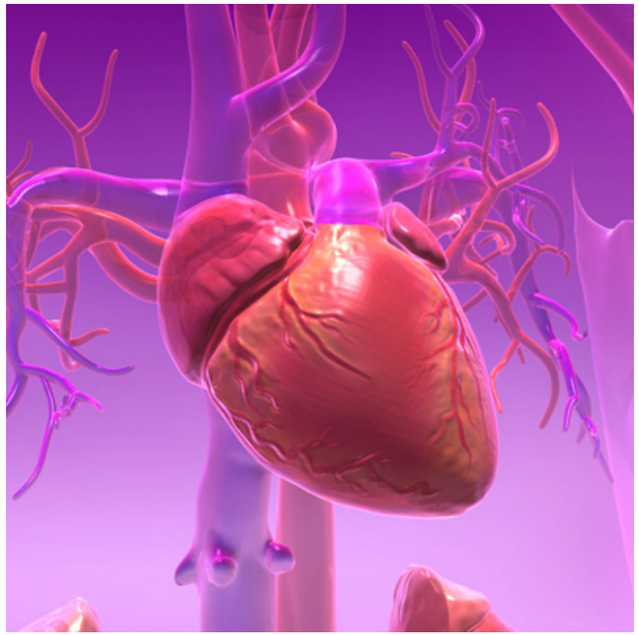
MED 9408

Beta Blockers, Calcium Channel Blockers, and Other Sympatholytics



Nicholas B. Norgard, PharmD

Learning Objectives

Predict the response—and explain the links that produce it

01 **Diagram** the mechanisms of all drug classes discussed in this lecture.

02 **Predict** each class's effects on heart rate, AV conduction, contractility, vascular tone, and renin release from its mechanism and compensatory responses.

03 **Distinguish** drugs within each class by receptor or tissue selectivity, intrinsic activity, binding reversibility, and clinically relevant pharmacokinetics.

04 **Relate** pharmacologic properties to therapeutic use, adverse-effect profile, and agent selection in hypertension, angina, HFrEF, and selected arrhythmias.

05 **Rationalize** the major adverse effects, contraindications, and drug interactions of each class mechanistically.

A framework for understanding every drug class

Connect mechanism, physiological effects, clinical benefits, and risks

1	2	3	4	5	6	7
Target	**Action**	**Tissue effect**	**Body response**	**Uses and outcomes**	**Safety**	**Pharmacokinetics**
Where does it act?	What does it do there?	What changes directly?	How does the body respond?	Who benefits, and how?	What could go wrong?	Does exposure change the answer?

Connect the answers

Target → Action → Tissue effect → Body response
Explain the direct effect, then account for compensation.

Connect these effects to **Uses and outcomes** and **Safety**. **Pharmacokinetics** changes the exposure that drives the response.

Mechanism explains a treatment’s rationale; clinical evidence establishes its outcomes.

Sympathetic Reflex to Low BP

Central control → peripheral receptors → cardiovascular effects

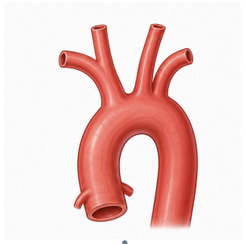
Central
Central α_2 agonists

→

Peripheral
α and β blockers

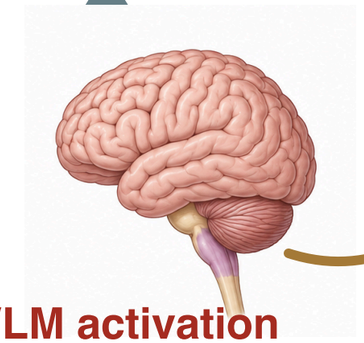
→

Effector
CCBs: heart and blood vessels



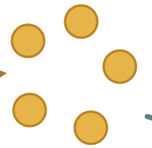
Baroreceptors
↓ BP → ↓ signal

Brainstem



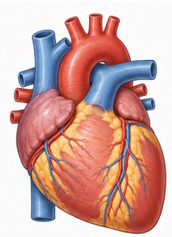
RVLM activation
↑ sympathetic outflow

Sympathetic efferent pathway

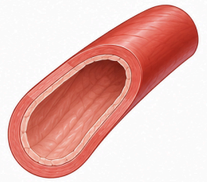


NE
Nerve terminals

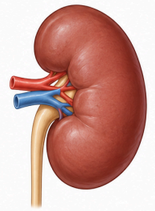
Adrenergic receptors

β_1 → 

Heart
↑ HR and contractility

α_1 → 

Blood vessels
Vasoconstriction

β_1 → 

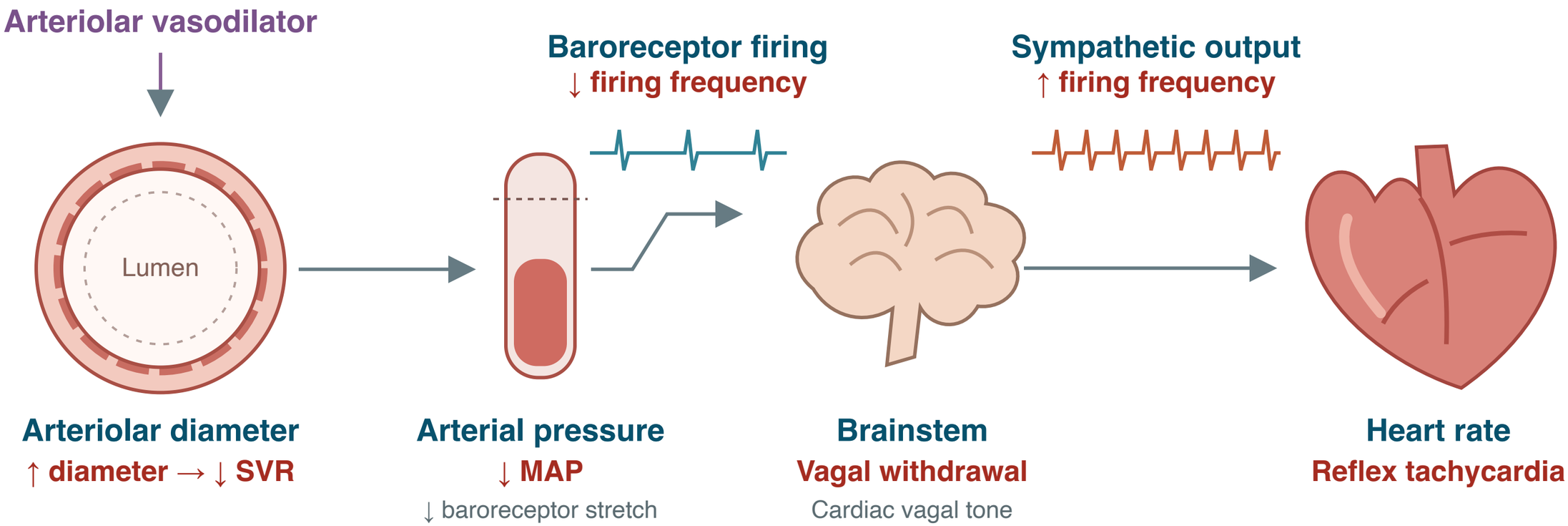
Kidney
↑ renin release

Cardiovascular effects: ↑ BP · ↑ HR · ↑ contractility · ↑ vascular tone

NE: mainly sympathetic nerve terminals · **Epinephrine:** mainly adrenal medulla → circulation

Baroreflex: Compensation for a Fall in Blood Pressure

Reflex tachycardia following arteriolar vasodilation



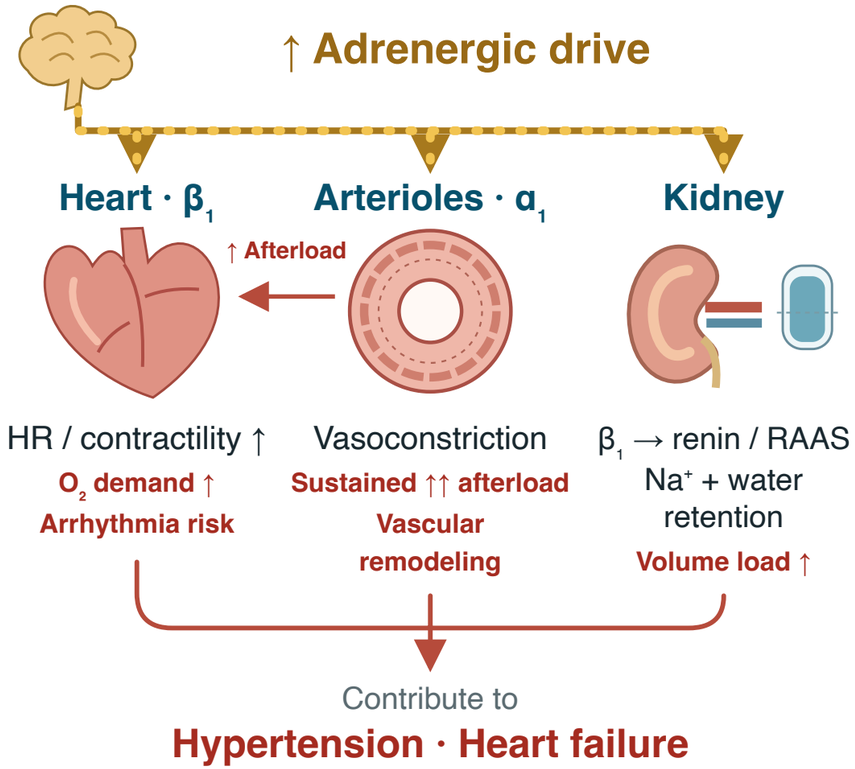
Dashed outlines mark baseline. Neural traces show firing frequency; timing is slowed for teaching.

Increased sympathetic outflow and vagal withdrawal produce reflex tachycardia.

Arteriolar vasodilation is the direct drug effect; reflex tachycardia is the baroreflex response.

Inappropriately High SNS Activity

"When good physiology goes bad" · Hypertension and heart failure



Gold: adrenergic drive · Red: cardiovascular stress.
Fluid retention and remodeling develop over longer timescales.

Aspect	Hypertension	HFrEF
Trigger	SNS overactivity contributes in many patients; hypertension has multiple causes.	Impaired pump function recruits SNS and RAAS compensation.
Hemodynamic effects	Vascular tone ↑; cardiac and renal sympathetic effects support pressure.	Initially supports circulation; sustained activation increases afterload and congestion.
Maladaptive changes	Vascular remodeling and endothelial injury.	β_1 downregulation, myocardial remodeling, fibrosis and cellular injury.
End-organ effects	LV hypertrophy, coronary disease, stroke and renal injury.	Progressive pump dysfunction and arrhythmias.

Sustained SNS activity adds cardiac work, pressure load, and volume load.

Signaling Cascades, Calcium Dynamics, and Physiologic Effects

α_1 · Vascular smooth muscle

Gq → PLC → IP_3
↑ SR Ca^{2+} release
Ca^{2+}–calmodulin → MLCK

→ **Contraction**

Arterioles: ↑ SVR

Veins: ↑ venous return

α_2 · Sympathetic neurons / brainstem

Gi/o → ↓ AC → ↓ cAMP

↓ Ca^{2+} entry / ↑ K^+ conductance
Parallel ion-channel effects

→ **↓ NE release**
Negative feedback

Brainstem (RVLM): ↓ neuronal activity → ↓ sympathetic outflow

β_1 · Heart and kidney

Gs → adenylyl cyclase → ↑ cAMP

SA / AV nodes
HCN + PKA / Ca^{2+} → ↑ rate, ↑ conduction

Myocardium
PKA → ↑ Ca^{2+} entry + SR release → ↑ force

Renal juxtaglomerular cells
cAMP / PKA → ↑ renin secretion

β_2 · Smooth muscle, metabolism, and secretion

Gs → adenylyl cyclase → ↑ cAMP → PKA

Smooth muscle
↓ MLCK → relaxation

Liver / skeletal muscle
↑ Glycogen breakdown

Secretory tissues
↑ Secretory activity

Vessels: vasodilation
Bronchi: bronchodilation
GI: ↓ wall tone / motility

Liver: ↑ glucose output
Muscle: fuel mobilization
Also: ↑ K^+ uptake, tremor

Pancreas: ↑ insulin
Eye: ciliary epithelium
↑ Aqueous humor formation

L-type Ca^{2+} channel
Voltage-gated · not adrenergic

Ca^{2+} entry
Tissue-specific effects →

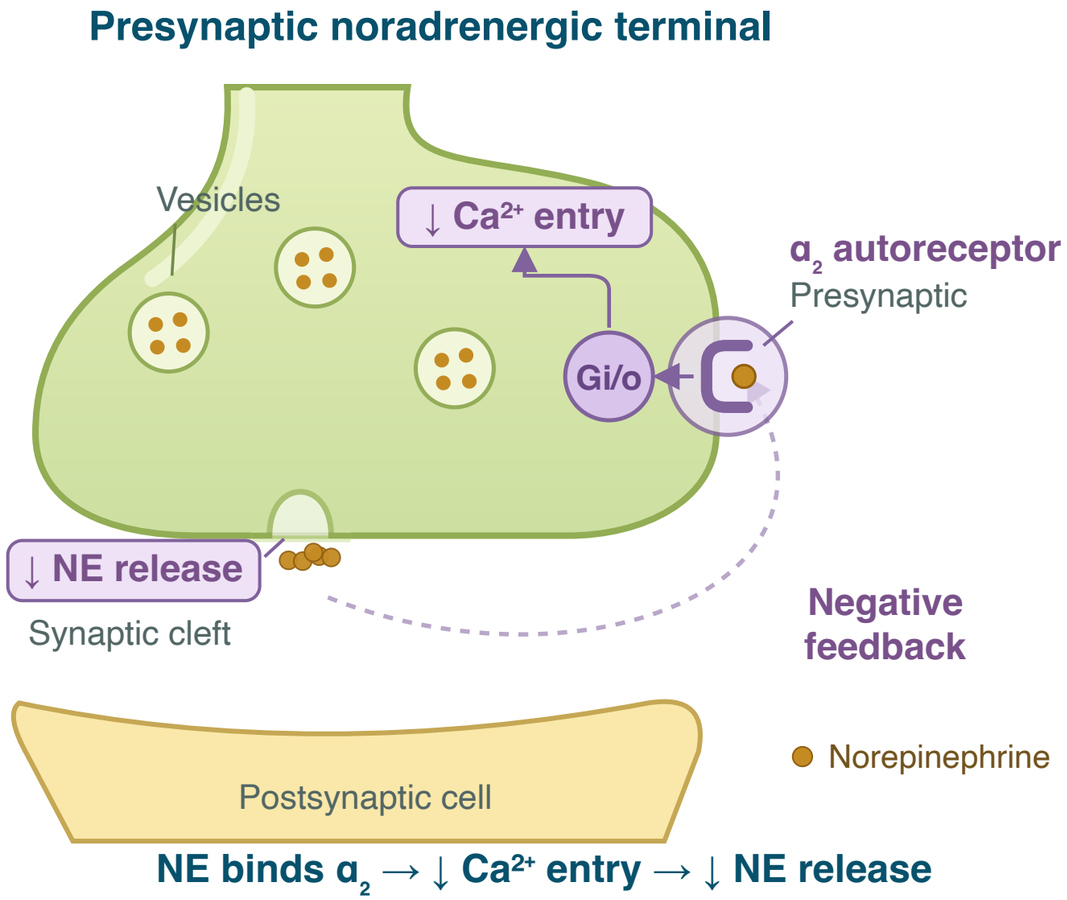
Vascular muscle
Contraction

SA / AV nodes
Depolarization / conduction

Myocardium
Ca^{2+} release → contraction

Central α_2-Adrenergic Agonists

"Inhibition through activation"



α_2 agonists activate this inhibitory receptor.

Central inhibitory receptors

Brainstem sympathetic-control networks, including the **rostral ventrolateral medulla (RVLM)**.

- **Gi/o:** ↓ adenylyl cyclase / cAMP
- **Parallel channel effects:** ↑ K^+ conductance and ↓ Ca^{2+} entry
- **Neuronal effect:** ↓ firing and transmitter release

Activating an inhibitory receptor produces **sympatholysis**.

Clonidine · Guanfacine · Methyldopa (after activation)

Central α_2 Agonists: Hemodynamic Effects

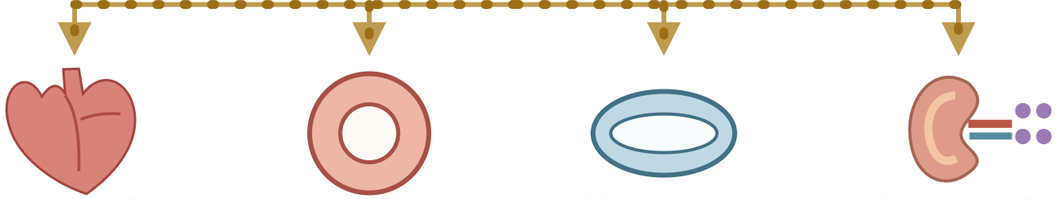
"Reducing sympathetic outflow from the CNS"

Before · Baseline

Central sympathetic activity

Brainstem / RVLM
Baseline outflow
Cardiac vagal tone

Baseline firing / NE release



Heart · β_1
Heart rate
Contractile drive

Arterioles · α_1
Arteriolar tone
SVR

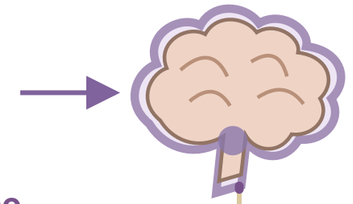
Veins · α_1
Venous tone
Venous return

Kidney · β_1
Renin release

Blood pressure — Baseline

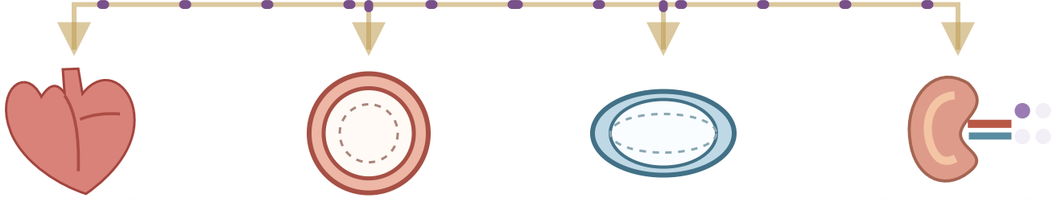
After · Central α_2 agonist

Central α_2 activation



Brainstem / RVLM
↓ sympathetic outflow
↑ cardiac vagal tone

↓ firing / NE release



Heart · β_1
↓ heart rate
↓ contractile drive

Arterioles · α_1
Vasodilation
↓ SVR

Veins · α_1
↑ capacitance
↓ venous return

Kidney · β_1
↓ renin release

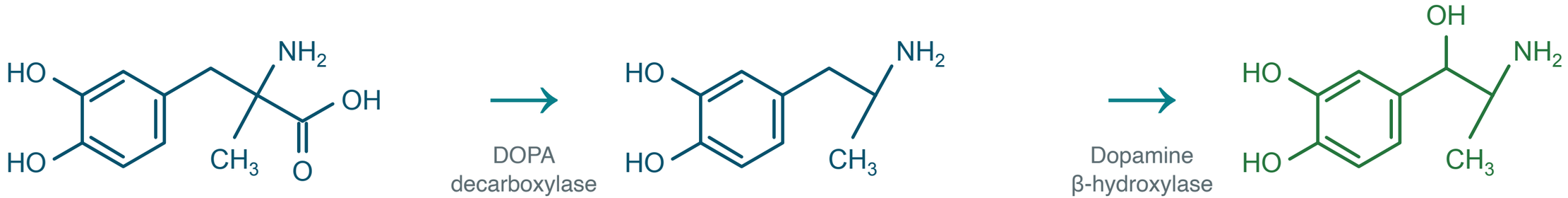
Blood pressure — **↓ BP**

Reduced sympathetic outflow lowers blood pressure.

Central sympatholysis blunts reflex tachycardia; net cardiac output may be maintained.

Methyldopa: Indirect Central α_2 Agonist

"A false neurotransmitter strategy"

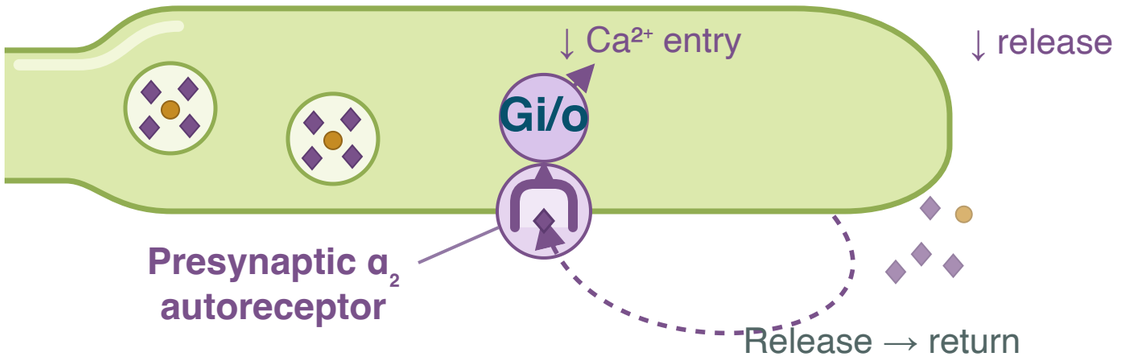


Methyldopa → **α-Methyldopamine** → **α-Methylnorepinephrine**

Before

After methyldopa

α-MeNE replaces vesicular NE



Central sympatholysis

Sympathetic outfall

↓ **sympathetic outflow**

↓ **BP**

Central network effect

● Norepinephrine (NE) ◆ α-Methylnorepinephrine (α-MeNE)

Presynaptic α_2 activation → ↓ Ca^{2+} entry → ↓ transmitter release.

Clonidine: Prototype Central α_2 Agonist

Broad receptor activity → widespread effects

CLONIDINE
α_2A · α_2B · α_2C + I_1 imidazoline

Brainstem

α_2A · medullary networks
I_1 imidazoline receptors
Rostral ventrolateral medulla

↓ sympathetic outflow

Presynaptic terminals

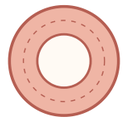
α_2A + α_2C
↓ NE release

Locus coeruleus

α_2A
↓ arousal

Sedation
Reduced alertness

Vascular muscle



α_2B
Vasoconstriction

Can oppose BP lowering
Pressor effect at high exposure

Less adrenergic stimulation across organs

Heart · β_1
↓ HR / contractile drive

Vessels · α_1
↓ vascular tone

Kidney · β_1
↓ renin release

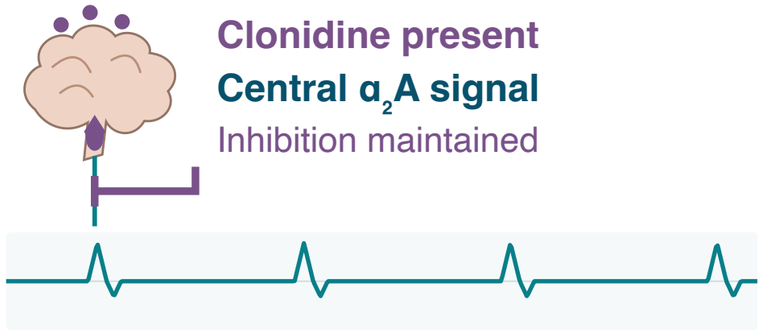
Central sympatholysis drives BP lowering

Broad effects limit tolerability: sedation, dry mouth, bradycardia / hypotension; abrupt withdrawal can cause rebound hypertension.

Clonidine Withdrawal: Loss of Central Inhibition

Falling drug exposure removes the central brake on sympathetic outflow

During treatment



Suppressed sympathetic firing

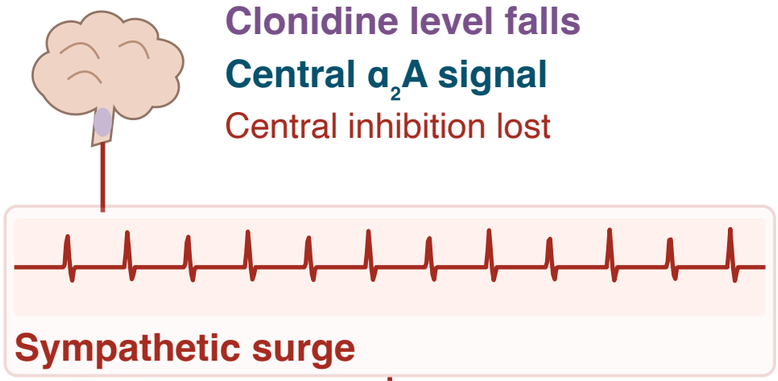
↓ NE release

Heart · β_1
↓ cardiac drive

Arterioles · α_1
↓ vascular tone

Lower BP

After abrupt cessation



↑ NE release

Heart · β_1
↑ HR / contractile drive

Arterioles · α_1
Constriction → ↑ SVR

Can cause rebound hypertension

Recognize the pattern

Missed doses or abrupt cessation followed by **hypertension, tachycardia, headache, agitation, tremor or sweating.**

Prevent the rebound

Taper rather than stop abruptly.

Faster heart rate + vasoconstriction → BP can rebound above baseline.

Strips show schematic sympathetic nerve firing; timing and magnitude are illustrative.

Excess drug effect: sedation + bradycardia / hypotension • **Withdrawal:** sympathetic activation + hypertension

Central α_2 Agonists: Agent Comparison

Clonidine vs Guanfacine vs Methyldopa

Guanfacine: lower BP-lowering potency per mg than clonidine; comparable BP control after titration.

Feature	Clonidine	Guanfacine	Methyldopa
Mechanism	Non-selective α_2 agonism + I_1 agonism	α_2A-preferring agonism	Converted to α-methylnorepinephrine
Therapeutic uses	Hypertension; autonomic symptoms of opioid withdrawal (off-label)	IR: hypertension ER: ADHD	Hypertension; established option in pregnancy
Formulation / exposure	Oral; weekly patch Patch onset: 2–3 days	Oral IR and ER	Oral; requires activation Renal clearance matters
Important adverse effects	Sedation, dry mouth, bradycardia / hypotension	**Less sedation than clonidine**; bradycardia / hypotension possible	Sedation; Coombs positivity, rare hemolysis; liver injury
Withdrawal	**Abrupt cessation → rebound hypertension**	Rebound hypertension can occur; taper	BP generally returns toward pretreatment levels
Distinguishing safety issue	Additive bradycardia with other rate-slowing drugs	CYP3A4 inhibitors ↑ exposure; inducers ↓ exposure	Avoid active liver disease, prior methyldopa liver injury, and MAO inhibitors

Alpha-Blockers

"Let's Vasodilate!!!"

Class	Examples	Receptor selectivity	Key pharmacologic features	Clinical use
Nonselective	Phentolamine Phenoxybenzamine	$\alpha_1 + \alpha_2$	Reversible / short acting (phentolamine) Irreversible / prolonged (phenoxybenzamine)	Catecholamine excess / pheochromocytoma; not routine HTN
α_1-selective	Prazosin Terazosin Doxazosin	α_1 over α_2	Competitive; preserves presynaptic α_2 feedback	HTN add-on in selected patients; terazosin / doxazosin also treat BPH
α_1A-preferring	Tamsulosin Silodosin	α_1A preference	Greater lower-urinary-tract selectivity; smaller BP effect	BPH; not antihypertensive therapy

Non-Selective Alpha Antagonists

"No Brakes, No Mercy: Total Alpha Blockade"

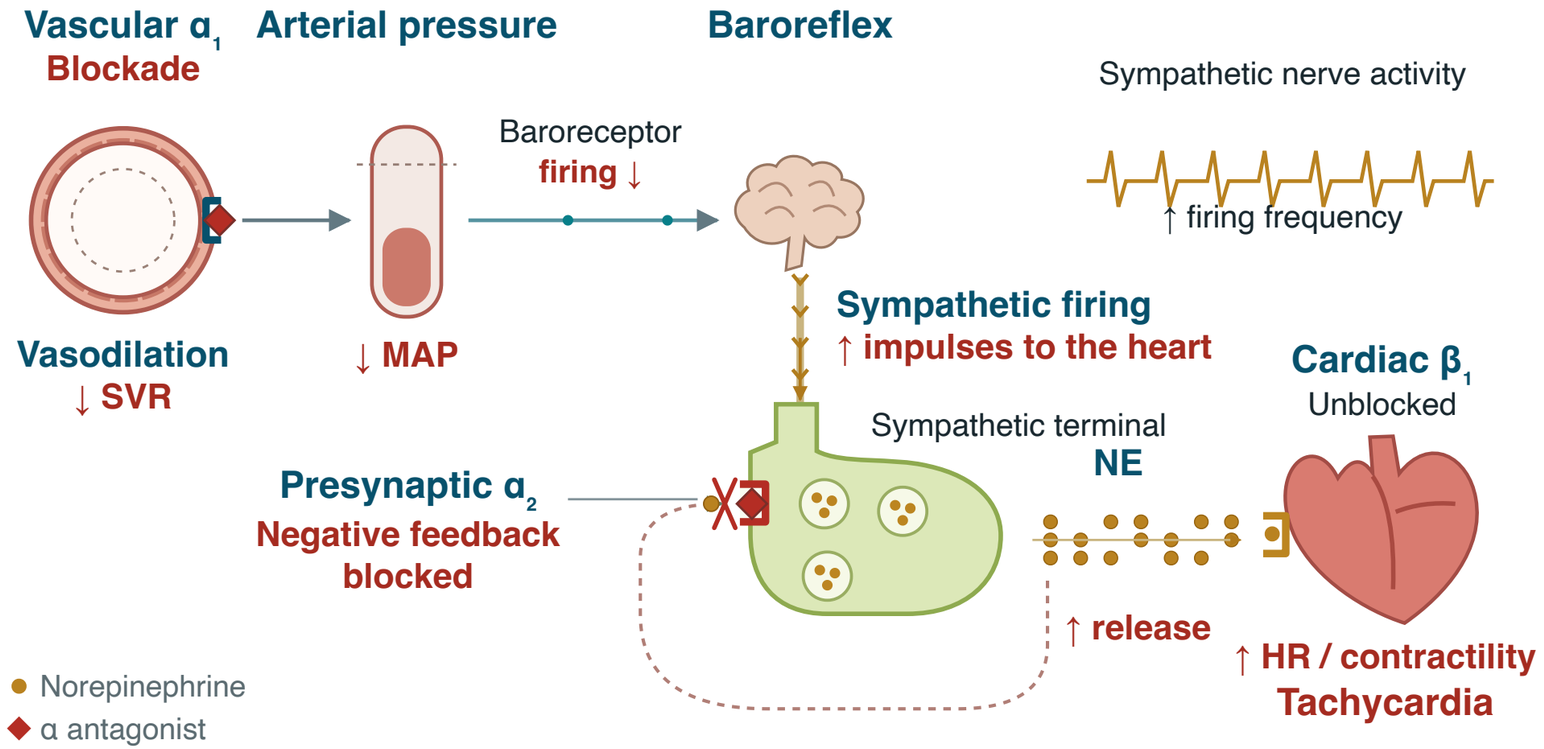
Drug	Mechanism	Clinical use	Key pharmacologic consequence
Phenoxybenzamine	Irreversible $\alpha_1 + \alpha_2$ antagonist	Pheochromocytoma: preoperative preparation	Oral; blockade persists for days. Recovery requires new functional receptors → prolonged benefit and hypotension risk.
Phentolamine	Reversible, competitive $\alpha_1 + \alpha_2$ antagonist	Acute catecholamine-mediated hypertension; norepinephrine extravasation	Rapid, brief parenteral effect. Local infiltration for extravasation; systemic use can cause marked tachycardia / hypotension.

Pheochromocytoma: α blockade before β blockade.

Add a β blocker for tachycardia only after adequate α blockade; β blockade first can worsen α-mediated vasoconstriction.

Non-Selective Alpha Antagonists

"Vasodilate but Watch the Heart Rate!!!"



Phentolamine · Phenoxybenzamine

Vasodilation + loss of α_2 feedback → greater cardiac β_1 stimulation

Adverse effects

- **Orthostatic hypotension**
  Loss of arterial and venous tone
- **Tachycardia / arrhythmias**
  Can precipitate myocardial ischemia
- **Prolonged hypotension**
  Especially with phenoxybenzamine
- Nasal congestion
- Diarrhea / abdominal cramps

Phentolamine: avoid in coronary artery disease / prior MI; severe hypotension and tachycardia increase ischemic risk.

Selective Alpha-1 Antagonists

Prazosin · Terazosin · Doxazosin

Blocks NE at **postsynaptic α_1 receptors** → ↓ smooth-muscle Ca^{2+} signaling.

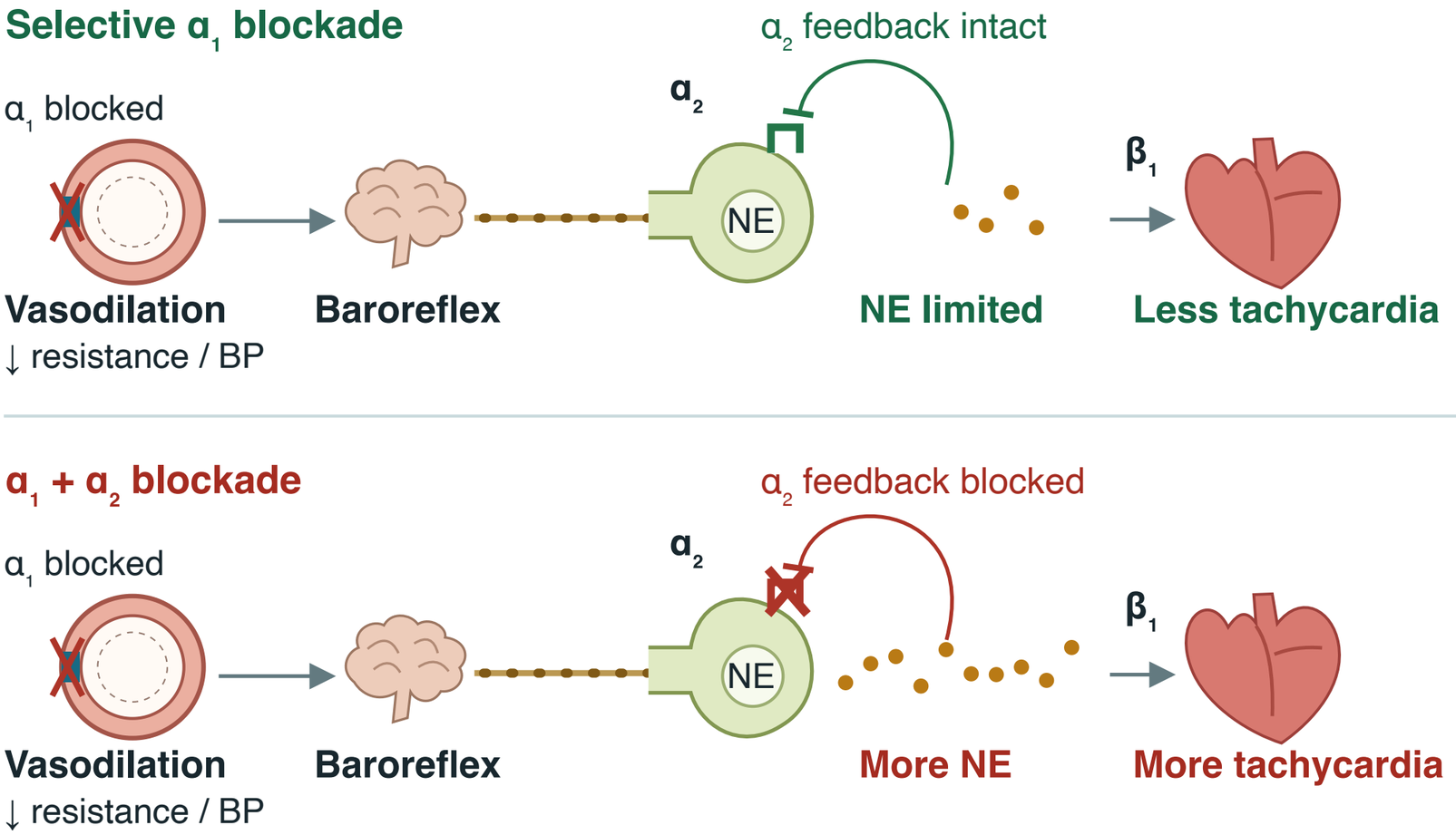
Arterial and venous relaxation
↓ SVR + ↓ venous return → ↓ BP

Presynaptic α_2 feedback is intact
Less NE release and less reflex tachycardia than with α_1 + α_2 blockade.

Plasma half-life

Prazosin	**2–3 h**
Terazosin	**~12 h**
Doxazosin	**~22 h**

Terazosin / doxazosin: usually once daily.



α_2 feedback limits the reflex response; it does not abolish it.

Selective Alpha-1 Antagonists

"Great for the Prostate, Cautious in Hypertension"

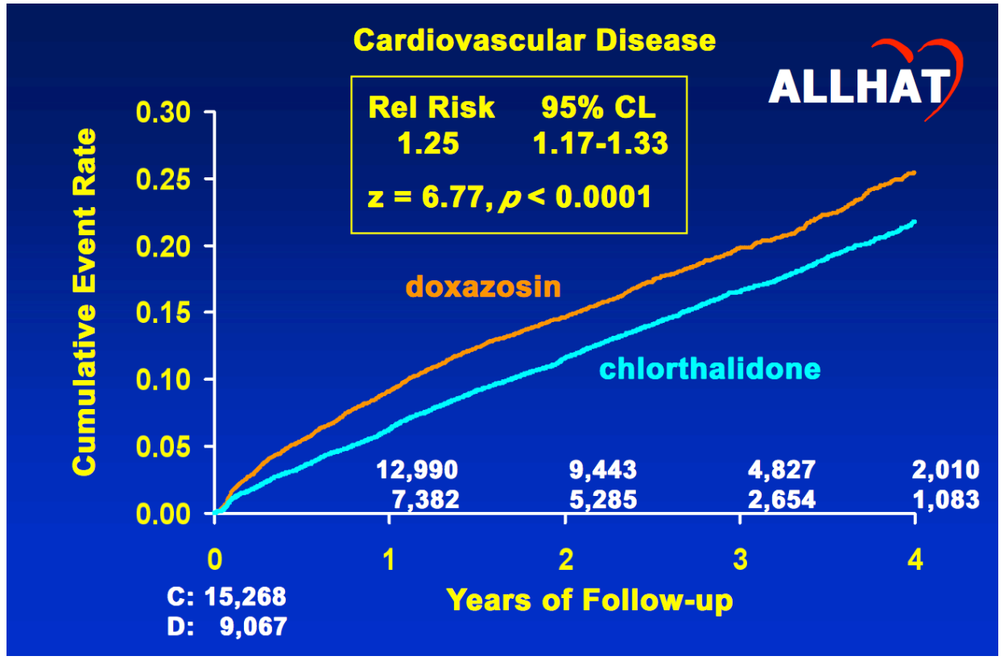
Hypertension

- **Not first-line therapy.**
- An add-on option in selected patients with uncontrolled BP.
- **Terazosin or doxazosin** may address concomitant BPH symptoms.

ALLHAT: doxazosin vs chlorthalidone

- No significant difference in fatal CHD / nonfatal MI.
- **Combined CVD risk ↑ 25%.**
- **Heart-failure risk approximately doubled.**
- **Stroke risk ↑ 19% (RR 1.19).**

The doxazosin arm was stopped early.



Combined cardiovascular disease

ALLHAT Collaborative Research Group · JAMA 2000

Heart failure: 8.13% vs 4.45%

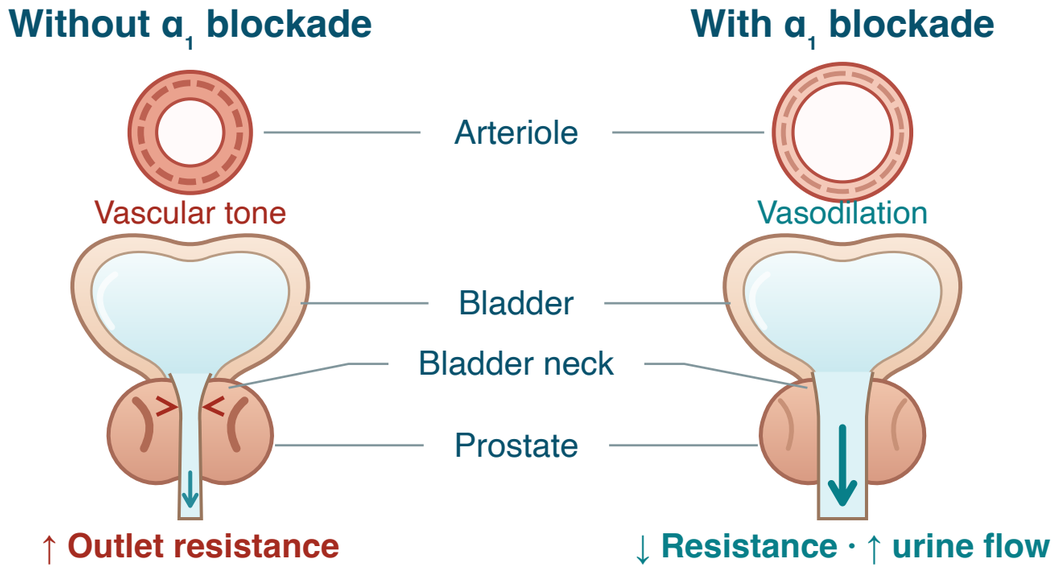
4-year rates · doxazosin vs chlorthalidone

α_1 Blockers: BPH Use and Blood Pressure

One mechanism in two tissues: urinary-outlet relaxation and vasodilation

Relax the urinary outlet

Prostate / bladder-neck smooth muscle relaxes → easier urine flow.



Symptom relief **without shrinking the prostate.**

Agents that also lower BP

Terazosin · Doxazosin
Established use for both hypertension and BPH symptoms.

Prazosin
Lowers BP; urinary use is off-label and is not a standard BPH choice.

Uroselective agents: BPH treatment

Tamsulosin · Silodosin
Prefer α_1A receptors in the urinary outlet.

Alfuzosin
Functional urinary selectivity.

Relatively small BP effects; **not hypertension therapy.**

α_1 Blockers: Shared Adverse Effects

Prazosin, terazosin, doxazosin, and uroselective agents — risk varies by drug

Orthostatic hypotension / syncope

α_1 blockade weakens reflex vascular constriction on standing.

Especially important with **prazosin, terazosin, and doxazosin**; uroselectivity does not eliminate risk.

Start low and titrate when required; bedtime first dosing for prazosin / terazosin. Rise slowly.

Additive hypotension

PDE5 inhibitors (e.g., sildenafil) and other BP-lowering drugs can increase symptomatic hypotension.

Other shared effects

Dizziness, headache, fatigue, and nasal congestion; fluid retention can occur.

Intraoperative floppy iris syndrome

A class concern, especially with tamsulosin.

Tell the eye surgeon about current or prior α_1-blocker use before cataract surgery.

Ejaculatory dysfunction

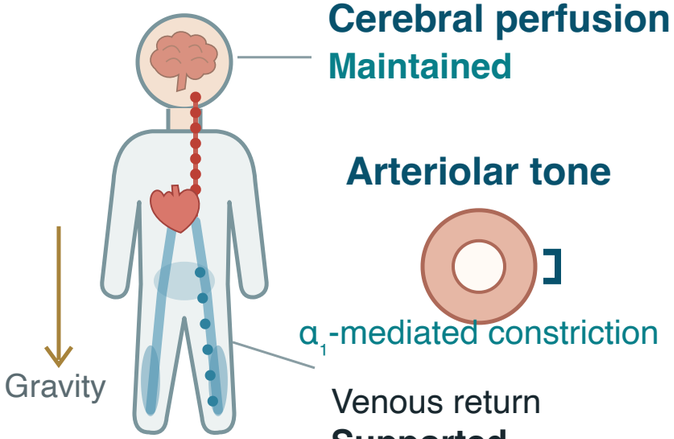
Especially associated with **tamsulosin / silodosin**; adverse-effect risk varies among agents.

Orthostatic Hypotension: α_1 Blockade and Gravity

Impaired vascular compensation on standing can reduce cerebral perfusion

Normal baroreflex

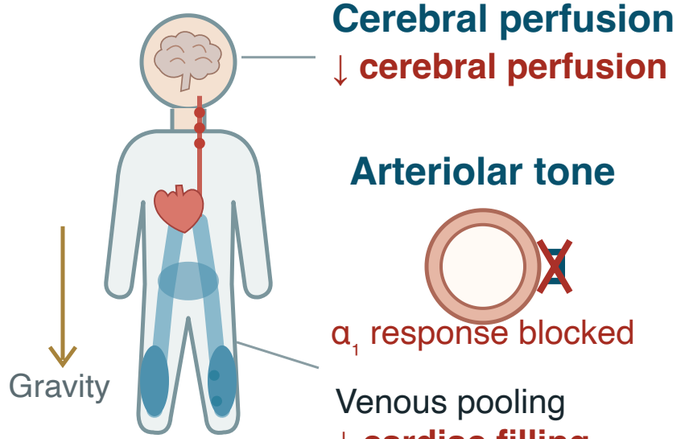
Standing → compensation



BP and cerebral perfusion maintained

With α_1 blockade

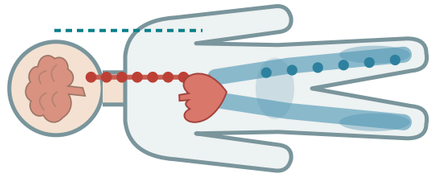
Standing → impaired compensation



Dizziness → possible syncope

Lying flat

"Taking gravity out of the equation"



Supine: smaller hydrostatic gradient

Cerebral perfusion improves

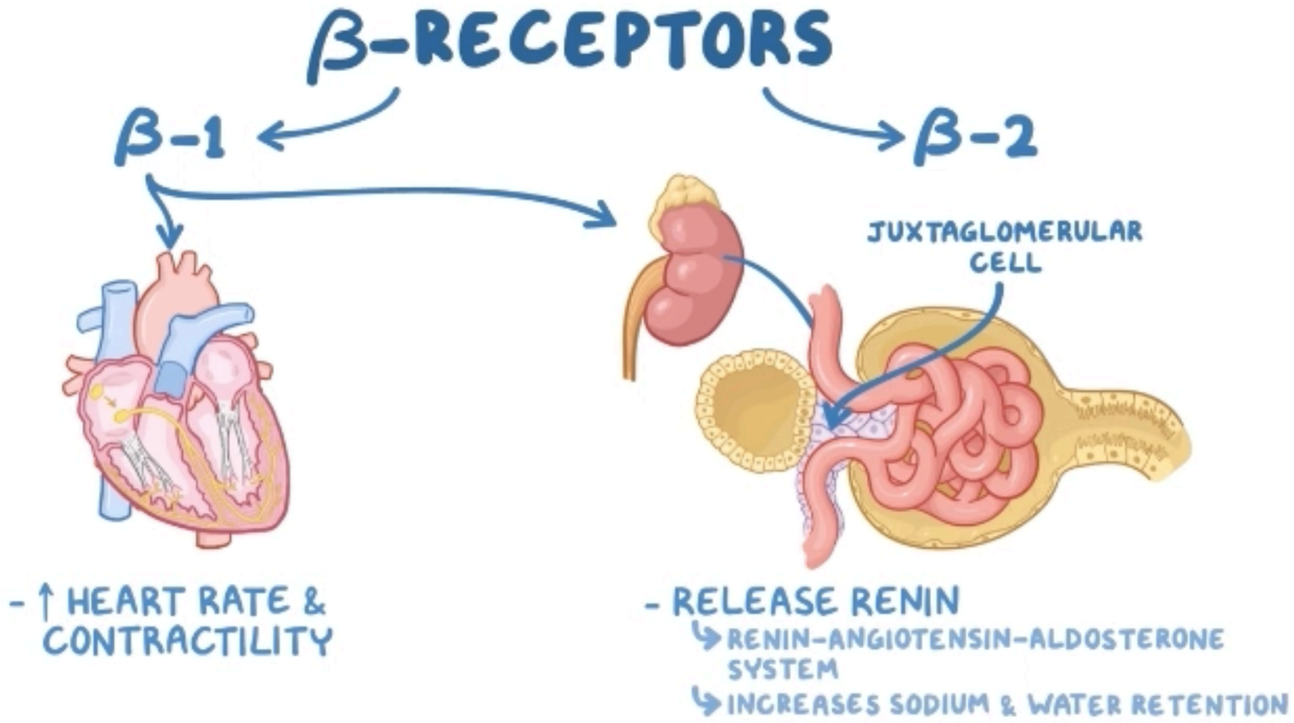
Sit or lie down at warning symptoms

Syncope results from transient cerebral hypoperfusion; becoming horizontal helps circulation recover.

α_1 blockade impairs the vascular compensation needed on standing.

Beta-Adrenergic Blockers

β_1 receptors connect cardiac stimulation to renin release



Blocking cardiac β_1 receptors

- ↓ heart rate and AV-nodal conduction
- ↓ catecholamine-stimulated contractility

Blocking renal β_1 receptors

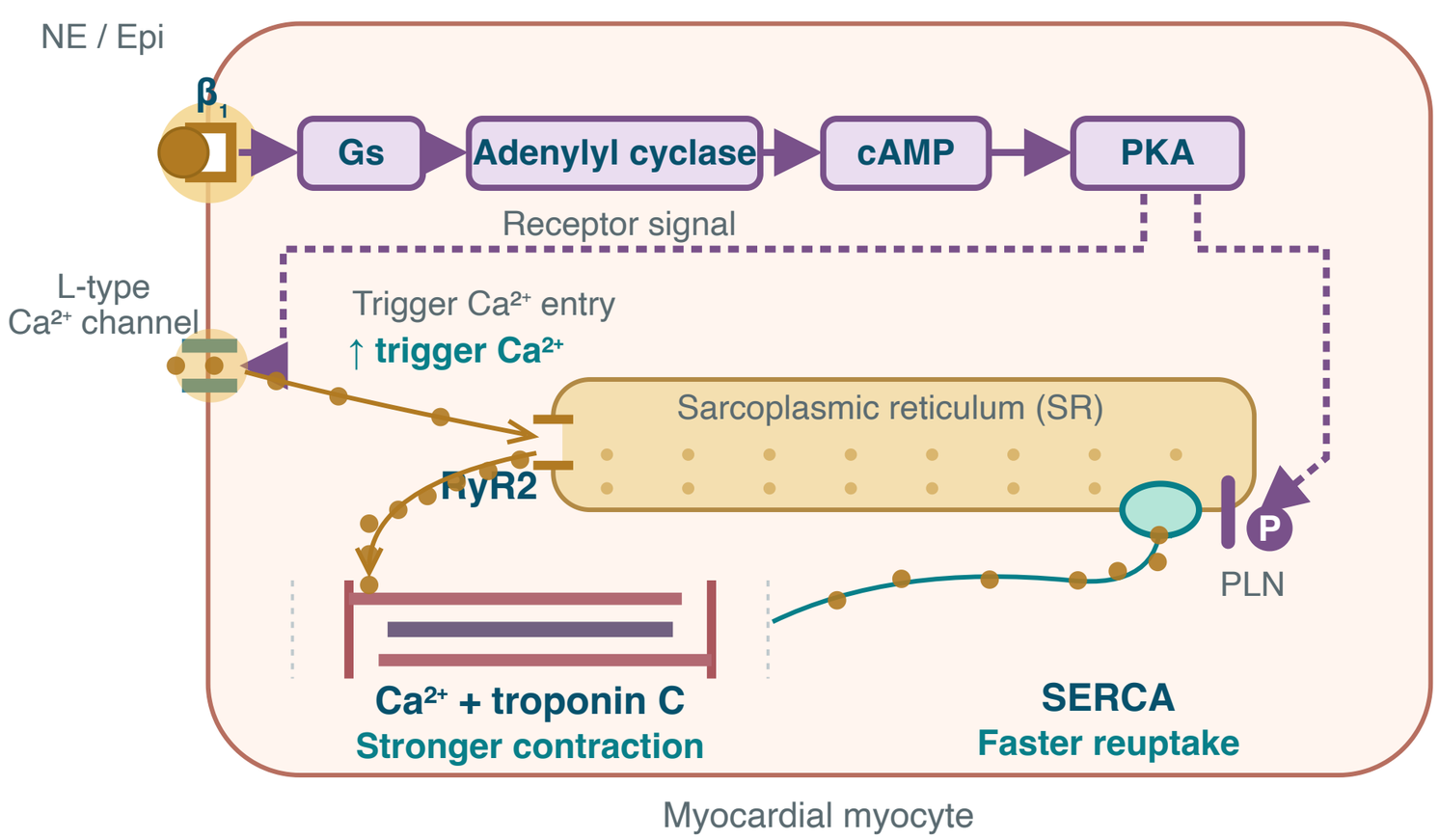
- ↓ renin release
- Less RAAS activation → less angiotensin II / aldosterone signaling

Competitive β antagonism reduces the response to catecholamines; effects depend on sympathetic tone.

β_1 Signaling: Contraction and Relaxation

β_1 activation drives cAMP / PKA enhancement of Ca^{2+} handling

1 · Basal beat | **2 · Add NE / Epi** | 3 · Add β_1 blocker



β_1 stimulation

NE / Epi binds the receptor.
Gs → adenylyl cyclase → cAMP → PKA

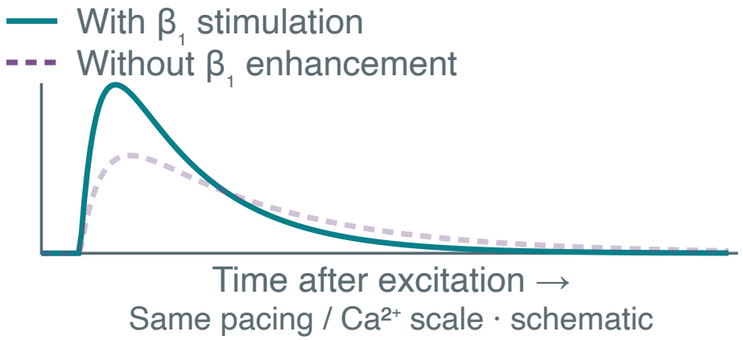
Stronger contraction

More trigger Ca^{2+} → more SR release.

Faster relaxation

PKA phosphorylates phospholamban.
Less SERCA inhibition → faster uptake.

Ca^{2+} during one beat

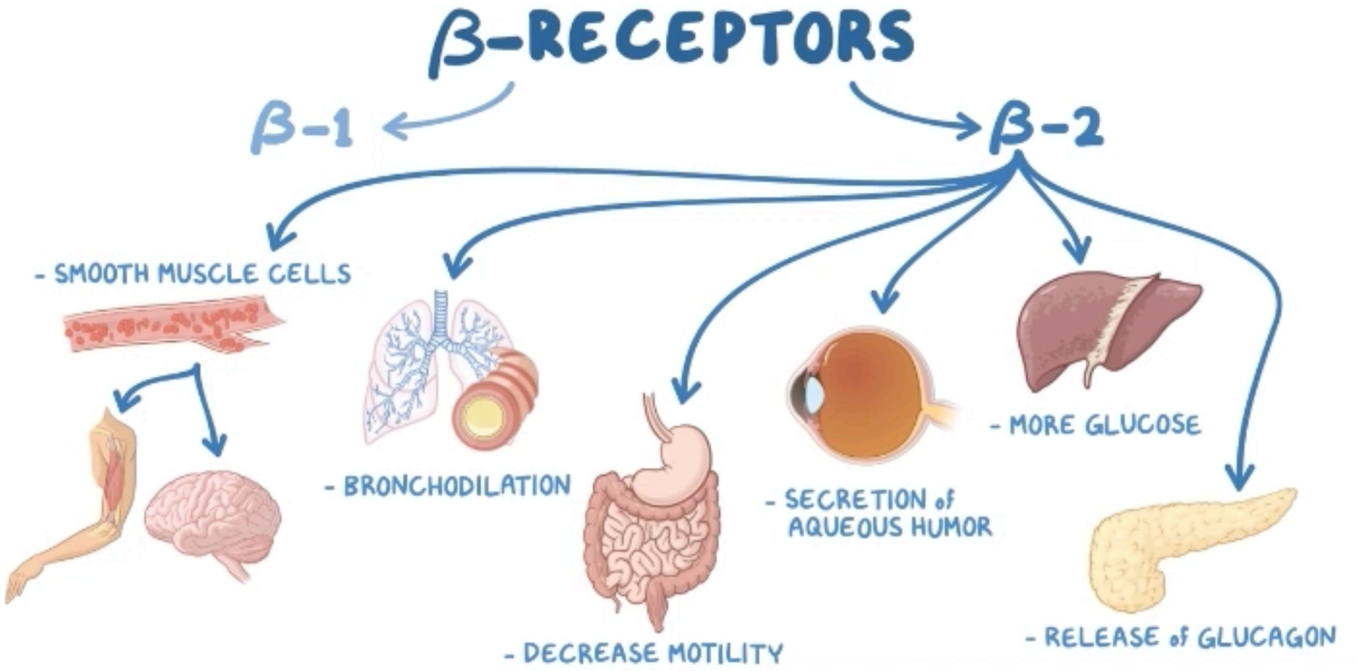


Same pacing / Ca^{2+} scale · schematic

β_1 activation increases Ca^{2+} delivery and speeds Ca^{2+} recovery through cAMP / PKA.

β_2 Receptors: Why Selectivity Matters

Nonselective blockade reaches beyond the heart



Consequences of β_2 blockade

- Bronchoconstriction; reduced response to inhaled β_2 agonists
- Loss of β_2-mediated vasodilation → cold extremities
- Hypoglycemia: reduced glycogenolysis → slower glucose recovery
- Metabolic risk: β_2 blockade can impair insulin release and contribute to insulin resistance

Ocular β blockade

- ↓ aqueous-humor production → ↓ intraocular pressure
- Topical timolol can still produce systemic effects

Cardiac β_1 blockade also masks tachycardia during hypoglycemia; sweating can remain.

Beta Blockers: Nonselective Agents

Receptor profile, exposure, and clinical distinctions

Drug	Receptors / ISA	Exposure	Clinical distinction
Propranolol	$\beta_1 + \beta_2$ No ISA	Lipophilic; hepatic metabolism IR and ER oral formulations	Migraine prevention, essential tremor; hyperthyroid symptoms
Nadolol	$\beta_1 + \beta_2$ No ISA	Hydrophilic; renal elimination Long duration	Adjust dosing for renal impairment
Timolol	$\beta_1 + \beta_2$ No ISA	Ophthalmic for glaucoma Systemic absorption occurs	Glaucoma; bronchospasm and bradycardia remain possible
Pindolol	$\beta_1 + \beta_2$ **ISA present**	Partial agonist	Rarely used clinically; less resting bradycardia

ISA = intrinsic sympathomimetic activity (partial agonism).

Beta-Blocker Selectivity: What Changes?

Shared β_1 effects · Different airway, vascular, and metabolic effects

Shared cardiac β_1 blockade

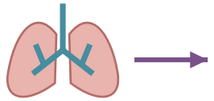
↓ heart rate / AV conduction
↓ catecholamine-stimulated contractility

Shared renal β_1 blockade

↓ renin release

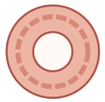
Nonselective · β_1 + β_2 blockade

Propranolol · Nadolol



Airways: β_2 blockade

Bronchospasm risk; ↓ bronchodilator response



Vessels: loss of β_2 dilation

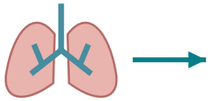
α_1 constriction less opposed → cold extremities

Metabolism: β_2 blockade

↓ glucose recovery / insulin release
Can impair glucose control

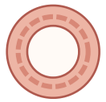
β_1-preferring · Less β_2 blockade

Metoprolol · Bisoprolol · Atenolol



Less interference with β_2 bronchodilation

Lower risk does not mean no risk.



Less loss of β_2-mediated dilation

Less α_1-predominant vasoconstriction.

Less potential for β_2 metabolic effects

Less interference with glucose recovery
and β_2-mediated insulin release

β_1 preference reduces potential β_2 effects; selectivity diminishes as exposure rises.

Beta Blockers: β_1-Preferring Agents

Cardioselectivity is relative and dose dependent

Drug	Key exposure feature	Clinical distinction
Metoprolol	Hepatic CYP2D6 Tartrate IR / succinate ER	**Succinate ER** is the formulation with HFrEF outcome evidence
Atenolol	Hydrophilic; renal elimination	Not preferred for uncomplicated HTN Accumulation with renal impairment
Bisoprolol	Renal + hepatic clearance	Evidence-based HFrEF agent
Esmolol	IV; rapid ester hydrolysis t½ ≈ 9 min	Rapid titration / rapid offset for acute HR and BP control
Nebivolol	Hepatic CYP2D6	NO-mediated vasodilation
Acebutolol	Active metabolite; renal clearance matters	ISA (partial agonism) Rarely used clinically

β_1 preference reduces β_2 blockade at usual exposure; increasing exposure can erode selectivity.

How Nonvasodilating Beta Blockers Lower Blood Pressure

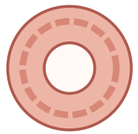
Hypertension treatment: acute ↓ CO → chronic SVR normalization with sustained ↓ CO / HR

ACUTE · initial response

↓ contractility + ↓ HR

Negative inotropy / chronotropy

↓ CO ≈ 20%



Baroreflex → α_1 vasoconstriction → ↑ SVR

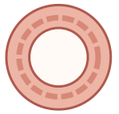
No direct vasodilator mechanism

CHRONIC · continued treatment

↓ renin → ↓ RAS activity

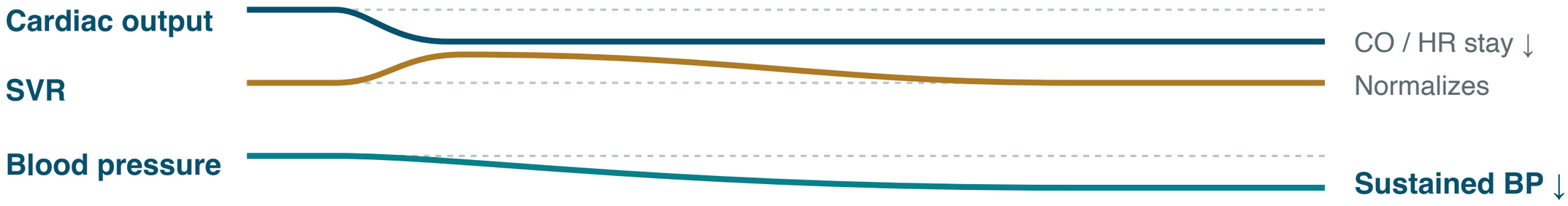
Less angiotensin II–mediated tone

Possible ↓ NE release*



SVR returns toward baseline

BP ≈ CO × SVR · CO = stroke volume × HR



Schematic time course; ≈20% is illustrative. *NE-release inhibition is a possible contributor, not a uniform class effect.

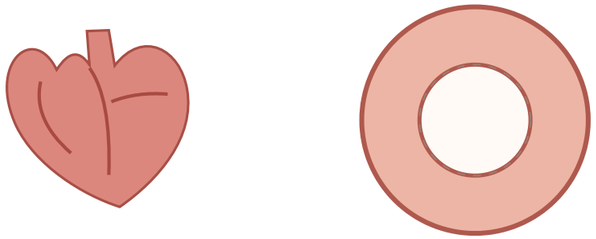
NOT first-line for uncomplicated hypertension.

Vasodilating Beta Blockers

β blockade plus vascular actions that lower resistance

Traditional β blocker

No added vasodilator mechanism



β blockade
↓ cardiac drive

Vascular tone
No direct relaxation

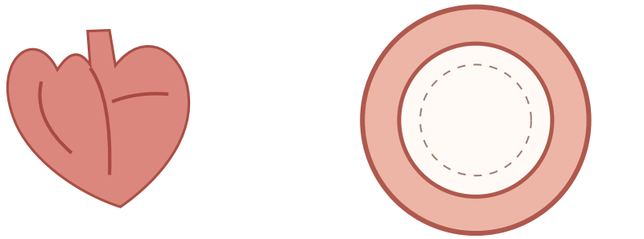
No direct α_1 / NO relaxation

Early SVR may rise reflexively

β blockade limits cardiac stimulation

Carvedilol · Labetalol

β_1 + β_2 blockade plus α_1 blockade



β blockade
↓ cardiac drive

Vasodilation
↓ SVR / afterload

α_1 block → ↓ Gq / IP_3 → relaxation

Labetalol β:α_1 ≈ 3:1 oral; 7:1 IV

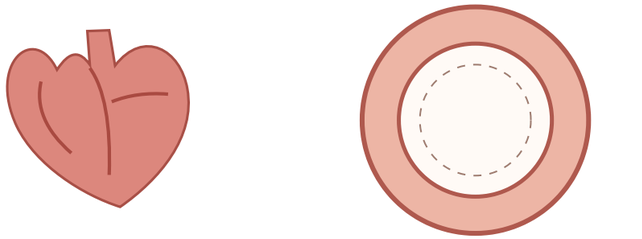
Carvedilol β:α_1 ≈ 2:1

Carvedilol: ↓ oxidative NO loss

+ NOS-dependent NO release*

Nebivolol

β_1 preference + endothelial NO



β blockade
↓ cardiac drive

Vasodilation
↓ SVR / afterload

↑ eNOS / NO → ↑ cGMP

Vascular smooth muscle relaxes

Depends on endothelial NO signaling

α_1 blockade reduces constrictor tone; carvedilol also preserves NO.

*NOS-dependent NO release: experimental evidence. The clinical impact of carvedilol's NO-related effects is not fully known.

Vasodilating Beta Blockers: Hemodynamic Profile

↓ SVR / afterload → preserved stroke volume and cardiac output

Traditional β blockers

Atenolol · Metoprolol

↓ HR + ↓ contractility

Less cardiac drive

No added vasodilation → early reflex ↑ SVR

No afterload relief to offset ↓ drive

↓ Cardiac output

Vasodilating β blockers

Carvedilol · Labetalol · Nebivolol

↓ HR + ↓ contractility

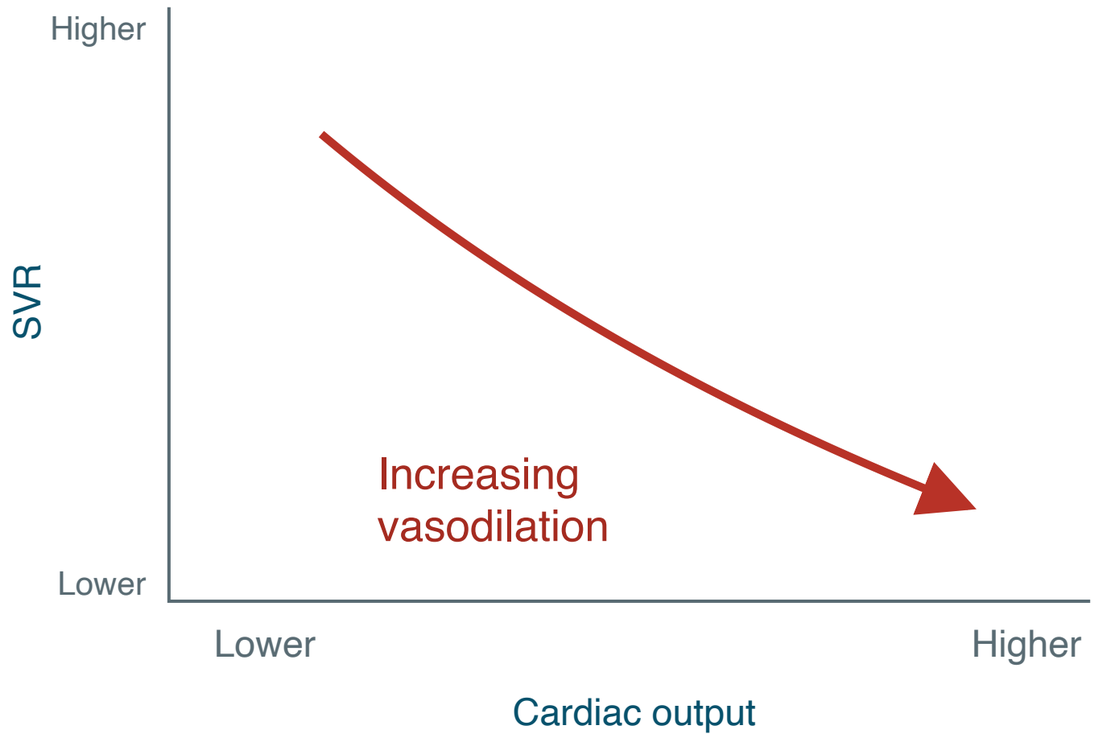
β blockade is still present

↓ SVR / afterload → easier ejection

Stroke volume preserved / ↑

Cardiac output better preserved

Same BP reduction, different hemodynamics



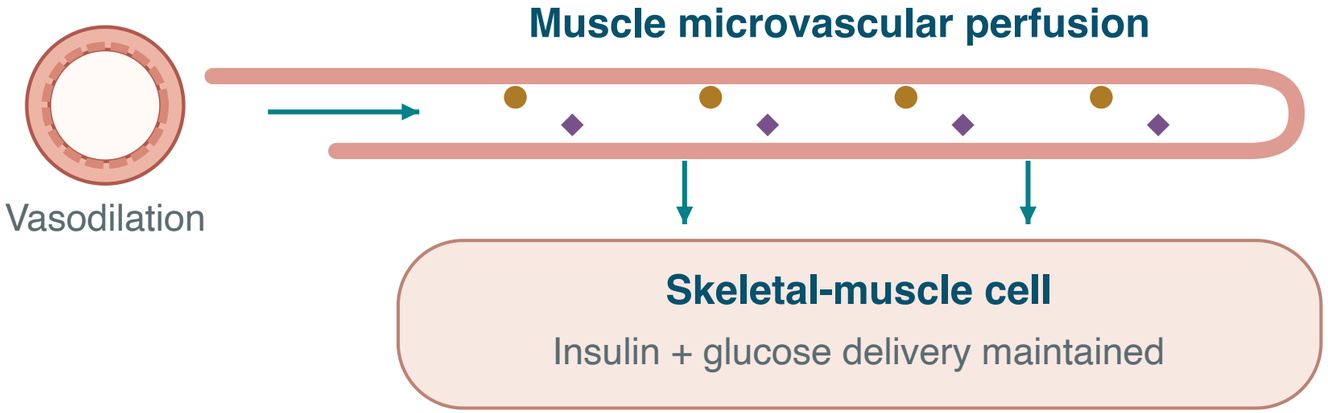
BP ≈ CO × SVR · CO = HR × SV

Vasodilating Beta Blockers: Metabolic Profile

Carvedilol: preserved muscle perfusion + antioxidant actions

Carvedilol · α_1 blockade

Less peripheral vasoconstriction



Preserved insulin-mediated glucose uptake

Additional intracellular antioxidant actions

↓ oxidative stress → support endothelial / cellular function*

Nebivolol

NO-mediated vasodilation
+ antioxidant effects

Supports muscle perfusion

Preserves insulin sensitivity

No α_1 blockade

GEMINI · 2004 ↗

Carvedilol vs metoprolol tartrate

HbA1c remained stable
Less adverse glycemic impact

When β blockade is indicated

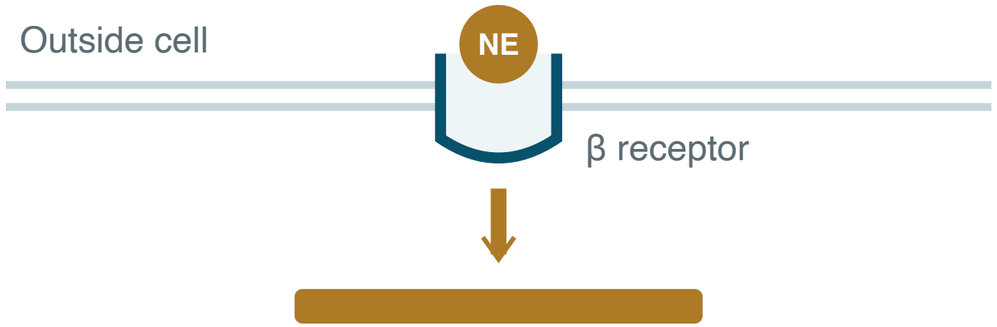
More metabolically neutral than traditional comparators. *Antioxidant contributions are proposed; their clinical share is not established.

Intrinsic Sympathomimetic Activity

Pindolol / acebutolol · Rarely used partial agonists

NE alone

Full agonist → strong stimulation

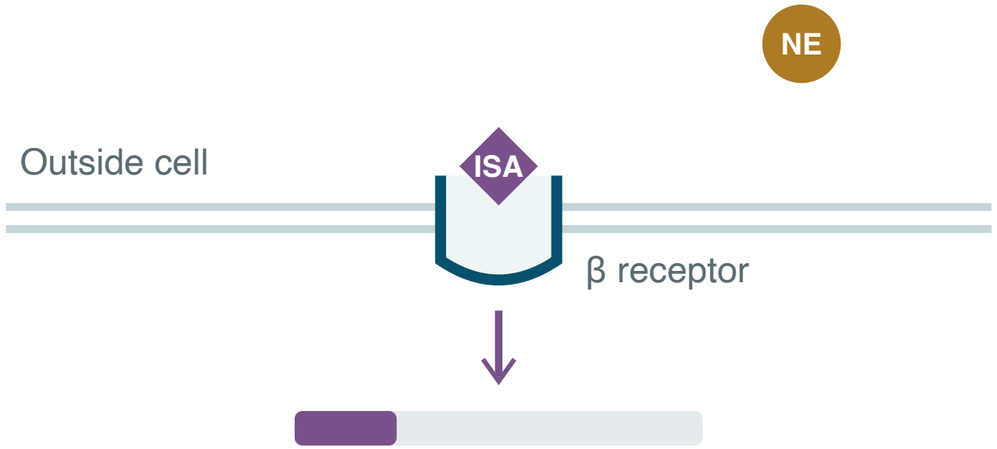


Strong receptor response

NE binds → receptor activation

NE + partial agonist

Compete for the same β receptor



Weak stimulation remains

NE cannot bind while ISA occupies the site.

Partial agonist: blocks NE's stronger response, but does not fully silence the receptor.

Potential benefits: less resting bradycardia and cardiac output reduction; may produce mild arterial vasodilation.

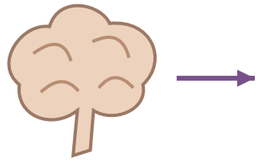
Why rare use? We usually want sympathetic suppression; ISA retains weak β-receptor stimulation.

Beta Blockers: Lipophilicity and CNS Penetration

Brain entry helps explain differences in adverse effects and therapeutic use

HIGH LIPOPHILICITY → GREATER BRAIN ENTRY | **HYDROPHILIC → LESS BRAIN ENTRY**

Propranolol	Metoprolol · Bisoprolol	Atenolol · Nadolol
Highly lipophilic · Readily crosses BBB	Intermediate lipid solubility	Low lipid solubility



CNS penetration

Lipid solubility facilitates blood–brain barrier entry. Propranolol readily enters.

Potential CNS effects

Sleep disturbance / vivid dreams
Rare hallucinations

Propranolol uses

Migraine prevention
Essential tremor

Hepatic metabolism

Metoprolol: CYP2D6 inhibition
↑ exposure → excessive β blockade

Renal elimination

Atenolol / nadolol accumulate as kidney function declines.

Mixed clearance

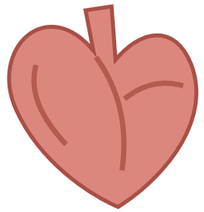
Bisoprolol: both renal and hepatic elimination

Beta Blockers: Contraindications and Cautions

Predict harm from the blocked physiological response

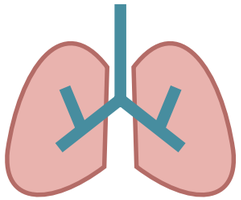
Severe bradycardia or advanced AV block

Further slowing can compromise cardiac output.



Cardiogenic shock or severe hypotension

The circulation may depend on adrenergic support.



Bronchospastic disease especially asthma

β_2 blockade can provoke bronchospasm and oppose rescue bronchodilation—even without current wheezing.

Additional cautions

Diabetes: hypoglycemia recognition / recovery

Verapamil / diltiazem: additive cardiac suppression

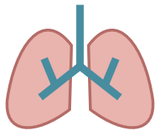
Stable heart failure is different from shock.

Beta Blockers: Major Adverse Effects

Cardiac, respiratory, metabolic, and withdrawal effects

Cardiac suppression

Bradycardia · AV block
Hypotension · early HF worsening



Airways and vessels

Bronchospasm · cold extremities
Greater concern with β_2 blockade

CNS effects

Lipophilicity → BBB penetration
Sleep disturbance · vivid dreams
Rare hallucinations

Metabolic effects

Impaired glucose control
- Less with carvedilol / nebivolol
- Can occur with cardioselective agents

All β blockers mask signs of hypoglycemia

Reduced quality of life

Fatigue / lethargy
Sexual dysfunction · Weight gain

Abrupt withdrawal

Tachycardia · hypertension · ischemia
Taper chronic therapy as appropriate

Severe toxicity: glucagon can bypass β receptors to support HR and contractility (adjunct).

Therapeutic Uses of Beta-Blockers

"The Sicker the Heart, the More Use for Beta-Blockade"

Cardiovascular

- Acute coronary syndromes
- Chronic stable angina
- Heart failure (HFrEF)*
- Tachyarrhythmias

Hypertension

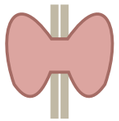
- Not first-line for uncomplicated HTN
- Second-line / add-on
- Hypertensive emergency (IV)

→ Esmolol and labetalol

Neurological

- Migraine prophylaxis
- Physical symptoms of anxiety

→ Lipophilic β blockers



Endocrine

- Hyperthyroidism symptom control

→ Propranolol

Ophthalmology

- Glaucoma (topical)

Essential tremor

- Propranolol

*HFrEF: metoprolol succinate, carvedilol, bisoprolol.

Beta Blockers for Ischemic Heart Disease

Maintaining the myocardial oxygen supply–demand balance

1 · Rest | 2 · Normal exertion | 3 · Exertion + blockage | **4 · Blockage + β blockade**

O_2 DEMAND

Work the heart must perform

Heart rate
Major determinant

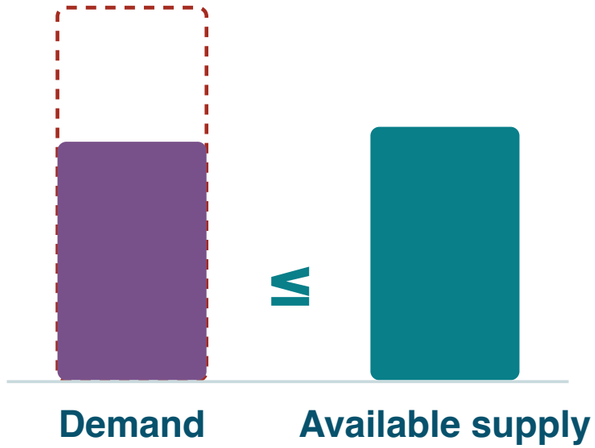
Contractility

Wall tension
Afterload · Preload

↓ HR + ↓ contractility
Blunted exertional HR rise
→ ↓ O_2 demand

β blockade: ↓ demand

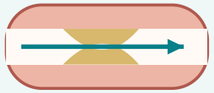
Demand fits the limited supply



Less myocardial ischemia

--- Demand before β blockade

O_2 SUPPLY



Coronary blockage

Coronary blood flow
Perfusion pressure
Diastolic time
Vessel patency

Arterial O_2 content

↓ HR → longer diastole
More time for LV perfusion

Coronary perfusion pressure ≈ diastolic BP – LVEDP

β blockers keep demand lower; they do not remove the coronary blockage.

Vasospastic angina: β blockers may worsen coronary spasm.

Chronic HFrEF: A Progressive Neurohormonal Disease

Persistent SNS activation drives injury, remodeling, and further loss of function

1 · Short-term compensation | 2 · Chronic injury | **3 · β blockade**

Ventricular dysfunction
↓ CO / reduced perfusion

→ **SNS + RAAS activation**
Neurohormonal drive remains present

→ **Less adrenergic injury**
Slower disease progression

Less chronic injury weakens the cycle of progression

Interrupt the progression

β blockade limits harmful β signaling

↓ Myocardial O_2 demand
↓ HR + ↓ adrenergic drive
Less cardiac workload

Recovery of β signaling
Less chronic overstimulation
Responsiveness can improve

Improved Ca^{2+} handling
Less adrenergic Ca^{2+} stress
Reduced arrhythmogenic drive

Less catecholamine toxicity
Less myocyte injury
Protection of viable myocardium

Less adverse remodeling
Slows progression
Reverse remodeling can develop

Renal β_1 blockade
↓ Renin release
Reduces RAAS activation

β blockade reduces chronic injury; ventricular function can improve over weeks to months.

HFrEF: Use β Blockers With Proven Outcomes

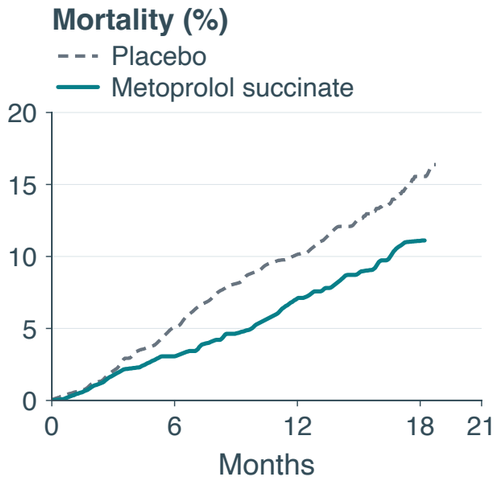
About one-third lower all-cause mortality in placebo-controlled HFrEF trials

Metoprolol succinate ER

MERIT-HF

↓ 34%

Relative mortality reduction



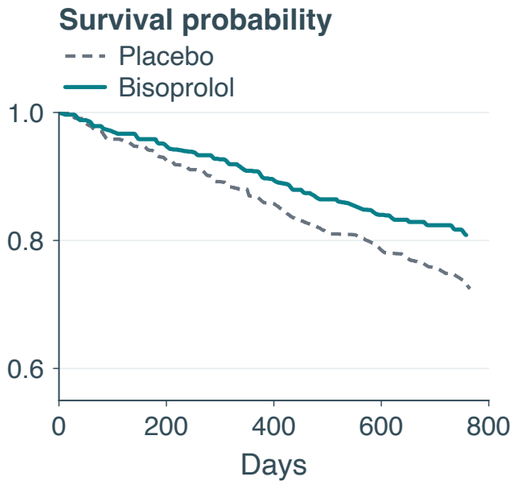
β_1 preference

Bisoprolol

CIBIS-II

↓ 34%

Relative mortality reduction



β_1 preference

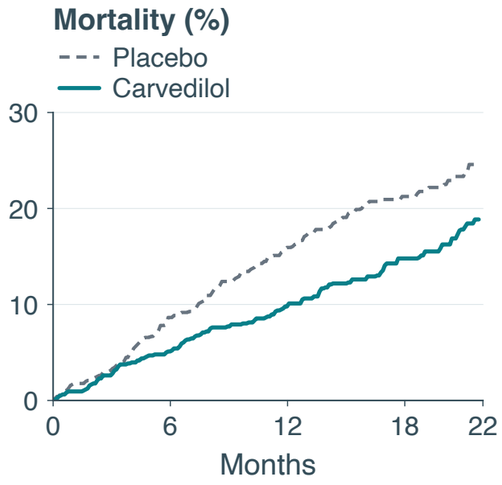
HFrEF: off-label

Carvedilol

COPERNICUS

↓ 35%

Relative mortality reduction

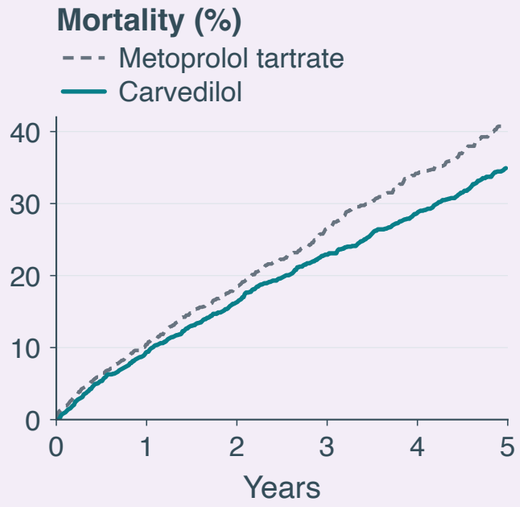


β_1 + β_2 and α_1 blockade

COMET

Active-comparator trial

Carvedilol vs metoprolol tartrate



17% lower mortality hazard

HR 0.83 · p = 0.0017

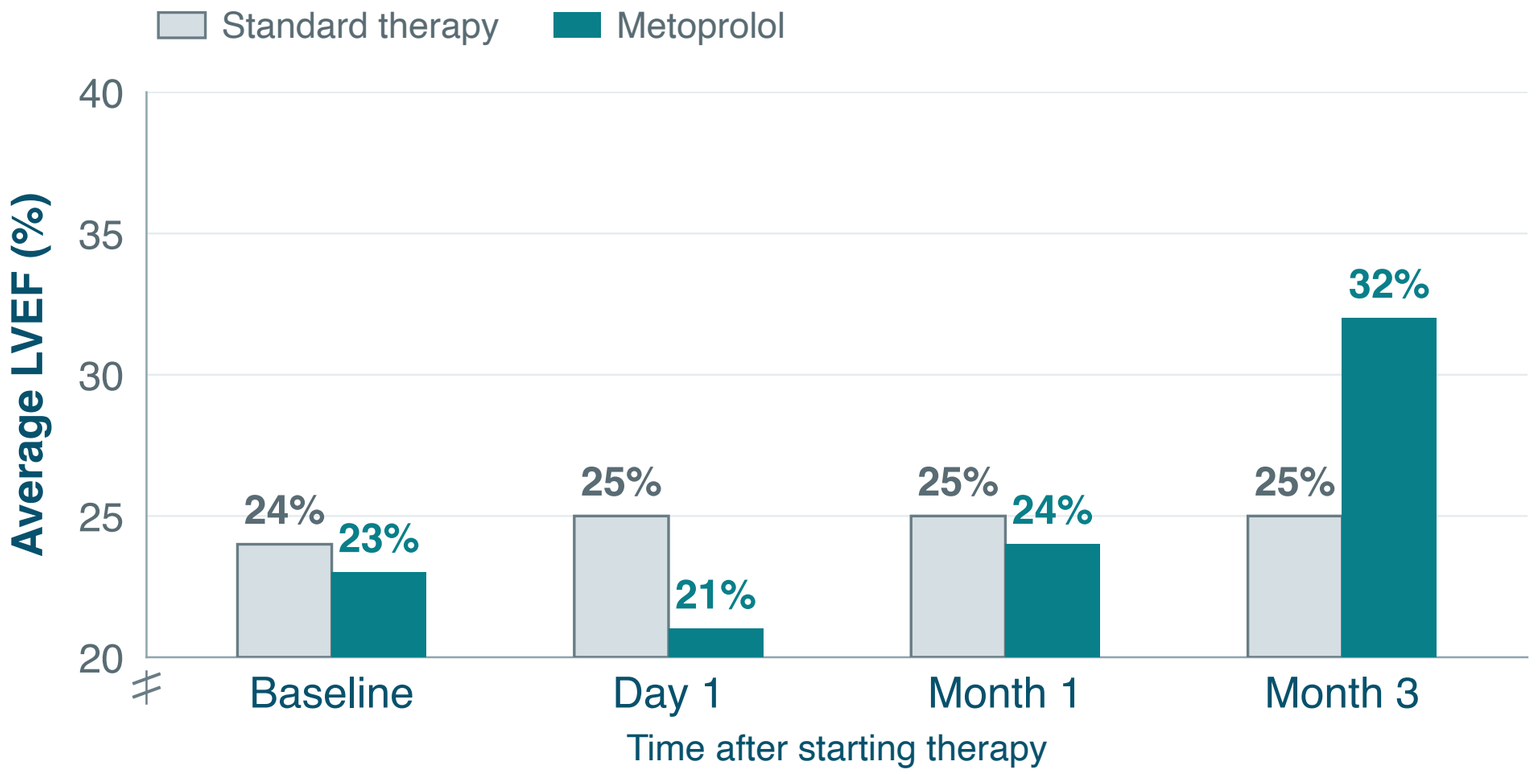
Evidence is formulation-specific.

Use the proven drug and formulation.

HFrEF: Early Effects and Long-Term Benefit

Possible early hemodynamic compromise → gradual improvement with continued therapy

Average LVEF over time



Hall et al. JACC 1995;25:1154–1161

Days to weeks

↓ Contractility + ↓ HR

Cardiac output can fall

Symptoms may worsen

1–3 months

LV function can improve

Less chronic SNS injury

Symptoms can stabilize

Continued therapy

HF symptoms improve

↓ HF hospitalization

↓ Mortality

Start low and go slow — continue and titrate as tolerated.

Clinical Application: HFrEF and Bronchospastic Disease

Apply receptor pharmacology to drug selection

A patient with ischemic HFrEF (LVEF 30%) is clinically stable and euvolemic.

The patient has moderate bronchospastic lung disease controlled with inhaled bronchodilators and has **no current wheezing** or signs of bronchospasm.

Which β blocker is most appropriate for this patient, and why?

A. Carvedilol

B. Metoprolol tartrate

C. Metoprolol succinate

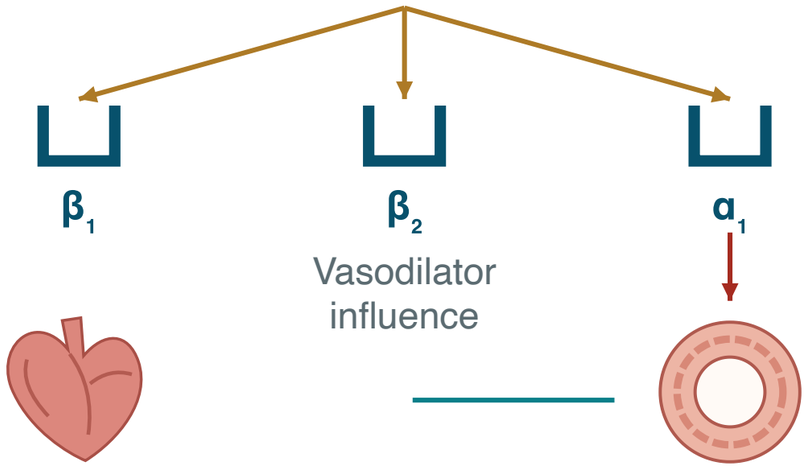
D. Propranolol

Beta Blockade During Acute Catecholamine Excess

The vascular α effect can remain while β effects are blocked

Catecholamine excess

Adrenergic stimulation reaches α and β receptors

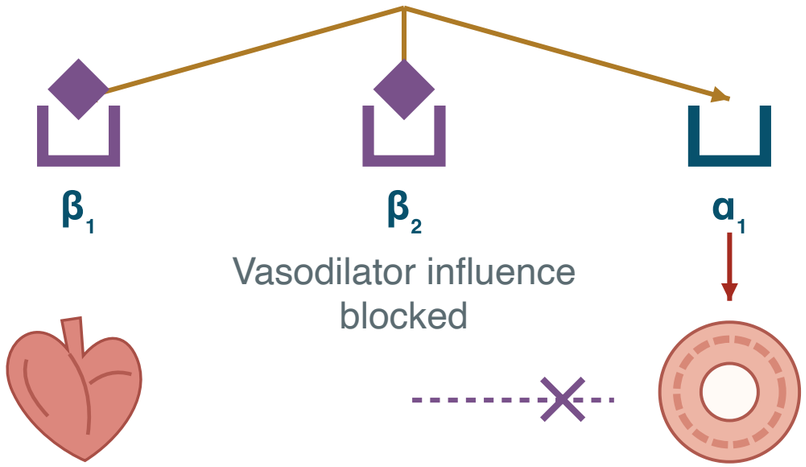


↑ cardiac stimulation

α-mediated constriction

Pure nonselective β blockade

“Unopposed α stimulation”



↓ β-mediated stimulation

α-mediated constriction

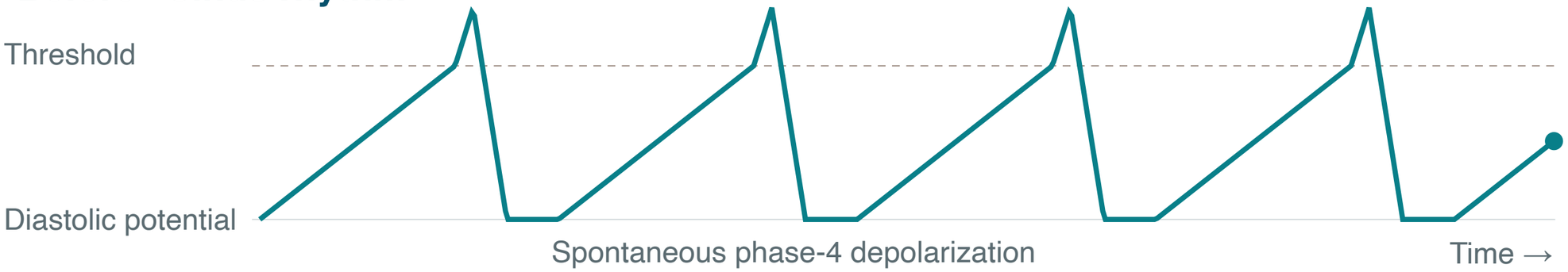
Causes of catecholamine excess

Acute cocaine / methamphetamine intoxication · Abrupt clonidine withdrawal

Ivabradine: Slowing Sinus-Node Automaticity

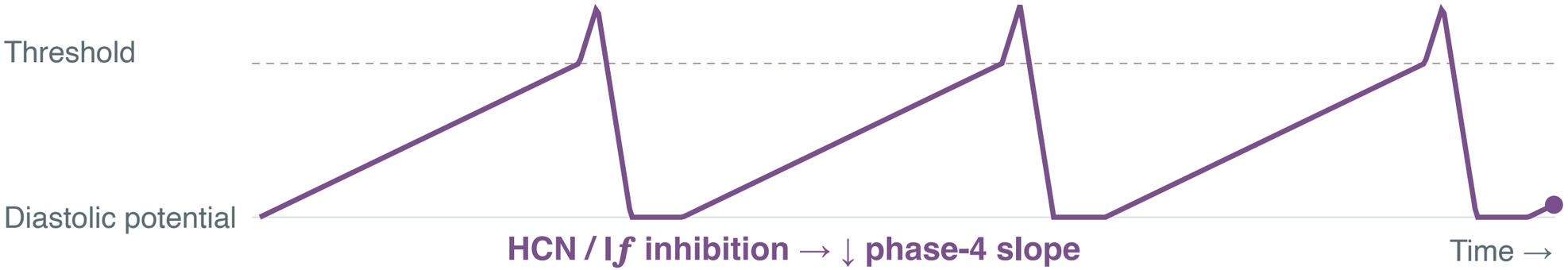
Beyond β blockade: HCN-channel inhibition further slows sinus rate

Before · Sinus rhythm



Baseline rate

After · Ivabradine



Lower sinus rate

Funny current carries mixed Na^+ / K^+ current. A slower sinus rate requires sinus rhythm; this is not AV-nodal blockade.

Ivabradine: Therapeutic Use and Safety

Additional sinus-rate slowing in selected patients with HFrEF

Therapeutic use

Adults with **stable, symptomatic chronic HFrEF**
LVEF ≤35% · Sinus rhythm · Resting HR ≥70/min

Add to maximally tolerated β-blocker therapy;
also an option when β blockers are contraindicated.

Benefit

Fewer hospitalizations for worsening HF.
I_f inhibition adds sinus-rate slowing without directly reducing contractility.

Safety

Bradycardia · Atrial fibrillation · Phosphenes (transient visual brightness).

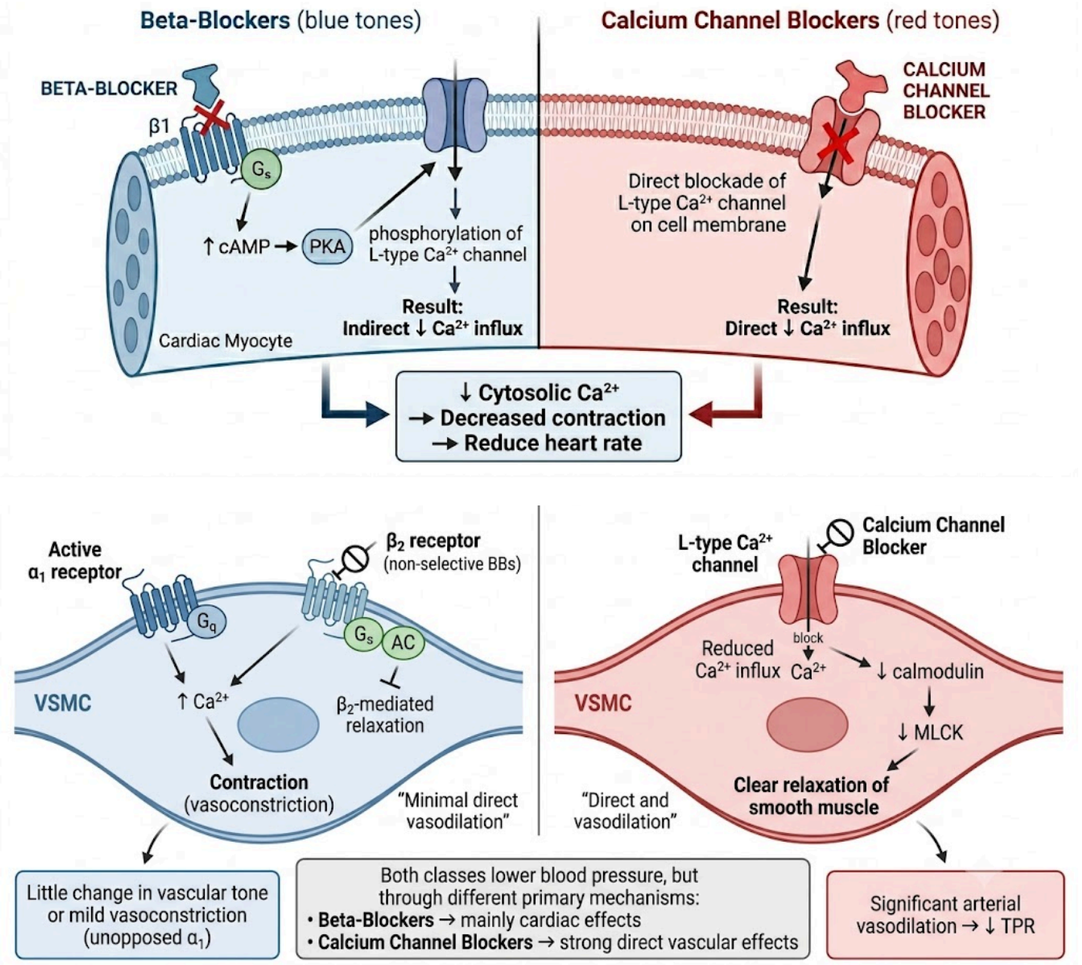
Avoid verapamil / diltiazem. Strong CYP3A inhibitors are contraindicated.
Do not use in acute decompensated HF.

Adult U.S. use: selected HFrEF patients · Not approved for angina

From Beta Blockers to Calcium Channel Blockers

Reducing intracellular calcium in the cardiovascular system

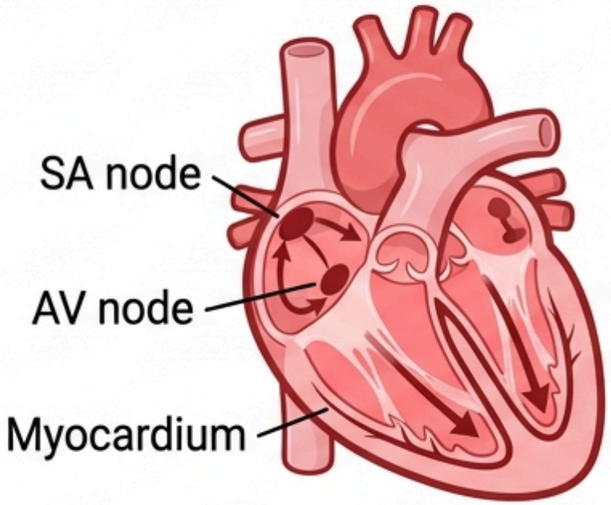
Aspect	β blockers	CCBs
Primary target	β_1 receptors Gs → cAMP → PKA	L-type Ca^{2+} channels
Effect on Ca^{2+}	Indirect: ↓ adrenergic enhancement of Ca^{2+} entry and release	Direct: ↓ Ca^{2+} entry
Main sites	Heart; vascular effects depend on the drug	Vasculature; heart effects depend on the drug
Clinical advantage	Limits injury from sustained sympathetic activation	Direct arteriolar vasodilation



Calcium Channel Blockers

Non-DHPs and DHPs: cardiac versus vascular effects

Non-dihydropyridines



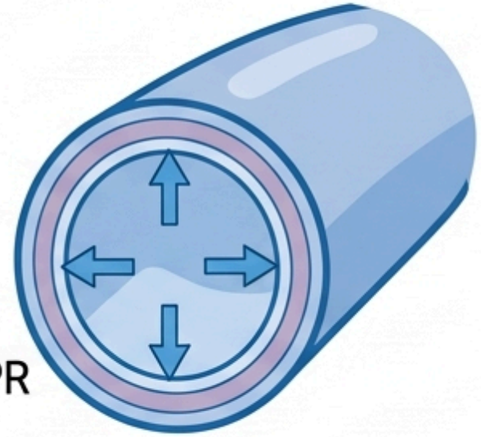
Verapamil
Diltiazem

↓ Heart rate
↓ Contractility
↓ AV conduction

Moderate vasodilation

Dihydropyridines

Amlodipine
Nifedipine
Felodipine
Nicardipine



Potent arterial vasodilation → ↓ TPR

Minimal direct cardiac effects (may cause reflex tachycardia)

Feature	Non-Dihydropyridines	Dihydropyridines
Primary Target	Heart >> Vessels	Vessels >> Heart
Main Clinical Effect	Rate control & negative inotropy	Potent vasodilation

Non-DHPs for AV-nodal rate control · DHPs for potent arteriolar vasodilation

Non-DHP CCBs: Normal LV Function

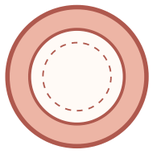
Direct cardiac depression + compensation = the observed response

1 · Direct drug effects | 2 · Add compensation | 3 · Net response

Direct drug effects

Verapamil · Diltiazem

↓ L-type Ca^{2+} entry



Arteriolar dilation
↓ BP
↓ SVR / afterload

↓ SA firing
↓ AV conduction
↓ Contractility

Compensation

Baroreflex

↓ BP → ↓ baroreceptor firing

↑ SNS drive to the heart

↑ HR / contractile drive

Opposes direct cardiac depression

Less resistance to LV ejection

Supports stroke volume

Changes loading, not inotropy

Net hemodynamics

Normal LV function

Heart rate

↔ Acutely → ↓ Chronically

↓ SVR / BP

Cardiac output often preserved

CO = HR × SV

↓ Afterload supports SV despite negative inotropy

Direct cardiac suppression remains

Verapamil: stronger negative inotropy · Diltiazem: less myocardial depression

Preserved cardiac output does not mean preserved contractility.

Non-DHP CCBs: Impaired LV Function

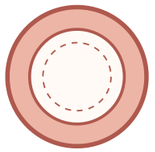
Reduced compensation can amplify cardiac suppression

1 · Direct drug effects | 2 · Add compensation | 3 · Net response

Direct drug effects

Verapamil · Diltiazem

↓ L-type Ca^{2+} entry



Arteriolar dilation

↓ BP

↓ SVR / afterload

↓ SA firing

↓ AV conduction

↓ Contractility

Low contractile reserve

Compensation

Baroreflex

↓ BP → ↓ baroreceptor firing

↑ SNS: heart + kidneys

SNS drive may remain high

Limited HR / contractile response

Less resistance to LV ejection

Supports stroke volume

May not preserve stroke volume

Net hemodynamics

Impaired LV function

Suppression can be greater

↓ HR + ↓ Contractility

↓ SVR; stroke volume can fall

Cardiac output can fall

CO = HR × SV

↑ LV filling pressure

HF may worsen

If CO falls: ↓ renal perfusion + ↑ renal SNS → ↑ RAAS → ↑ afterload + fluid retention → worse HF

Verapamil: stronger negative inotropy · Diltiazem: less myocardial depression

Avoid both drugs in LV systolic dysfunction, even before overt HF.

Non-DHP CCBs: Therapeutic Uses

Verapamil · Diltiazem

Angina

- Chronic stable angina
- Vasospastic angina

Arrhythmias

- Selected SVT conversion
- AF / flutter rate control

Hypertension

- Not first-line for uncomplicated HTN

Hypertrophic CM

- Symptom relief
- Selected patients

Pulmonary

- Vasoreactive PAH only
- Diltiazem · specialist care

Neurological

- Cluster-headache prevention
- Verapamil · off-label

Drug	IV Intravenous	IR Immediate release · oral	SR Sustained release · oral
Verapamil	✓	✓	✓
Diltiazem	✓	✓	✓

Non-DHP CCBs for Ischemic Heart Disease

Maintaining the myocardial oxygen supply–demand balance

1 · Rest | 2 · Normal exertion | 3 · Exertion + stenosis | **4 · Stenosis + CCB** | 5 · Vasospasm | 6 · Spasm + CCB

O_2 DEMAND

Work the heart must perform

Heart rate
Major determinant

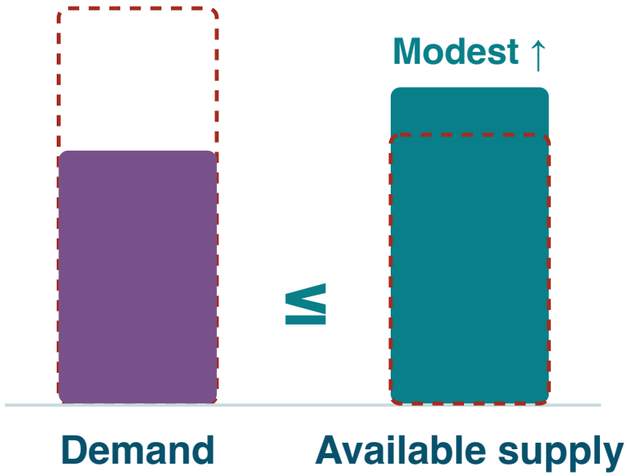
Contractility

Wall tension
Afterload · Preload

↓ HR + ↓ contractility
↓ Afterload → ↓ O_2 demand

Non-DHP CCB effects

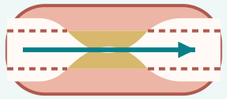
↓ Demand + modest ↑ supply



Less myocardial ischemia

--- Before non-DHP CCB

O_2 SUPPLY



Coronary dilation
Stenosis remains

Coronary blood flow
Perfusion pressure
Diastolic time
Vessel patency

Arterial O_2 content

Coronary dilation → ↑ supply
↓ HR → longer diastole

Coronary perfusion pressure ≈ diastolic BP – LVEDP

Demand reduction predominates; coronary dilation adds a smaller supply benefit.

Non-DHP CCBs: Major Drug Interactions

The double threat: AV-nodal suppression + altered drug exposure

🔴 Avoid / high concern

🟡 Adjust / monitor

Drug / class	Interaction → clinical risk	Graded action
β blockers	Additive cardiac depression → Bradycardia, AV block, HF	🔴 **Avoid IV combination** Oral use: careful selection
Ivabradine	CYP3A4 inhibition + HR slowing → Excessive bradycardia	🔴 **Avoid combination**
Digoxin	P-gp inhibition + AV-nodal slowing → ↑ Levels, bradycardia / block	🟡 **Monitor level + HR** Reduce dose as needed
Simvastatin / lovastatin	CYP3A4 inhibition → ↑ statin levels → Myopathy / rhabdomyolysis	🟡 **Limit dose** Simvastatin ≤10; lovastatin ≤20 mg/day
Colchicine	CYP3A4 + P-gp inhibition → Colchicine toxicity	🟡 **Reduce dose or avoid** Renal / hepatic function matters
Strong CYP3A4 inhibitors	↑ CCB exposure → Bradycardia, hypotension	🟡 **Reduce CCB dose or avoid** Check the specific inhibitor
Dabigatran / Rivaroxaban	P-gp and/or CYP3A4 inhibition → ↑ Exposure / bleeding	🟡 **Check drug + renal function** Avoid some combinations

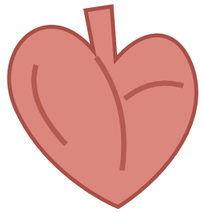
Verapamil + diltiazem: CYP3A4 and P-gp **substrates**
Moderate CYP3A4 inhibitors · Also inhibit P-gp

Non-DHP CCBs: Contraindications

When negative inotropy and nodal slowing become dangerous

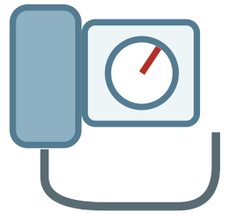
Symptomatic bradycardia or advanced AV block

Further sinus / AV-nodal slowing can compromise cardiac output.



LV systolic dysfunction with or without overt HF

Negative inotropy can ↓ output and make HF clinically apparent.



Severe hypotension or cardiogenic shock

Further ↓ BP and contractility can compromise organ perfusion.

Important distinctions

High-grade AV block / sick sinus syndrome: unless a functioning pacemaker is present.

β blockers: additive cardiac suppression

Bradycardia · AV block · Negative inotropy

Avoid in LV systolic dysfunction, even before overt HF.

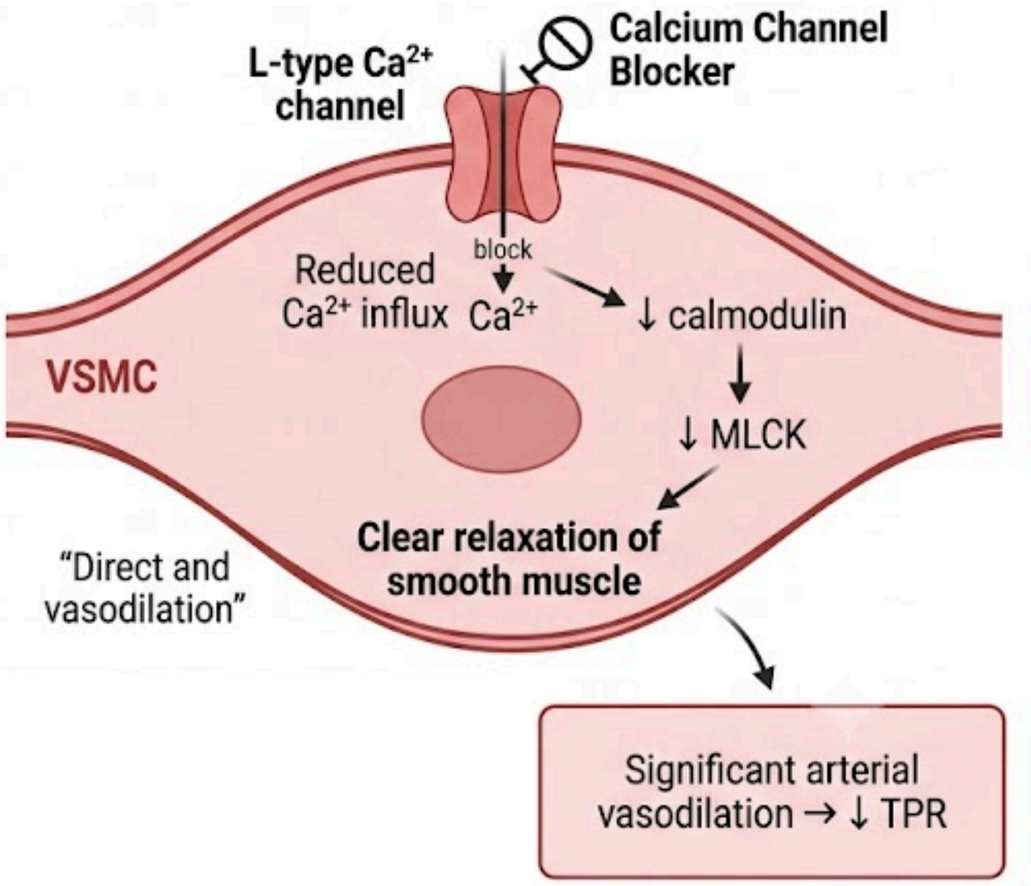
Verapamil versus Diltiazem: Adverse Effects

Constipation is a particularly useful distinction

Adverse effect	Verapamil	Diltiazem
Constipation	**More prominent**; can be severe	Less common
Bradycardia / AV block	Clinically important	Clinically important
HF / negative inotropy	Stronger cardiac depression	Less depression; HFrEF risk remains
Hypotension	Can occur	Can occur
Peripheral edema	Can occur	Can occur
Headache / flushing / dizziness	Can occur	Can occur
Hyperprolactinemia	**8.5% prevalence**	Not a typical adverse effect

Dihydropyridine CCBs

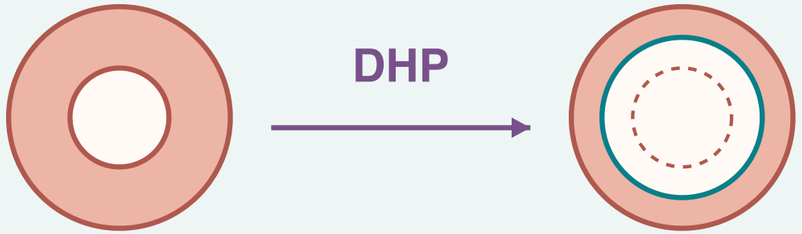
Extreme vascular selectivity



Vessels » Heart

Direct effects at usual doses

Strong arteriolar dilation



Peripheral: ↓ SVR and afterload

Coronary: ↓ resistance to flow

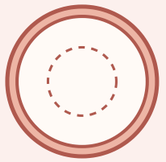
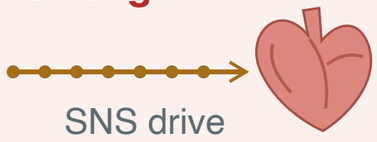
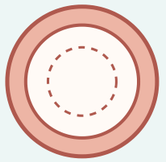
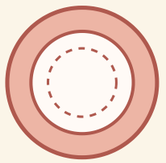
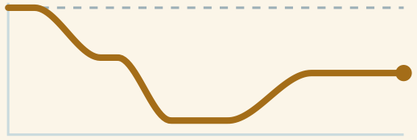
Minimal direct cardiac effects

SA / AV nodes: little slowing

Myocardium: little depression

DHPs: Vasodilation and the Baroreflex

Speed and magnitude of the BP fall determine the reflex response

Formulation	Vasodilation	BP over time	Baroreflex → heart	Clinical consequence
IR nifedipine Rapid oral onset		Abrupt / large fall 	**Strong reflex**  SNS drive	**↑ O_2 demand + ↓ perfusion** Can worsen ischemia Avoid for acute BP lowering
Long-acting oral Amlodipine Nifedipine ER		Gradual, sustained fall 	**Smaller reflex**  SNS drive	**Less reflex stimulation** Safer chronic BP control than IR nifedipine
Titrated IV Nicardipine Clevidipine		Excess fall → adjust 	**↑ HR → reassess**  SNS drive	**Monitor BP and HR** ↑ HR / excessive ↓ BP: Adjust or stop infusion

↓ BP → ↓ Baroreceptor firing → ↑ SNS → ↑ HR / contractility

Dihydropyridine CCBs: Therapeutic Uses

Clinical uses of predominantly vascular calcium-channel blockade

Hypertension

- Long-acting DHPs
- First-line options

Hypertensive emergency

- IV nicardipine / clevidipine
- Titrate; monitor BP + HR

Angina

- Chronic stable angina
- Coronary vasospasm

Pulmonary

- Selected vasoreactive PAH
- Specialist-directed therapy

Raynaud phenomenon

- Relief of digital vasospasm

Aneurysmal SAH

- Enteral nimodipine
- Improves neurological outcomes

Amlodipine vs chlorthalidone: similar fatal CHD / nonfatal MI; heart failure was more frequent with amlodipine.

DHP CCBs for Ischemic Heart Disease

Long-acting therapy: ↓ afterload + coronary vasodilation

1 · Rest | 2 · Normal exertion | 3 · Exertion + stenosis | **4 · Stenosis + DHP** | 5 · Vasospasm | 6 · Spasm + DHP

O_2 DEMAND

Work the heart must perform

Heart rate
Major determinant

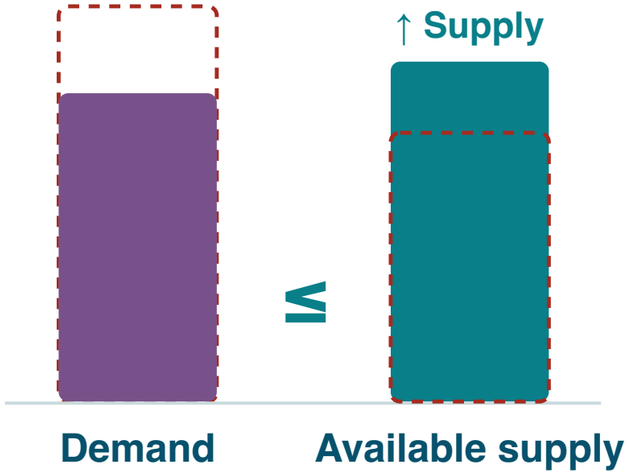
Contractility

Wall tension
Afterload · Preload

↓ Afterload → ↓ O_2 demand
Little direct cardiac slowing

Long-acting DHP effects

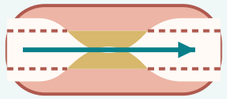
↓ Afterload + ↑ coronary flow



Less myocardial ischemia

--- Before long-acting DHP

O_2 SUPPLY



Coronary dilation
Stenosis remains

Coronary blood flow
Perfusion pressure
Diastolic time
Vessel patency

Arterial O_2 content

Coronary dilation → ↑ supply
↓ Coronary resistance

Coronary perfusion pressure ≈ diastolic BP – LVEDP

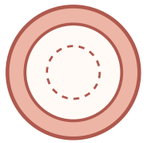
DHPs lower demand through afterload relief and increase supply through coronary dilation.

DHPs: When Vasodilation Becomes Dangerous

The clinical setting and formulation matter

Acute coronary syndromes

Avoid immediate-release nifedipine



Rapid vasodilation → ↓ BP

↑ Reflex SNS

↓ Coronary perfusion pressure

↑ HR / contractility

↑ O_2 demand **↓ O_2 supply**

Worsening ischemia

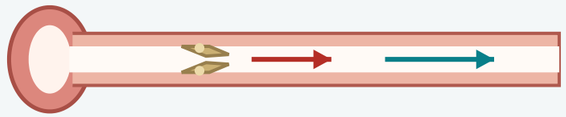
Tachycardia also shortens coronary filling time.

Severe aortic stenosis

Same valve · wider arterioles

Before DHP

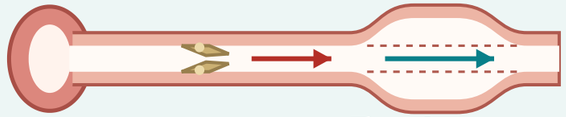
BP



LV Narrow valve Arteriole

After DHP

↓ BP



LV Still narrow **↓ Resistance**

Flow cannot rise enough

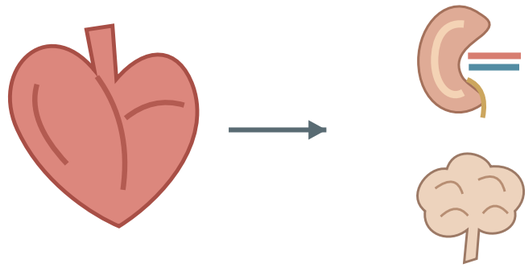
↓ BP → ↓ brain / heart perfusion

Hypotension / syncope

IV nicardipine / clevidipine: **contraindicated in severe AS**

Cardiogenic shock

Low output + hypotension



Organ perfusion already low

Further ↓ SVR / BP

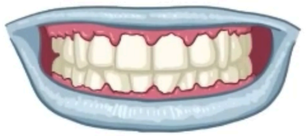
↓ Tissue perfusion

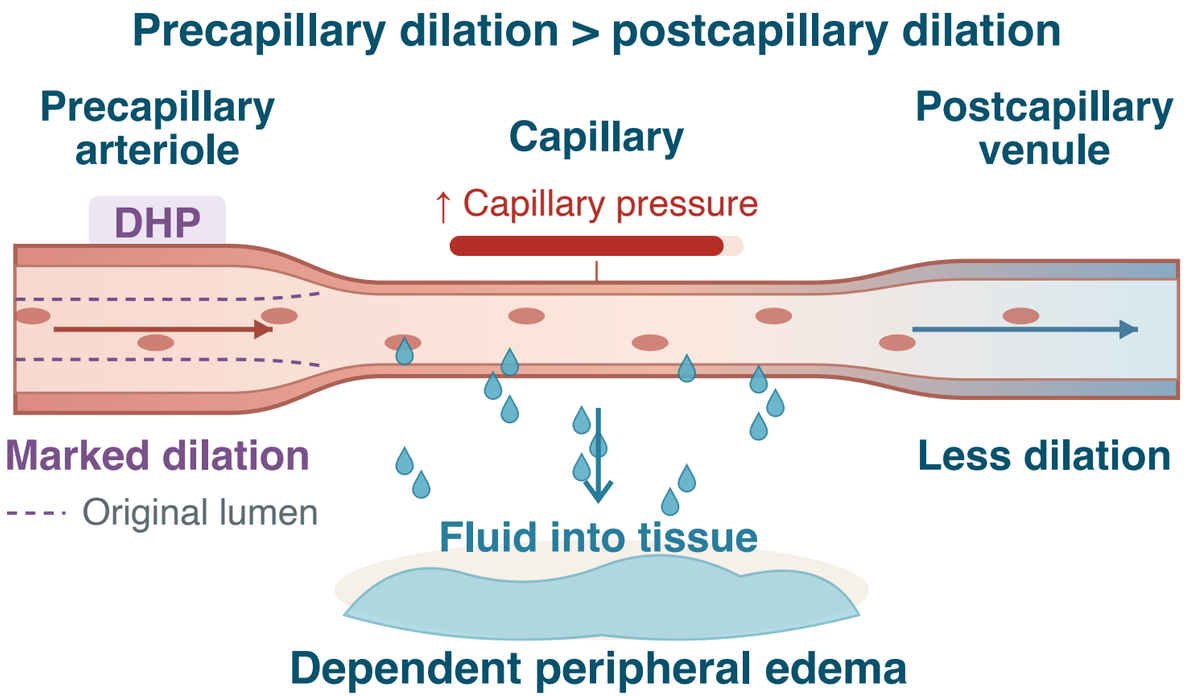
Worsening shock

Dihydropyridine CCBs: Adverse Effects

Open arteries, but swollen legs

- **Dependent peripheral edema**
  Dose-related; usually reflects fluid redistribution, not generalized volume overload
- **Management**
  Lower dose, leg elevation, compression; adjust therapy when needed
- **Reflex tachycardia / hypotension**
- **Headache, flushing, dizziness**
  Related to vasodilation
- **Gingival overgrowth**
  Particularly associated with nifedipine



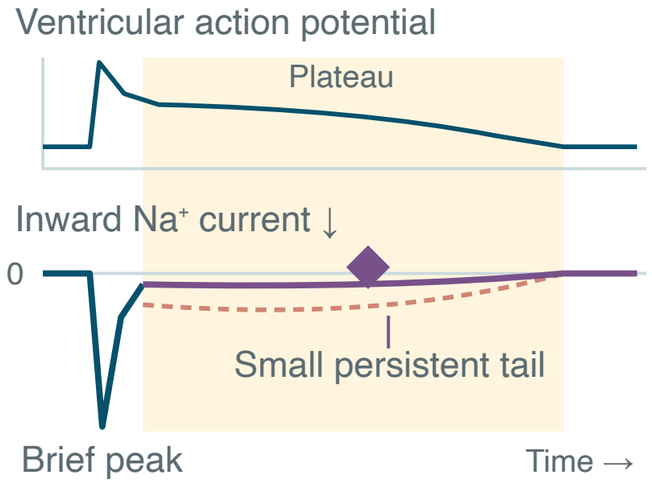


Ranolazine: Inhibiting Late Sodium Current

Late Na^+-current inhibition · Proposed pathway to angina relief

1 · Normal beat | 2 · Ischemia | 3 · Ca^{2+} overload | **4 · Ranolazine**

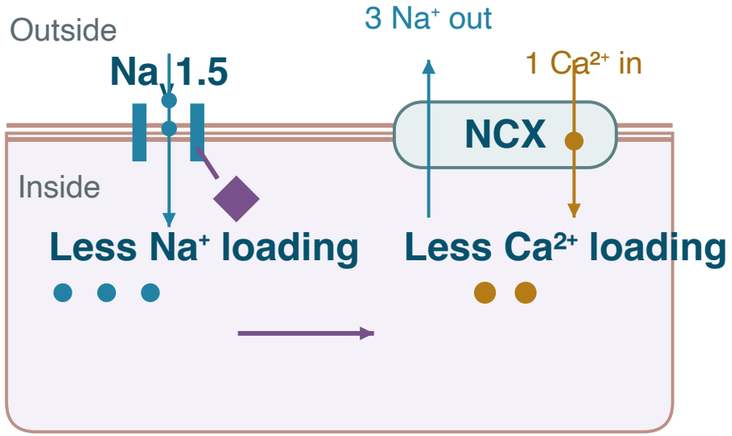
Na^+ entry



Ranolazine inhibits late I_{Na}

Dashed red = before treatment

Na^+–Ca^{2+} coupling

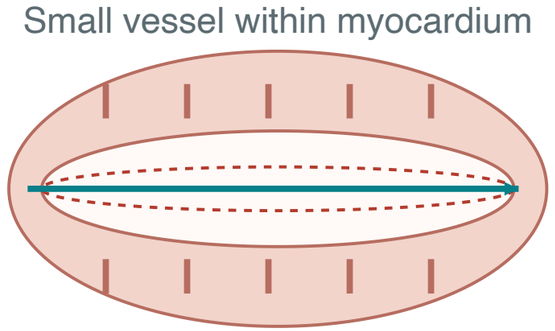


↓ Na^+-dependent Ca^{2+} loading

Less drive for reverse Ca^{2+} entry

Ca^{2+} removal better supported

Diastolic tension



Proposed: less vessel compression

May improve O_2 supply

Less tension + Ca^{2+} cycling

May reduce cellular energy cost

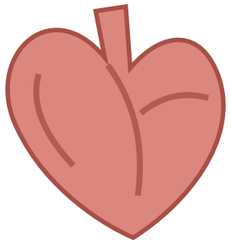
Proposed pathway: less Na^+ / Ca^{2+} overload → less diastolic tension and vessel compression.

Clinical hallmark: angina relief with minimal HR / BP change

Exact antianginal mechanism undetermined · Separate action: I_{Kr} blockade → QT prolongation

Ranolazine: Therapeutic Use

Key feature: antianginal benefit with minimal hemodynamic effects



Chronic stable angina

Relief of symptoms

Minimal hemodynamic effects

Little change in heart rate or BP.
Useful when low HR or BP
limits other antianginal agents.

Persistent angina

Add when symptoms persist despite
β blocker, CCB, or long-acting nitrate therapy.

Scheduled therapy for chronic symptom control · Not an acute rescue drug

Ranolazine: Adverse Effects and Safety

QT prolongation, drug interactions, and organ function guide safe use

Adverse effect / safety concern	Clinical point
Common adverse effects	Dizziness · Headache · Nausea · Constipation
QT prolongation	I_{Kr} inhibition; dose-related QT prolongation Review QT risk and other QT-prolonging drugs
CYP3A interactions	Strong inhibitors and CYP3A inducers: **contraindicated** Verapamil / diltiazem: **maximum ranolazine 500 mg twice daily**
Liver cirrhosis	**Contraindicated**
Renal impairment	Monitor renal function; acute renal failure can occur Discontinue if acute renal failure develops

Antianginal Selection: Follow the Patient's Physiology

Heart rate, BP, ventricular function, and mechanism narrow the choice

Drug class	Effect that helps	Patient context	Main limit
β blocker	↓ HR / contractility → ↓ O_2 demand	Exertional angina; elevated HR or another cardiac indication	Bradycardia / block; bronchospasm; HFrEF evidence is agent specific
DHP CCB	Arteriolar dilation → ↓ afterload; coronary dilation	Angina with hypertension or vasospasm; add-on to β blockade	Hypotension / edema; abrupt vasodilation can provoke reflex tachycardia
Verapamil / diltiazem	↓ HR / AV conduction / contractility; vasodilation	Angina with useful rate slowing and suitable LV function	Bradycardia / block; HFrEF; additive effects with β blockers
Ranolazine	Late Na^+-current inhibition; little HR / BP change	Persistent angina when low HR or BP limits other treatment	QT prolongation; CYP3A interactions; organ function

Nitrates are also antianginal drugs and will be discussed separately.

> **Optional antianginal deep dive** ↗ Mechanisms, drug comparisons, and clinical cases

Persistent or changing chest pain also requires assessment of ischemic risk and the underlying coronary disease.

Clinical Application: Angina, Bradycardia, and Hypertension

Which additional drug best fits the hemodynamics?

A 60-year-old man had an ACS and coronary stent 6 years ago. He now reports **predictable exertional angina 3–4 times weekly**, relieved by rest or sublingual nitroglycerin.

Current therapy includes metoprolol succinate 100 mg/day, lisinopril 10 mg/day, aspirin and atorvastatin.

HR 58/min · BP 155/95 mm Hg · LVEF 55%
No rest pain or recent change in symptom pattern.

Which additional drug is the best choice for this patient?

A. Increase metoprolol

B. Add verapamil

C. Add amlodipine

D. Add ranolazine

Change the Hemodynamics, Change the Choice

The same patient, a different presentation

The same patient has persistent stable exertional angina, but this time:
HR 58/min · BP 106/66 mm Hg.

He is already taking a tolerated β-blocker regimen. LVEF is preserved.

QT interval, renal / hepatic function and drug interactions have been reviewed and do not preclude treatment.

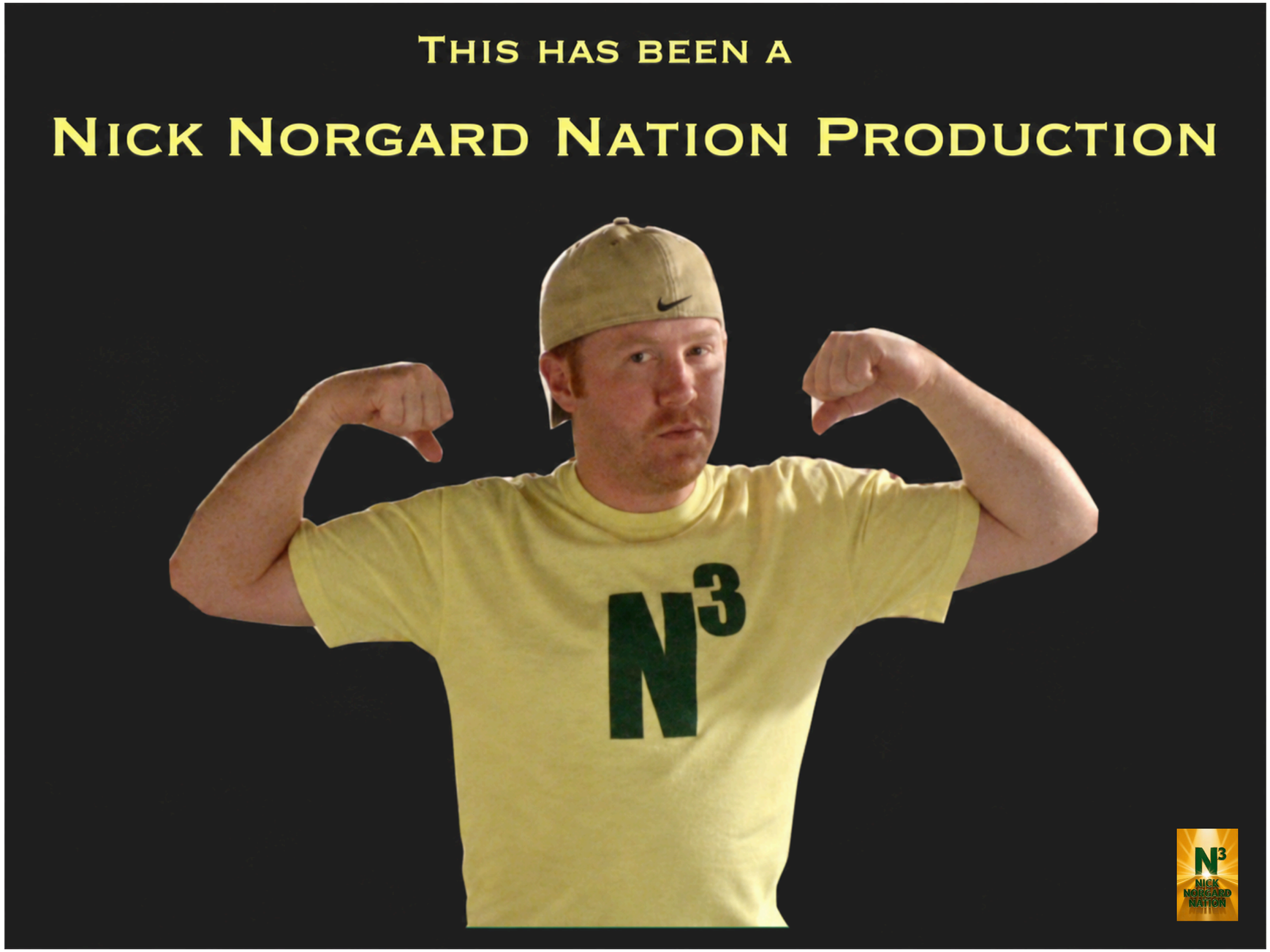
Which additional drug is the best choice for this patient?

A. Increase metoprolol

B. Add verapamil

C. Add amlodipine

D. Add ranolazine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