Cardio-Vascular Pharmacology

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Drugs used to treat Hypertension

Antihypertensive Drugs

DIURETICS

Amiloride MIDAMOR
Bumetanide BUMEX
Chlorthalidone HYGROTON
Eplerenone INSPRA
Ethacrynic acid EDECRIN
Furosemide LASIX
Hydrochlorothiazide MICROZIDE
Indapamide LOZOL
Metolazone MYKROX, ZAROXOLYN
Spironolactone ALDACTONE
Triamterene DYRENIUM
Torsemide DEMADEX

β-BLOCKERS

Acebutolol SECTRAL
Atenolol TENORMIN
Betaxolol KERLONE
Bisoprolol ZEBETA
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Penbutolol LEVATOL
Pindolol VISKEN
Propranolol INDERAL LA, INNOPRAN XL
Timolol BLOCADREN

ACE INHIBITORS

Benazepril LOTENSIN
Captopril CAPOTEN
Enalapril VASOTEC
Fosinopril MONOPRIL
Lisinopril PRINIVIL, ZESTRIL
Moexipril UNIVASC
Quinapril ACCUPRIL
Perindopril ACEON
Ramipril ALTACE
Trandolapril MAVIK

ANGIOTENSIN II RECEPTOR BLOCKERS

Azilsartan medoxomil EDARBI
Candesartan ATACAND
Eprosartan TEVETEN
Irbesartan AVAPRO
Losartan COZAAR
Olmesartan BENICAR
Telmisartan MICARDIS
Valsartan DIOVAN

RENIN INHIBITORS

Aliskiren TEKTURNA

CALCIUM CHANNEL BLOCKERS

Amlodipine NORVASC
Clevidipine CLEVIPREX
Diltiazem CARDIZEM, CARTIA, DILACOR
Felodipine PLENDIL
Isradipine DYNACIRC CR
Nicardipine CARDENE
Nifedipine ADALAT, NIFEDIAC, PROCARDIA
Nisoldipine SULAR
Verapamil CALAN, ISOPTIN, VERELAN

α-BLOCKERS

Doxazosin CARDURA
Prazosin MINIPRESS
Terazosin HYTRIN

OTHERS

Clonidine CATAPRES, DURACLON
Fenoldopam CORLOPAM
Hydralazine APRESOLINE
Methyldopa ALDOMET
Minoxidil LONITEN
Nitroprusside NITROPRESS

α-ADRENOCEPTOR–BLOCKING AGENTS

- *Prazosin*, *doxazosin*, *and terazosin* produce a competitive block of α1-adrenoceptors.
- They decrease peripheral vascular resistance and lower arterial BP by causing relaxation of both arterial and venous smooth muscle.
- These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.
- Reflex tachycardia and postural hypotension often occur at the onset of treatment.
- Due to weaker outcome data and their side effect profile, α-blockers are no longer recommended as initial treatment for hypertension.

α-/β-ADRENOCEPTOR–BLOCKING AGENTS

- *Labetalol and carvedilol block α1, β1, and β2* receptors.
- *Carvedilol, although an effective antihypertensive, is mainly* used in the treatment of heart failure.
- *Labetalol is used in the management* of gestational hypertension and hypertensive emergencies.

CENTRALLY ACTING ADRENERGIC DRUGS

A. Clonidine

- ***α2 agonist*** → inhibition of sympathetic vasomotor centers → ↓ sympathetic outflow to the periphery → ↓ TPR and ↓ blood pressure.
- *T*reatment of HT that has not responded to treatment with two or more drugs.
- *Clonidine does not decrease* renal blood flow or glomerular filtration ⇨ useful in the treatment of hypertension complicated by renal disease.
- *Clonidine is* absorbed well after *oral* administration and is excreted by the kidney.
- It is also available in a transdermal patch.
- Adverse effects include sedation, dry mouth, and constipation.
- Rebound hypertension occurs following abrupt withdrawal of *clonidine*.

B. Methyldopa

- *α2 agonist , converted to* methylnorepinephrine centrally → ↓ adrenergic outflow from the CNS.
- The most common side effects : *sedation* and drowsiness.
- Its use is limited due to adverse effects and the need for multiple daily doses.
- It is mainly used for management of hypertension in pregnancy, where it has a record of safety.

VASODILATORS

- The direct-acting smooth muscle relaxants, (*hydralazine* and *minoxidil), are not used as primary* drugs to treat hypertension.
- Act by producing relaxation of vascular smooth muscle, primarily in arteries and arterioles ⇨ ⬇TPR ⇨ ⬇ BP.
- Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction in predisposed individuals.
- Vasodilators also increase plasma renin concentration, resulting in sodium and water retention.
- *Hydralazine* is accepted to use for management of HT in pregnancy.
- Adverse effects of *hydralazine include headache,* tachycardia, nausea, sweating, arrhythmia, and precipitation of angina.

HYPERTENSIVE EMERGENCY

- Hypertensive emergency is a rare but life-threatening situation characterized by:
  - severe elevations in BP (systolic > 180 mm Hg or diastolic > 120 mm Hg)
  - with evidence of progressive target organ damage (ex. stroke, myocardial infarction).

- Hypertensive emergencies require :
  - timely blood pressure reduction
  - with treatment administered IV to prevent or limit target organ damage.

- A variety of medications are used, including:
  - calcium channel blockers (*nicardipine and clevidipine),*
  - *nitric oxide vasodilators (nitroprusside* and *nitroglycerin),*
  - *adrenergic receptor antagonists (phentolamine, esmolol, and labetalol),*
  - *the vasodilator hydralazine,*
  - *and the dopamine* agonist *fenoldopam.*

RESISTANT HYPERTENSION

- Resistant hypertension is defined as blood pressure that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic.

- The most common causes of resistant hypertension are:
  - poor compliance,
  - excessive ethanol intake,
  - concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome),
  - concomitant medications (sympathomimetics, NSAIDs, or antidepressants)
  - insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.

Drugs used to treat Heart Failure

ACE INHIBITORS
Captopril CAPOTEN
Enalapril VASOTEC
Fosinopril MONOPRIL
Lisinopril PRINIVIL, ZESTRIL
Quinapril ACCUPRIL
Ramipril ALTACE

ANGIOTENSIN RECEPTOR BLOCKERS
Candesartan ATACAND
Losartan COZAAR
Telmisartan MICARDIS
Valsartan DIOVAN

ALDOSTERONE ANTAGONISTS
Eplerenone INSPRA
Spironolactone ALDACTONE

β–ADRENORECEPTOR BLOCKERS
Bisoprolol ZEBETA
Carvedilol COREG, COREG CR
Metoprolol succinate TOPROL XL
Metoprolol tartrate LOPRESSOR

DIURETICS
Bumetanide BUMEX
Furosemide LASIX
Metolazone ZAROXOLYN
Torsemide DEMADEX

DIRECT VASO - AND VENODILATORS
Hydralazine APRESOLINE
Isosorbide dinitrate DILATRATE-SR, ISORDIL
FDC Hydralazine/Isosorbide dinitrate BIDIL

INOTROPIC AGENTS
Digoxin LANOXIN
Dobutamine DOBUTREX
Milrinone PRIMACOR

Therapeutic strategies in HF

Chronic HF is typically managed by :

• fluid limitations (less than 1.5 to 2 L daily);

• low dietary intake of sodium (less than 2000 mg/d);

• treatment of comorbid conditions;

• and judicious use of diuretics, inhibitors of the RAAS, and inhibitors of the sympathetic nervous system. Inotropic agents are reserved for acute HF signs and symptoms in mostly the inpatient setting.

• Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nondihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible.

Drugs used to treat Heart Failure

VASO- AND VENODILATORS

➢ **Nitrates** are commonly used venous dilators to reduce preload for patients with chronic HF.

➢ Arterial dilators, such as ***hydralazine*** *reduce systemic arteriolar resistance* and decrease afterload.

➢ If the patient is intolerant of ACE inhibitors or β-blockers, or if additional vasodilator response is required, a combination of *hydralazine and isosorbide dinitrate* may be used.

INOTROPIC DRUGS

➢ Positive inotropic agents enhance cardiac contractility and, thus, increase cardiac output.

➢ Although these drugs act by different mechanisms, the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.

- تعزز هذه العوامل قلوصية القلب فتزيد بذلك النتاج القلبي
- على الرغم من أن هذه الأدوية تعمل باليات مختلفة، فإن التأثير المقوي للقلب ينجم عن زيادة تركيز الكالسيوم في سيتوبلاسما الخلية والذي يحفز قلوصية العضلة القلبية.

1. Digitalis glycosides

- They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are used in treating HF.
- The digitalis glycosides have a low therapeutic index.
- The most widely used agent is *digoxin*

- مركبات يمكنها أن تزيد قلوصية عضلة القلب ولذا تستعمل لعلاج قصور القلب. وأكثرها شيوعا الديجوكسين.
- تمتلك هذه المركبات هامش علاجي ضيق.

Pharmacokinetics:

- *Digoxin is available in oral and injectable formulations.*
- It has a large volume of distribution, because it accumulates in muscle.
- *Digoxin has a long half-life of 30 to 40 hours.*
- *It is* mainly eliminated intact by the kidney.

- متوفر بشكل فموي وحقني.
- تمتلك حجم توزع كبير، وعمر نصفي طويل.
- يطرح كما هو بشكل رئيسي عن طريق الكلية.

1. Digitalis glycosides

Mechanism of action:

a. Regulation of cytosolic calcium concentration:

- By inhibiting the Na+/K+-adenosine triphosphatase (ATPase) enzyme, *digoxin reduces the ability of the myocyte to actively pump* Na+ from the cell

b. Increased contractility of the cardiac muscle:

- *Digoxin* increases the force of cardiac contraction, causing cardiac output to more closely resemble that of the normal heart.
- Vagal tone is also enhanced, so both heart rate and myocardial oxygen demand decrease.

1- تنظيم تركيز الكالسيوم السيتوبلاسمي: بتثبيط مضخة الصوديوم/بوتاسيوم حيث ينقص الديجوكسين قدرة الخلية القلبية على ضخ الصوديوم من الخلية.

2- زيادة قلوصية عضلة القلب: يزيد الديجوكسين قوة تقلص القلب ليصبح اقرب إلى قوة القلب الطبيعي. يعزز توتر المبهم فينقص معدل ضربات القلب وحاجة القلب للاوكسيجين.

1. Digitalis glycosides

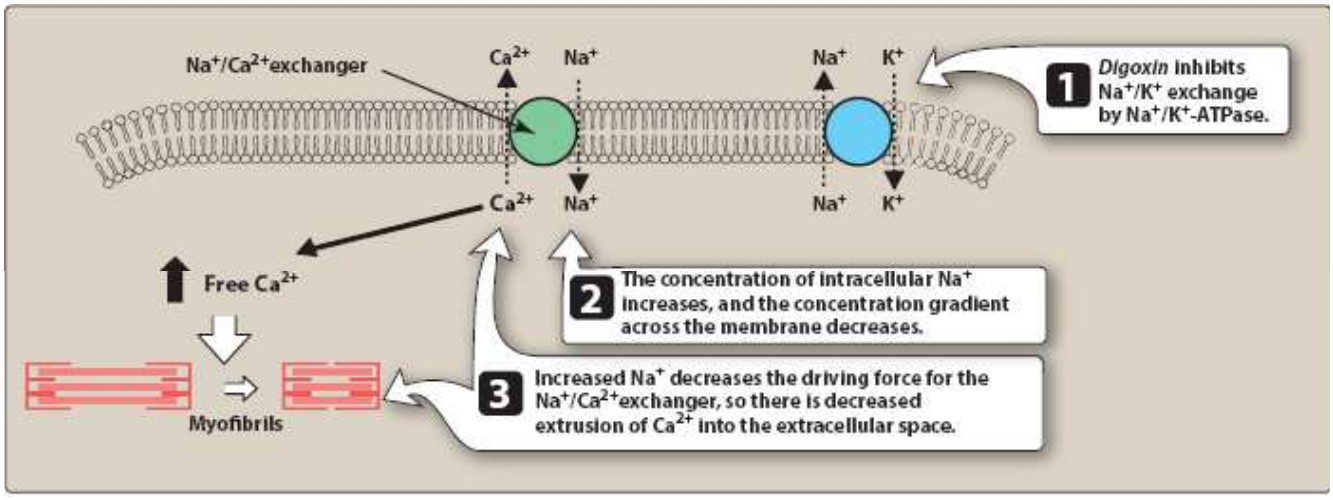


Figure 19.8
Mechanism of action of *digoxin*. ATPase = adenosine triphosphatase.

1. Digitalis glycosides

Therapeutic uses:

- *Digoxin therapy is indicated in patients with* severe HF after initiation of ACE inhibitor, β-blocker, and diuretic therapy.
- Patients with mild to moderate HF often respond to treatment with ACE inhibitors, β-blockers, aldosterone antagonists, direct vaso- and venodilators, and diuretics and may not require *digoxin*.

- توصف المعالجة بالديجوكسين لمرضى قصور القلب الشديد بعد البدء بالمعالجة بمثبطات الأنزيم المحول للأنجيوتنسين وحاصرات بيتا والمدرات.

- لمرضى قصور القلب الخفيف الى المتوسط غالبا ما يستجيبون للأدوية الأخرى ومن الممكن ألا يحتاجون للديجوكسين.

1. Digitalis glycosides

Adverse effects:

- *Digoxin toxicity is one of the most common adverse drug reactions*
- *N*ausea, and vomiting may be initial indicators of toxicity. Blurred vision, yellowish vision , and various cardiac arrhythmias
- Toxicity can often be managed by discontinuing *digoxin, determining* serum potassium levels.
- Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to *digoxin (digoxin immune Fab), which bind and inactivate the* drug.

- التسمم بالديجوكسين أكثرها شيوعا، من أعراضه: الغثيان، الاقياء، تشوش الرؤية، الرؤية المصفرة، ولا نظميات قلبية.

- غالبا ما يتم تدبير التسمم بالديجوكسين بإيقاف الديجوكسين وتحديد المستويات المصلية للبوتاسيوم.

- يمكن أن تتطلب السمية الشديدة المؤدية الى تسرع قلب بطيني استعمال مضادات اللا نظميات، و استعمال أضداد للديجوكسين كي ترتبط وتزيل تفعيل الديجوكسين

1. Digitalis glycosides

Adverse effects:

- *Digoxin is a substrate of P-gp, and inhibitors* of P-gp, such as *clarithromycin, verapamil, and amiodarone, can* significantly increase *digoxin levels, necessitating a reduced dose of digoxin.*
- *Digoxin should also be used with caution with other drugs* that slow AV conduction, such as β-blockers, *verapamil, and diltiazem.*
- Patients receiving thiazide or loop diuretics may be prone to hypokalemia that predispose a patient to *digoxin toxicity*.

- بما أن الديجوكسين ركازة لـ غليكوبروتين، فان تناول مثبطات هذا البروتين مثل كلاريترومايسين، فيراباميل، أميوداروون يمكن أن يزيد مستويات الديجوكسين مما يستدعي إنقاص جرعة الديجوكسين.

- يجب استعمال الديجوكسين بحذر مع الأدوية التي تبطئ التوصيل الأذيني البطيني مثل حاصرات بيتا، الفيراباميل، والديلتيازيم.

- مدرات العروة والمدرات التيازيدية يمكن ان تسبب نقص بوتاسيوم الدم الذي يسبب التسمم بالديجوكسين.

2. β-Adrenergic agonists

- β-Adrenergic agonists, such as *dobutamine* and *dopamine, improve cardiac performance by* causing positive inotropic effects.
- *Dobutamine is the* most commonly used inotropic agent other than *digoxin.*
- β-Adrenergic agonists lead to an increase in intracellular cyclic adenosine
- Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting.

- مقلدات بيتا مثل الدوبوتامين والدوبامين تحسن الأداء القلبي من خلال تأثيراتها المقوية للقلب.
ويعد الدوبوتامين اكثرها شيوعا.
- يؤدي استعمالها الى زيادة تركيز الادينوزين الحلقي داخل الخلوي.
- تعطى بالتسريب الوريدي في حالات قصور القلب الحاد.

2. β-Adrenergic agonists

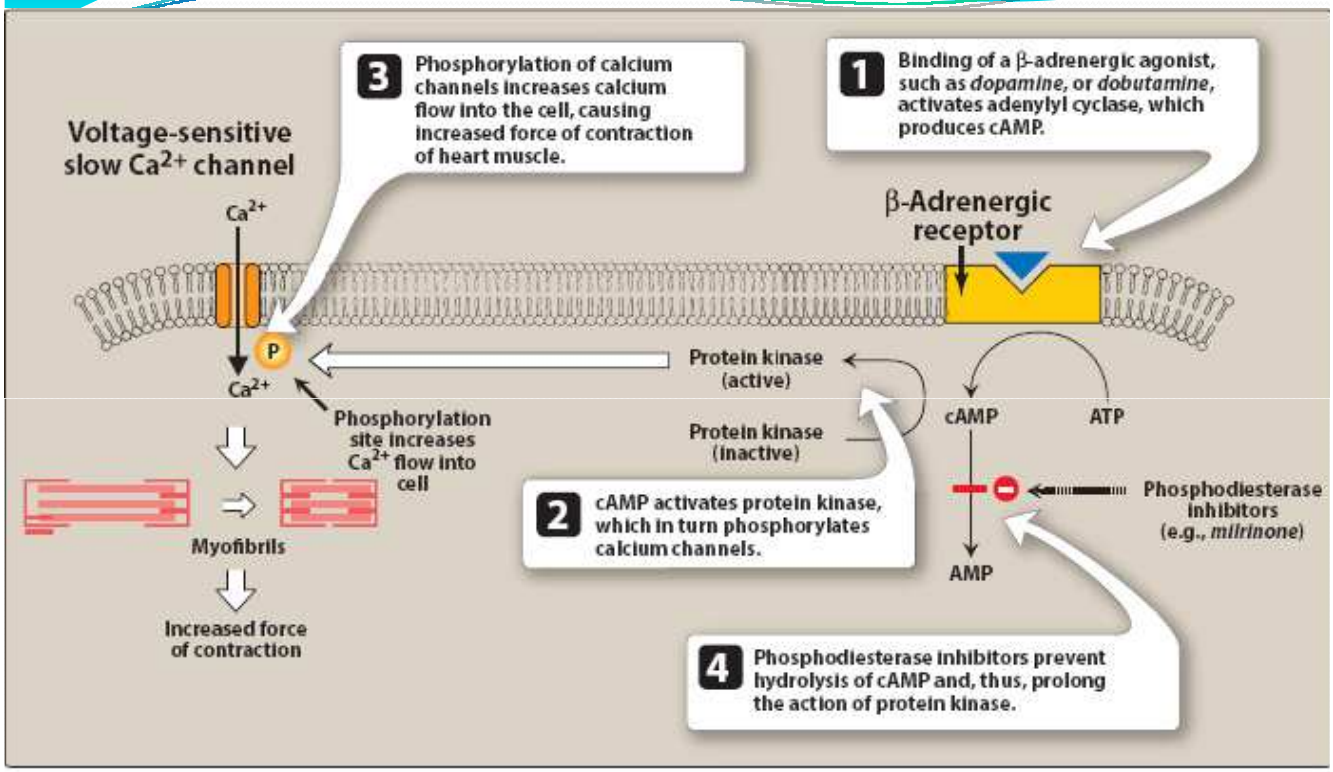
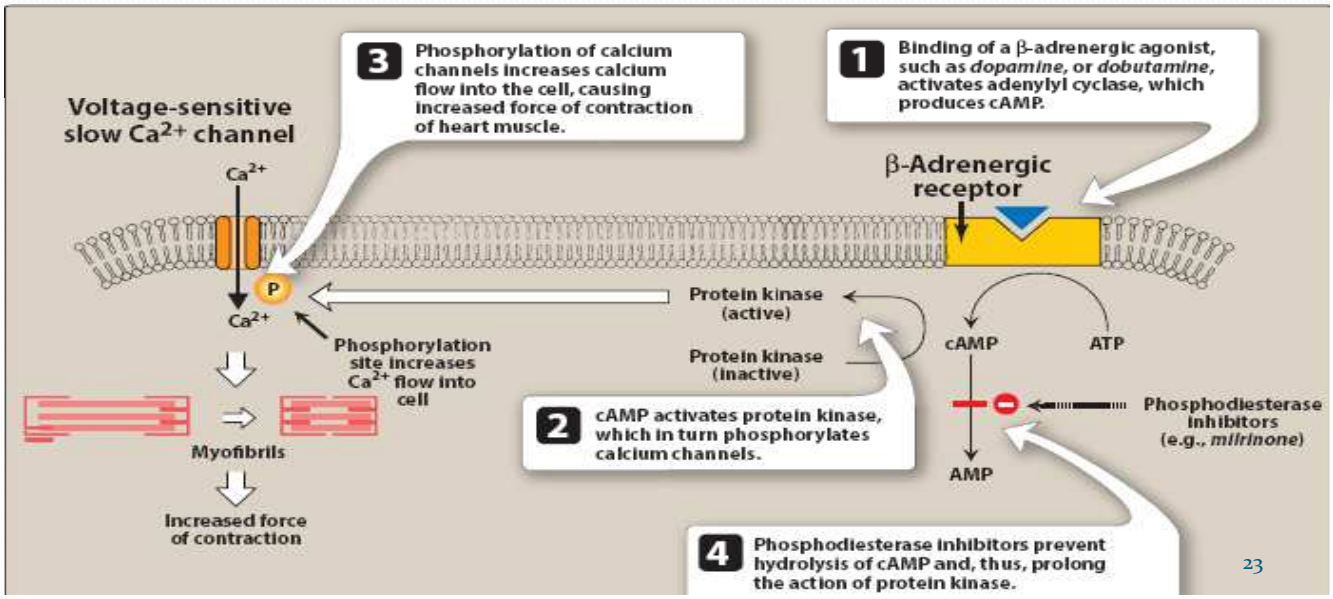


Figure 19.10
Sites of action by β-adrenergic agonists on heart muscle. AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; P = phosphate.

3. Phosphodiesterase inhibitors

➢ *Milrinone is a phosphodiesterase inhibitor that* increases the intracellular concentration of cAMP, this results in an increase of intracellular calcium and, therefore, cardiac contractility.

- تزيد هذه الأدوية تركيز الادينوزين الحلقي داخل الخلوي مما يؤدي الى زيادة الكالسيوم داخل الخلوي وبالتالي القلوصية القلبية .



ORDER OF THERAPY

➢ HF classified into four stages, from least severe to most severe.

1. In patients with overt HF, loop diuretics are often introduced first for relief of signs or symptoms of volume overload.
2. ACE inhibitors or ARBs are added after the optimization of diuretic therapy.
3. β-blockers were added after optimization of ACE inhibitor or ARB therapy
4. most patients newly diagnosed with HF are initiated on both low doses of an ACE inhibitor and β-blocker after initial stabilization.
5. *Digoxin, aldosterone antagonists, and fixed-dose hydralazine and isosorbide dinitrate are initiated in patients who continue to have HF symptoms* despite optimal doses of an ACE inhibitor and β-blocker.

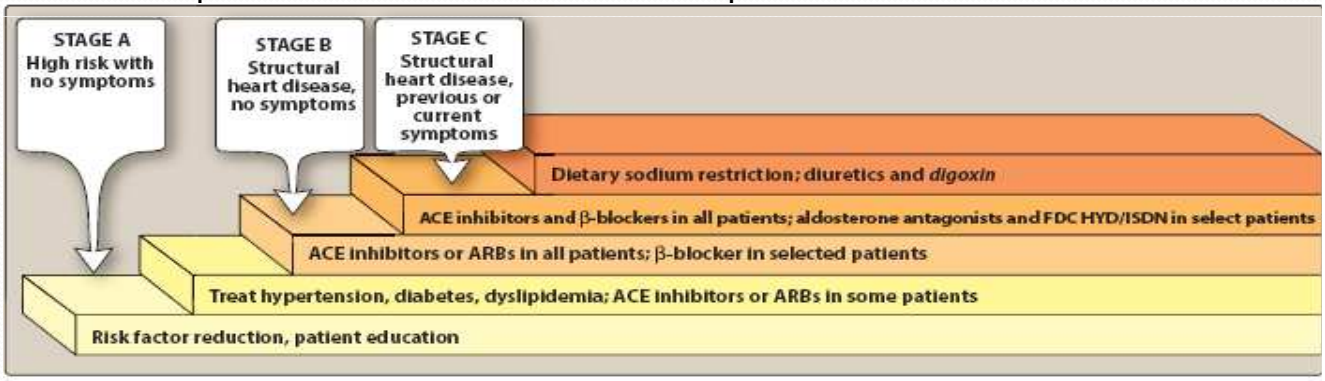


Figure 19.11
Treatment options for various stages of HF. ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; FDC = fixed dose combination; HYD = hydralazine; ISDN = isosorbide dinitrate. Stage D (refractory symptoms requiring special interventions) is not shown.

Drugs used to treat Angina

Typical angina pectoris

- All patients with IHD and angina should:
  - receive **guideline-directed medical therapy**
  - with emphasis on **lifestyle modifications** (smoking cessation, physical activity, weight management)
  - and **management of modifiable risk factors** (hypertension, diabetes, dyslipidemia) to reduce cardiovascular morbidity and mortality.

β-BLOCKERS
Atenolol TENORMIN
Bisoprolol ZEBETA
Metoprolol LOPRESSOR, TOPROL XL
Propranolol INDERAL, INDERAL LA
CALCIUM CHANNEL BLOCKERS (DIHYDROPYRIDINES)
Amlodipine NORVASC
Felodipine PLENDIL
Nifedipine PROCARDIA XL
CALCIUM CHANNEL BLOCKERS (NONDIHYDROPYRIDINE)
Diltiazem CARDIZEM
Verapamil CALAN, ISOPTIN
NITRATES
Nitroglycerin NITRO-BID, NITRO-DUR, NITROLINGUAL, NITROSTAT
Isosorbide dinitrate DILATRATE-SR, ISORDIL
Isosorbide mononitrate IMDUR, ISMO
SODIUM CHANNEL BLOCKER
Ranolazine RANEXA

Figure 21.1
Summary of antianginal drugs.

ORGANIC NITRATES

- These compounds cause a reduction in myocardial oxygen demand, followed by relief of symptoms.

- They are effective in stable, unstable, and variant angina.

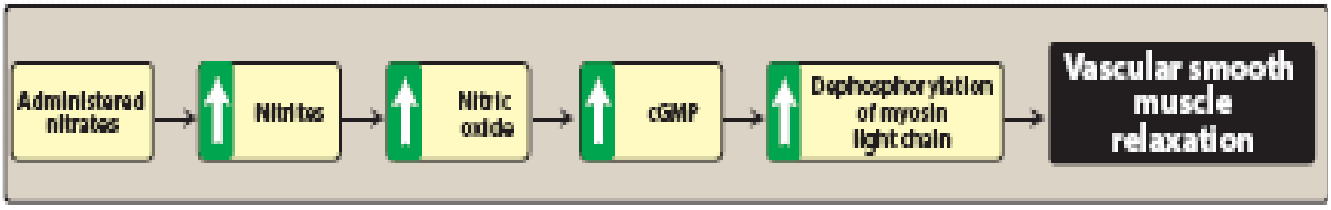
A. Mechanism of action

- Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP).

- Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation.

- Nitrates such as nitroglycerin cause dilation of the large veins, which reduces preload (venous return to the heart) and, therefore, reduces the work of the heart.

- Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.



B. Pharmacokinetics

- Nitrates differ in their **onset of action** and **rate of elimination**.
- The onset of action varies from 1 minute for nitroglycerin to 30 minutes for isosorbide mononitrate.
- For prompt relief of an angina attack precipitated by exercise or emotional stress, sublingual (or spray form) nitroglycerin is the drug of choice.
- All patients suffering from angina should have nitroglycerin on hand to treat acute angina attacks.
- Significant first-pass metabolism of nitroglycerin occurs in the liver. Therefore, it is commonly administered via the sublingual or transdermal route (patch or ointment), thereby avoiding the hepatic first-pass effect.

B. Pharmacokinetics

- Isosorbide mononitrate owes its improved bioavailability and long duration of action to its stability against hepatic breakdown.
- Oral isosorbide dinitrate undergoes denitration to two mononitrates, both of which possess antianginal activity.

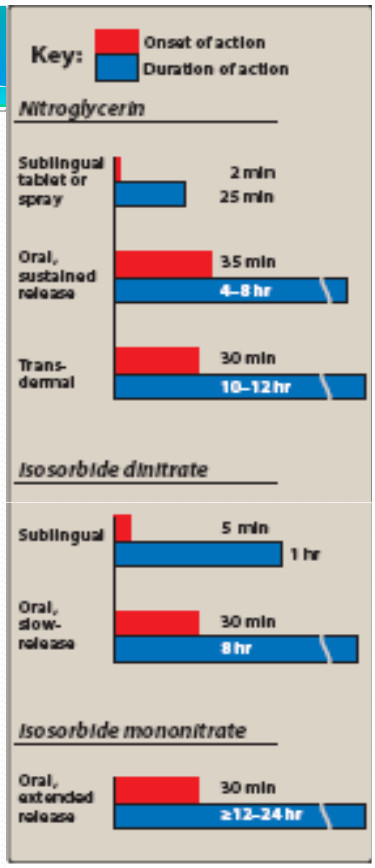


Figure 21.6
Time to peak effect and duration of action for some common organic nitrate preparations.

C. Adverse effects

- **Headache** is the most common adverse effect of nitrates.
- **High doses of nitrates** can also cause **postural hypotension, and tachycardia**.
- **Phosphodiesterase type 5 inhibitors** such as *sildenafil* **potentiate** the action of the nitrates. (To preclude the dangerous hypotension that may occur, **this combination is contraindicated**).
- **Tolerance to the actions of nitrates develops rapidly** as the blood vessels become **desensitized to vasodilation**.
- Tolerance can be overcome by providing **a daily "nitrate-free interval"** to restore sensitivity to the drug.

C. Adverse effects

- This **interval of 10 to 12 hours is usually taken at night** because demand on the heart is decreased at that time.
- **Nitroglycerin patches are worn for 12 hours and then removed for 12 hours.**

SODIUM CHANNEL BLOCKER

- Ranolazine inhibits the late phase of the sodium current (late INa), improving the oxygen supply and demand equation.

- Inhibition of late INa reduces intracellular sodium and calcium overload, thereby improving diastolic function.

- Ranolazine has antianginal as well as antiarrhythmic properties.

- It is indicated for the treatment of chronic angina and may be used alone or in combination with other traditional therapies.

- It is most often used in patients who have failed other antianginal therapies.

SODIUM CHANNEL BLOCKER

- Ranolazine is extensively metabolized in the liver, mainly by the CYP3A family and also by CYP2D6.

- It is also a substrate of P-glycoprotein.

- As such, ranolazine is subject to numerous drug interactions.

- In addition, ranolazine can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.