PHARM.D • YEAR 3

Medicinal Chemistry

CHAPTER 7.1

Antihypertensive Agents

PPT CHAPTER COVER



Hypertension: mechanisms and organ risk

Arterial pressure reflects cardiac output and systemic vascular resistance.

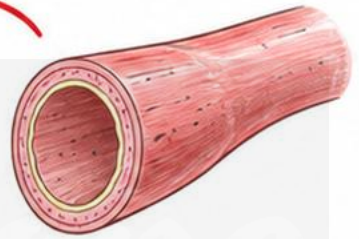
Sustained hypertension increases risk of cardiac, cerebral, renal and vascular injury.

Heart – cardiac output (CO)

- Sympathetic activity contributes to regulation.
- Circulating volume influences cardiac output.



Arterial pressure = CO × SVR

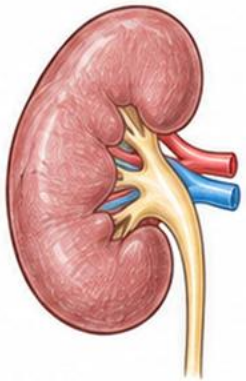


Vessels – systemic vascular resistance (SVR)

- Sympathetic activity contributes to regulation.
- The renin–angiotensin–aldosterone system contributes to regulation.

Guideline note

The PDF uses an older staging framework; numerical thresholds vary between current guidelines and should not be presented as a universal modern standard.



Kidney – fluid balance and RAAS

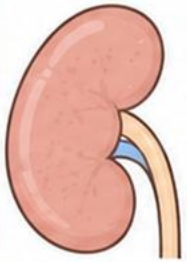
- Circulating volume contributes to regulation.
- The renin–angiotensin–aldosterone system contributes to regulation.

Medicinal chemistry and use

- Antihypertensive chemistry spans several scaffolds and targets.
- Clinical selection requires patient-specific assessment; these pages focus on drug identity, mechanisms and structural features rather than prescribing.

Antihypertensive classes: target map.

1. Volume



Diuretics
reduce sodium and volume burden.

↓ Sodium reabsorption

↓

↓ Extracellular fluid volume

2. Renin-angiotensin system (RAAS)

Angiotensinogen

↓

Angiotensin I (Ang I)

↓ ACE — ACE inhibitors block this conversion.

Angiotensin II (Ang II)

↓

AT1 receptor — ARBs block AT1 receptor effects, NOT formation of Ang II.

↓

Vasoconstriction and other effects

3. Sympathetic system

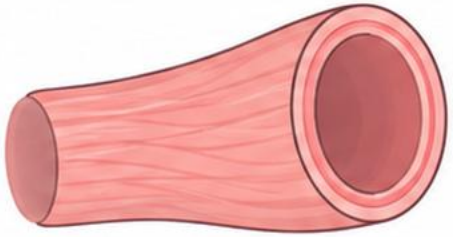


Beta blockers
reduce selected sympathetic effects.

Central sympatholytics
reduce sympathetic outflow.

Peripheral neuronal blockers or catecholamine-depleting drugs
have distinct mechanisms.

4. Vascular smooth muscle



Calcium-channel blockers
reduce calcium-dependent vascular or cardiac activity.

Direct vasodilators
act on vascular smooth muscle through different pathways.

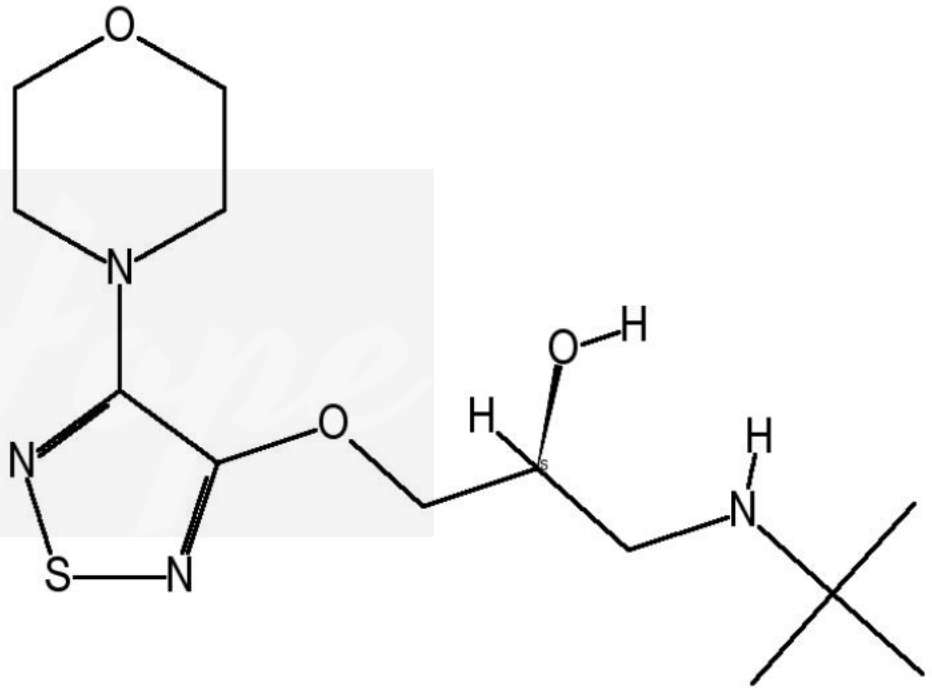
The chapter's brand examples include several classes, but they are not interchangeable.
Relate each class to its target before comparing scaffold or adverse effects.

Timolol: beta-blocker chemistry

Structure and composition

- Timolol is a non-selective beta blocker with an aryloxypropanolamine-related side chain, a 1,2,5-thiadiazole ring and a morpholine substituent.
- Its correct free-base formula is $C_{13}H_{24}N_4O_3S$.
- The active stereochemical form has an S-configured alcohol centre.

$C_{13}H_{24}N_4O_3S$



Verified molecular structure

Pharmacological actions

- Beta blockade affects heart rate and contractility.
- Ophthalmic timolol also reduces aqueous-humour production.

Important adverse effects

- Bradycardia, conduction effects and bronchospasm are important concerns.

Additional point

- Systemic effects can occur after eye-drop use.
- The PDF's diphenylmethanol description is incorrect for timolol.

Beta-blocker SAR: timolol example

Aryloxypropanolamine-related arrangement

The aryloxypropanolamine-related arrangement provides an aromatic or heteroaromatic region, an ether linkage, a hydroxyl-bearing three-carbon chain and a basic amino group.

Alcohol stereochemistry

Alcohol stereochemistry strongly influences receptor recognition.

N-alkyl substituent

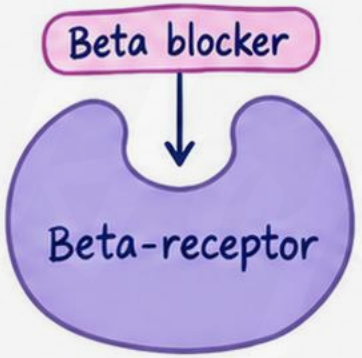
The bulky N-alkyl substituent supports beta-receptor affinity.

Heteroaromatic region and morpholine

The heteroaromatic region and morpholine alter physicochemical properties.

Pharmacophore domains (in words)

- Aromatic or heteroaromatic region
- Ether linkage
- Hydroxyl-bearing THREE-CARBON chain
- Basic amino group



A shared side-chain motif does not prove identical selectivity or partial-agonist behaviour across all beta blockers.

Nonselectivity and clinical relevance

Timolol is non-selective, so beta2-related bronchospasm remains relevant.

Key distinction

Distinguish the pharmacophore from the complete molecule.

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