

Chapter 2 – Nitrates and Newer Antianginals

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“When the remedy is used for a long time, the dose requires to be increased before the effect is produced.”

Brunton, 1867!^[1]

The Nature of Angina of Effort

Besides the classic and well-described constricting chest pain with its characteristic radiation that is brought on by effort in those with symptomatic coronary artery disease, and its diagnostic relief by cessation of effort, there are a series of crescendo and decrescendo events that precede and follow the anginal pain (Fig. 2-1). The crescendo events constitute the ischemic cascade of Nesto,^[2] to which must be added postischemic stunning,^[3] often ignored.

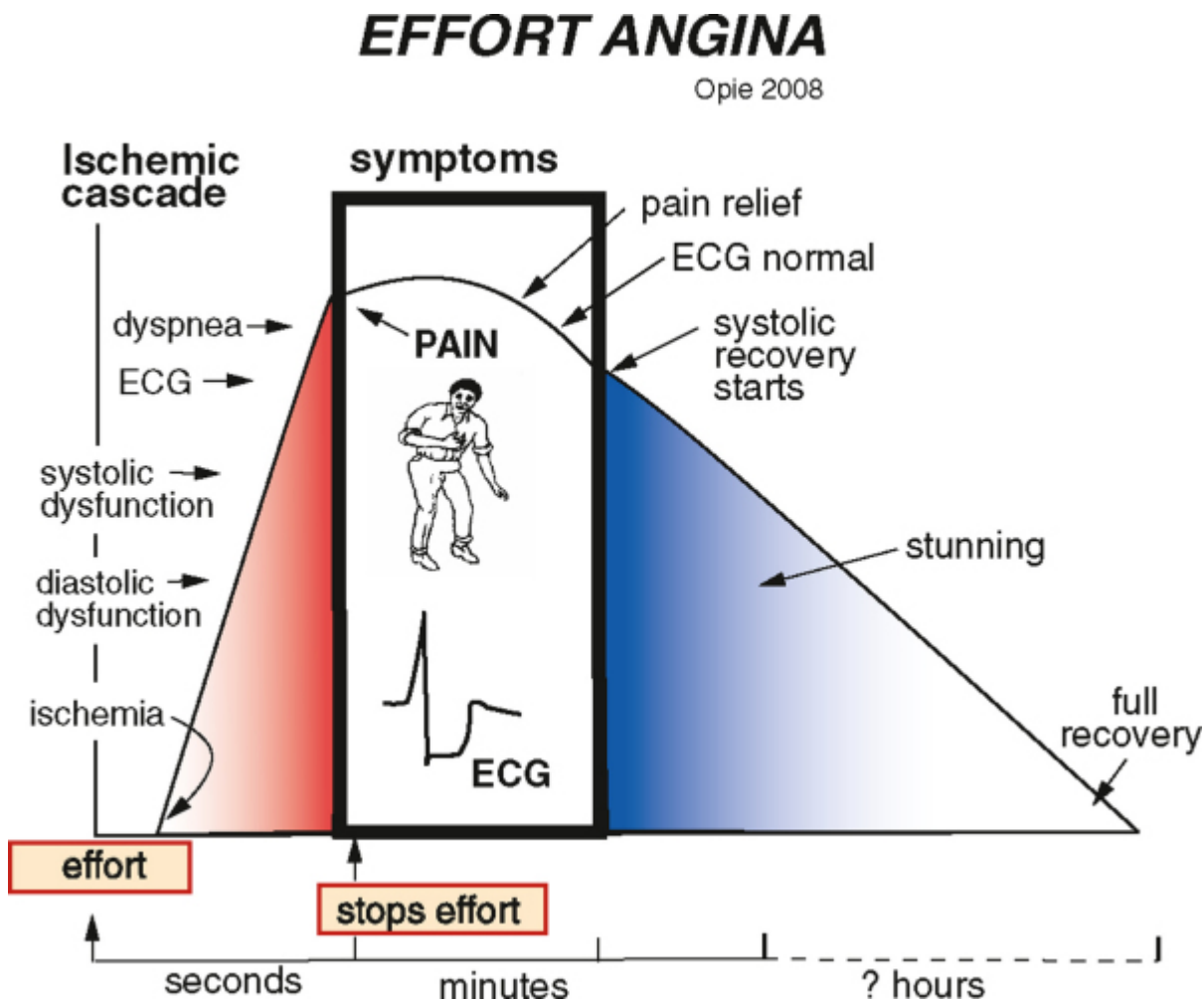


Figure 2-1 The ischemic cascade leading to the chest pain of effort angina followed by a period of mechanical stunning with slow recovery of full function. (For basic concepts see Nesto.[2]) (ECG, electrocardiogram.) (Figure © L.H. Opie, 2008.)

The initial imbalance between the oxygen supply and demand leads to inadequate myocardial blood flow (myocardial ischemia) that, in turn, sets off a series of metabolic changes. A deficit of high-energy phosphates leads to loss of potassium and gain of sodium and calcium, with rapid onset of diastolic dysfunction. A little later this is followed by systolic dysfunction, electrocardiographic changes, shortness of breath, and then the onset of anginal chest pain, which stops the effort. In the recovery period, the electrocardiogram reverts to normal shortly after pain relief, but systolic recovery can be delayed for at least 30 minutes (stunning).

This chapter focuses on the antianginal effects of nitrates, one of *four major classes of antianginals*, including β -blockers and calcium channel blockers (CCBs) (Fig. 2-2). Mechanistically, nitrates and CCBs are coronary vasodilators, with nitrates also reducing the preload and CCBs the afterload. β -Blockers reduce oxygen demand by slowing the heart and by a negative inotropic effect. Metabolic antianginals constitute the new fourth class, acting by metabolic modulation without major hemodynamic effects. Antianginals should be viewed a part of a global antiatherosclerotic attack by statins, aspirin, and angiotensin-converting enzyme (ACE) inhibitors to constitute an effective alternative or additive to percutaneous coronary intervention (PCI).[4]

ACTION OF ANTIANGINALS

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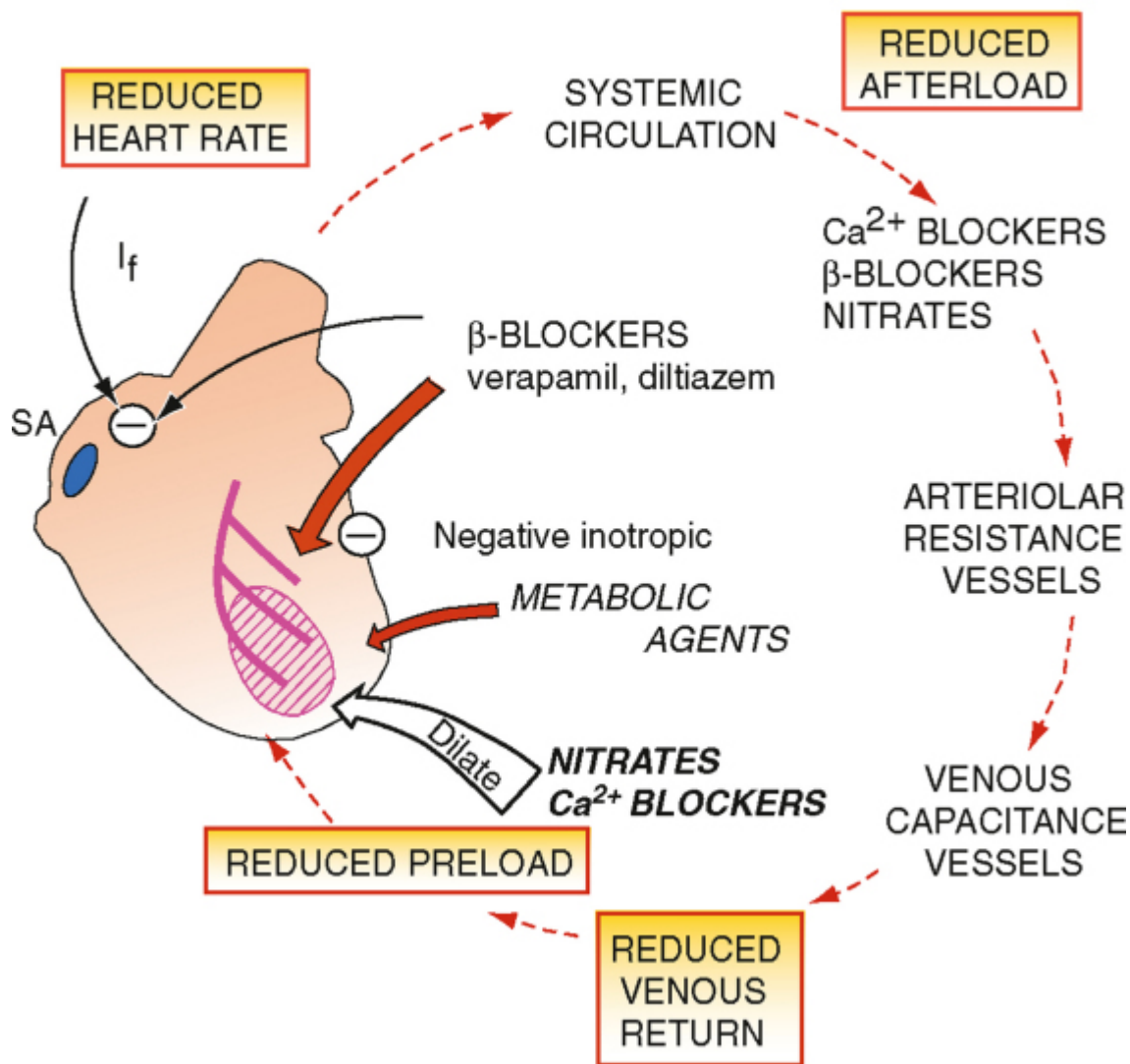


Figure 2-2 Proposed antianginal mechanisms for the major four classes of antianginal agents: nitrates, β -blockers, calcium channel blockers, and metabolic agents (for details of metabolic agents, see Fig. 2-7). (SA, sinoatrial.) (Figure © L.H. Opie, 2008.)

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Mechanisms of Nitrate Action in Angina

Nitrates provide an exogenous source of the vasodilator nitric oxide, a very short-lived free radical (NO^{\bullet} , usually given as NO), thereby inducing coronary vasodilation even when endogenous production of NO is impaired by coronary artery disease. Thus nitrates act differently from the other classes of antianginals (see Fig. 2-2). *Chronic use of nitrates produces tolerance, a significant clinical problem.* The main focus of current clinical work remains on strategies to minimize or prevent the development of tolerance, with the major emphasis on the adverse role of excess NO that produces harmful peroxynitrite.^[5] The thrust of basic work has shifted to endogenously produced NO as a ubiquitous physiologic messenger, as described by the winners of the 1998 Nobel Prize for Medicine, namely Furchgott, Ignarro, and Murad.^[6] Although endogenously produced NO has many functions (such as a role in vagal neurotransmission) quite different from the NO derived from exogenous nitrates, there are important shared vasodilatory effects.

Vasodilatory effects, coronary and peripheral.

A distinction must be made between antianginal and coronary vasodilator properties. Nitrates preferentially dilate large coronary arteries and arterioles greater than $100\ \mu\text{m}$ in diameter^[7] to (1) redistribute blood flow along collateral channels and from epicardial to endocardial regions, and (2) relieve coronary spasm and dynamic stenosis, especially at epicardial sites, including the coronary arterial constriction induced by exercise. Thereby exercise-induced myocardial ischemia is relieved. Thus nitrates are “effective” vasodilators for angina; dipyridamole and other vasodilators acting more distally in the arterial tree are not, rather having the risk of diverting blood from the ischemic area—a “coronary steal” effect.

The additional peripheral hemodynamic effects of nitrates, originally observed by Lauder Brunton,^[1] cannot be ignored. Nitrates do reduce the afterload, in addition to the preload, of the heart (Fig. 2-3). The arterial wave reflection from the periphery back to the aorta is altered in such a way that there is “true” afterload reduction, with the aortic systolic pressure falling even though the brachial artery pressure does not change.^[8]

ACTION OF NITRATES ON CIRCULATION

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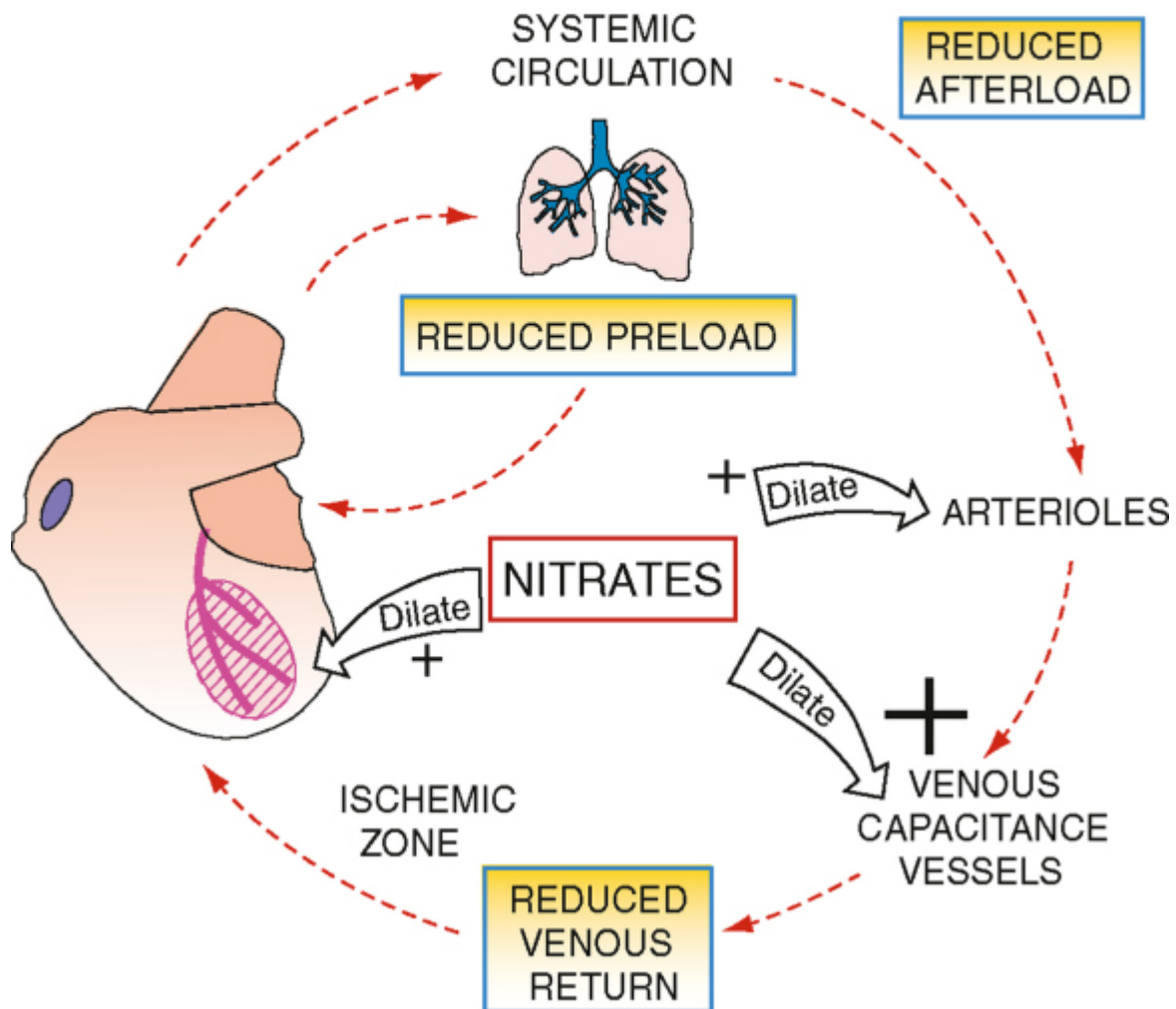


Figure 2-3 Schematic diagram of effects of nitrate on the circulation. The major effect is on the venous capacitance vessels, with additional coronary and peripheral arteriolar vasodilatory benefits.

(Figure © L.H. Opie, 2008.)

Reduced oxygen demand.

Nitrates increase the venous capacitance, causing pooling of blood in the peripheral veins and thereby a reduction in venous return and in ventricular volume. There is less mechanical stress on the myocardial wall and the myocardial oxygen demand is reduced. Furthermore, a fall in the aortic systolic pressure also reduces the oxygen demand.

Endothelium and vascular mechanisms.

The fundamental mechanism of nitrate biologic effect is the enzyme-mediated release of highly unstable NO^* from the nitrate molecule (Fig. 2-4). An intact vascular endothelium is required for the vasodilatory effects of some vascular active agents (thus acetylcholine physiologically vasodilates but constricts when the endothelium is damaged). Nitrates vasodilate whether or not the endothelium is physically intact and/or functional (although their vasodilator effects are attenuated by endothelial dysfunction). Prolonged nitrate therapy with formation of peroxynitrite may, however, inhibit endothelial NO synthase, which is one of

several postulated mechanisms of nitrate tolerance.^[5] Similarly, long-term continuous use of long-acting nitrates may cause endothelial dysfunction mediated by free radicals^[9]; whether this problem extends to aggravation of preexisting endothelial dysfunction is uncertain. Thus nitrate tolerance and endothelial dysfunction have partially shared pathogenetic mechanisms. Nitrates, after entering the vessel wall, are bioconverted to release nitric oxide (NO[•]), which stimulates guanylate cyclase to produce cyclic GMP (see Fig. 2-4). Calcium in the vascular myocyte falls, and vasodilation results. Sulfhydryl (SH) groups are required for such formation of NO[•] and the stimulation of guanylate cyclase. Nitroglycerin powerfully dilates when injected into an artery, an effect that is probably limited in humans by reflex adrenergic-mediated vasoconstriction. Hence (1) nitrates are better venous than arteriolar dilators, and (2) there is an associated adrenergic reflex tachycardia^[10] that can be attenuated by concurrent β-blockade.

NITRATE MECHANISMS

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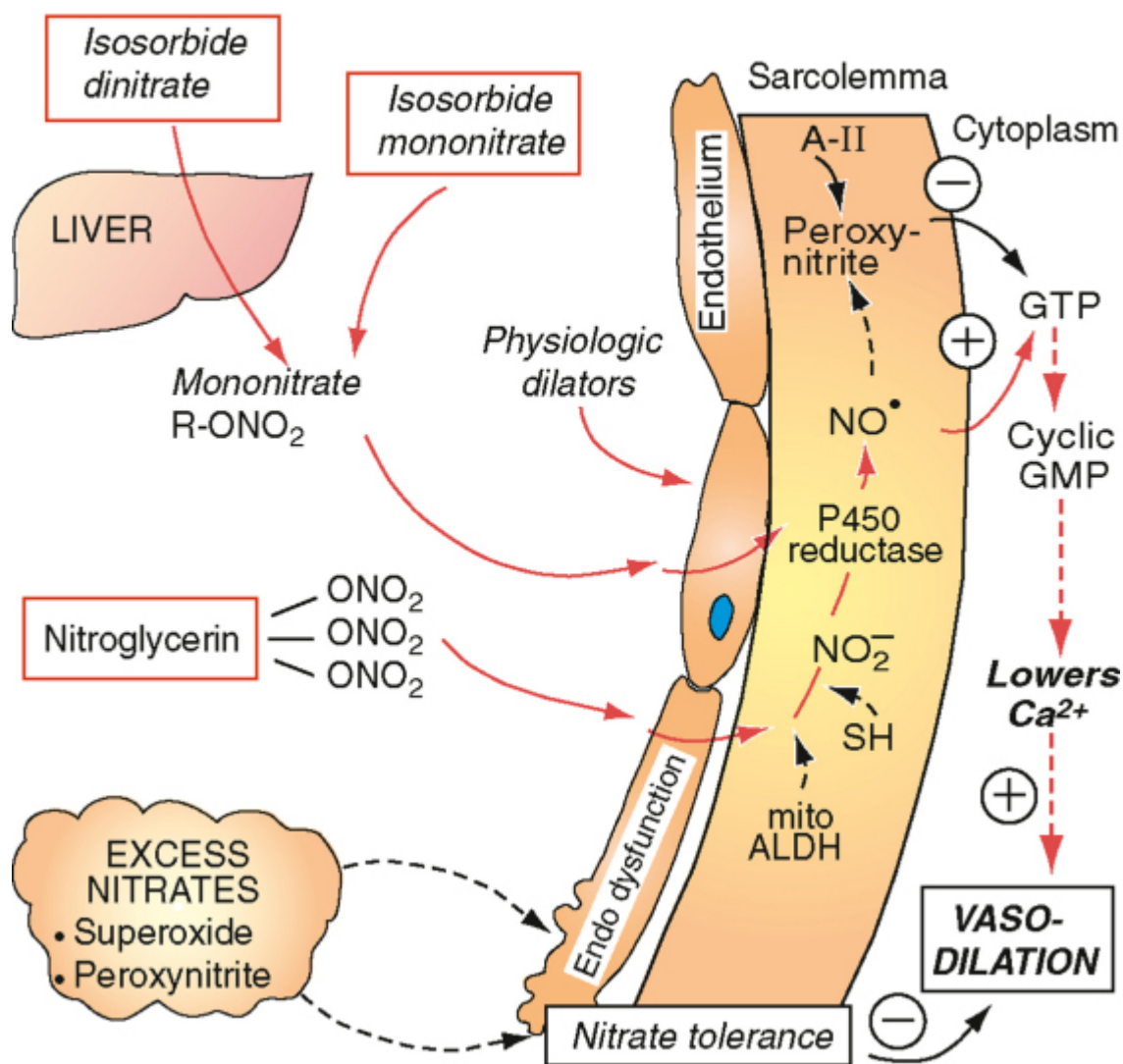


Figure 2-4 Effects of nitrates in generating NO[•] and stimulating guanylate cyclase to cause vasodilation. To explain nitrate tolerance, current emphasis is on the generation of peroxynitrite and superoxide, which ultimately inhibit the conversion of GTP to cyclic GMP. Note that mononitrates bypass hepatic metabolism and the mitochondrial aldehyde dehydrogenase-2 (mito ALDH) step required for bioactivation of nitroglycerin. (A-II, angiotensin II; endo, endothelial; GMP, guanosine monophosphate; GTP, guanosine triphosphate; P450, cytochrome P-450; SH, sulfhydryl.) (Figure © L.H. Opie, 2008.)

Antiaggregatory effects.

Organic nitrates mimic the effects of endogenous NO[•] in inhibiting and potentially reversing platelet aggregation.^{[3],[11],[12]} These effects are mediated primarily via the classical pathway of stimulation of activation of soluble guanylate cyclase (see Fig. 2-4).

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Pharmacokinetics of Nitrates

Bioavailability and half-lives.

The various nitrate preparations differ so much that each needs to be considered separately. As a group, nitrates are absorbed from the mucous membranes, the skin, and the gastrointestinal tract. All organic nitrates undergo serial enzymatic denitration, releasing NO[•]. The prototype agent, nitroglycerin, has pharmacokinetics that are not well understood. It rapidly disappears from the blood, with a half-life of only a few minutes, largely by extrahepatic mechanisms that convert the parent molecule to longer acting and active dinitrates.^[13] Isosorbide dinitrate, in contrast, must first be converted in the liver to active mononitrates (see Fig. 2-4) that have half-lives of about 4 to 6 hours with ultimate renal excretion. The mononitrates are completely bioavailable without any hepatic metabolism, with half-lives of 4 to 6 hours. In reality, knowledge of pharmacokinetics is of limited interest, because of the highly variable relationship between the plasma concentrations of the nitrates, the levels of their active metabolites, and the onset and duration of pharmacologic action that matter most to the clinician.^[13] Of the many nitrate preparations (Table 2-1), sublingual nitroglycerin remains the “gold standard” for acute anginal attacks.^[14] In practice, patients are often also given long-acting nitrates. “No matter which long-acting preparation is used, physicians should prescribe the drug in a manner to decrease the likelihood of nitrate tolerance. This involves an on-off strategy of at least a 10-hour nitrate free interval each day.”^[14] This policy does, however, entertain the risk of precipitation of angina during the nitrate-free interval, which is often at night.

Table 2-1 -- Nitrate Preparations, Doses, and Duration of Effects

Compound	Route	Preparation and Dose	Duration of Effects and Comments
Amyl nitrite	Inhalation	2–5 mg	10 sec–10 min; for diagnosis of LV outflow obstruction in hypertrophic cardiomyopathy.
Nitroglycerin (trinitrin, TNT, glyceryl trinitrate)	<p>(a) Sublingual tablets</p> <p>(b) Spray</p> <p>(c) Ointment</p> <p>(d) Transdermal patches</p> <p>(e) Oral; sustained release</p> <p>(f) Buccal</p> <p>(g) Intravenous infusion (discontinued in USA)</p>	<p>0.3–0.6 mg up to 1.5 mg</p> <p>0.4 mg/metered dose</p> <p>2%; 6 × 6 inches or 15 × 15 cm or 7.5–40 mg</p> <p>0.2–0.8 mg/hr: patch on for 12 hr, patch off for 12 hr</p> <p>2.5–13 mg; 1–2 tablets 3 × daily</p> <p>1–3-mg tablets 3 × daily</p> <p>5–200 mcg/min (care with PVC)</p> <p>Tridil 0.5 mg/ml or 5.0 mg/ml Nitro-Bid IV 5 mg/ml</p>	<p>Peak blood levels at 2 min; t_{1/2} about 7 min; for acute therapy of effort or rest angina. Keep tightly capped.</p> <p>Similar to tablets at same dose. Apply 2 × daily; 6-hr intervals; effect up to 7 hr after first dose. No efficacy data for chronic use.</p> <p>Effects start within minutes and last 3–5 hr. No efficacy data for second or third doses during chronic therapy.</p> <p>4–8 hr after first dose; no efficacy data for chronic therapy.</p> <p>Effects start within minutes and last 3–5 hr. No efficacy data for second or third doses during chronic therapy.</p> <p>In unstable angina, increasing doses are often needed to overcome tolerance. High-concentration solutions contain propylene glycol; cross-</p>

Compound	Route	Preparation and Dose	Duration of Effects and Comments
			reacts with heparin.
Isosorbide dinitrate (= sorbide nitrate) Isordil	(a) Sublingual (b) Oral tablets (c) Spray (d) Chewable (e) Oral; slow release (f) Intravenous infusion (g) Ointment	2.5–15 mg 5–80 mg 2–3 × daily 1.25 mg on tongue 5 mg as single dose 40 mg once or 2 × daily 1.25–5.0 mg/hr (care with PVC) 100 mg/24 hr	Onset 5–10 min, effect up to 60 min or longer. Up to 8 hr (first dose; then tolerance) with 3 × or 4 × daily doses; 2 × daily 7 hr apart may be effective but data inadequate. Rapid action (2–3 min). Exercise time increased for 2 min–2½ hr. Up to 8 hr (first dose; 2 × daily not superior to placebo). May need increasing doses for unstable angina at rest. Not effective during continuous therapy.
Isosorbide 5-mononitrate	Oral tablets	20 mg 2 × daily (7 hr apart)	12–14 hr after chronic dosing for 2 wk.
		120–240 mg 1 × daily (slow release)	Efficacy up to 12 hr after 6 wk.
Pentaerythritol tetranitrate	Sublingual	10 mg as needed	No efficacy data.

For references, see previous editions and text.

IV, intravenous; LV, left ventricular; PVC, polyvinyl chloride tubing, $t_{1/2}$, half-life.

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Nitrate Interactions with Other Drugs

Many of the potential interactions of nitrates are pharmacodynamic, involving potentiation of vasodilatory effects, as with the CCBs. However, the chief example of vasodilator interactions is with the selective phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil, used in treatment of erectile dysfunction. All can cause serious hypotensive reactions when combined with nitrates (Fig. 2-5). Hence the package insert of each agent forbids coadministration to patients taking nitrates in any form either regularly or intermittently. For example, sildenafil decreases the blood pressure by about 8.4/5.5 mm Hg, and by much more in patients taking nitrates. The exertion of sexual intercourse also stresses the cardiovascular system further. As a group, these drugs also should not be given with α -adrenergic blockers. In case of *inadvertent PDE-5-nitrate combinations*, administration of an α -adrenergic agonist or even of norepinephrine may be needed.

SERIOUS NITRATE-DRUG INTERACTION

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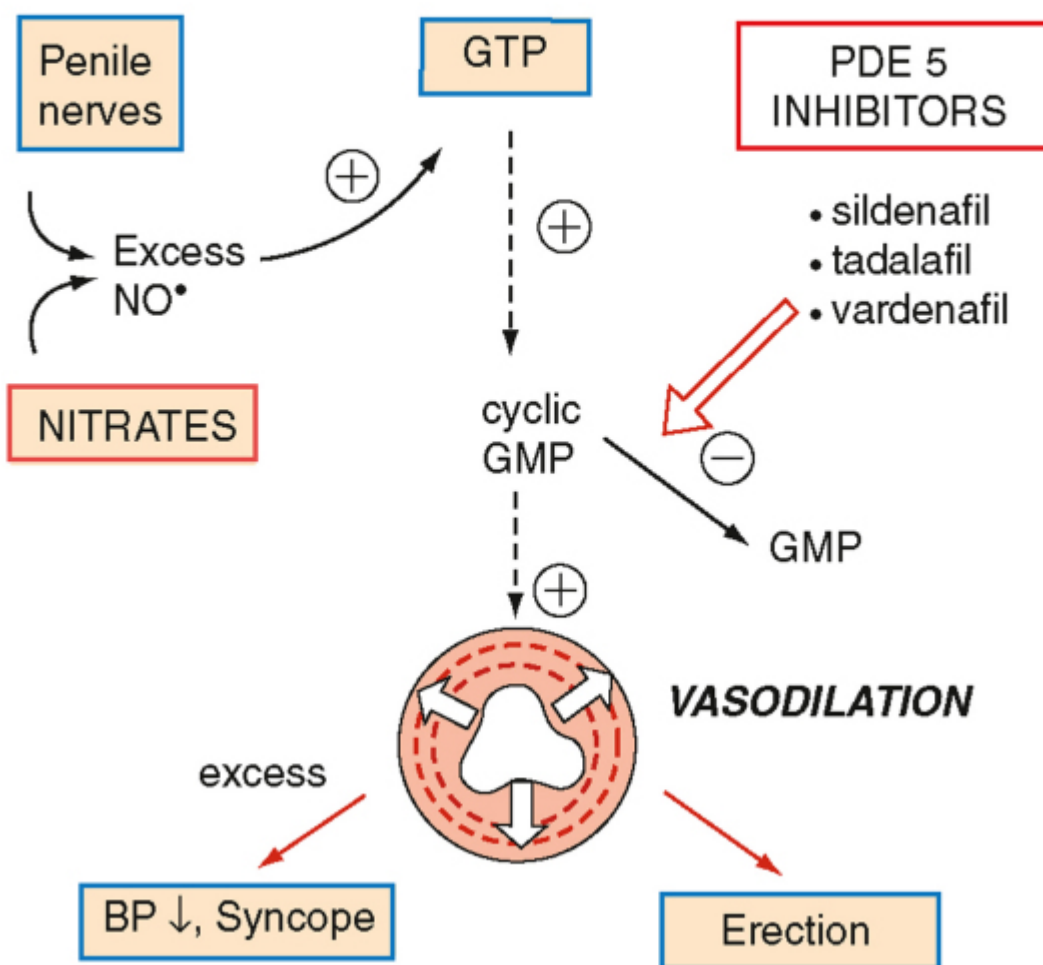


Figure 2-5 A serious nitrate-drug interaction. The mechanism of normal erection involves penile vasodilation mediated by GTP and cyclic GMP. The phosphodiesterase-5 (PDE 5) inhibitors such as sildenafil (Viagra) act by inhibiting the enzymatic breakdown of penile cyclic GMP to GMP with increased vasodilation. This is not confined to the penis, and peripheral vasodilation, added to that caused by nitrates, gives rise to an excess fall of blood pressure (BP) and possible syncope. Hence the use of PDE 5 inhibitors in any patient taking nitrates is contraindicated. (GMP, guanosine monophosphate; GTP, guanosine triphosphate).

(Figure © L.H. Opie, 2008.)

An essential question for males with acute coronary syndrome.

Whenever a male patient presents with an anginal attack or acute coronary syndrome, whether or not precipitated by sexual intercourse, then one essential question is: "Have you recently taken Viagra or Levitra or Cialis (the trade names for sildenafil, vardenafil, and tadalafil)?" If so, how soon can a nitrate be given? In clinical practice, nitrates may be started 24 hours after sildenafil.^[14] Likewise, for vardenafil, a 24-hour interval can be inferred from data in the package insert. For the longer acting tadalafil, the corresponding interval is 48 hours.^[15]

Beneficial combination with hydralazine.

There is a beneficial interaction between nitrates and hydralazine (at least in congestive heart failure) whereby the latter helps to lessen nitrate tolerance,^[16] probably acting through inhibition of free radical formation. This may explain why the combination of nitrates and hydralazine is effective in heart failure and is now approved for use in the United States as BiDil (NitroMed, Inc.) for self-identified black patients with heart failure (see Chapter 6, p. 184). Approval was based in part on results of the African-American Heart Failure Trial (A-HeFT) showing that BiDil gave a 43% reduction in death and a 39% reduction in hospitalizations.^[17] The combination used was isosorbide dinitrate 20 mg and hydralazine 37.5 mg, both given three times daily.

High-dose intravenous nitroglycerin: is heparin resistance relevant?

The infusion rate of nitroglycerin required to produce heparin resistance is relatively high (>350 mcg/min), and such infusion rates should not ordinarily be required. With lower doses, no significant interaction was found.^[18]

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Short-Acting Nitrates for Acute Effort Angina

Sublingual nitroglycerin is very well established in the initial therapy of angina of effort, yet may be ineffective, frequently because the patient has not received proper instruction or because of severe headaches. When angina starts, the patient should rest in the sitting position (standing promotes syncope, lying enhances venous return and heart work) and take sublingual nitroglycerin (0.3 to 0.6 mg) every 5 minutes until the pain goes or a maximum of 4 to 5 tablets have been taken. *Nitroglycerin spray* is an alternative mode of oral administration, which is more acceptable to some patients. It vasodilates sooner than does the tablet, which might be of special importance in those with dryness of the mouth.^[19]

Isosorbide dinitrate may be given *sublingually* (5 mg) to abort an anginal attack and then exerts antianginal effects for about 1 hour. Because the dinitrate requires hepatic conversion to the mononitrate, the onset of antianginal action (mean time: 3.4 minutes) is slower than with nitroglycerin (mean time: 1.9 minutes), so that the manufacturers of the dinitrate recommend sublingual administration of this drug only if the patient is unresponsive to or intolerant of sublingual nitroglycerin. After oral ingestion, hemodynamic and antianginal effects persist for several hours. Single doses of isosorbide dinitrate confer longer protection against angina than can single doses of sublingual nitroglycerin (see Table 2-1).

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Long-Acting Nitrates for Angina Prophylaxis

Long-acting nitrates are not continuously effective if regularly taken over a prolonged period, unless allowance is made for a nitrate-free or -low interval (Table 2-2). Worsening of endothelial dysfunction is a potential complication of long-acting nitrates that should be avoided.^[9] Hence the common practice of routine use of long-acting nitrates for patients with effort angina^[20] may have to be re-evaluated.

Table 2-2 -- Interval Therapy for Effort Angina by Eccentric Nitrate Dosage Schedules Designed to Avoid Tolerance

Preparation	Dose	Reference
Isosorbide dinitrate (Dilatrate-SR)	30 mg at 7 AM, 1 PM ^[*]	Thadani & Lipicky (1994) ^[†]
Isosorbide mononitrate (Monoket, Ismo, Elantan)	20 mg at 8 AM and 3 PM	Parker (1993) ^[23]
Isosorbide mononitrate, extended-release (Imdur)	120–240 mg daily	Chrysant (1993) ^[24]
Transdermal nitrate patches	7.5–10 mg/12 hr patches removed after 12 hr	DeMots (1989) ^[51]
Phasic-release nitroglycerin patch	15 mg, most released in first 12 hr ^[‡]	Parker (1989) ^[§]

* No data for other doses; efficacy of second dose not established.

† Cardiovasc Drugs Ther 1994;8:625–633.

‡ No data for other doses.

§ Eur Heart J 1989;10(Suppl A):43–49.

Isosorbide dinitrate (oral preparation) is frequently given for the prophylaxis of angina. An important question is whether regular therapy with isosorbide dinitrate gives long-lasting protection (3 to 5 hours) against angina. In a crucial placebo-controlled study, exercise duration improved significantly for 6 to 8 hours after single oral doses of 15 to 120 mg isosorbide dinitrate, but for only 2 hours when the same doses were given repetitively 4 times daily.^[21] Marked tolerance develops during sustained therapy, despite much higher plasma isosorbide dinitrate concentrations during sustained than during acute therapy.^[21] With the extended-release formulation of isosorbide dinitrate (*Tembirds*), eccentric twice-daily treatment with a 40-mg dose administered in the morning and 7 hours later was not superior to placebo in a large multicenter study.^[22] Nonetheless, eccentric dosing schedules of isosorbide dinitrate are still often used in an effort to avoid tolerance.

Mononitrates have dosage and effects similar to those of isosorbide dinitrate. Nitrate tolerance, likewise a potential problem, can be prevented or minimized when rapid-release preparations (*Monoket*, *Ismo*, *Elantan*) are given twice daily in an eccentric pattern with doses spaced by 7 hours.^[23] Using the *slow-release preparation* (*Imdur*), a dose range from 30 to 240 mg once daily was tested for antianginal activity. Only 120 and 240 mg daily improved exercise times at 4 and 12 hours after administration, even after 42 days of daily use.^[24] These high doses were reached by titration over 7 days. A daily dose of 60 mg, still often used, was ineffective.

Transdermal nitroglycerin patches are designed to permit the timed release of nitroglycerin over a 24-hour period. Despite initial claims of 24-hour efficacy, major studies have failed to show prolonged improvement.

Limitations: Side Effects and Nitrate Failure

Side Effects

Hypotension is the most serious and headache the most common side effect (Table 2-3). Headaches characteristically occur with sublingual nitroglycerin, and at the start of therapy with long-acting nitrates.^[14] Often the headaches pass while antianginal efficacy is maintained, yet headaches may lead to loss of compliance. Concomitant aspirin may protect from the headaches and from coronary events. In chronic lung disease, arterial hypoxemia may result from vasodilation and increased venous admixture. Occasionally, prolonged high-dose therapy can cause *methemoglobinemia* (see Table 2-3), which reduces the oxygen-carrying capacity of the blood and the rate of delivery of oxygen to the tissues. Treatment is by intravenous methylene blue (1 to 2 mg/kg over 5 minutes).

Table 2-3 -- Precautions and Side Effects in Use of Nitrates

Precautions
Nitroglycerin tablets should be kept in <i>airtight containers</i> . Nitrate sprays are inflammable.
Common Side Effects
<i>Headaches</i> frequently limit dose. Arterial tolerance may exceed that in the veins. Therefore, headaches may cease while antianginal venous efficacy is sustained. Headaches often respond to aspirin. Facial flushing. Sublingual nitrates may cause halitosis.
Serious Side Effects
<i>Syncope</i> and <i>hypotension</i> from reduction of preload and afterload; alcohol or cotherapy with vasodilators may augment hypotension. Treat by recumbency. <i>Tachycardia</i> frequent, but unexplained <i>bradycardia</i> occasionally occurs in acute MI. Hypotension may cause cerebral ischemia. Prolonged high dosage can cause <i>methemoglobinemia</i> (nitrate ions can oxidize hemoglobin to methemoglobin); treat with intravenous methylene blue (1–2 mg/kg). High-dose intravenous nitrates can induce <i>heparin resistance</i> .
Contraindications
In angina caused by <i>hypertrophic obstructive cardiomyopathy</i> , nitrates may exaggerate outflow obstruction and are contraindicated except for diagnosis.
<i>Acute inferior MI</i> with right ventricular involvement: here a fall in the filling pressure may lead to hemodynamic and clinical deterioration. <i>Viagra</i> (or similar agents) may lead to excess hypotension or even acute MI.
Relative Contraindications
In <i>cor pulmonale</i> and arterial hypoxemia, nitrates decrease arterial O ₂ tension by venous admixture. Although <i>glaucoma</i> is usually held to be a contraindication, there is no objective evidence to show any increase in intraocular pressure (possible exception: amyl nitrite). <i>Cardiac tamponade</i> or constrictive pericarditis or tight mitral stenosis; the already compromised diastolic filling may be aggravated by reduced venous return.
Tolerance
Shown experimentally and clinically. Continuous therapy and high-dose frequent therapy lead to tolerance that eccentric dosage may avoid. Cross-tolerance occurs between the various formulations.
Withdrawal Symptoms
Established in munition workers, in whom withdrawal may precipitate symptoms and sudden death. Some evidence for a similar clinical syndrome.
Therefore, long-term nitrate therapy should be gradually discontinued.
Recurrence of anginal pain in nitrate-free intervals during sustained therapy occurs in some patients, but is less common with β -blocker cotherapy.



Failure of Nitrate Therapy

In contrast to the marked beneficial effects of sublingual nitroglycerin in reversing attacks of angina pectoris, long-acting nitrates are only moderately effective in reducing frequency of angina pectoris or in relieving symptoms in patients with heart failure. Apart from issues of noncompliance, the principal reason for limitation of therapeutic response to nitrates can be categorized as NO resistance, “true” nitrate tolerance, or nitrate pseudo-tolerance, alone or in combination (Table 2-4).

Table 2-4 -- Factors Limiting Responsiveness to Organic Nitrates

Anomaly	Principal Mechanisms	Effects
NO resistance	“ Scavenging ” of NO	De novo hyporesponsiveness
	Dysfunction of soluble guanylate cyclase	
“True” nitrate tolerance	(1) Impaired bioactivation of nitrates	Progressive attenuation of nitrate effect?
	(2) Increased clearance of NO by O ₂ ⁻	Worsening of endothelial dysfunction
Nitrate pseudo-tolerance	Increased release of vasoconstrictors (angiotensin II catecholamines, endothelin)	“Rebound” during nitrate-free periods

NO, nitric oxide.

Management of apparent failure of nitrate therapy.

After exclusion of tolerance and poor compliance (headaches), therapy is stepped up (Table 2-5) while excluding aggravating factors such as hypertension, thyrotoxicosis, atrial fibrillation, and anemia.

Table 2-5 -- Proposed Step-Care for Angina of Effort

1. General. History and physical examination to exclude valvular disease, anemia, hypertension, thromboembolic disease, thyrotoxicosis, and heart failure. Check risk factors for coronary artery disease (smoking, hypertension, blood lipids, diabetes, obesity). Must stop smoking. Check diet.
2. Prophylactic drugs. Give aspirin, statins, and ACE inhibitors. Control BP.
3. Intermittent short acting nitrates, as needed to control pain. Combination therapy with β-blockers (sometimes CCBs) standard practice.
4. Prophylactic long-acting nitrates are currently under question (endothelial dysfunction). If used, give in eccentric doses known to avoid tolerance. Intermittent short-acting nitrates can still be added.
5. Primary antianginal drug. β-Blocker if prior infarct or heart failure. Otherwise level of evidence only C.[73] May use CCB (preferably verapamil as in INVESTI[57] or diltiazem or long-acting dihydropyridine).
6. Triple therapy. Short-acting nitrates plus β-blockers plus CCBs (preferably long-acting dihydropyridine as in ACTIONI[20]). Care with combination of verapamil or diltiazem with β-blockers (see Fig. 1-4). Watch for hypotension.
7. Consider novel drugs: metabolic agents or ivabradine. Ranolazine is licensed for use in combination with amlodipine, β-blockers, or nitrates. Trimetazidine is often used in Europe in a similar manner or as a primary drug. Perhexiline is widely used in Australia and New Zealand. Ivabradine to reduce heart rate is becoming available.

8. PCI with stenting may be attempted at any stage in selected patients, especially for highly symptomatic single-vessel disease.

9. Consider bypass surgery after failure to respond to medical therapy or for left mainstem lesion or for triple-vessel disease, especially if reduced LV function. Even response to medical therapy does not eliminate need for investigation.

10. Nitrate failure. This may occur at any of the above steps. Consider nitrate tolerance or worsening disease or poor compliance.

ACE, angiotensin-converting enzyme; BP, blood pressure; CCB, calcium channel blocker; LV, left ventricular; PCI, percutaneous coronary intervention.

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Nitrates for Acute Coronary Syndromes

Large trials of oral and cutaneous nitrates have failed to show a consistent reduction in mortality in either unstable angina/non–ST-elevation myocardial infarction (MI) or in ST-elevation MI. Therefore, the primary goal of nitrate therapy is pain relief or management of associated acute heart failure^[25] or severe hypertension.

Intravenous nitroglycerin is very effective in the management of pain in patients with acute coronary syndromes, although without properly controlled trials. Nitroglycerin should be infused at an initial rate of 5 mcg/min (or even 2.5 mcg/min in patients with borderline hypotension), utilizing nonadsorptive delivery systems. While earlier studies utilized progressive uptitration of infusion rates to relief of pain (with eventual rates of >1000 mcg/min in some patients), this strategy should be limited in general, because of the risks of tolerance induction and subsequent “rebound.” Given that even 10 mcg/min nitroglycerin induces some degree of tolerance within 24 hours,^[26] a maximal infusion rate of 16 mcg/min is recommended in most cases.^[27] Nitrate patches and nitroglycerin ointment should not be used. Intravenous therapy, which can be titrated upward as needed, is far better for control of pain.

Percutaneous coronary intervention.

Intracoronary nitroglycerin is often used to minimize ischemia, for example, due to coronary spasm. Some nitrate solutions contain high levels of potassium that may precipitate ventricular fibrillation.

Nitrate contraindications.

With right ventricular involvement in acute myocardial infarction (AMI), a nitrate-induced fall in left ventricular (LV) filling pressure may aggravate hypotension. A systolic blood pressure (BP) less than 90 mm Hg is a contraindication. Recent ingestion of sildenafil or its equivalent means that nitrate therapy must be delayed or avoided (see Nitrate Interactions with Other Drugs, p. 42).

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Acute Heart Failure and Acute Pulmonary Edema

No clear guidelines exist regarding management of *acute decompensated heart failure*. In an observational study on more than 65,000 patients, intravenous nitroglycerin gave outcomes similar to the more modern and expensive intravenous nesiritide and better results than dobutamine.^[28] However, the patients were not equally matched for BP at entry, so that randomized controlled trials are needed to develop practice guidelines.

In *acute pulmonary edema* from various causes, including AMI, nitroglycerin can be strikingly effective, with some risk of precipitous falls in BP and of tachycardia or bradycardia. Sublingual nitroglycerin in repeated doses of 0.8 to 2.4 mg every 5 to 10 minutes can relieve dyspnea within 15 to 20 minutes, with a fall of LV filling pressure and a rise in cardiac output.^[29] Intravenous nitroglycerin, however, is usually a better method to administer nitroglycerin, as the dose can be rapidly adjusted upward or downward depending upon the clinical and hemodynamic response. Infusion rates required may be higher than the maximal use for AMI (i.e., above 200 mcg/min), but this is based on the idea of brief infusion when pulmonary edema is present without systemic hypotension. A similar approach has been validated with intravenously infused isosorbide dinitrate.^[30]

In contrast, the infusion of nitroglycerin at lower rates, in combination with *N*-acetylcysteine (NAC), was as effective as a diuretic-based treatment regimen in unselected patients with acute pulmonary edema.^[31]

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Congestive Heart Failure

Both short- and long-acting nitrates are used as unloading agents in the relief of symptoms in acute and chronic heart failure. Their dilating effects are more pronounced on veins than on arterioles, so they are best suited to patients with raised pulmonary wedge pressure and clinical features of pulmonary congestion. The combination of high-dose isosorbide dinitrate (60 mg four times daily) plus hydralazine was better than placebo in decreasing mortality, yet nonetheless inferior to an ACE inhibitor in severe congestive heart failure (CHF).^[32] Dinitrate-hydralazine may therefore be chosen when a patient cannot tolerate an ACE inhibitor, or it may be added to the therapy of heart failure, the latter indication being well validated in black patients.^[17]

Nitrate tolerance remains a problem. Intermittent dosing, designed to counter periods of expected dyspnea (at night, anticipated exercise), is one sensible policy.^[33] Escalating doses of nitrates provide only a short-term solution and should be avoided in general. A third possible option is cotherapy with ACE inhibitors plus carvedilol plus hydralazine, which might blunt nitrate tolerance (Fig. 2-6). *Nitrate patches* have given variable results in CHF.

NITRATE TOLERANCE AND ENDOTHELIAL DYSFUNCTION

Opie 2008

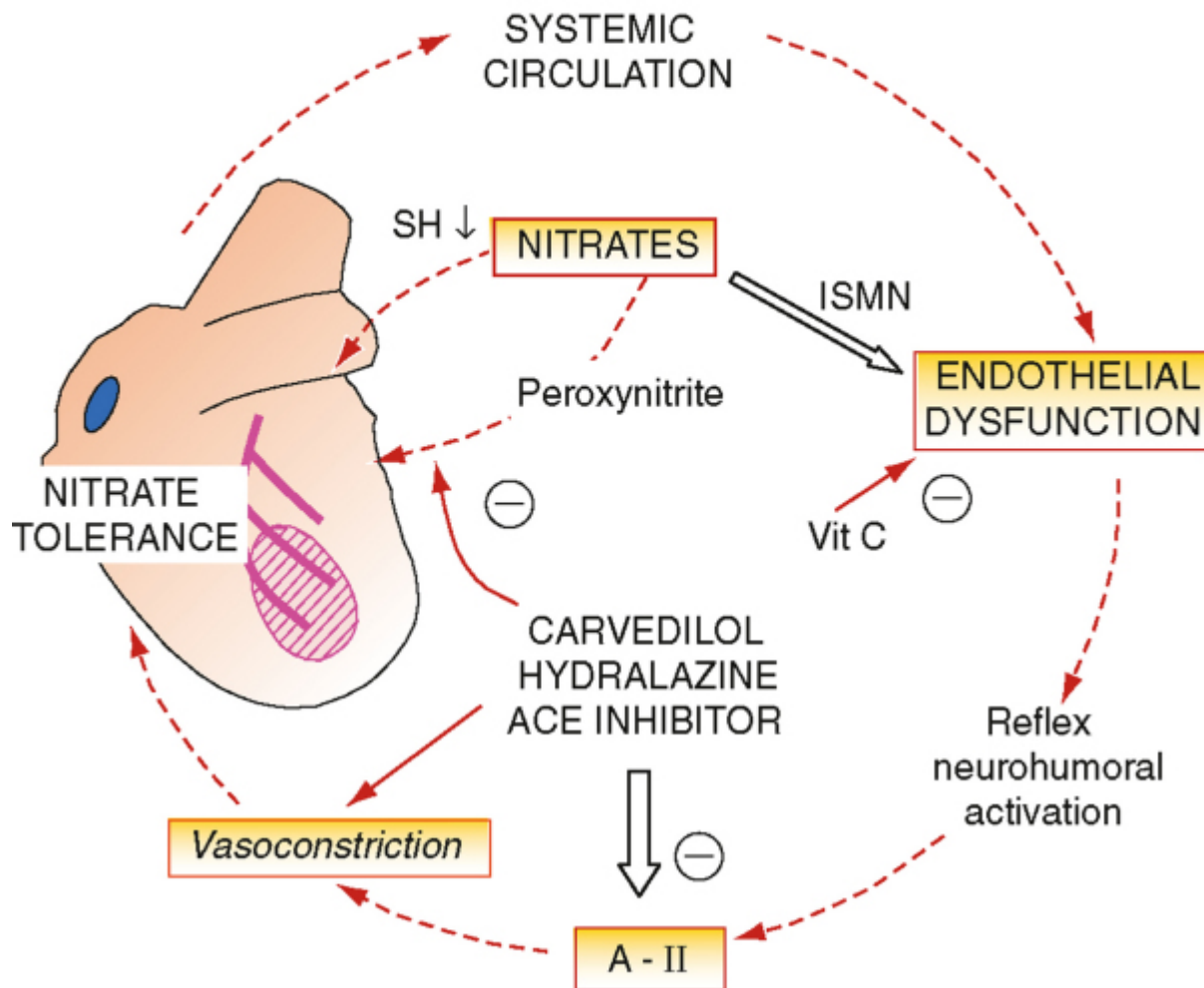


Figure 2-6 Current proposals for therapy of nitrate tolerance. (For cellular mechanisms of peroxynitrite, see Fig. 2-3.) Carvedilol, vitamin C (Vit C), and hydralazine may all lessen free radical formation. Isosorbide dinitrate and hydralazine have proven long-term effects in heart failure patients. Angiotensin-converting enzyme (ACE) inhibitors oppose the neurohumoral activation that is thought to occur as a result of nitrate-induced vasodilation, possibly involving reflex arterial constriction and impaired renal blood flow. (A-II, angiotensin II; ISMN, isosorbide mononitrate; SH, sulfhydryl.) (Figure © L.H. Opie, 2008.)

Nitrate Tolerance and Nitric Oxide Resistance

Nitrate Tolerance

Nitrate tolerance often limits nitrate efficacy. Thus longer acting nitrates, while providing higher and better sustained blood nitrate levels, paradoxically often seem to lose their efficacy with time. This is the phenomenon of nitrate tolerance (see Fig. 2-6). A number of hypotheses have been proposed to account for development of nitrate tolerance. These may be summarized as follows:

1. *Impaired bioconversion of nitrates to active form.*^{[27],[34],[35]} The donor nitrate compound undergoes intracellular transformation to release the active NO[•] moiety that stimulates guanylate cyclase to produce vasodilatory cyclic GMP (see Figs. 2-4 and 2-6). Induction of tolerance to nitroglycerin is associated with impairment of its bioconversion to glyceryl-1,2-dinitrate, with decreased release of NO[•].^[26] In the case of nitroglycerin, the mitochondrial enzyme aldehyde dehydrogenase may be the key enzyme in the initial phase of the biotransformation of nitroglycerin to release NO.^{[35],[36]} This enzyme, when inactivated, may promote nitroglycerin tolerance.^[35] Nitrate bioconversion can also be mediated by another major enzyme, cytochrome P-450 (CYP) reductase of the endoplasmic reticulum. This enzyme activates the long-acting nitrates, isosorbide mono- and dinitrates, thereby bypassing aldehyde dehydrogenase.^[35] Decreased activity of either of these key enzymes may result from and is associated with increased production of free radicals.^{[35],[37]}
2. *Free radical hypothesis and endothelial dysfunction.* Prolonged nitrate administration can lead to incremental formation of superoxide and peroxynitrite.^[34] These, in turn, have multiple adverse effects, including inhibition of guanylyl cyclase with decreased formation of vasodilatory cyclic GMP (see Fig. 2-5); impaired endothelial function^{[34],[38]}; and decreased activity of mitochondrial aldehyde dehydrogenase.^[37] A further twist to the free radical hypothesis lies in the multiple possible sources of the free radicals, including increased mitochondrial production of superoxide, an added indicator of a prominent role for mitochondrial dysfunction in nitrate tolerance.^[37] The free radical hypothesis would explain why nitrate tolerance can be lessened acutely by concurrent therapy with vitamin C^{[9],[39],[40]} or hydralazine.^{[35],[38],[41]} Other agents that reduce oxidative stress include statins, ACE inhibitors, and angiotensin receptor blockers (ARBs).^[38]

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Prevention and Limitation of Nitrate Tolerance

In effort angina, many studies now show that symptomatic tolerance can be lessened by interval dosing. Eccentric twice-daily doses of isosorbide mononitrate (Monoket, Ismo) or once-daily treatment with 120 or 240 mg of the extended-release formulation of mononitrate (Imdur) maintain clinical activity but may nonetheless lead to endothelial dysfunction.^[9] Of the possible drug therapies, hydralazine is logical, especially in CHF, because (1) there are strong trial data favoring the nitrate-hydralazine combination^[17]; and (2) the hydralazine may overcome the impact of free radical formation. There is considerable evidence that nitrate effects on blood vessels and platelets are sulfhydryl dependent.^{[42],[43]} Concomitant therapy with sulfhydryl donors such as NAC potentiates nitroglycerin effects, both hemodynamically^[44] and on platelet aggregation.^[45] Concomitant nitroglycerin/NAC therapy may also limit tolerance induction clinically,^[46] while improving outcomes in unstable angina pectoris.^[47] Addition of an ACE inhibitor is also logical (see previous section) but sometimes disappointing. Simple procedures are folic acid supplementation, supplemental L-arginine,^[48] and vitamin C.^[9] Rapidly increasing blood nitrate levels may temporarily overcome tolerance. Overall, present data do not give assurance that cotherapy with NAC, ACE inhibitors, carvedilol, folic acid, L-arginine, or vitamin C can prevent tolerance. Chronically, the BiDil study suggests that hydralazine could be protective in the setting of congestive failure.^[17] While there is strong evidence that nitrate-free intervals limit tolerance, they may be associated with rebound or the “zero-hour phenomenon” (see later).

Nitrate Cross-Tolerance

Short- and long-acting nitrates are frequently combined. In patients already receiving isosorbide dinitrate, addition of sublingual nitroglycerin may give a further therapeutic effect, albeit diminished. Logically, as discussed in previous editions of this book, tolerance to long-acting nitrates should also cause cross-tolerance to short-acting nitrates, as shown for the capacitance vessels of the forearm, coronary artery diameter, and in exercise tolerance during intravenous nitroglycerin therapy.

Nitrate Pseudo-Tolerance and Rebound

Rebound is the abrupt increase in anginal frequency during accidental nitrate withdrawal (e.g., displacement of an intravenous infusion) or during “nitrate-free” periods.^{[49],[50]} Nitrate pseudo-tolerance probably accounts for the zero-hour phenomenon, whereby patients receiving long-acting nitrate therapy experience worsening of angina just prior to routine administration of medication.^[51] The underlying mechanisms are unopposed vasoconstriction (angiotensin II, catecholamines, and endothelin) during nitrate withdrawal with attenuation of the net vasodilator effect of NO.^[41]

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Nitric Oxide Resistance

This may be defined as de novo hyporesponsiveness to NO effects, whether vascular or antiaggregatory. It also occurs with other “direct” donors of NO, such as sodium nitroprusside. The occurrence of NO resistance accounts for the finding that some patients with heart failure respond poorly to infused NO donors, irrespective of prior nitrate exposure.^[52] The mechanisms of NO resistance in platelets relate primarily to incremental redox stress mediated by superoxide anion release.^[53] There is a close association between NO resistance and endothelial dysfunction as in acute coronary syndromes.^[54] Platelet resistance to NO is an adverse prognostic marker.^[55]

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Step-Care for Angina of Effort

A full history and physical examination is required to exclude all remediable factors (see Table 2-5), not forgetting aortic stenosis, which may be symptomatically occult in the elderly. Risk factors and lifestyle must be vigorously managed, and aspirin, statins, and an ACE inhibitor given if there are no contraindications.^[56] Long-acting nitrates are generally no longer the basis of symptomatic control of angina but are rather brought in when β -blockers and/or CCBs still allow anginal attacks.^[35] A new alternative is a metabolically active agent. PCI and bypass surgery are increasingly taken as escape routes when coronary anatomy is appropriate. However, conservative management gives outcome results as good as PCI.^[4] There are no long-term outcome studies on the benefits of nitrates alone in angina pectoris.

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Combination Therapy for Angina

Existing data are inadequate to evaluate the overall efficacy of combinations of nitrates plus β -blockers and/or CCBs, when compared with optimal therapy with each other or with any one agent alone. The COURAGE study reflects current American therapeutic practice.^[4] Almost all patients received a statin and aspirin, 86% to 89% a β -blocker, and 65% to 78% an ACE inhibitor or ARB. Nitrate use declined from 72% at the start to 57% at 5 years. However, only 43% to 49% of patients were given a CCB, even though first-line therapy with the CCB verapamil in those with effort angina or prior infarction was identical in outcome with β -blockade by atenolol.^[57]

Beta-blockade and long-acting nitrates are often combined in the therapy of angina (see Table 2-5). Both β -blockers and nitrates decrease the oxygen demand, and nitrates increase the oxygen supply; β -blockers block the tachycardia caused by nitrates. β -Blockade tends to increase heart size, and nitrates to decrease it.

CCBs and short-acting nitroglycerin are often combined. In a double-blind trial of 47 patients with effort angina, verapamil 80 mg three times daily decreased the use of nitroglycerin tablets by 25% and prolonged exercise time by 20%.^[58] No outcome data have been reported. *CCBs and long-acting nitrates* are also often given together, however, again without support from outcome trial data.

Nitrates, β -blockers, and CCBs (usually dihydropyridines) may also be combined as triple therapy. The ACTION study was a very large outcome study in which long-acting nifedipine GITS (Procardia XL, Adalat CC) was added to preexisting antianginal therapy, mostly β -blockers (80%) and nitrates (57% nitrates as needed, and 38% daily nitrates).^[20] The CCB reduced the need for coronary angiography or bypass surgery, and new heart failure. In hypertensive patients, added nifedipine gave similar but more marked benefits plus stroke reduction.^[59] There are two lessons to be learned. First, dual medical therapy by β -blockers and nitrates is inferior to triple therapy (added dihydropyridine CCBs); and, second, hypertension in stable angina needs vigorous antihypertensive therapy as in triple therapy. However, we would argue that “optimal medical therapy” should consider a metabolically active agent.

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Metabolic and Other Newer Antianginal Agents

The metabolic antianginal agents have antianginal activity not mediated by or associated with hemodynamic changes. Their protective mechanisms oppose the basic metabolic mechanisms operative in the myocardial ischemia that is the basis of angina (Fig. 2-7).

NOVEL ANTIANGINALS

Opie 2008

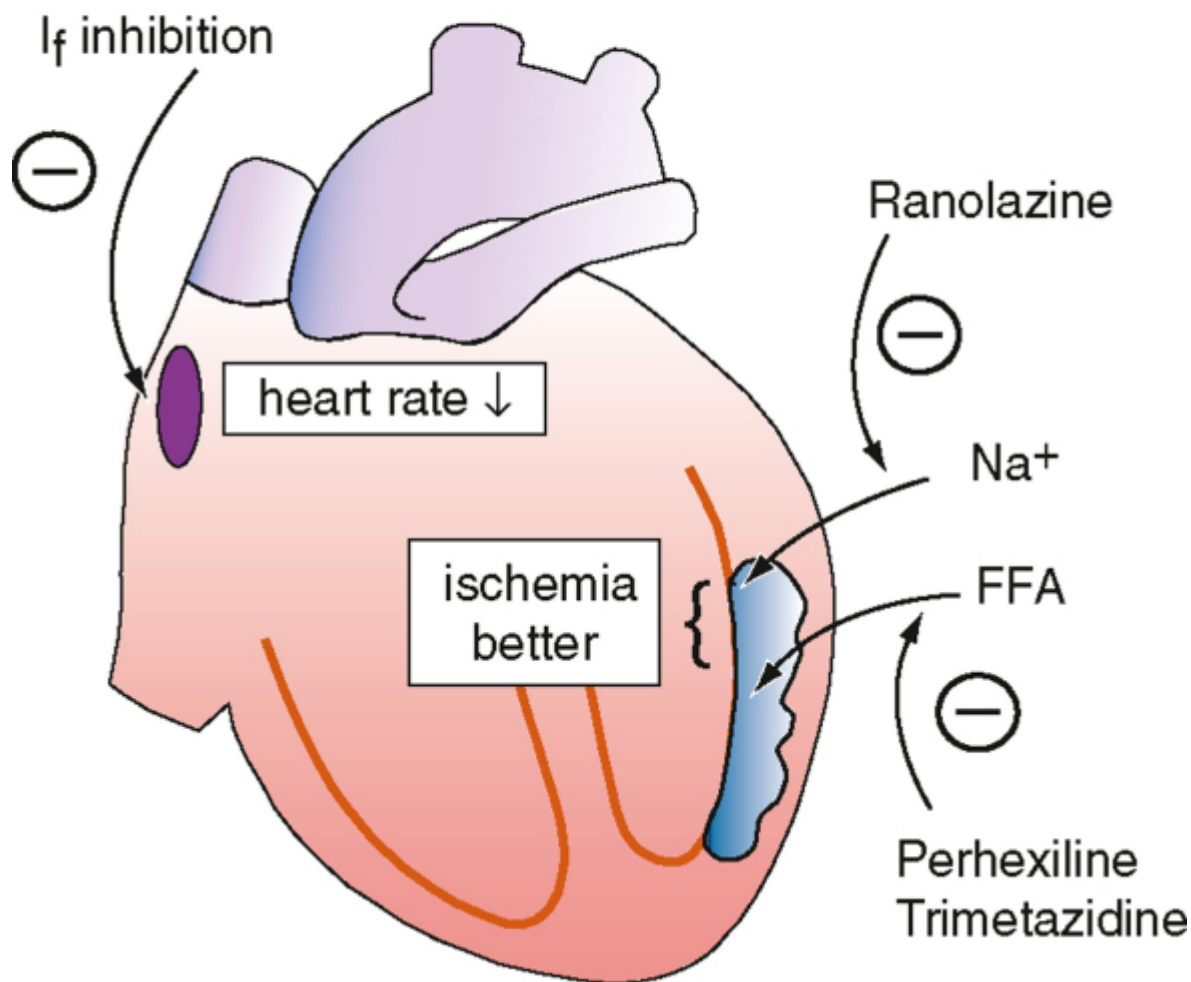


Figure 2-7 Novel antianginal agents work in different ways. Hyperpolarization-activated current (I_f) inhibition by ivabradine decreases myocardial oxygen demand by decreasing the heart rate. Ranolazine decreases the inflow of sodium by the slow sodium current during ischemia and thereby lessens the intracellular sodium and calcium load. Perhexiline inhibits free fatty acid (FFA) oxidation at the level of the enzyme CPT-1. Trimetazidine inhibits fatty acid oxidation at the level of the mitochondrial long-chain oxidation and, in addition, improves whole body insulin sensitivity. (Figure © L.H. Opie, 2008.)

Ranolazine (registered in the United States as Ranexa) is a metabolically active antianginal, originally thought to act by inhibition of oxygen-wasting fatty acid metabolism, thereby increasing the metabolism of protective glucose.^[60] Currently, however, the postulated major mechanism is inhibition of the slow inward sodium current whereby sodium enters the ischemic cells, then dragging in calcium ions, with their proischemic effects, by sodium-calcium exchange. Ranolazine is approved by the U.S. Food and Drug Administration for chronic effort angina, and may be used in combination with amlodipine, β -blockers, or nitrates. At present it should be used only when there is no adequate response to other antianginals because of the risk of QT prolongation. Thus cotherapy with the CCBs diltiazem and verapamil is not advised.

Update: New Content Added

Date Added: 08 July 2009

Ranolazine now approved by the FDA for use in chronic effort angina with further new studies in acute coronary syndrome (non–ST segment elevation myocardial infarction)

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Summary

Ranolazine is now registered by the U.S. Food and Drug Administration (FDA) as Ranexa for use in chronic effort angina with a starting dose of 500 mg twice daily up to 1000 mg twice daily. For cautions regarding drug interactions, see text of chapter 2, page 54. There have also been further studies in patients with acute coronary syndromes (ACS).

In the parent study on 6560 patients with ACS and non–ST segment elevation myocardial infarction, the major benefit of adding ranolazine to standard therapy was a reduction in recurrent ischemia.^[1] In the subgroup of patients ($n = 3565$) with prior chronic angina,^[2] the benefits of ranolazine given during ACS were reduced recurrent ischemia, less worsening of angina, and less need for medication increase. There was also better exercise tolerance after 8 months of follow-up.

A glycometabolic effect was found in 4918 of the total patients in another subgroup study, which tested the effects of ranolazine given during ACS on subsequent hyperglycemia as often follows ACS.^[3] In patients without diabetes at baseline, the incidence of hyperglycemia and increase of hemoglobin A_{1c} at 4 months after ACS was reduced. In diabetic patients, follow-up for 1 year showed that patients who had received ranolazine had lower hemoglobin A_{1c} values (14.2% vs. 20.6%; $P < .001$).

This update can be found on page 52 of the text.

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Ranolazine cautions. Although the U.S. package insert warns about prolongation of the QT_c interval, in a recent large trial on patients with acute coronary syndromes no proarrhythmic effects were noted.^[61]

However, ranolazine should still be avoided in those patients with prior QT prolongation, or taking other drugs that prolong the QT interval (see Fig. 8-6). Being metabolized by the hepatic isoenzyme CYP 3A, drugs inhibiting this enzyme (ketoconazole, diltiazem, verapamil, macrolide antibiotics, human immunodeficiency virus protease inhibitors, and grapefruit juice) and chronic liver disease may all increase ranolazine blood levels and hence QT prolongation.

Trimetazidine is widely used as an antianginal drug in Europe but not in the United States or the United Kingdom. It is a partial inhibitor of fatty acid oxidation without hemodynamic effects. Short-term studies have demonstrated significant benefits, including a reduction in weekly angina episodes and improved exercise time, but large, long-term trials are needed.^[62] An interesting proposal is that, because it acts independently of any BP reduction, trimetazidine could be used in place of nitrates as an antianginal in patients with erectile dysfunction to allow free use of sildenafil and similar agents.

Perhexiline inhibits fatty acid oxidation at the level of CPT-1, the enzyme that transports activated long-chain fatty acids into the mitochondria. Although it was previously widely used, hepatotoxicity and peripheral neuropathy became limitations in the 1980s. The subsequent realization that these side effects resulted mainly from slow hepatic hydroxylation, and that their incidence could be reduced by measuring blood levels and lowering doses if needed, has led to a resurgence of use in refractory angina in Australia and New Zealand.^[49,63–66] Elsewhere, perhexilene is not widely used. It should theoretically be ideal for the combination of angina and heart failure.^[65]

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Other Newer Antianginal Agents

Ivabradine is a blocker of the pacemaker hyperpolarization-activated current (I_f), hence acting not directly on the metabolism but indirectly by decreasing the heart rate and hence the metabolic demand of the heart. Its antianginal potency is similar to that of β -blockade^[67] and amlodipine.^[68] There is no negative inotropic effect or BP reduction as with β -blockers, nor any rebound on cessation of therapy.^[64] *Ivabradine* is licensed in the United Kingdom and other European countries for use in angina when β -blockers are not tolerated or are contraindicated. Theoretically there is less risk of severe sinus node depression than with β -blockade because only one of several pacemaker currents is blocked, whereas β -blockade affects all. The downside is that the I_f is also found in the retina, explaining the uncommon disturbance of nocturnal vision with flashing lights (phosphenes)^[69] that is often transient but that could impair driving at night. *Ivabradine* is under test in a large angina outcome trial, which will also evaluate its addition to β -blockade.

Update: New Content Added

Date Added: 16 April 2009

Antianginal effect of ivabradine added to β -blockade in effort angina

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Summary

In this double-blinded antianginal trial, 889 patients with stable angina receiving atenolol 50 mg/day were randomly assigned to receive ivabradine 5 mg bid for 2 months, increased to 7.5 mg bid for a further 2 months, or placebo.^[1] Patients underwent treadmill exercise tests at the trough of drug activity using the standard Bruce protocol for randomization and at 2 and 4 months. Total exercise duration at 4 months increased by 24.3 ± 65.3 seconds in the ivabradine group compared with 7.7 ± 63.8 seconds with placebo ($P < .001$). The combination of ivabradine 7.5 mg bid and atenolol at the commonly used dosage in clinical practice in patients with chronic stable angina pectoris produced additional efficacy with no untoward effect on safety or tolerability.

An accompanying editorial points out that this is a new antianginal combination and that it is unknown whether the addition of ivabradine to prior maximal doses of β -blockers would reduce angina further.^[2] This study also raises the issue of whether reducing heart rate is a modifiable risk factor in effort angina that could be translated into reduction of mortality and morbidity.

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Nicorandil (not available in the United States) has a double cellular mechanism of action, both acting as a potassium channel activator and having a nitrate-like effect, which may explain why its antianginal effects may be limited by tolerance induction. It is a nicotinamide nitrate, acting chiefly by dilation of the large coronary arteries, as well as by reduction of pre- and afterload. It is widely used as an antianginal agent in Japan. In the IONA study, 5126 patients with stable angina were followed for a mean of 1.6 years. Major

coronary events, including acute coronary syndrome, were reduced.[70]

Update: New Content Added

Date Added: 05 December 2008

Heart rate reduction by ivabradine in coronary heart disease

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The BEAUTIFUL (Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease and Left Ventricular Dysfunction) study was presented at the European Congress of Cardiology in September 2008. The hypothesis was that ivabradine, a heart rate-reducing drug available in Europe but not in the U.S., would benefit patients with coronary heart disease with left ventricular dysfunction (left ventricular ejection fraction <40%). Entry heart rate had to be >60 beats/min in sinus rhythm. Otherwise, patients (almost 11,000) received standard current therapy (aspirin, 94%; statin, 72%; angiotensin-converting enzyme inhibitor, 89%; β -blocker, 83%; diuretics including aldosterone blocker, 92%).

The trial tested the hypothesis that ivabradine 5-7.5 mg twice daily added to current therapy could reduce the primary combination end point, cardiovascular death or admission to the hospital for new-onset or worsening heart failure (primary hypothesis; nonsignificant result), or the secondary end point, admission to the hospital for myocardial infarction, fatal or nonfatal.[1] None of these results was significant. In a predetermined subgroup defined after the start of the trial with an initial heart rate >70 beats/min, admission for myocardial infarction was reduced (HR 0.64, CI 0.49-0.84, $P = .001$; absolute reduction from 4.9% to 3.1% over 2 years), as was coronary revascularization (HR 0.70, CI 0.52-0.93, $P = .016$). Ivabradine was effective in that subgroup by reducing heart rate in patients with a high heart rate at baseline.

The authors conclude that in patients with coronary artery disease and left ventricular dysfunction, ivabradine can be safely combined with a β -blocker, with a low rate of ocular side effects (0.04%), and in the subgroup with a high heart rate (>70 beats/min), coronary outcomes are improved.

Critical Evaluation: As the authors point out, strictly speaking, the improved coronary artery outcomes in patients (treated by ivabradine plus beta-blockade) with heart rates of 70 bpm [beats/min] or more ... deserve confirmation in a prospective study.¹ Presumably, there would be fewer subgroups, which statistically weaken the present findings according to Smith, Professor of Medicine at the University of North Carolina, the discussant of this trial at the European Congress of Cardiology. Nonetheless, the finding of reduced admission to the hospital for myocardial infarction in the ivabradine group was highly significant ($P < 0.001$) and is hypothesis-generating. Overall, this study is expected to kindle much interest in the role of a high heart rate as an adverse but treatable prognostic risk factor in such patients.[2]

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Are Nitrates Really Safe?

In contrast to the reasonable data for the safety of β -blockers and CCBs in effort angina,^[71] logic would say that nitrate therapy that leads to excess production of free radicals, endothelial dysfunction, tachycardia, and renin-angiotensin activation may not be safe.^[37] Analyses of two large databases showed that nitrate use was associated with increased mortality, with hazard ratios of 1.6 and 3.8.^[72] At present the best policy may lie in adding short-acting nitrates to β -blockers and/or CCBs plus the standard cardioprotective drugs such as aspirin, ACE inhibitors, and statins,^[35] as in the EUROPA study (see Chapter 5).

SUMMARY

1. **Mechanisms of action.** Nitrates act by venodilation and relief of coronary vasoconstriction (including that induced by exercise) to ameliorate anginal attacks. They are also arterial dilators, and reduce aortic systolic pressure. Their unloading effects also benefit patients with CHF with high LV filling pressures.
2. **Intermittent nitrates for effort angina.** Sublingual nitroglycerin remains the basic therapy, usually combined with a β -blocker and/or a CCB with careful assessment of lifestyle, BP, and blood lipid profile. As the duration of action lasts for only minutes, nitrate tolerance is unusual because of the relatively long nitrate-free intervals between attacks. Intermittent isosorbide dinitrate has a delayed onset of action due to the need for hepatic transformation to active metabolites, yet the duration of action is longer than with nitroglycerin.
3. **For anginal prophylaxis,** some newer nitrate preparations are not substantial advances over the old, especially the nitrate patches, which clearly predispose to tolerance by sustained blood nitrate levels. The mononitrates are an advance over dinitrates because they eliminate variable hepatic metabolism on which the action of the dinitrates depends, and because the dose schedules required to avoid symptomatic tolerance have been well defined. The longer the duration of nitrate action, the more likely is tolerance to develop, thus therapy effectively turns into a balancing act between duration of action and avoidance of tolerance. Increasing data show that endothelial dysfunction is a possible side effect of prolonged prophylactic long-acting nitrate therapy, hence introducing a reserve into such use.
4. **For unstable angina at rest,** a nitrate-free interval is not possible, and short-term treatment for 24 to 48 hours with intravenous nitroglycerin is frequently effective with, however, escalating doses often required to overcome tolerance.
5. **In early-phase AMI,** we suggest that intravenous nitrates be specifically reserved for more complicated patients.
6. **During the treatment of CHF,** tolerance also develops, so that nitrates are often reserved for specific problems such as acute LV failure, nocturnal dyspnea, or anticipated exercise. However, isosorbide dinitrate combined with hydralazine is now licensed for heart failure in self-defined black subjects.
7. **Acute pulmonary edema.** Nitrates are an important part of the overall therapy, acting chiefly by preload reduction.
8. **Nitrate tolerance.** The current understanding of the mechanism of tolerance focuses on both free radical formation (superoxide and peroxynitrite) and impaired bioconversion of nitrate to active NO. During the treatment of effort angina by isosorbide dinitrate or mononitrate, substantial evidence suggests that eccentric doses with a nitrate-free interval largely avoid clinical tolerance, but endothelial dysfunction remains a long-term hazard. Besides addition of hydralazine (see earlier), other less well-tested measures include administration of carvedilol, statins, ACE inhibitors, and vitamin C.

9. *Serious interaction with sildenafil-like agents.* Nitrates can interact very adversely with such agents, now often used to alleviate erectile dysfunction. The latter is common in patients with cardiovascular disease, being a manifestation of endothelial dysfunction. The coadministration of these PDE-5 inhibitors with nitrates is therefore contraindicated. Every male presenting with acute coronary syndrome should be questioned about recent use of these agents (trade names: Viagra, Levitra, Cialis). If so, there has to be an interval of 24 to 48 hours (the longer interval for Cialis) before nitrates can be given therapeutically with reasonable safety but still with great care.

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