroke	Decreased	Moderate	No effect	Moderate
Combined Risk of CV Mortality, Nonfatal MI, and Stroke	No effect	Moderate	Decreased	Moderate
Atrial Fibrillation	No effect	High	No effect	High
Total Hospitalizations	No effect	Moderate	No effect	Moderate
Angina-Related Hospitalizations	No effect	High	No effect	High
HF-Related Hospitalizations	Decreased	High	No effect	Moderate
Revascularization	Decreased	High	No effect	Moderate

DRI: Aliskiren

- Aliskiren binds to the $S3^{bp}$ binding pocket of renin, essential for its activity. Binding to this pocket prevents the conversion of angiotensinogen to angiotensin I.

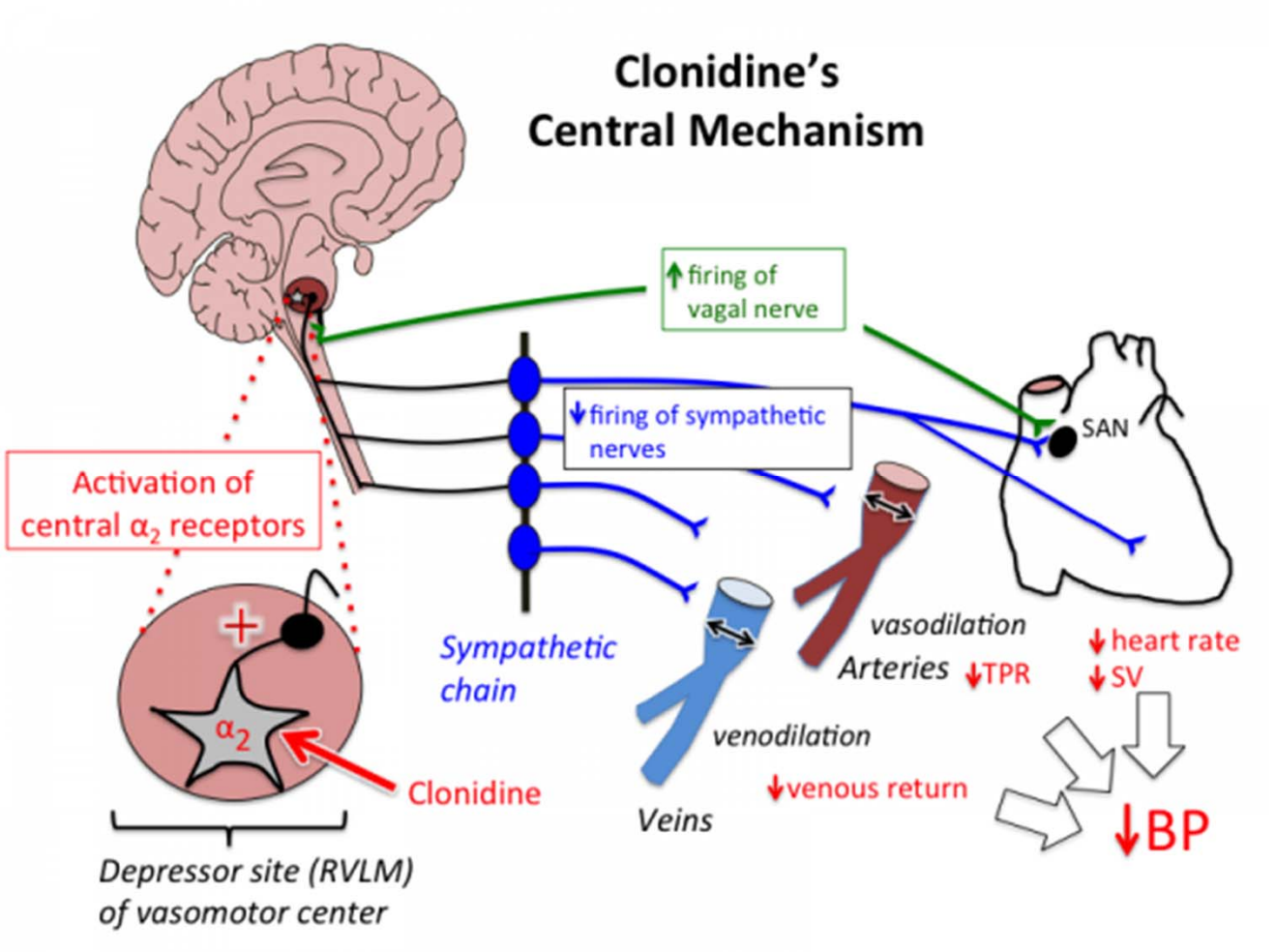
Possible side effects:
Angioedema
Hyperkalemia (particularly when used with ACE inhibitors in diabetic patients)
Hypotension (particularly in volume-depleted patients)
Diarrhea and other GI symptoms
Headache
Dizziness
Cough
Rash
Elevated uric acid, gout, and renal stones
Rarely: allergic swelling of the face, lips or tongue and difficulty breathing

Contraindications:
Pregnancy: other drugs such as ACE inhibitors, also acting on the renin-angiotensin system have been associated with fetal malformations and neonatal death.
Breast feeding: during animal studies, the drug has been found present in milk.

Centrally acting sympatholytic drugs

- α2 agonists
  - clonidine
  - guanabenz
  - guanfacine
  - α-methyldopa

In pregnancy α-methyldopa is the first choice of drug.



I1 (imidazoline) receptor agonists: I1 receptors mediate sympatho-inhibitory effect

Side effects: dry mouth, sedation, impared mental acuity, rebound hypertension

Centrally acting α_2 agonists

- Alpha-Methyldopa: a prodrug
  - Precursor of Dopamine and NA
  - MOA: Converted to alpha methyl noradrenaline which acts on alpha-2 receptors in brain and causes inhibition of adrenergic discharge in medulla – fall in PVR and fall in BP
  - Various adverse effects – cognitive impairement, postural hypotension, positive coomb`s test etc. – Not used therapeutically now except in Hypertension during pregnancy
- Clonidine: Imidazoline derivative, partial agonist of central alpha-2 receptor
  - Not frequently used now because of tolerance and withdrawal hypertension
- Guanfacine, guanabenz

Peripheral α_1 adrenergic receptor antagonists

- Non selective alpha blockers are not used in chronic essential hypertension (phenoxybenzamine, phentolamine), only used sometimes as in phaechromocytoma
- Specific alpha-1 blockers like prazosin, terazosin and doxazosine are used
- PRAZOSIN is the prototype of the alpha-blockers
- Reduction in t.p.r and mean BP – also reduction in venomotor tone and pooling of blood – reduction in CO
- Does not produce tachycardia as presynaptic auto (alpha-2) receptors are not inhibited – autoregulation of NA release remains intact

Peripheral α_1 adrenergic receptor antagonists

- Adverse effects:
  - Prazosin causes postural hypotension – start 0.5 mg at bed time with increasing dose and upto 10 mg daily
  - Fluid retention in monotherapy
  - Headache, dry mouth, weakness, dry mouth, blurred vision, rash, drowsiness and failure of ejaculation in males
- Current status:
  - Several advantages – improvement of carbohydrate metabolism – diabetics, lowers LDL and increases HDL, symptomatic improvement in BHP
  - But not used as first line agent, used in addition with other conventional drugs which are failing – diuretic or beta blocker
- Doses: Available as 0.5 mg, 1 mg, 2.5 mg, 5 mg etc. dose:1-4 mg thrice daily (Minipress/Prazopress)

Directly acting vasodilators

- Calcium antagonists (e.g. **nifedipine**, **diltiazem**, **verapamil**): block Ca^{2+} entry in response to depolarisation. Common adverse effects include ankle swelling and (especially with verapamil) constipation.
- K_{ATP} channel activators (e.g. **minoxidil**): open membrane potassium channels, causing hyperpolarisation. Ankle swelling and increased hair growth are common.
- Drugs that increase cytoplasmic cyclic nucleotide concentrations by:
  - - increasing adenylyl cyclase activity, for example prostacyclin (**epoprostenol**), $ß_2$-adrenoceptor agonists, adenosine
  - - increasing guanylyl cyclase activity: nitrates (e.g. **glyceryl trinitrate**, **nitroprusside**)
  - - inhibiting phosphodiesterase activity (e.g. **sildenafil**).

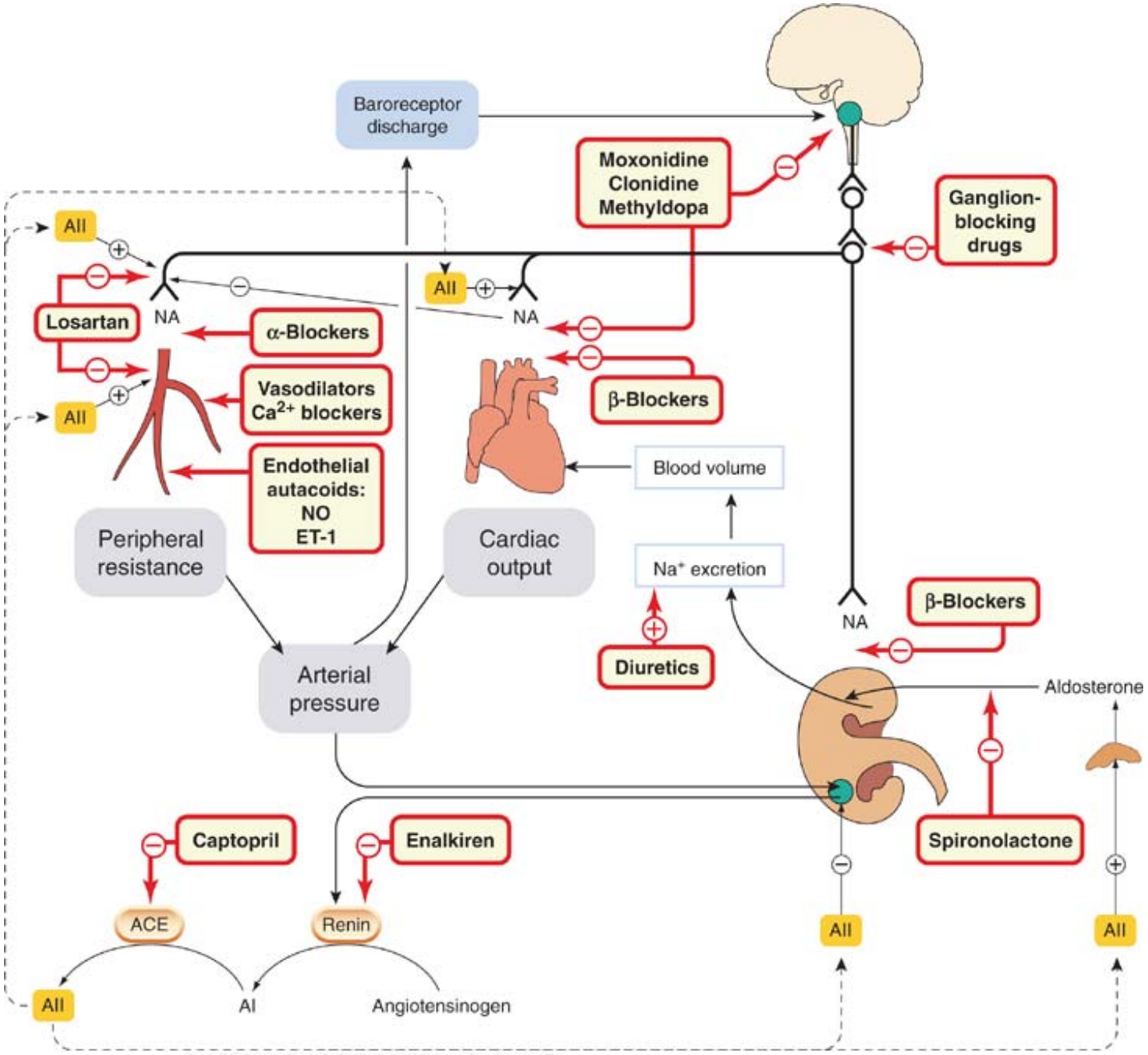
Indirectly acting vasodilators

- Drugs that interfere with the sympathetic nervous system (e.g. α_1-adrenoceptor antagonists). Postural hypotension is a common adverse effect.
- Drugs that block the renin-angiotensin system:
  - - renin inhibitors (e.g. **aliskiren**)
  - - angiotensin-converting enzyme inhibitors (e.g. **ramipril**); dry cough may be troublesome
  - - AT_1 receptor antagonists (e.g. **losartan**).
- Drugs or mediators that stimulate endothelial NO release (e.g. acetylcholine, bradykinin).
- Drugs that block the endothelin system:
  - - endothelin synthesis (e.g. phosphoramidon)
  - - endothelin receptor antagonists (e.g. **bosentan**).

Vasodilators with unknown mechanism:
alcohol, propofol, hydralazine

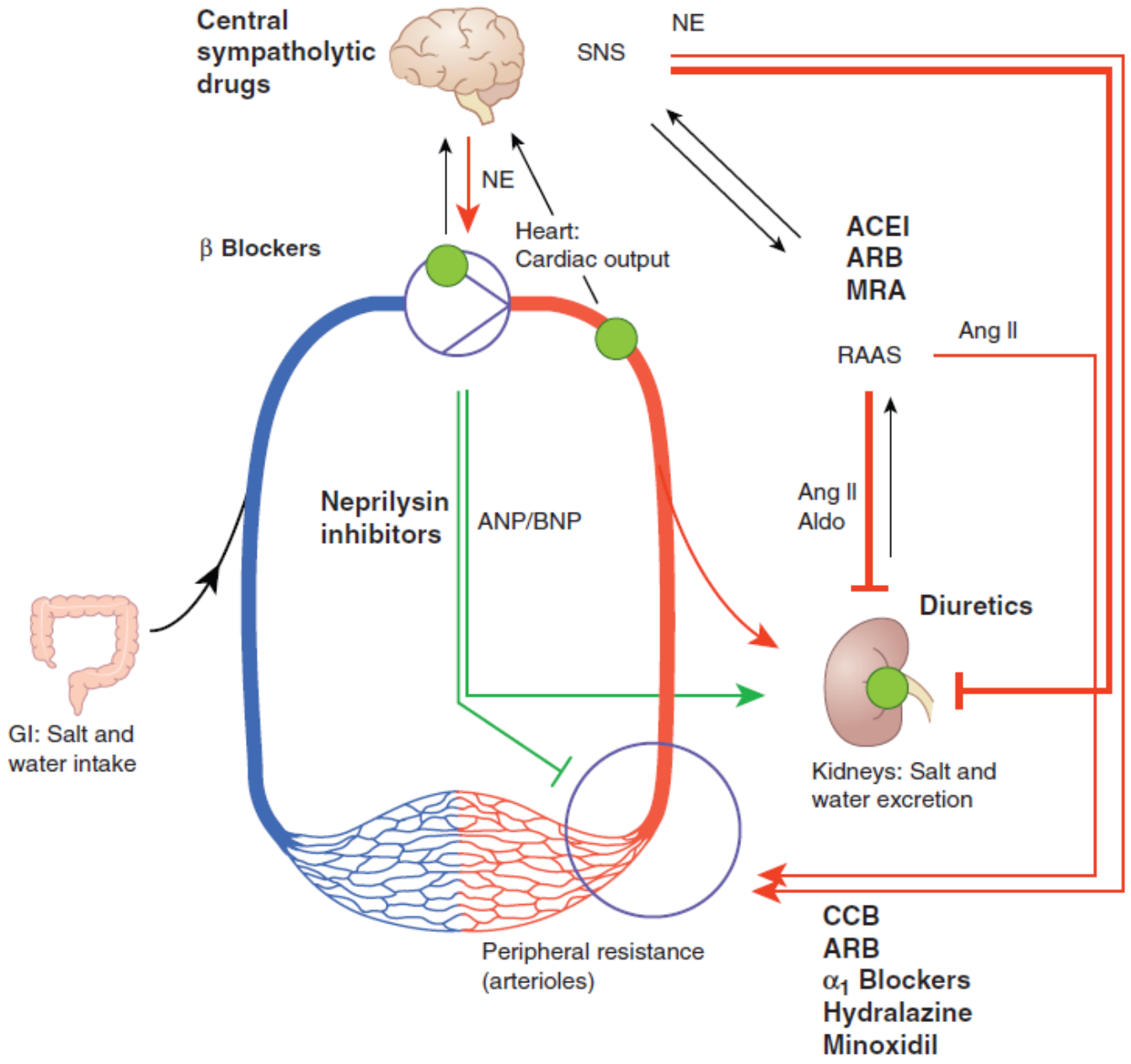
Clinical use of antihypertensive drugs

Group of drug	Main indication	Possible indication	Main contraindication	Possible contraindication
Thiazides	Heart failure, elder patient, systolic hypertension	DM	Gout	Dyslipidaemia, sexually active males
Beta blockers	Angina pectoris, after AMI, tachicardia	Heart failure, gravidity, DM, glaucoma, aortic aneurism, ES	Asthma, COPD, II./III. AV block	Dislipidaemia, sport, peripheral blood vessel disease, psoriasis
Alfa-1 blockers	Prostate hypertrophy	Metabolic sy., dyslipidaemia		Orthostatic hypotension, aortic aneurism, congestive heart failure
ACEI	Heart failure, Left ventricle dysfunction, after AMI, diabetic nephropathy	IHD	Gravidity, Bilateral renal artery stenosis, hyperkalaemia	Aortic stenosis
AT1 blockers	Heart failure, Left ventricle dysfunction, diabetic nephropathy		Gravidity, bilateral renal artery stenosis, hyperkalaemia	Aortic stenosis
Ca^{++} antagonists	Angina pectoris, elder patient, systolic hypertension	Peripheral blood vessel disease	II./III. AV block	Congestive heart failure, aortic aneurism, aortic stenosis
Imidazoline I-1 rec blocker		Diabetes mellitus, metabolic syndrome	II./III. AV block	
Centrally acting alfa-2 rec agonists	Gravidity	Aortic aneurism	II./III. AV block, depression, liver disease	
Direct vasodilators		Therapy resistent hypertonia, hypertonic crisis	Aorta/mitral valve stenosis	IHD, aortic aneurism, cerebrovascular ischaemia

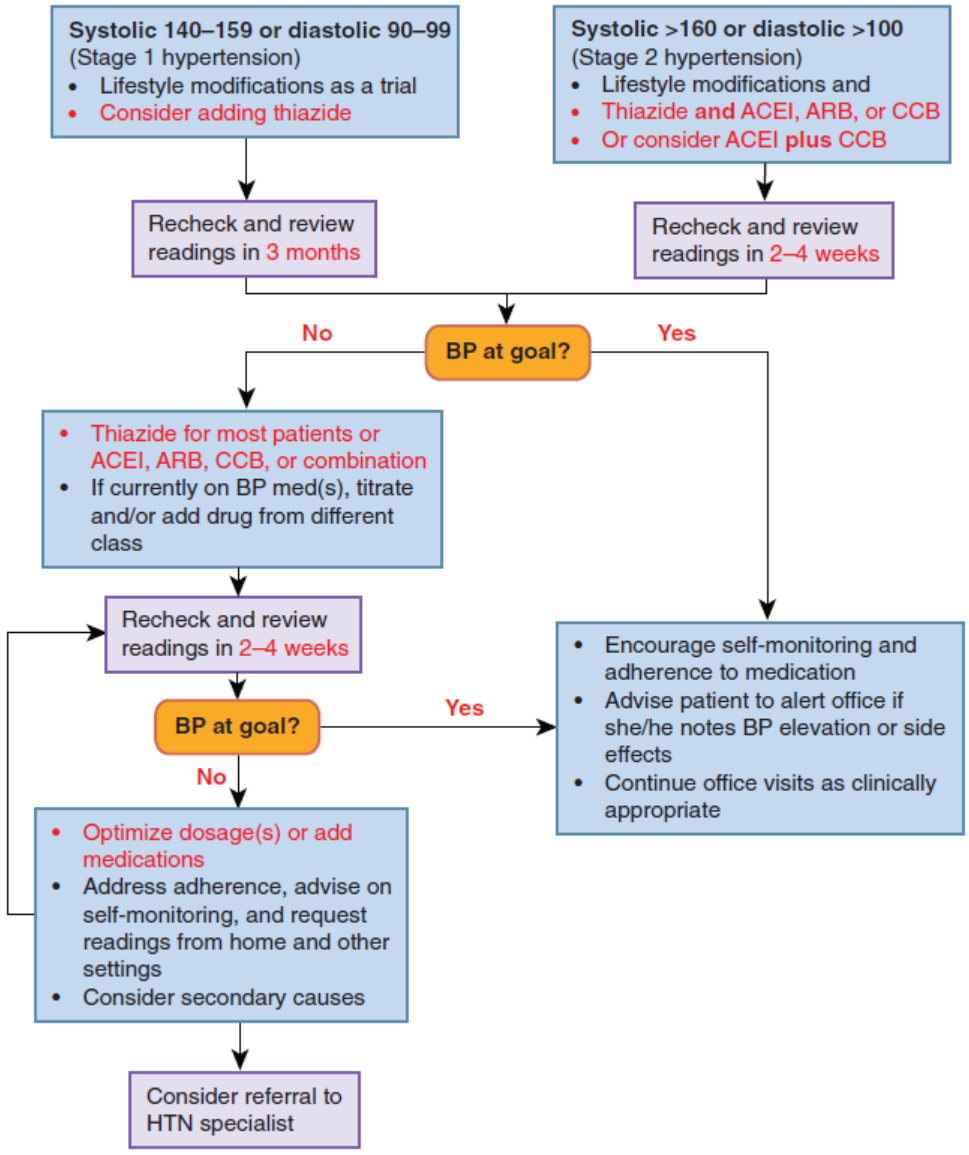


HEMODYNAMIC EFFECTS OF LONG-TERM ADMINISTRATION OF ANTIHYPERTENSIVE AGENTS

	HEART RATE	CARDIAC OUTPUT	TOTAL PERIPHERAL RESISTANCE	PLASMA VOLUME	PLASMA RENIN ACTIVITY
Diuretics	↔	↔	↓	–↓	↑
Sympatholytic agents					
Centrally acting	–↓	–↓	↓	–↑	–↓
α_1 Blockers	–↑	–↑	↓	–↑	↔
β Blockers					
No ISA	↓	↓	–↓	–↑	↓
ISA[a]	↓↑	↔	↓	–↑	–↓
Arteriolar vasodilators	↑	↑	↓	↑	↑
Ca^{2+} channel blockers	↓ or ↑	↓ or ↑	↓	–↑	–↑
ACEIs	↔	↔	↓	↔	↑
AT_1 receptor blockers	↔	↔	↓	↔	↑
Renin inhibitor	↔	↔	↓	↔	↓ (but renin ↑)


Central sympatholytic drugs
NE
SNS
NE
β Blockers
Heart: Cardiac output
ACEI
ARB
MRA
Ang II
RAAS
Ang II
Aldo
Neprilysin inhibitors
ANP/BNP
Diuretics
GI: Salt and water intake
Kidneys: Salt and water excretion
Peripheral resistance (arterioles)
CCB
ARB
α1 Blockers
Hydralazine
Minoxidil

Treatme ertension



Treatment of hypertensive crisis

- Commonly utilized agents
  - Nitroprusside
  - Nitroglycerin
  - Esmolol
  - Labetalol
  - Hydralazine
  - Nicardipine or Clevidipine (new agent)