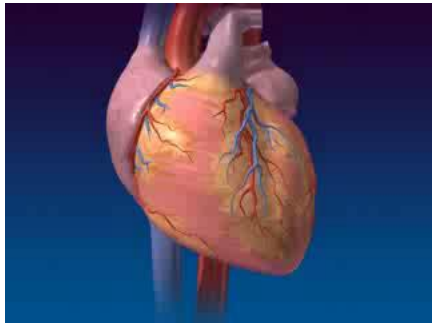
Cardiovascular Drugs

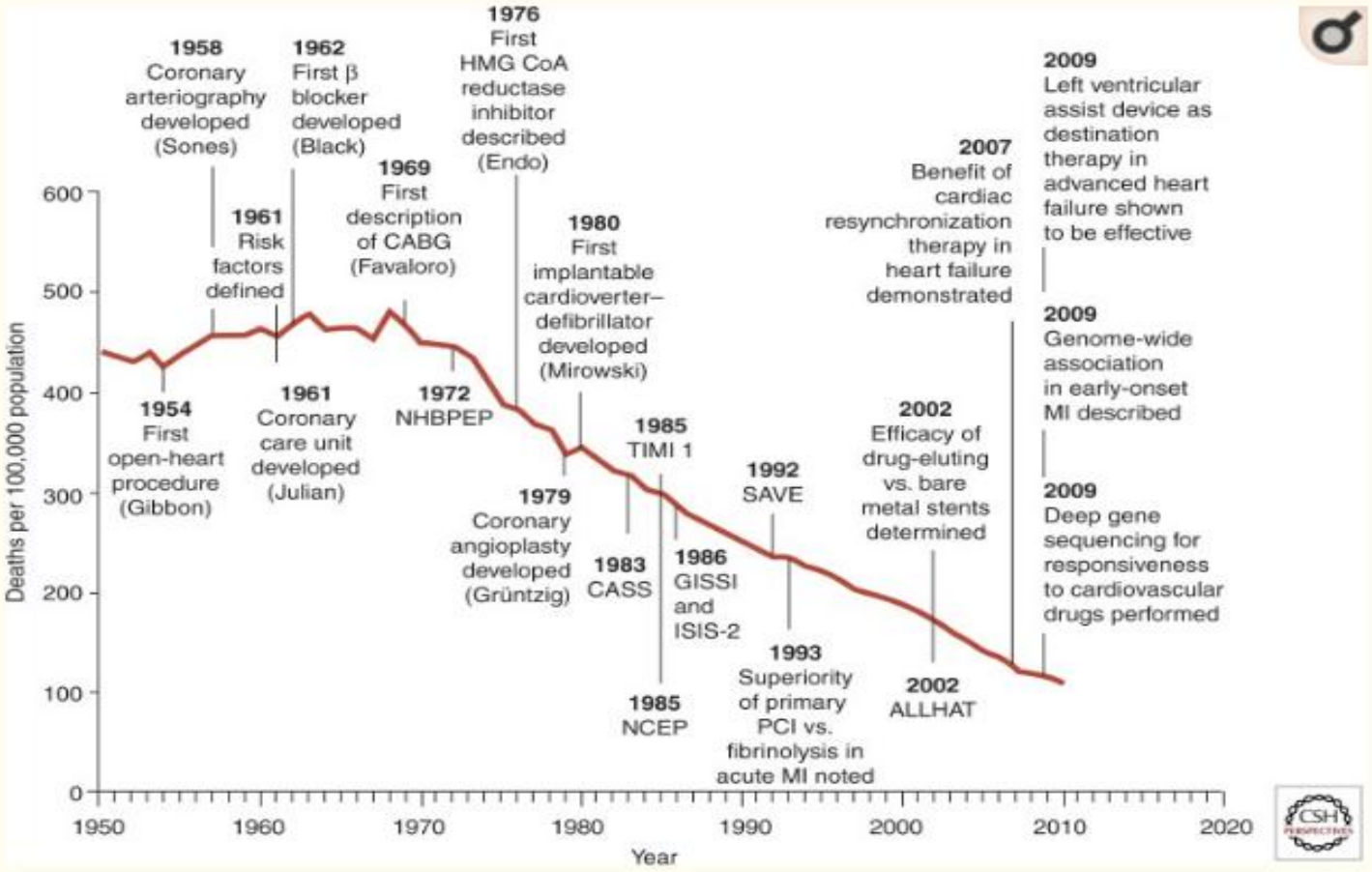


Definition

- Drugs having their major action on heart or blood vessels, or those used primarily for cardiovascular disorders are designated cardiovascular drugs.

- They can act directly on the cardiovascular structures or through autonomic/central nervous system, kidney, autacoids or hormones which regulate cardiovascular function.

Cardiovascular disease constitutes the largest single cause of death in the industrialized countries. As with cancer, which is a distant second in terms of mortality, cardiovascular disease morbidity increases with age, accounting for about two-thirds of all deaths in persons over 75. Even though some diseases affect primarily the heart and other diseases effect the vascular system, they cannot be divorced from each other. This obvious interdependence makes a unified imperative. One of the major diseases, atherosclerosis, affects and ultimately damages the heart, kidneys, and other organs.

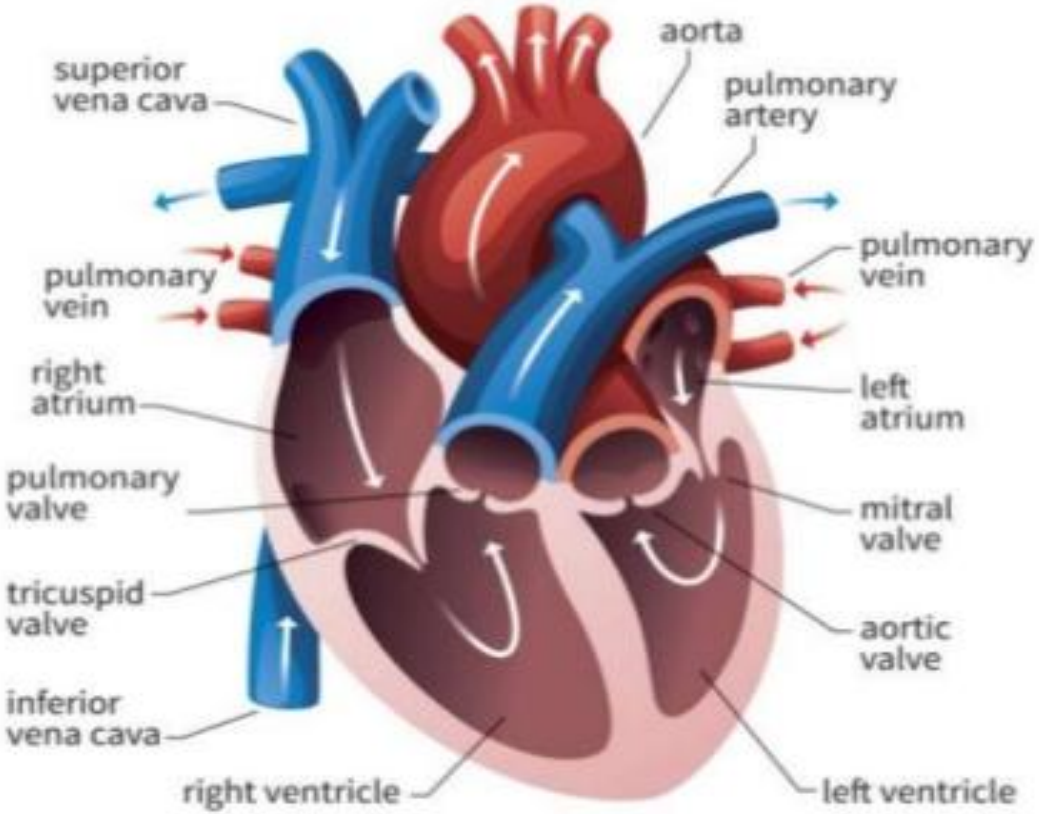


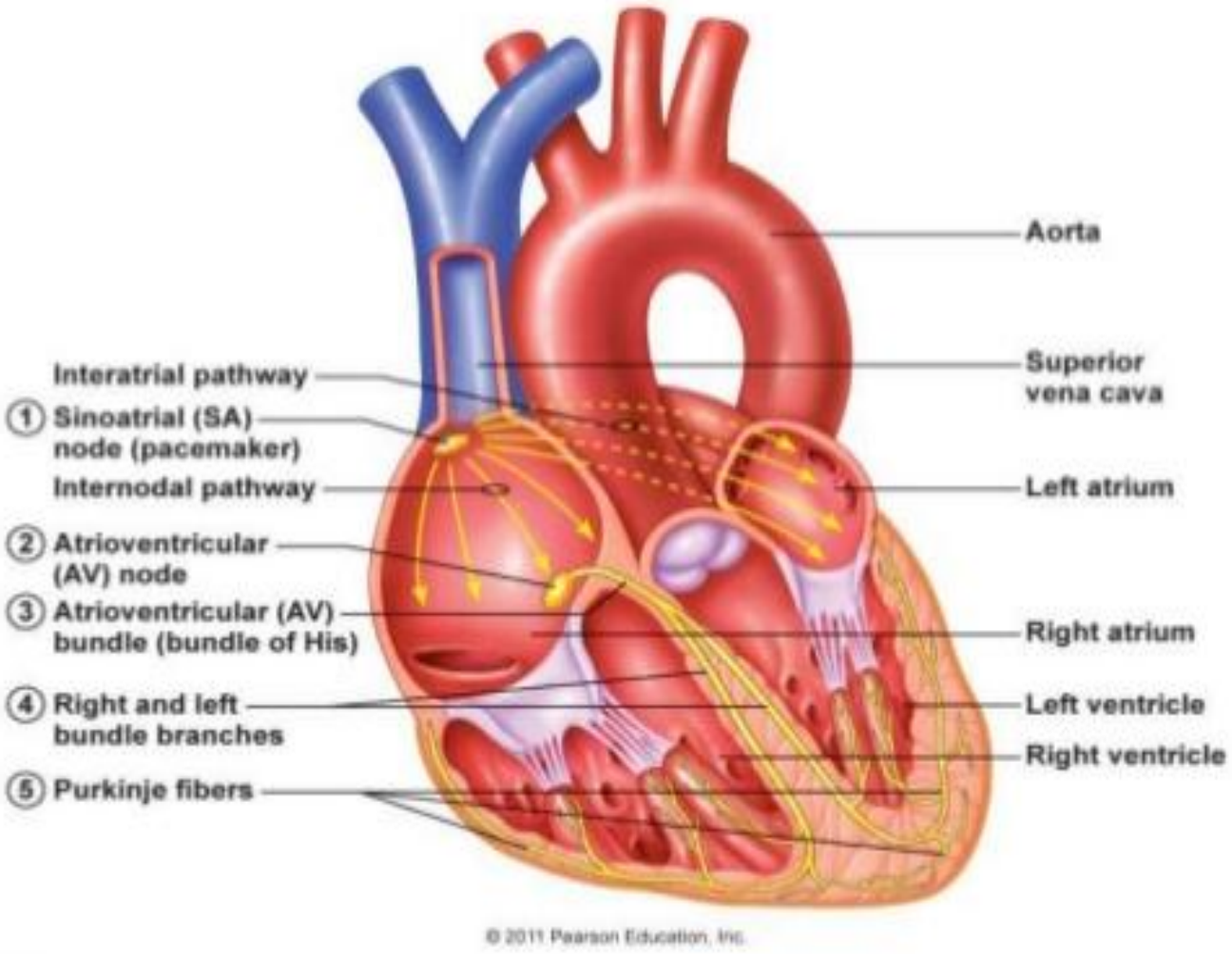
Figure

Decline in deaths from cardiovascular disease in relation to scientific advances. (From Mabel and Braunwald 2012; reproduced, with permission.)

G. Gromo, J. Mann, J.D. Fitzgerald, "Cardiovascular Drug Discovery: A Perspective from a Research-Based Pharmaceutical Company" Cold Spring Harb Perspect Med. 2014, 4(6) a014092

Structure of the Heart




Aorta
Interatrial pathway
Superior vena cava
1 Sinoatrial (SA) node (pacemaker)
Internodal pathway
Left atrium
2 Atrioventricular (AV) node
3 Atrioventricular (AV) bundle (bundle of His)
Right atrium
4 Right and left bundle branches
Left ventricle
Right ventricle
5 Purkinje fibers
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Main Diseases of the Cardiovascular System

- Angina Pectoris
- Hypertension
- Cardiac Arrhythmias
- Congestive Heart Failure (CHF)

ANTIANGINAL DRUGS

- Antianginal drugs prevent, abort or terminate attacks of angina pectoris.
- Angina Pectoris is a pain syndrome due to induction of an adverse oxygen supply/demand situation in a portion of the myocardium.

***The risk factors for the development of angina pectoris and CHD are genetic predisposition, age, male sex, and a series of reversible risk factors. The most important factors include high-fat and cholesterol-rich diets, lack of exercise, inability to retain normal cardiac function under increased exercise tolerance, tobacco and smoking (because nicotine is a vasoconstrictor), excessive alcohol drinking, carbohydrate and fat metabolic disorders, diabetes, hypertension, obesity, and the use of drugs that produce vasoconstriction or enhanced oxygen demand.

Classification of Antianginal Drugs

1. Nitrates:

(a) Short acting: *Glyceryl trinitrate* (GTN, Nitroglycerine)
(b) Long acting: *Isosorbide dinitrate* (short acting by sublingual route*), Isosorbide mononitrate*, *Erythrityl tetranitrate, Pentaerythritol tetranitrate*.

2. Calcium Channel Blockers:

(a) Phenyl alkylamines: *Verapamil, Gallopamil*
(b) Benzothiazepine: *Diltiazem*
(c) Dihydropyridines: *Nifedipine, Felodipine, Amlodipine, Isradipine, Nitrendipine, Nimodipine, Lacidipine*, and others.

3. β Blockers:

*Propranolol, Metoprolol, Atenolo*l and others.

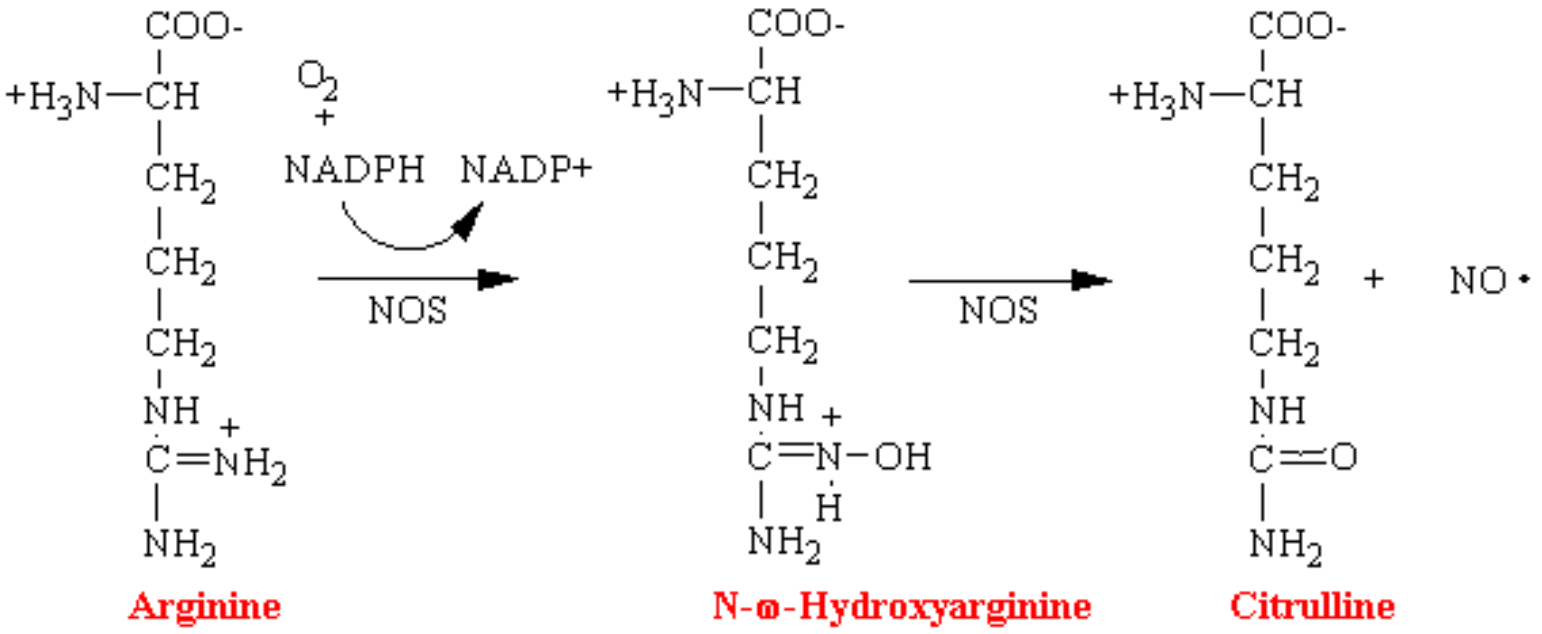
4. Others: Nonspesific Coronary Dilators

Organic Nitrates

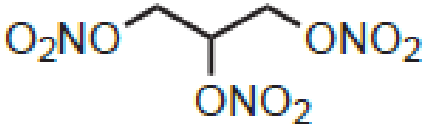
- The organic nitrates and nitrites are dilators of arterial and venous smooth muscle. The vasodilation results in decreased left and right ventricular end-diastolic pressure, which are greater on a percentage basis than is the decrease in systemic arterial pressure. Net systemic vascular resistance is usually relatively unaffected; heart rate is unchanged or slightly increased; and pulmonary vascular resistance is consistently reduced. These drugs correct the inadequacy of myocardial oxygenation by increasing the supply of oxygen to ischemic myocardium by direct dilatation of the coronary vasculature and by decreasing the oxygen demand by a reduction in cardiac work. The latter results from the decrease in vascular pressure enabling the heart to pump blood easier.

Mechanism of Action

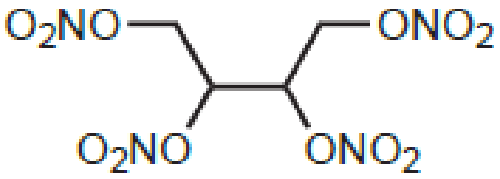
- Nitric oxide (NO) has been shown to be an important messenger in many signal transduction processes. This free radical gas is naturally produced endogenously from arginine in a complete reaction that is catalyzed by nitric oxide synthetase (NOS).



Nitrovasodilators



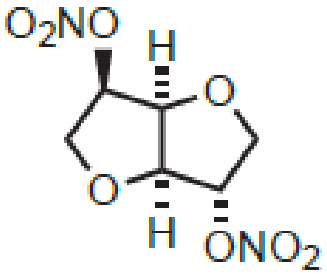
Glyceryl Trinitrate



Erythrityl Tetranitrate

Amyl Nitrite

Pentaerythritol Tetranitrate

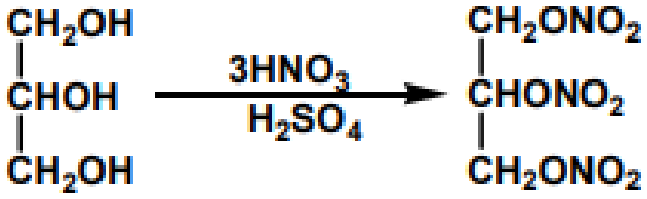


Isosorbide Dinitrate

PHARMACEUTICAL PREPARATIONS AND DOSAGE FORMS Organic nitrates are administered by inhalation; by infusion; as sublingual, chewable, and sustained-release tablets; as capsules; as transdermal disks; and as ointments.

Rapid acting compounds

(Glyceryl trinitrate)



(Glyceryl trinitarte)

It is dispensed in sublingual, buccal, and trans-dermal preparations (patch).

Onset of action is 2 minutes and lasts for half an hour

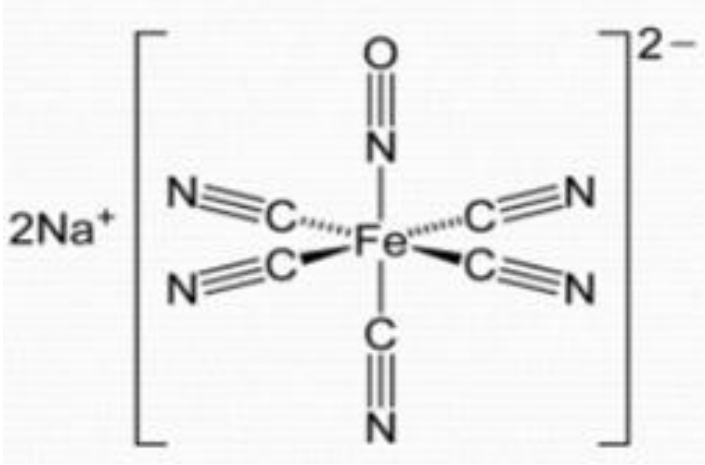
It is an effective antianginal because it causes redistribution of coronary blood flow to ischemic regions of the heart.

Glyceryl trinitrate, or nitroglycerine, is a dense sweet-smelling oil that is highly explosive.

Buccal absorption is rapid, offering almost instantaneous relief of sufficient duration (<30 min) for the emergency. In order to get continuous blood levels different and innovative dosage forms are being developed. Because nitroglycerin is efficiently absorbed through the skin, this has led to the introduction of nitroglycerin skin patches. These patches contain the drug in a form which results in its continuous release.

Sodium Nitroprusside

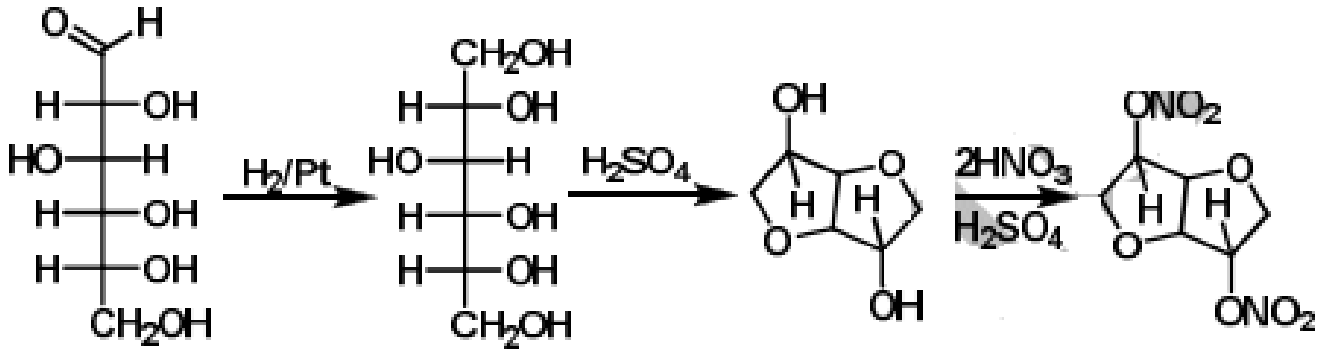
$Na_2Fe(CN)_5NO$ Nipride®, Nipruss®



- Rapidly and consistently acting vasodilator
- Relaxes both resistance and capacitance of vessels (decrease in venous return)
- Produces decrease in cardiac work and no reflex tachycardia.
- Improves ventricular function in heart failure by reducing preload
- MOA: RBCs convert nitroprusside to NO – relaxation also by non-enzymatically to NO by glutathione
- Uses: Hypertensive Emergencies, 50 mg is added to 500 ml of saline/glucose and infused slowly with 0.02 mg/min initially and later on titrated with response (wrap with black paper)
- Adverse effects: All are due release of cyanides (thiocyanate) – palpitation, pain abdomen, disorientation, psychosis, weakness and lactic acidosis.

Slow acting compounds

Diluted Isosorbride dinitrate (Isordil)



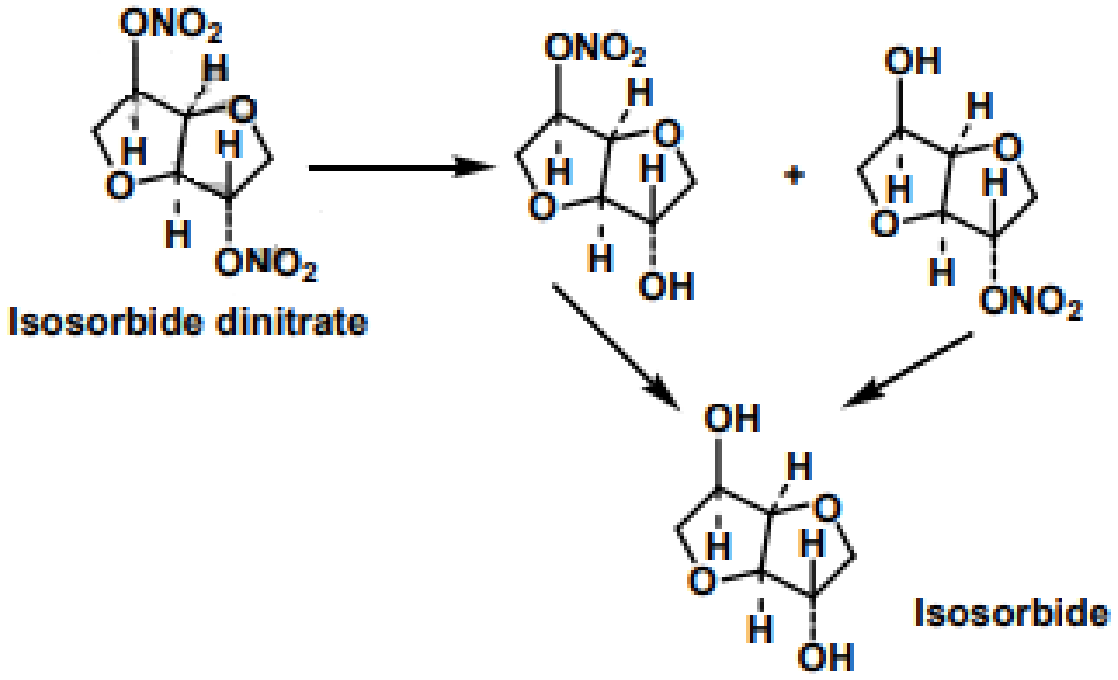
1,4:3,6-Dianhydro-D-sorbitol dinitrate

Isosorbide dinitrate is used for *prophylaxis or* treatment of acute angina in the form of sublingual tablets.

Its onset of action is 3 min. and duration is one hour.

5-isomer is still potent vasodilator, its plasma half life of about 4.5 hours is much longer than isosorbide dinitrate itself, the extended half life owing to the metabolite's resistance to other metabolism indicates that it may be contributed to the prolonged duration of action of isosorbide

Metabolism of isosorbide dinitrate

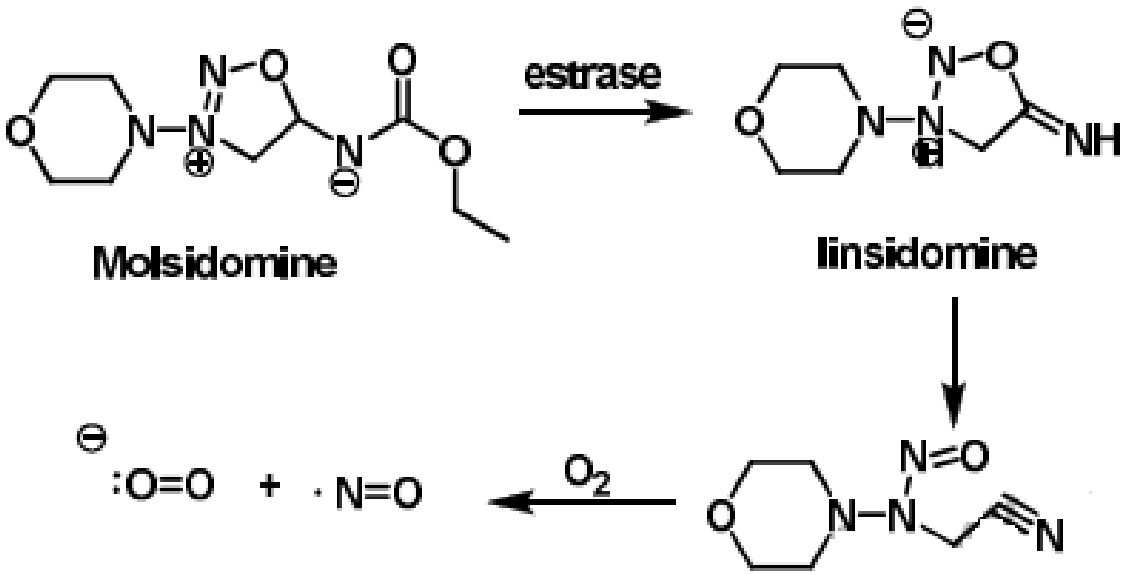


2-Nitric Oxide Donor

N-ethoxy carbonyl-3-morpholino sydnone imine

Corvaton®, Molsicor®

Molsidomine (Corvaton)



Molsidomine is an oral nitric oxide donor known as sydnone imine, a mesionic compound soluble in both water and organic solvents

Molsidomine has a slower onset and longer duration of action than conventional nitrates because the relatively slow rate of conversion to linsidomine which has rapid onset and shorter duration.

Used in treatment of stable angina