Drug Targets in the Cardiovascular System

1. Introduction

The cardiovascular system (CVS) comprises the heart and blood vessels and is responsible for the transport of blood, oxygen, and nutrients throughout the body. Many cardiovascular diseases (CVDs) arise due to dysfunctions in this system and are treated with drugs targeting specific molecules or receptors involved in its regulation.

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2. Key Drug Targets in the Cardiovascular System

A. Receptors

1. Adrenergic Receptors (α and β)

- **α_1-receptors**: Cause vasoconstriction → ↑ blood pressure
  - *Antagonists*: Prazosin, Doxazosin (used in hypertension)
- **β_1-receptors**: Found in the heart → ↑ heart rate and force
  - *Antagonists (β-blockers)*: Atenolol, Metoprolol (used in hypertension, angina, arrhythmia)
- **β_2-receptors**: Bronchodilation and vasodilation
  - *Agonists*: Not commonly used for CVS but important in lungs

2. Angiotensin II Receptors (AT_1)

- Vasoconstriction, sodium retention → ↑ BP
  - *Blockers (ARBs)*: Losartan, Valsartan

3. Muscarinic Receptors (M_2)

- Decrease heart rate
  - *Agonists*: Rarely used
  - *Antagonists*: Atropine (used in bradycardia)

B. Ion Channels

1. Calcium Channels (L-type)

- Involved in cardiac muscle contraction and vascular tone
  - *Blockers*: Amlodipine, Verapamil, Diltiazem

- *Use*: Hypertension, angina, arrhythmias

2. Potassium Channels

- Regulate cardiac repolarization
  - *Blockers*: Amiodarone, Sotalol
  - *Use*: Antiarrhythmic

3. Sodium Channels

- Responsible for cardiac depolarization
  - *Blockers*: Lidocaine, Quinidine (Class I antiarrhythmics)

C. Enzymes

1. Angiotensin-Converting Enzyme (ACE)

- Converts Angiotensin I → Angiotensin II
  - *Inhibitors*: Enalapril, Ramipril
  - *Use*: Hypertension, heart failure

2. HMG-CoA Reductase

- Key enzyme in cholesterol biosynthesis
  - *Inhibitors*: Statins (Atorvastatin, Simvastatin)
  - *Use*: Hyperlipidemia

3. Phosphodiesterase (PDE3 & PDE5)

- Degrades cAMP/cGMP, regulating heart and vessel tone
  - *Inhibitors*: Milrinone (PDE3, heart failure), Sildenafil (PDE5, pulmonary hypertension)

D. Transporters and Channels

1. Na^+/K^+-ATPase

- Maintains cardiac cell membrane potential
  - *Inhibitors*: Digoxin
  - *Effect*: ↑ intracellular calcium → ↑ cardiac contractility
  - *Use*: Congestive heart failure, atrial fibrillation

2. Sodium-Calcium Exchanger

- Affected indirectly by drugs like Digoxin

E. Hormonal Systems

1. Renin-Angiotensin-Aldosterone System (RAAS)

- Targeted at multiple points:
  - *Renin inhibitors*: Aliskiren
  - *ACE inhibitors*: Enalapril, Lisinopril
  - *AT_1 receptor blockers (ARBs)*: Losartan
  - *Aldosterone antagonists*: Spironolactone

2. Natriuretic Peptide System

- Promotes natriuresis and vasodilation
  - *Drug*: Sacubitril (Neprilysin inhibitor used with valsartan)

F. Platelet and Coagulation Pathways

1. Cyclooxygenase (COX)

- Produces thromboxane A2 → platelet aggregation
  - *Inhibitor*: Aspirin (low dose)
  - *Use*: MI prevention, stroke prevention

2. $P2Y_{12}$ Receptor (ADP receptor)

- Promotes platelet activation
  - *Antagonists*: Clopidogrel, Ticagrelor

3. Glycoprotein IIb/IIIa Receptor

- Final common pathway for platelet aggregation
  - *Inhibitors*: Abciximab, Eptifibatide

G. Diuretic Targets (Renal)

- Act on kidney tubules to reduce blood volume and pressure:

- **Loop Diuretics**: Furosemide (Na^+-K^+-$2Cl^-$ symporter)
- **Thiazide Diuretics**: Hydrochlorothiazide (Na^+/Cl^- symporter)
- **K^+-Sparing Diuretics**: Spironolactone (aldosterone receptor antagonist)

3. Summary Table of Drug Targets

Target	Drug Class	Example Drugs	Clinical Use
β_1-receptor	β-blockers	Metoprolol, Atenolol	HTN, Angina, CHF
ACE enzyme	ACE inhibitors	Enalapril, Ramipril	HTN, CHF
AT_1 receptor	ARBs	Losartan, Valsartan	HTN
L-type Ca^{2+} channel	CCBs	Amlodipine, Verapamil	HTN, Angina
HMG-CoA reductase	Statins	Atorvastatin	Hyperlipidemia
Na^+/K^+-ATPase	Cardiac glycosides	Digoxin	CHF, Arrhythmia
$P2Y_{12}$ receptor	Antiplatelets	Clopidogrel	MI, Stroke
COX enzyme	Antiplatelet	Aspirin	CAD, Stroke
PDE5	PDE inhibitors	Sildenafil	Pulmonary HTN
Neprilysin	Neprilysin inhibitor	Sacubitril	CHF