Anti-Anginal Drugs

Atherosclerosis

- Atherosclerotic lesions in coronary arteries can obstruct blood flow.
- leading to an imbalance in myocardial oxygen supply and demand that presents as stable angina or an acute coronary syndrome (myocardial infarction [MI] or unstable angina).
- Spasms of vascular smooth muscle may also inhibit cardiac blood flow, reducing perfusion and causing ischemia and anginal pain.

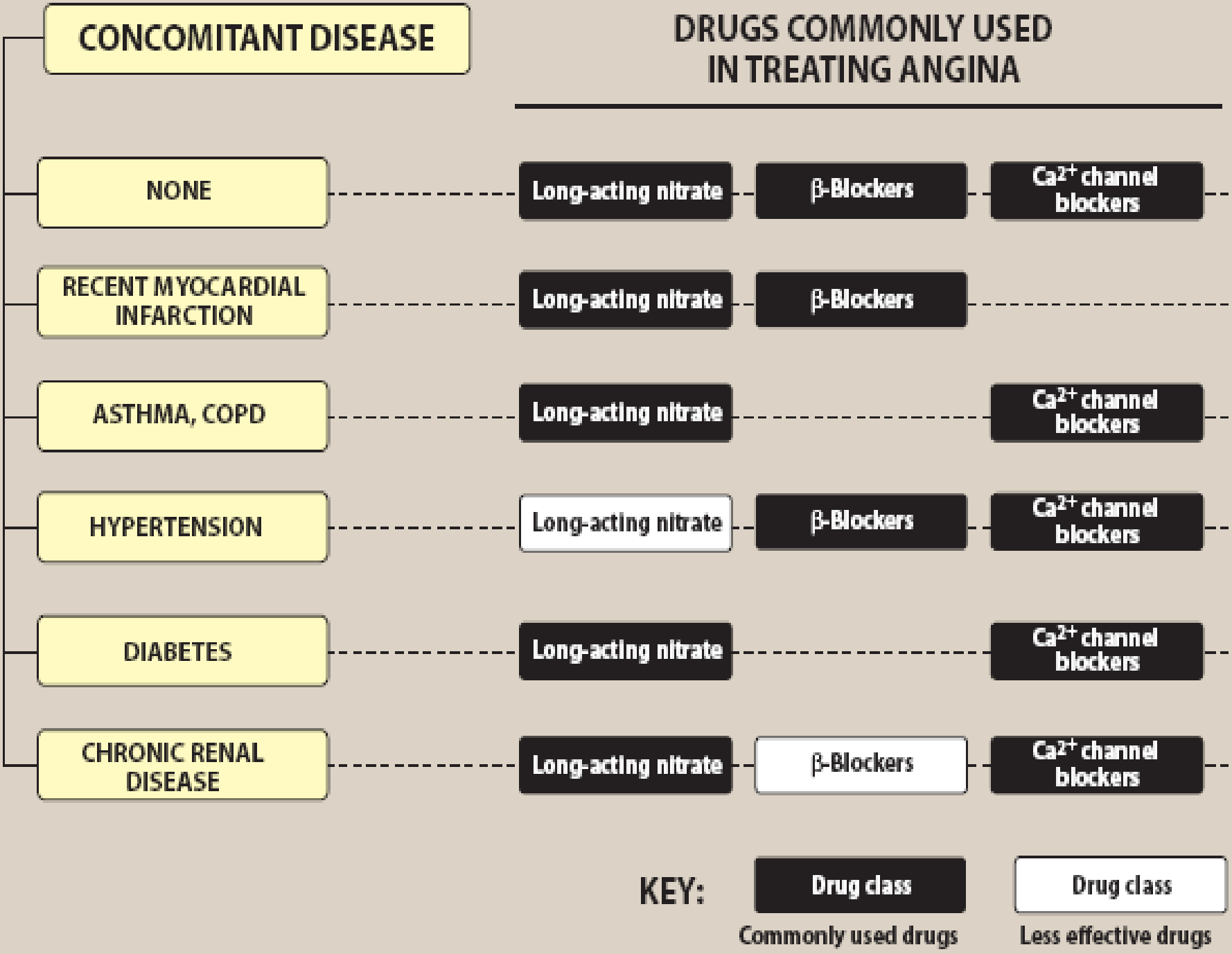
Angina Pectoris

- Typical angina pectoris is a characteristic:
- ➢ Sudden, severe, crushing chest pain that may radiate to the neck, jaw, back, and arms.
- ➢ Patients may also present with dyspnea or
- Atypical symptoms such as indigestion, nausea, vomiting, or diaphoresis.
- Angina different types caused by varying combinations of increased myocardial demand and decreased myocardial perfusion.

Treatment Strategies

- Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina:
- **β-blockers.**
- **Calcium Channel Blockers.**
- **Organic Nitrates.**
- **The sodium channel–blocking drug, ranolazine.**

✓ These agents help to balance the cardiac oxygen supply and demand equation by affecting blood pressure, venous return, heart rate, and contractility.


CONCOMITANT DISEASE
DRUGS COMMONLY USED IN TREATING ANGINA
NONE
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
RECENT MYOCARDIAL INFARCTION
Long-acting nitrate
β-Blockers
ASTHMA, COPD
Long-acting nitrate
Ca2+ channel blockers
HYPERTENSION
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
DIABETES
Long-acting nitrate
Ca2+ channel blockers
CHRONIC RENAL DISEASE
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
KEY:
Drug class
Commonly used drugs
Drug class
Less effective drugs

Organic Nitrates

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

❖ **Main Mechanism of action:**

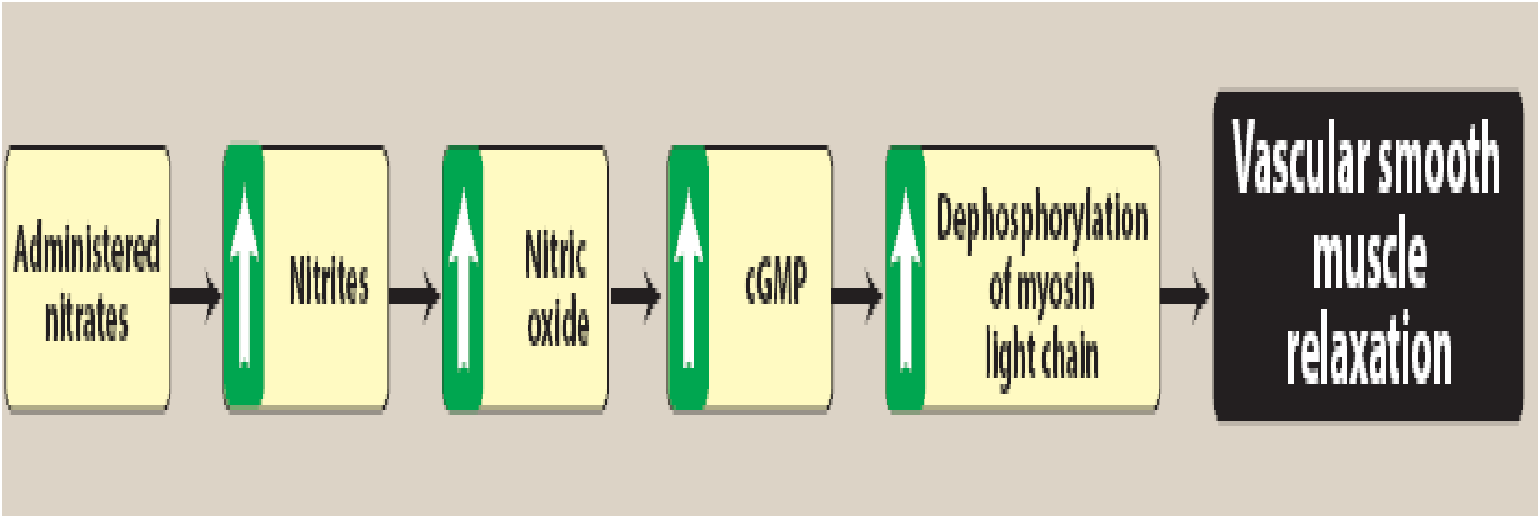
- Organic **nitrates** relax vascular smooth muscle by their intracellular conversion to **nitrite ions** and then to **nitric oxide**, which activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP).

✓ 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.

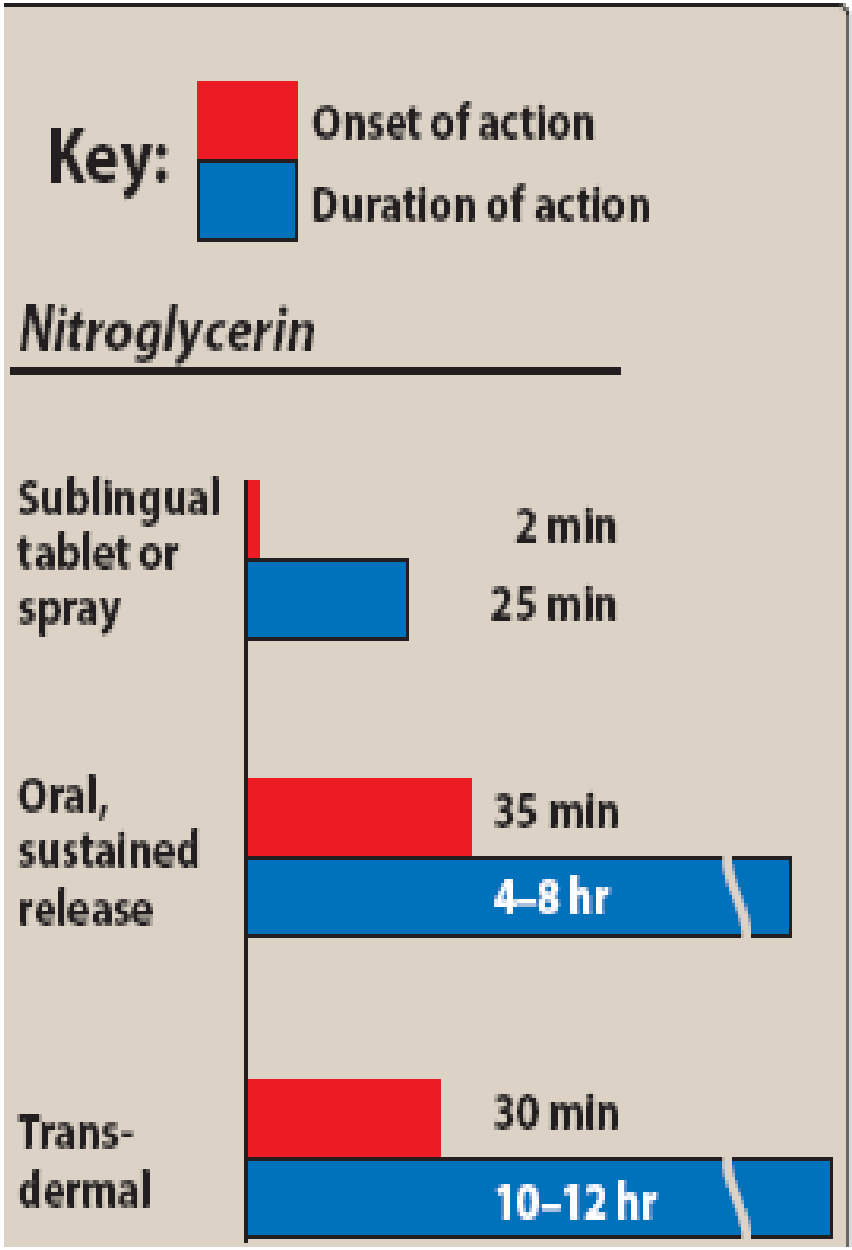
Mechanism of Action of Nitrates

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

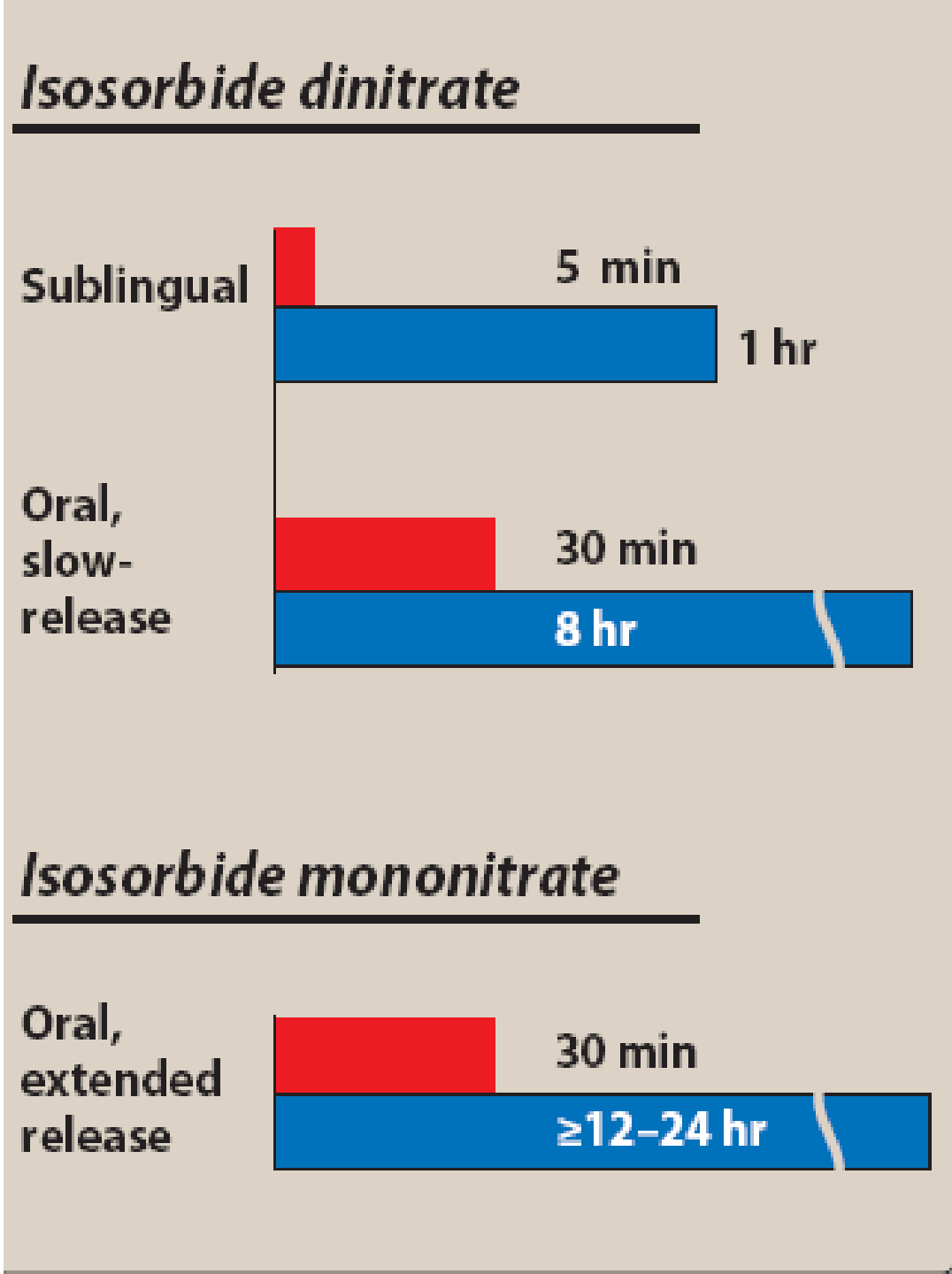


Pharmacokinetics

- ✓ Nitrates differ in their onset of action and rate of elimination.
- 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.
- ✓ Sublingual or transdermal route (patch or ointment), avoiding the hepatic first-pass effect.



- **Isosorbide Mononitrate** 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.



Adverse effects

- **Headache** is the most common adverse effect of nitrates.
- **High doses** …..postural hypotension, facial flushing, and tachycardia.

✓ Phosphodiesterase type 5 inhibitors as **sildenafil** potentiate the action of the nitrates Dangerous hypotension ……. **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. 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.

- Nitrate-free interval in these patients should occur in the late afternoon.

β-adrenergic blockers

- ✓ The β-adrenergic blockers **decrease the oxygen demands** of the myocardium by blocking β1 receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure.
- These agents reduce myocardial oxygen demand during **exertion and at rest.**
- ✓ Can reduce both the frequency and severity of angina attacks.
- β-Blockers can be used to **increase exercise duration and tolerance** in patients with effort-induced angina.
- ✓ β-Blockers are recommended as **initial antianginal** therapy in all patients unless contraindicated.
- ✓ β-Blockers reduce the risk of death and MI in patients who have had a **prior MI** and also improve mortality in patients with **hypertension** and **heart failure** with reduced ejection fraction.

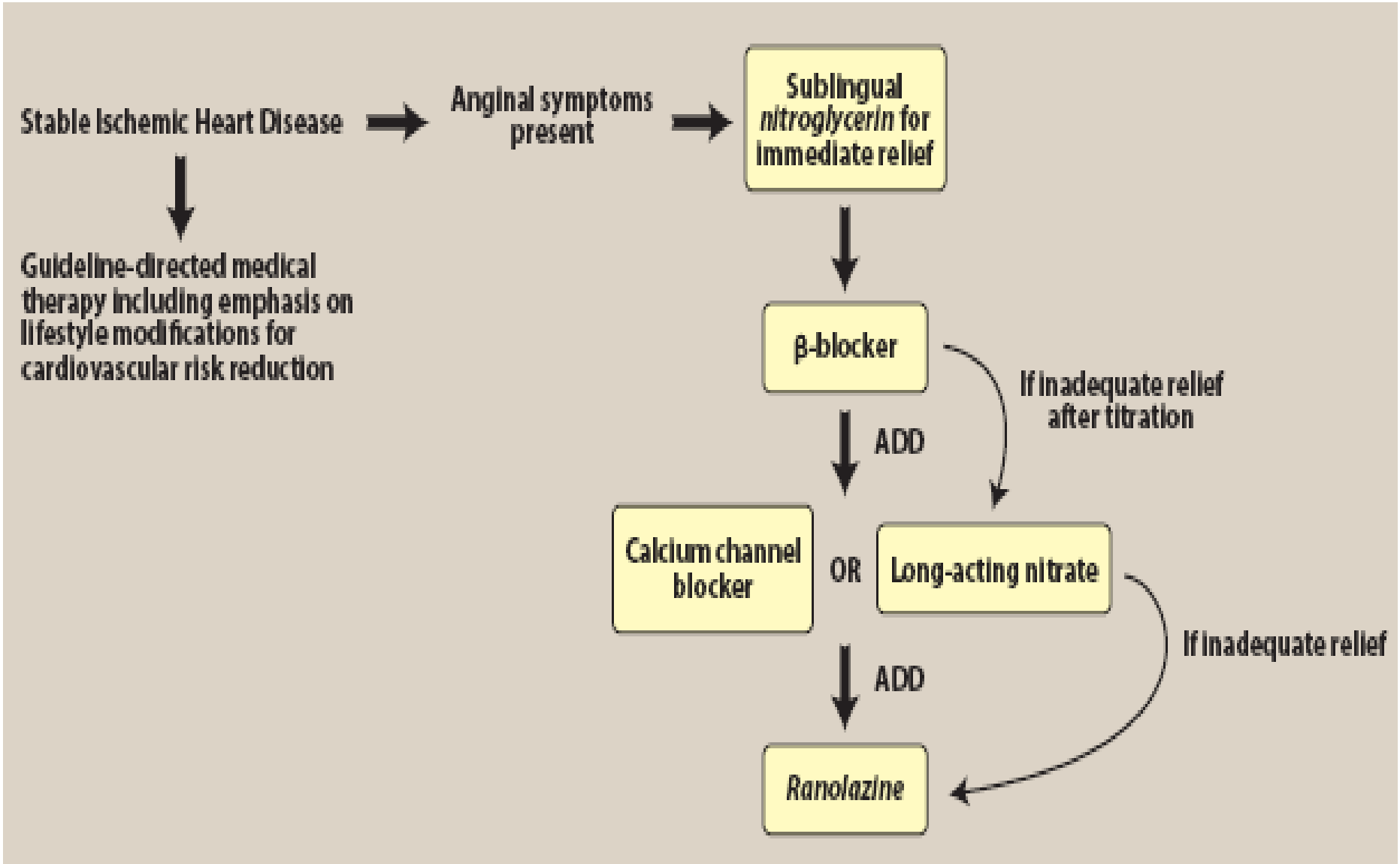
- **Propranolol is the prototype for this class of compounds, but it is not cardioselective**

✓ **Metoprolol and Atenolol, are preferred.**

- **All β-blockers are nonselective at high doses and can inhibit β2 receptors.**

  - **β-Blockers should be avoided in patients with severe bradycardia.**
  - **Nonselective β-blockers should be avoided in patients with asthma.**
  - **It is important not to discontinue β-blocker therapy abruptly.**
  - **The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.**

Treatment Algorithm for Improving Symptoms in Patients With Stable Angina.



Calicum Channel Blockers

- **Calcium is essential for muscular contraction.**
- **Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces.**
- **This promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia.**
- **The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds.**

Calcium channel blockers

- These agents primarily affect the **resistance** of peripheral and coronary arteriolar smooth muscle.
- In the treatment of effort-induced angina, calcium channel blockers reduce myocardial **oxygen consumption** by decreasing **vascular resistance**, thereby decreasing **afterload.**
- All calcium channel blockers lower blood pressure.

Dihydropyridine calcium channel blockers

- **Amlodipine** an oral dihydropyridine, functions mainly as an arteriolar vasodilator.

✓ This drug has minimal effect on cardiac conduction. The vasodilatory effect of amlodipine is useful in the treatment of variant angina caused by spontaneous coronary spasm.

- **Nifedipine** is another agent in this class; it is usually administered as an extended-release oral formulation.

Nondihydropyridine calcium channel blockers

- **Verapamil** slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand.
- Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator.

✓ Verapamil is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities.

- **Diltiazem** also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator.
- Nondihydropyridine calcium channel blockers can worsen heart failure due to their negative inotropic effect, and their use should be avoided in this population.

Sodium Channel Blockers

- **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.

- **Ranolazi**ne 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.

- Ranolazine is extensively **metabolized** in the liver.
- Ranolazine is subject to numerous drug **interactions**.