



Department of Vermont Health Access

Therapeutic Class Review Nitrates and Nitrites

Overview/Summary

The nitrates and nitrites are a class of vasodilating agents primarily indicated for the acute treatment, prophylaxis and management of angina pectoris due to coronary artery disease. Myocardial ischemia develops when there is an imbalance between myocardial oxygen supply and demand which can lead to symptoms such as angina pectoris. Nitrates and nitrites effectively reduce myocardial oxygen demand by causing vascular smooth muscle relaxation, resulting in peripheral vasodilation.² Vasodilation can also lead to side effects, such as headache and flushing. Various formulations are available that differ in both onset and duration of action, which dictates their role in treatment of acute, stable and unstable angina.¹⁻²

The nitrates, isosorbide dinitrate in combination with hydralazine in particular, also serve a role in the management of heart failure as an adjunct to standard treatment.³⁻⁶ Furthermore, intravenous nitroglycerin is indicated for blood pressure control during cardiovascular procedures while either intravenous or sublingual nitroglycerin is beneficial in the management of patients with acute myocardial infarction.²

Frequently repeated or continuous exposure to organic nitrates leads to a decrease in their pharmacological effects. The development of tolerance limits the efficacy of all chronic nitrate therapies regardless of route of administration. Nitrate-free interval dosing can limit the degree of tolerance associated with chronic use.¹

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Amyl nitrite*	Nitrites	✓
Isosorbide dinitrate (Dilatrate-SR [®] , Isordil [®] *)	Nitrates	✓
Isosorbide mononitrate (Imdur [®] *, Ismo [®] *, Monoket [®] *)	Nitrates	✓
Nitroglycerin (Minitran [®] *, Nitro-Bid [®] , Nitro-Dur [®] *, Nitrolingual [®] , NitroMist [®] , Nitrostat [®] *)	Nitrates	✓

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications⁷⁻²³

Indication	Amyl Nitrite	Isosorbide Dinitrate*†	Isosorbide Mono-nitrate†	Nitroglycerin		
				Sublingual Tablet/Spray	Injection	Capsule, Trans-dermal†
Acute relief of angina pectoris	✓			✓		
Acute prophylaxis of angina pectoris due to coronary artery disease				✓		
Control of congestive					✓	

Indication	Amyl Nitrite	Isosorbide Dinitrate*†	Isosorbide Mononitrate†	Nitroglycerin		
				Sublingual Tablet/Spray	Injection	Capsule, Transdermal†
heart failure in the setting of acute myocardial infarction						
Induction of intraoperative hypotension					✓	
Prevention of angina pectoris due to coronary artery disease		✓	✓			✓
Treatment of angina pectoris due to coronary artery disease		✓	✓ ‡			
Treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and β -blockers					✓	
Treatment of perioperative hypertension					✓	

*Because the onset of action of sublingual isosorbide dinitrate is significantly slower than that of sublingual nitroglycerin, sublingual isosorbide dinitrate is not the drug of first choice for aborting an acute anginal episode.

†The onset of action of oral isosorbide dinitrate (immediate or sustained-release), oral isosorbide mononitrate, oral nitroglycerin capsules, or transdermal nitroglycerin is not sufficiently rapid for these products to be useful in aborting an acute anginal episode.

‡Monoket® and equivalents.

Pharmacokinetics

Table 3. Pharmacokinetics⁷⁻²³

Generic Name	Bioavailability (%)	Onset (minutes)	Duration	Active Metabolites	Half-Life
Amyl nitrite	Not reported	0.5	3 to 15 minutes	Not reported	Not reported
Isosorbide dinitrate sublingual tablet	40 to 50	2 to 10	1 to 2 hours	2-mononitrate, 5-mononitrate	1 to 4 hours
Isosorbide dinitrate extended-release capsule/tablet	Not reported	60	Up to 8 hours	2-mononitrate, 5-mononitrate	1 to 4 hours
Isosorbide dinitrate tablet	10 to 90	45 to 60	4 to 6 hours	2-mononitrate, 5-mononitrate	1 to 4 hours
Isosorbide mononitrate extended-release tablet	100	30 to 60	12 hours	None	4 hours
Isosorbide mononitrate tablet	100	30 to 60	5 to 7 hours	None	4 hours
Nitroglycerin injection	Not reported	Immediate	3 to 5 minutes	1,2- dinitroglycerols, 1,3-dinitroglycerols	1 to 4 minutes
Nitroglycerin ointment	Not reported	15 to 60	2 to 12 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1 to 4 minutes
Nitroglycerin sublingual tablet	40	1 to 3	30 to 60 minutes	1,2- dinitroglycerols, 1,3-dinitroglycerols	1 to 4 minutes

Generic Name	Bioavailability (%)	Onset (minutes)	Duration	Active Metabolites	Half-Life
Nitroglycerin sustained-release capsule	Not reported	20 to 45	4 to 8 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1 to 4 minutes
Nitroglycerin transdermal patch	Not reported	40 to 60	18 to 24 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1 to 4 minutes
Nitroglycerin lingual spray	Not reported	2	30 to 60 minutes	1,2- dinitroglycerols, 1,3-dinitroglycerols	1 to 4 minutes

Clinical Trials

Isosorbide mononitrate has demonstrated statistically significant improvement in exercise duration over placebo in patients with stable angina.²⁴⁻²⁶ The efficacy of intravenous nitroglycerin has been demonstrated in patients with angina unresponsive to standard therapy with a reduction in angina episodes, doses of sublingual nitroglycerin and morphine sulfate ($P<0.001$).²⁷ Isosorbide dinitrate in combination with hydralazine has shown a 34% reduction in mortality in patients with heart failure compared to placebo ($P<0.028$).²⁸ More specifically in African American patients, this combination of vasodilators produced a lower mortality rate of 6.2 vs 10.2% for placebo.²⁹

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Stable Angina				
Parker et al ²⁴ ISMN 5 mg BID vs ISMN 10 mg BID vs ISMN 20 mg BID vs placebo	DB, PC, PG Patients with stable angina	N=214 3 weeks	Primary: Total exercise duration and time to moderate angina Secondary: Not reported	Primary: Patients underwent testing prior to exercise as well as two and seven hours after each dose on days one and 14. Additionally, on days seven and 21, testing was performed two hours after the first dose. ISMN, at all doses, showed improvement over placebo at two and seven hours after the morning dose and two hours after the second dose on day one. Active treatment prolonged exercise duration over placebo treatment at two hours postdose for each of the two daily doses. ISMN 20 mg was the only strength that demonstrated increased exercise duration seven hours after administration, which occurred on day 14. Overall, there were fewer episodes of angina noted in the ISMN 20 mg group (<i>P</i> values not reported). Secondary: Not reported
Thadani et al ²⁵ ISMN 20 mg BID vs placebo Patients were allowed to continue β -blocker therapy.	DB, MC, PC, PG, RCT Patients with stable exertional angina who stopped treadmill exercise secondary to angina pectoris	N=116 2 weeks	Primary: Total exercise duration (time to moderately severe angina) Secondary: Magnitude of ST-segment depression, heart rate, SBP, DBP, number of anginal attacks, number of nitroglycerin doses	Primary: A statistically significant improvement in total exercise duration was observed at both the morning and afternoon dose compared to placebo (<i>P</i> <0.01). Secondary: The magnitude of ST-segment depression was comparable in both the ISMN and placebo groups (1.2±0.1 vs 1.2±0.2 mm; <i>P</i> >0.2). Heart rate and SBP, during the period of exercise, was determined to be similar among the groups. Additionally, the number of anginal attacks and doses of nitroglycerin were no different per group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Chrysant et al²⁶</p> <p>ISMN ER 30 mg QAM</p> <p>vs</p> <p>ISMN ER 60 mg QAM</p> <p>vs</p> <p>ISMN ER 120 mg QAM</p> <p>vs</p> <p>ISMN ER 240 mg QAM</p> <p>vs</p> <p>placebo</p>	<p>DB, RCT</p> <p>Patients with stable effort-induced angina</p>	<p>N=313</p> <p>6 weeks</p>	<p>Primary:</p> <p>Mean change from baseline in total exercise time (serial exercise testing immediately prior to and four and two hours after administration, on days one, seven, 14, 28 and 42)</p> <p>Secondary:</p> <p>Adverse effects</p>	<p>Primary:</p> <p>A significant improvement in mean total exercise time of 30 to 50 seconds was shown in all active treatment groups compared to the placebo group at four and 12 hours postdose ($P<0.01$). The mean changes from baseline in total exercise time in patients on ISMN ER 120 or 240 mg surpassed patients on placebo by about 50 to 60 seconds at four hours postdose ($P<0.01$), and by 30 to 35 seconds 12 hours after dosing ($P\leq 0.05$).</p> <p>There was no meaningful difference in response found between active treatment and placebo at 24 hours after administration, thus no indication that ISMN ER induced rebound angina.</p> <p>Secondary:</p> <p>The most common adverse effect among active treatment groups was transient headache.</p>
<p>Bray et al³⁰</p> <p>NTG administered buccally</p> <p>vs</p> <p>NTG administered sublingually</p>	<p>DB, MC</p> <p>Patients with proven chronic stable exercise-induced angina</p>	<p>N=Not reported</p> <p>Duration not reported</p>	<p>Primary:</p> <p>Efficacy</p> <p>Secondary:</p> <p>Not reported</p>	<p>Primary:</p> <p>The two formulations had comparable effects on acute attacks of angina pectoris.</p> <p>Secondary:</p> <p>Not reported</p>
<p>Ryden et al³¹</p> <p>NTG administered buccally</p> <p>vs</p> <p>NTG administered sublingually</p>	<p>MC, XO</p> <p>Patients with stable angina pectoris</p>	<p>N=126</p> <p>2 weeks</p>	<p>Primary:</p> <p>Efficacy</p> <p>Secondary:</p> <p>Ease of use, patient preference</p>	<p>Primary:</p> <p>Buccal formulation resulted in 31% less acute anginal attacks compared to the sublingual formulation ($P<0.001$). Prophylaxis was effective in 74% of patients taking buccal NTG compared to 66% of sublingual-treated patients ($P<0.05$).</p> <p>Secondary:</p> <p>There was no difference in ease of use reported in 67% of patients, whereas 19% of patients indicated that sublingual NTG was easier and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Demots et al³²</p> <p>NTG 0.2 mg/hour or 0.4 mg/hour TD for 12 hours (Group A)</p> <p>vs</p> <p>NTG 0.6 mg/hour or 0.8 mg/hour TD for 12 hours (Group B)</p> <p>vs</p> <p>placebo</p> <p>The concurrent use of β-blockers was greater in Group A.</p>	<p>DB, RCT</p> <p>Patients with chronic stable angina</p>	<p>N=206</p> <p>4 weeks</p>	<p>Primary: Effectiveness in chronic stable angina (serial treadmill testing performed zero, four, eight and 12 hours after patch application at baseline and on days one, 15 and 29)</p> <p>Secondary: Adverse reaction</p>	<p>14% of patients indicated that buccal NTG was easier. Overall, 65% of patients preferred buccal NTG and 19% of patients preferred sublingual NTG ($P<0.05$). As far as prophylactic use, buccal administration was again preferred by more patients (81%) than sublingual administration (4%; $P<0.05$).</p> <p>Primary: Improved walking times were observed in both Group A and Group B over the placebo group at all testing points after short-term administration. Results were statistically significant for Group A at 12 hours and for Group B at four, eight and 12 hours (P values not reported).</p> <p>At weeks two and four, walking times were again greater in Group B over the placebo group at all testing points with the four hour test time at week two and the eight hour test time at week two and four reaching statistical significance (P values not reported). Group A did not demonstrate increased duration in walking time long-term.</p> <p>Secondary: Active therapy was generally tolerated well. An increase in non-exertional angina during the patch-off interval was reported in nine patients.</p>
Unstable Angina				
<p>Dellborg et al³³</p> <p>NTG IV for 24 hours</p> <p>vs</p> <p>NTG administered buccally every 4 hours</p>	<p>RCT</p> <p>Patients admitted to the coronary care unit due to unstable angina</p>	<p>N=29</p> <p>24 hours</p>	<p>Primary: Efficacy</p> <p>Secondary: Adverse effects</p>	<p>Primary: Efficacy was comparable in the two groups.</p> <p>Secondary: Less adverse effects (headache, hemodynamic intolerance) were associated with buccal NTG than IV NTG although the differences were not significant.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kaplan et al ²⁷ NTG IV 10 µg/minute increased by 10 µg/minute every 5 minutes to 50 µg/minute then increased by 50 µg/minute per each episode of angina	OL, OS Patients with angina at rest unresponsive to standard therapy including oral or topical nitrates and β-blockers	N=35 24 hours	Primary: Clinical response Secondary: Not reported	Primary: NTG therapy reduced the number of episodes of angina at rest from 3.5±0.4 to 0.3±0.1, reduced doses of sublingual NTG from 1.9±0.3 to 0.4±0.1 mg/day and decreased morphine sulfate use from 5.5±1.3 to 0.4±0.2 mg/day (<i>P</i> <0.001 for all). Complete response, defined as no rest angina, was achieved in 25 patients, while eight patients experienced >50% reduction in episodes and two patients were nonresponders. Secondary: Not reported
Karlberg et al ³⁴ NTG IV titrated from 1.5 mL/hour in <1 hour to a maximum of 12 mL/hour vs placebo	DB, PC, RCT Patients with recent onset of chest pain, suggestive of myocardial ischemia or worsening of previously stable angina pectoris and clinical evidence of underlying coronary artery disease	N=143 48 hours	Primary: Reduction in ongoing signs of myocardial ischemia (>2 angina attacks responding to one to three sublingual NTG tablets and lasting <20 minutes [AP1], or one angina attack lasting >20 minutes, despite three sublingual NTG tablets [AP2]), leukocyte activation, inhibition of platelet aggregation Secondary: Adverse effects	Primary: Treatment with NTG IV resulted in fewer patients (13) experiencing ongoing signs of ischemia (AP1+AP2) than patients treated with placebo (25; <i>P</i> <0.03). There were significantly less patients on active treatment that required >2 sublingual NTG tablets compared to patients receiving placebo (12 vs 22; <i>P</i> <0.005). There was no significant difference found between groups in regards to leukocyte activation or inhibition of platelet aggregation. Secondary: Active treatment was stopped in seven patients compared to zero in the placebo group (<i>P</i> <0.001). Five patients terminated therapy prematurely because of headache while two patients stopped because of a decrease in BP and bradycardia.
Heart Failure				
Cohn et al ²⁸ V-HeFT I Hydralazine 300 mg daily plus	AC, DB, PC, RCT Men with	N=642 3 years	Primary: Mortality Secondary:	Primary: There was a 34% risk reduction in mortality by two years in the hydralazine plus ISDN group compared to the placebo group (<i>P</i> <0.028).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ISDN 160 mg daily vs prazosin 20 mg daily vs placebo	impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic		Effect on left ventricular function	Cumulative mortality rates of 25.6 and 36.2% were observed in the hydralazine plus ISDN group at two and three years respectively, compared to 34.3 and 46.9% in the placebo group (<i>P</i> value not reported). The results found in the prazosin group were similar to the placebo group. Secondary: A significant increase in the LVEF was reported at eight weeks and one year in the hydralazine plus ISDN treatment group, but not in either the prazosin or placebo groups.
Cohn et al ³⁵ V-HeFT II Hydralazine 75 mg plus ISDN 40 mg QID vs enalapril 10 mg BID	DB, RCT Men between 18 and 75 years of age receiving digoxin and diuretic therapy for heart failure	N=804 2 years	Primary: Mortality, body oxygen consumption at peak exercise, LVEF Secondary: Not reported	Primary: Mortality after two years was significantly lower in the enalapril arm (18%) than in the hydralazine plus ISDN arm (25%; <i>P</i> =0.016). Body oxygen consumption at peak exercise was increased only by hydralazine plus ISDN treatment and was significantly greater at 13 weeks, six months and two years (<i>P</i> =0.01, <i>P</i> =0.02 and <i>P</i> =0.02, respectively). LVEF, which increased with both regimens during the two years after randomization, increased more (<i>P</i> =0.026) during the first 13 weeks in the hydralazine plus ISDN arm. Secondary: Not reported
Taylor et al ²⁹ A-HeFT Hydralazine/ISDN 37.5/20 mg TID titrated up to hydralazine/ISDN 75/40 mg TID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for	N=1,050 18 months (mean duration of follow-up was 10 months)	Primary: A composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, and quality of life changes Secondary: Individual	Primary: From a range of possible scores of -6 to 2 for the composite endpoint, patients in the active treatment group achieved a significantly better score of -0.1±1.9 compared to -0.5±2.0 in the placebo group (<i>P</i> =0.01). Secondary: There was a significantly higher mortality rate in the placebo group compared to the hydralazine/ISDN group (6.2 vs 10.2%; <i>P</i> =0.02). Survival was increased by 43% in the active treatment group (HR, 0.57; <i>P</i> =0.02). This led to the early termination of the trial. Compared to the placebo group, the rate of first hospitalization for heart

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	at least 3 months and evidence of left ventricular dysfunction within the prior 6 months		components of the primary composite score	<p>failure was significantly reduced in the hydralazine/ISDN group (16.4 vs 24.4%; $P=0.001$).</p> <p>There was a significant improvement in quality of life scores found with the hydralazine/SDN group when compared to the placebo group (-5.6 ± 20.6 vs -2.7 ± 21.2; $P=0.02$).</p>
<p>Taylor et al³⁶ A-HeFT</p> <p>Hydralazine/ISDN 37.5/20 mg TID titrated up to hydralazine/ISDN 75/40 mg TID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Post-hoc analysis of A-HeFT</p>	<p>N=1,050</p> <p>Mean duration of follow-up was 18 months</p>	<p>Primary: Cause specific mortality, event free survival (time to either death or first hospitalization and time to first hospitalization for heart failure)</p> <p>Secondary: Subgroup analysis</p>	<p>Primary: Cardiovascular deaths were significantly reduced in the treatment group compared to the placebo group (5.0 vs 8.5%; $P=0.027$). Pump failure death was also significantly reduced (75%) compared to the placebo group (0.8 vs 3.0%; $P=0.012$). There were no significant differences between the groups for other causes of death.</p> <p>In the treatment group event-free survival (death or first hospitalization for heart failure) was significantly improved compared to the placebo group (HR, 0.63; 95% CI, 0.49 to 0.81; $P<0.001$).</p> <p>The time to first hospitalization for heart failure was also significantly reduced (HR, 0.61; 95% CI, 0.46 to 0.80; $P<0.001$).</p> <p>Secondary: A consistent beneficial effect was seen in the treatment sub groups (age, sex, baseline BP, history of chronic renal insufficiency, presence of diabetes, cause of heart failure, and baseline medication use) on primary composite score and event-free survival.</p>
<p>Yancy et al³⁷ X-A-HeFT</p> <p>Hydralazine/ISDN 37.5/20 mg TID titrated up to hydralazine/ISDN 75/40 mg TID</p> <p>vs</p>	<p>ES, OL</p> <p>Patients previously enrolled in A-HeFT with NYHA class I to IV heart failure symptoms while</p>	<p>N=158</p> <p>12 months or until hydralazine/ISDN approved by the FDA</p>	<p>Primary: Compliance with study drug, safety, tolerability</p> <p>Secondary: Change in NYHA association class, death, hospitalization</p>	<p>Primary: Compliance in the treatment group averaged $87\pm 25\%$, with no significant difference when compared to the placebo group.</p> <p>There were no significant differences in adverse events between the groups.</p> <p>Secondary: No significant difference was seen in hospitalizations from heart failure</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	receiving background therapy and satisfying the A-HeFT inclusion criteria		for heart failure	<p>according to randomization.</p> <p>The greatest improvement in heart failure symptoms occurred in NYHA class III (at baseline) compared to other classes ($P<0.001$).</p> <p>Overall most patients were unchanged with 24% showing improved NYHA class and 9% showing a worsening.</p>

Drug regimen abbreviations: BID=twice daily, ER=extended release, IV=intravenous, QAM=every morning, QID=four times daily, TD=transdermal, TID=three times daily

Study abbreviations: AC=active-controlled, DB=double-blind, ES=extension study, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover

Miscellaneous abbreviations: Trial, BP=blood pressure, DBP=diastolic blood pressure, FDA=Food and Drug Administration, LVEF=left ventricular ejection fraction, HR=hazard ratio, ISDN=isosorbide dinitrate, ISMN=isosorbide mononitrate, NTG=nitroglycerin, NYHA=New York Heart Association, SBP=systolic blood pressure

Special Populations**Table 5. Special Populations**⁷⁻²³

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Amyl nitrite	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Isosorbide dinitrate	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Renal dose adjustment is required; during hemodialysis, dose should be administered post-dialysis or a supplemental dose of 10 to 20 mg should be administered.	Not studied in hepatic dysfunction.	C	Unknown
Isosorbide mononitrate	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Nitroglycerin	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

Adverse Drug Events**Table 6. Adverse Drug Events (%)**⁷⁻²³

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate ER	Isosorbide Mononitrate	Nitroglycerin
Cardiovascular					
Abnormal heart sound	-	-	≤5	-	-
Aggravated angina pectoris	-	-	≤5	-	-
Angina pectoris	-	-	-	<1	-
Arrhythmia	-	-	≤5	<1	-
Atrial fibrillation	-	-	≤5	<1	-
Bradycardia	-	-	≤5	-	-
Bundle branch block	-	-	≤5	-	-

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate ER	Isosorbide Mononitrate	Nitroglycerin
Cardiac failure	-	-	≤5	-	-
Extrasystole	-	-	≤5	-	-
Flushing	✓	-	≤5	-	✓
Heart murmur	-	-	≤5	-	-
Hypertension	-	-	≤5	-	-
Hypotension	✓	✓	≤5	<1	✓
Migraine	-	-	≤5	-	-
Myocardial infarction	-	-	≤5	-	-
Palpitation	✓	-	≤5	<1	✓
Postural hypotension	✓	-	-	<1	✓
Premature ventricular contraction	-	-	-	<1	-
Q wave abnormality	-	-	≤5	-	-
Rebound hypertension	-	✓	-	-	✓
Supraventricular tachycardia	-	-	-	<1	-
Syncope	✓	✓	✓	<1	✓
Tachyarrhythmia	✓	-	-	-	-
Tachycardia	-	-	≤5	-	-
Ventricular tachycardia	-	-	≤5	-	-
Central Nervous System					
Anxiety	-	-	≤5	<1	-
Confusion	-	-	≤5	<1	-
Decreased libido	-	-	≤5	-	-
Depression	-	-	≤5	-	-
Dizziness	✓	✓	8 to 11	3 to 5	✓
Headache	✓	✓	38 to 57	17 to 35	✓
Impotence	-	-	≤5	<1	-
Insomnia	-	-	≤5	<1	-
Lightheadedness	✓	-	-	-	✓
Nervousness	-	-	≤5	<1	-
Neuritis	-	-	≤5	-	-
Paresis	-	-	≤5	-	-
Paresthesia	-	-	≤5	-	-
Purpura	-	-	≤5	-	-
Somnolence	-	-	≤5	-	-
Vertigo	-	-	≤5	-	✓
Dermatological					
Acne	-	-	≤5	-	-
Anaphylactoid reactions	-	-	-	-	✓
Contact dermatitis	-	-	-	-	✓*
Exfoliative dermatitis	-	-	-	-	✓
Photophobia	-	-	≤5	-	-
Pruritus	-	-	≤5	<1 to 2	-
Rash	✓	-	≤5	<1 to 2	✓
Skin nodule	-	-	≤5	-	-
Endocrine and Metabolic					
Edema	-	-	≤5	<1	-
Gastrointestinal					
Abdominal pain	-	-	≤5	<1 to 2	-
Constipation	-	-	≤5	-	-
Diarrhea	-	-	≤5	<1 to 2	-

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate ER	Isosorbide Mononitrate	Nitroglycerin
Dyspepsia	-	-	≤5	<1	-
Flatulence	-	-	≤5	-	-
Gastric ulcer	-	-	≤5	-	-
Gastritis	-	-	≤5	-	-
Hemorrhagic gastric ulcer	-	-	≤5	-	-
Loose stools	-	-	≤5	-	-
Nausea	✓	-	≤5	2 to 4	✓
Vomiting	✓	-	≤5	2 to 4	✓
Genitourinary					
Dysuria	-	-	-	<1	-
Polyuria	-	-	≤5	-	-
Renal calculus	-	-	≤5	-	-
Urinary tract infection	-	-	≤5	-	-
Hematologic					
Hemolytic anemia	✓	-	-	-	-
Hypochromic anemia	-	-	≤5	-	-
Methemoglobinemia	✓	✓	✓	✓	✓
Thrombocytopenia	-	-	≤5	-	-
Laboratory Test Abnormalities					
Elevated SGOT	-	-	≤5	-	-
Elevated SGPT	-	-	≤5	-	-
Musculoskeletal					
Arthralgia	-	-	≤5	<1	-
Asthenia	✓	-	≤5	<1	-
Muscle weakness	-	-	≤5	-	-
Musculoskeletal pain	-	-	≤5	-	-
Myalgia	-	-	≤5	-	-
Respiratory					
Bronchitis	-	-	≤5	<1	-
Bronchospasm	-	-	≤5	-	-
Coughing	-	-	≤5	-	-
Dyspnea	✓	-	≤5	-	-
Increased sputum	-	-	≤5	-	-
Nasal congestion	-	-	≤5	-	-
Pharyngitis	-	-	≤5	-	-
Pneumonia	-	-	≤5	<1	-
Pulmonary infiltration	-	-	≤5	-	-
Rales	-	-	≤5	-	-
Rhinitis	-	-	≤5	-	-
Sinusitis	-	-	≤5	-	-
Upper-respiratory tract infection	-	-	-	1 to 4	-
Other					
Abnormal hair texture	-	-	≤5	-	-
Abnormal vision	-	-	≤5	-	-
Agitation	-	-	-	<1	-
Atrophic vaginitis	-	-	≤5	-	-
Back pain	-	-	≤5	-	-
Bacterial infection	-	-	≤5	-	-
Blurred vision	-	-	-	<1	-
Breast pain	-	-	≤5	-	-
Chest pain	-	-	≤5	-	-

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate ER	Isosorbide Mononitrate	Nitroglycerin
Cold sweat	-	-	-	<1	-
Collapse	-	-	-	-	✓
Conjunctivitis	-	-	≤5	-	-
Diplopia	-	-	-	<1	-
Dry mouth	-	-	≤5	-	-
Dyscoordination	-	-	-	<1	-
Earache	-	-	≤5	-	-
Fatigue	-	-	≤5	1 to 4	-
Fever	-	-	≤5	-	-
Flu-like symptoms	-	-	≤5	-	-
Frozen shoulder	-	-	≤5	-	-
Glossitis	-	-	≤5	-	-
Hemorrhoids	-	-	≤5	-	-
Hot flashes	-	-	≤5	-	-
Hyperuricemia	-	-	≤5	-	-
Hypoesthesia	-	-	≤5	<1	-
Hypokalemia	-	-	≤5	-	-
Hypokinesia	-	-	-	<1	-
Impaired concentration	-	-	≤5	-	-
Increased appetite	-	-	-	<1	-
Increased sweating	-	-	≤5	-	-
Intermittent claudication	-	-	≤5	-	-
Leg ulcer	-	-	≤5	-	-
Malaise	-	-	≤5	<1	-
Melena	-	-	≤5	-	-
Moniliasis	-	-	≤5	-	-
Myositis	-	-	≤5	-	-
Nightmares	-	-	-	<1	-
Pallor	-	-	-	-	✓
Paranoia	-	-	≤5	-	-
Ptosis	-	-	≤5	-	-
Restlessness	✓	-	-	-	✓
Rigors	-	-	≤5	<1	-
Tendon disorder	-	-	≤5	-	-
Tenesmus	-	-	-	<1	-
Tinnitus	-	-	≤5	-	-
Tooth disorder	-	-	-	<1	-
Tremor	-	-	≤5	-	-
Tympanic membrane perforation	-	-	≤5	-	-
Varicose veins	-	-	≤5	-	-
Viral infection	-	-	≤5	-	-
Weakness	-	-	-	-	✓

ER=extended release, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase

*Topical formulations only.

✓ Percent not specified.

- Event not reported or incidence <1%.

Contraindications/Precautions⁷⁻²⁰

Amyl nitrite is contraindicated in patients with a hypersensitivity to nitrates, severe anemia, head injury, angle-closure glaucoma, postural hypotension and head trauma or cerebral hemorrhage. Amyl nitrite should be used with caution in patients with coronary artery disease, hypotension or increased intracranial pressure.

All nitrates are contraindicated in patients allergic to organic nitrates. Intravenous nitroglycerin is contraindicated in patients with pericardial tamponade, restrictive cardiomyopathy, or constrictive pericarditis. As noted in the drug interactions in Table 7, sildenafil can amplify the vasodilatory effects of nitrates resulting in severe hypotension. Nitrates may aggravate angina caused by hypertrophic cardiomyopathy. With the exception of intravenous nitroglycerin, the benefits of nitrates for acute myocardial infarction and congestive heart failure have not been established and patients must be monitored for potential hypotension and tachycardia. Even small doses of nitrates can cause severe hypotension which may be accompanied by paradoxical bradycardia and increased angina pectoris; therefore, they should not be used in patients that are volume depleted or already hypotensive. The effect of sublingual nitroglycerin may be diminished as tolerance to isosorbide dinitrate and other formulations of nitroglycerin develops.

Drug Interactions

Table 7. Drug Interactions⁷

Drug(s)	Interaction	Mechanism
Nitrates and nitrites	Dihydroergotamine	The metabolism of dihydroergotamine is decreased thus increasing its bioavailability. The dose of the dihydroergotamine may need to be decreased.
Nitrates and nitrites	Sildenafil, tadalafil, vardenafil	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.

Dosage and Administration

Table 8. Dosing and Administration⁷⁻²³

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Amyl nitrite	<u>Acute relief of angina pectoris:</u> One to six inhalations holding capsule under nose, repeat in three to five minutes as needed	Safety and efficacy in children have not been established.	Inhalant
Isosorbide dinitrate sublingual tablet	<u>Prevention or treatment of angina pectoris due to coronary artery disease:</u> 2.5 to 5 mg every five to 10 minutes to maximum of three doses in 15 to 30 minutes or 15 minutes prior to activity	Safety and efficacy in children have not been established.	Sublingual tablet: 2.5 mg 5 mg
Isosorbide dinitrate extended-release capsule/tablet	<u>Prevention or treatment of angina pectoris due to coronary artery disease:</u> Extended-release capsule/tablet: 40 mg every eight to 12 hours; maximum, 160 mg daily; a daily dose-free interval of at least 18 hours is advisable to minimize tolerance	Safety and efficacy in children have not been established.	Extended-release capsule: 40 mg Extended-release tablet: 40 mg
Isosorbide dinitrate tablet	<u>Prevention or treatment of angina pectoris due to coronary artery disease:</u> Initial, 5 to 20 mg two to three times daily; maintenance, 10 to 40 mg two to three times daily; a daily dose-free interval of at least 14 hours is advisable to minimize tolerance	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg 30 mg 40 mg
Isosorbide mononitrate	<u>Prevention or treatment of angina pectoris due to coronary artery</u>	Safety and efficacy in children have not been	Extended-release tablet:

Therapeutic Class Review: nitrates and nitrites

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
extended-release tablet	<u>disease:</u> Initial, 30 to 60 mg daily may increase to 120 mg daily; rarely, 240 mg daily may be required	established.	30 mg 60 mg 120 mg
Isosorbide mononitrate tablet	<u>Prevention or treatment of angina pectoris due to coronary artery disease:</u> Tablet: 20 mg twice daily given seven hours apart	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg
Nitroglycerin injection	<u>Control of congestive heart failure in the setting of acute myocardial infarction, induction of intraoperative hypotension, treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and β-blockers or treatment of perioperative hypertension:</u> 5 μ g/minute, increase by 5 μ g/minute every three to five minutes to 20 μ g/minute; if no response at 20 μ g/minute increase by 10 μ g/minute every three to five minutes, up to 200 μ g/minute	Safety and efficacy in children have not been established.	Vial: 0.1 mg/mL 0.2 mg/mL 0.4 mg/mL 5 mg/mL
Nitroglycerin ointment	<u>Prevention of angina pectoris due to coronary artery disease</u> Initial, 1/2 inch (7.5 mg) twice daily, second dose applied six hours later; dose may be doubled then doubled again	Safety and efficacy in children have not been established.	Ointment: 2%
Nitroglycerin sublingual tablet	<u>Acute relief of angina pectoris:</u> One tablet dissolved under tongue or in the buccal pouch at the first sign of an acute angina attack, may repeat every five minutes up to three doses in a 15-minute period <u>Acute prophylaxis of angina pectoris due to coronary artery disease:</u> One tablet five to 10 minutes prior to activity	Safety and efficacy in children have not been established.	Sublingual tablet: 0.3 mg 0.4 mg 0.6 mg
Nitroglycerin sustained-release capsule	<u>Prevention of angina pectoris due to coronary artery disease</u> 2.5 to 6.5 mg three to four times daily	Safety and efficacy in children have not been established.	Sustained-release capsule: 2.5 mg 6.5 mg
Nitroglycerin transdermal patch	<u>Prevention of angina pectoris due to coronary artery disease</u> Initial, 0.2 to 0.4 mg/hour up to 0.8 mg/hour with a patch-off period of 10 to 12 hours	Safety and efficacy in children have not been established.	Transdermal patch: 0.1 mg/hr 0.2 mg/hr 0.3 mg/hr 0.4 mg/hr 0.6 mg/hr 0.8 mg/hr
Nitroglycerin sublingual spray	<u>Acute relief of angina pectoris:</u> One to two sprays onto or under	Safety and efficacy in children have not been	Sublingual spray: 400 μ g

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	tongue no more than three sprays in a 15-minute period <u>Acute prophylaxis of angina pectoris due to coronary artery disease:</u> One to two sprays onto or under tongue five to 10 minutes prior to activity	established.	

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that guidelines addressing the treatment of stable angina are presented globally, addressing the role of various medication classes in the treatment of this diseases. Due to the complexity of treatment regimens for unstable angina, myocardial infarction and heart failure the associated guideline summaries focus on the role of nitrates in disease management. Additionally The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2003) recommends intravenous nitroglycerine, at a rate of 5 to 100 µg/minute, among the treatment options for the management of hypertensive emergencies, particularly in the setting of coronary ischemia. The onset and duration of action of intravenous nitroglycerine are two to five minutes and five to ten minutes, respectively.³⁸

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American College of Cardiology /American Heart Association: 2007 Chronic Angina Focused Update of the 2002 Guidelines³⁹ for the Management of Patients With Chronic Stable Angina (2007)⁴⁰	<ul style="list-style-type: none"> Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. Patients with hypertension and established coronary artery disease should be treated with blood pressure medication(s) as tolerated, including angiotensin converting enzyme (ACE) inhibitors and/or β-blockers with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. Angiotensin receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction and have a LVEF of ≤40%. ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. Aldosterone blockade is recommended in patients post-myocardial

Clinical Guideline	Recommendation(s)
	<p>infarction without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF $\leq 40\%$ and have either diabetes or heart failure.</p> <ul style="list-style-type: none"> • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
<p>European Society of Cardiology: Management of Stable Angina Pectoris (2006)⁴¹</p>	<p><u>Therapy to improve prognosis</u></p> <ul style="list-style-type: none"> • Aspirin 75 mg once daily is recommended in all patients without contraindications. • Statin therapy is recommended for all patients with coronary disease. • ACE inhibitor therapy is recommended for patients with indications for ACE inhibition including hypertension, heart failure, left ventricular dysfunction and history of myocardial infarction with left ventricular dysfunction and diabetes. • β-blocker therapy is recommended in patients with history of myocardial infarction or heart failure. • Class IIa evidence includes ACE inhibition in patients with angina and proven coronary disease, clopidogrel in patients with stable angina who are not candidates for aspirin and high dose statin therapy in high risk patients with proven coronary disease. • Class IIb evidence includes fibrates in patients with low high density lipoprotein cholesterol and high triglycerides who have diabetes or metabolic syndrome. • Calcium channel blockers may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction and who do not have heart failure. <p><u>Therapy to improve symptoms and/or reduce ischemia</u></p> <ul style="list-style-type: none"> • Short-acting nitroglycerin therapy is recommended for acute symptom relief and situational prophylaxis. • Test the effects of a β1 blocker and titrate to full dose; consider the need for 24-hour protection against ischemia. • If β-blockers are not effective or not tolerated, attempt monotherapy with a calcium channel blocker, long-acting nitrate or nicorandil*. • If the effects of β-blocker therapy are insufficient, add a dihydropyridine calcium channel blocker. • Class IIa evidence includes a sinus node inhibitor in the case of β-blocker intolerance, or a long-acting nitrate or nicorandil* in place of a calcium channel blocker in the case of insufficient response to calcium channel blocker monotherapy or combination therapy with a calcium channel blocker and β-blocker. • Class IIb evidence includes the use of metabolic agents where available as add-on therapy or in place of conventional therapy when conventional therapy is not tolerated. <p><u>Treatment of syndrome X</u></p> <ul style="list-style-type: none"> • Therapy with nitrates, β-blockers and calcium channel blockers alone or in combination is recommended. • Statin therapy is recommended in patients with hyperlipidemia. • ACE inhibitors are recommended in patients with hypertension.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> Class IIa evidence includes a trial of other anti-anginal agents such as nicorandil* and metabolic agents. <p><u>Treatment of vasospastic angina</u></p> <ul style="list-style-type: none"> Treatment with calcium channel blockers is recommended in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.
<p>American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-segment Elevation Myocardial Infarction (2007)⁴²</p>	<p><u>Clinical assessment</u></p> <ul style="list-style-type: none"> Patients with suspected acute coronary syndrome should be instructed to take no more than one dose of sublingual nitroglycerin for chest pain or discomfort. If additional doses are required for persistent or worsening pain, emergency medical attention should be sought. Additional nitroglycerin may be taken every five minutes for a total of three doses while awaiting an ambulance. Patients with chronic stable angina should be instructed that if symptoms are significantly improved after the first dose of sublingual nitroglycerin, doses can be repeated every five minutes if needed for a total of three doses. If pain does not completely resolve after three doses, immediate medical attention should be sought. Instructions for sublingual nitroglycerin administration may be individualized for patients who are known to have frequent angina episodes. The frequency and characteristics of symptoms, as well as the typical response time should be evaluated to determine an appropriate plan. <p><u>Immediate management</u></p> <ul style="list-style-type: none"> Low-risk patients that are referred to outpatient stress testing should be given medications such as sublingual nitroglycerin, aspirin and/or β-blockers as a preventative measure prior to receiving test results. <p><u>Anti-ischemic therapy</u></p> <ul style="list-style-type: none"> Sublingual nitroglycerin (0.4 mg) should be given to patients with Unstable Angina and Non-ST-segment Elevation Myocardial Infarction (UA/NSTEMI) and continuing angina every five minutes as needed for up to three doses. An evaluation of the need for intravenous nitroglycerin, if not contraindicated, should then be performed. An evaluation as to whether to administer intravenous nitroglycerin should be performed after alternative mortality-reducing interventions with agents such as β-blockers or ACE inhibitors have been utilized. Intravenous nitroglycerin is indicated during the first 48 hours after UA/NSTEMI and continuing ischemia, heart failure or hypertension. The recommended starting dose of intravenous nitroglycerin is 10 μg/minute and then titrated by 10 μg/minute every three to five minutes until patient is either asymptomatic or a response in blood pressure is seen. Once the dose has reached 20 μg/minute and no response has been noted, an increase of 10 and then 20 μg/minute may be used. In the absence of relief of symptoms, the goal is to achieve a response in blood pressure. Once this is reached, the dose of intravenous nitroglycerin should then be decreased and the dosing intervals should be extended. The maximum dose of intravenous nitroglycerin has not been established although it is generally considered to be 200 μg/minute. Topically or orally administered nitrates are considered options for

Clinical Guideline	Recommendation(s)
	<p>patients without persistent refractory ischemic symptoms but who require additional treatment for angina.</p> <ul style="list-style-type: none"> Once patients have been symptom-free for 12 to 24 hours intravenous nitroglycerin doses should be decreased and converted to oral or topical nitrates. Nitrates should not be given under the following circumstances: in patients with UA/NSTEMI with systolic blood pressure <90 or ≥30 mm Hg below baseline, in cases of severe bradycardia (<50 beats per minute), in patients with tachycardia (>100 beats per minute) in asymptomatic heart failure or right ventricular infarction. Nitrates are also contraindicated within 24 hours of receiving sildenafil or 48 hours of taking tadalafil. The appropriate time between vardenafil utilization and nitrate administration has not been established. Nitrate-free intervals are recommended in patients on oral or topical nitrates and decreases in intravenous doses should be attempted whenever possible to avoid tolerance. <p><u>Post-UA/NSTEMI</u></p> <ul style="list-style-type: none"> All patients post-UA/NSTEMI should be given sublingual or spray nitroglycerin . Sublingual nitroglycerin should be used for anginal discomfort that has not been relieved by discontinuation of activity or removal from a stressful event. If symptoms persist or worsen after five minutes emergency medical services should be contacted. Doses can be repeated every five minutes if needed for three total doses while patient is lying down or sitting. <p><u>Long-term medical therapy and secondary prevention</u></p> <ul style="list-style-type: none"> Nitroglycerin is recommended to treat ischemic symptoms. <p>Note: A focused update to the 2007 guideline was published in 2011; however, the recommendations for the nitrates and nitrites were not updated and remain current to the 2007 guideline.⁴³</p>
<p>European Society of Cardiology: Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes (2007)⁴⁴</p>	<ul style="list-style-type: none"> β-Blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia and are usually well tolerated. Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes. Calcium channel blockers provide symptom relief in patients already receiving nitrates and β-blockers; they are useful in patients with contraindications to β-blockade and in the subgroup of patients with vasospastic angina. Nifedipine, or other dihydropyridines, should not be used unless combined with β-blockers. Intravenous nitrates may be considered in patients with non-ST-segment elevation acute coronary syndrome who require hospitalization. Once symptoms are controlled, a non-parenteral alternative should be used at intermittent dosing intervals to avoid tolerance. Patients with non-ST-segment elevation acute coronary syndrome should be initiated on sublingual or intravenous nitroglycerin with caution given to those with systolic blood pressure <90 mm Hg.
<p>American College of Cardiology/American Heart Association:</p>	<p><u>Initial emergency department management</u></p> <ul style="list-style-type: none"> Sublingual nitroglycerin 0.4 mg should be given to patients with ongoing ischemic discomfort every five minutes for three total doses. After three

Clinical Guideline	Recommendation(s)
<p>Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction–Pharmacological Management (2004)⁴⁵</p>	<p>doses, assess need for intravenous nitroglycerin.</p> <ul style="list-style-type: none"> Intravenous nitroglycerin is indicated for relief of ongoing ischemic discomfort, control of hypertension or management of pulmonary congestion. <p><u>Hospital management–medication assessment</u></p> <ul style="list-style-type: none"> Intravenous nitroglycerin is indicated during the first 48 hours for treatment of persistent ischemia, hypertension or congestive heart failure, provided that therapy does not preclude treatment with β-blockers or ACE inhibitors. Nitroglycerin after 48 hours can be useful for recurrent angina or persistent congestive heart failure provided that therapy does not preclude treatment with β-blockers or ACE inhibitors. <p>Note: Focused updates to the 2004 guideline were published in 2007 and 2009; however, the recommendations for the nitrates and nitrites were not updated and remain current to the 2004 guideline.⁴⁶⁻⁴⁷</p>
<p>National Institute for Health and Clinical Excellence: Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)⁴⁸</p>	<p><u>Patients with prior myocardial infarction without heart failure</u></p> <ul style="list-style-type: none"> Calcium channel blockers, nitrates, and potassium channel activators* have no effect on premature mortality and can be used for management of risk factors such as hypertension in patients intolerant to a β-blocker and an ACE inhibitor.
<p>American College of Cardiology/American Heart Association: Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)³ and Diagnosis and Management of Heart Failure in Adults (2009 Focused Update)⁴</p>	<ul style="list-style-type: none"> The addition of a combination of hydralazine and a nitrate is reasonable for patients with heart failure who are already taking an ACE inhibitor and β-blocker for symptomatic heart failure, but who have persistent symptoms. A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of heart failure and reduced LVEF who cannot be given an ACE inhibitor or an ARB because of drug intolerance, hypotension, or renal insufficiency. The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African American, with moderate to severe symptoms on optimal therapy with ACE inhibitors, β-blockers and diuretics. Combination of fixed-dose hydralazine and isosorbide dinitrate to a standard regimen for heart failure, including ACE inhibitors and β-blockers, is recommended in order to improve outcomes for patients self-described as African American, with New York Heart Association (NYHA) functional class III or IV heart failure. Any potential benefit in other patients has yet to be evaluated. Patients with heart failure should be given nitrates and β-blockers for the treatment of angina. Vasodilators (i.e., intravenous nitroglycerin, nitroprusside or nesiritide) can be beneficial when added to diuretics and/or in those who do not respond to diuretics alone in patients with severely symptomatic fluid overload in the absence of systemic hypotension.
<p>Heart Failure Society of America: Heart Failure Society</p>	<ul style="list-style-type: none"> Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE inhibitors for African Americans with heart failure and reduced LVEF.

Clinical Guideline	Recommendation(s)
<p>of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)⁵</p>	<ul style="list-style-type: none"> • In patients with reduced LVEF, combination hydralazine and an oral nitrate may be considered when ACE inhibitors are not tolerated due to hyperkalemia or renal insufficiency or ARBs are not tolerated due to cough or angioedema. • May be considered in non–African American patients with left ventricular dysfunction who remain symptomatic despite optimized standard therapy. • Addition of the combination of hydralazine and isosorbide dinitrate should be considered in African American patients with heart failure and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with ACE inhibitors and β-blocker or unable to tolerate a β-blocker. • In patients admitted with acute decompensated heart failure, intravenous nitroglycerin, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in the absence of symptomatic hypotension. • Intravenous vasodilators (nitroglycerin or nitroprusside) and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. • Intravenous vasodilators (nitroglycerin, nesiritide or nitroprusside) can be considered in patients with acute decompensated heart failure who have persistent symptoms despite aggressive treatment with diuretics and standard oral therapy. • Nitrates should be considered in patients with heart failure when additional medication is needed for anginal symptoms.
<p>European Society of Cardiology: European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2008)⁶</p>	<ul style="list-style-type: none"> • Patients should be counseled on the possible role of sublingual nitrates as prophylaxis agents against dyspnea and chest pain during sexual activity. • Isosorbide dinitrate in combination with hydralazine may be considered for the management of heart failure in cases of intolerance to ACE inhibitors and ARBs. Addition of the combination isosorbide dinitrate and hydralazine should be considered in patients with persistent symptoms despite treatment with an ACE inhibitor, β-blocker and an ARB or aldosterone antagonist. • Vasodilators are recommended at an early stage for patients with acute heart failure without symptomatic hypotension or serious valvular disease. Intravenous nitrates and nitroprusside are recommended in patients with systolic blood pressure >110 mm Hg and may be used with caution in patients with systolic blood pressure 90 to 110 mm Hg. • Vasodilators and loop diuretics are recommended in decompensated chronic heart failure. • In hypertensive heart failure, vasodilators are recommended with close monitoring and low-dose diuretic treatment in patients with volume overload or pulmonary edema.

*Agent not currently available in the United States.

Conclusions

Nitrates and nitrites are indicated for the acute, prophylactic and chronic treatment of angina pectoris due to coronary artery disease. Intravenous nitroglycerin is additionally Food and Drug Administration Approved (FDA)-approved for the control of congestive heart failure in the setting of myocardial infarction, induction of intraoperative hypotension, treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and β -blockers and treatment of perioperative hypertension. Since all nitrates have the same pharmacologic effects, product selection is based on desired onset and duration of action. Nitroglycerin sublingual tablets have long demonstrated their utility as a treatment for acute angina due to

their rapid onset of action. The nitroglycerin sublingual spray possesses no known clinical advantage over the sublingual tablets. Nitroglycerin, when administered buccally every four hours, has shown similar efficacy to intravenous administration over a 24-hour period in patients with unstable angina.³³ Both isosorbide mononitrate and isosorbide dinitrate are available generically. Furthermore, nitroglycerin extended-release capsules, injection, ointment, sublingual tablets, and transdermal patches are all available generically.

The phosphodiesterase inhibitors, used for erectile dysfunction, are contraindicated in all patients on nitrite or nitrate therapy. The potential for tolerance, and therefore loss of pharmacologic effect, is common to all nitrate formulations. Nitrate tolerance is minimized by ensuring a nitrate-free period and/or use of the lowest effective dose. Transient headache is an adverse effect most often associated with nitrites and nitrates.

The beneficial effects of nitrates for the management of chronic stable angina are evident, although there is no known advantage over β -blockers or calcium channel blockers. Tolerance further limits the chronic use of this class of medications and as a result, they are considered second-line to β -blockers for chronic stable angina.³⁹⁻⁴² The efficacy of isosorbide dinitrate and hydralazine is further recognized in clinical practice guidelines for the management of congestive heart failure.³⁻⁶ Furthermore, sublingual and intravenous nitroglycerin are both recommended in unstable angina, myocardial infarction and acute coronary syndromes.⁴²⁻⁴⁸

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Nitrostat	362	405	52.53%	\$5,931.66	\$14.65
Isosorbide mononitrate ER	124	246	31.91%	\$8,040.82	\$32.69
Nitroglycerin transdermal	25	39	5.06%	\$1,638.05	\$42.00
Nitroglycerin	52	28	3.63%	\$430.27	\$15.37
Isosorbide dinitrate	17	25	3.24%	\$383.98	\$15.36
Isosorbide mononitrate	9	12	1.56%	\$531.33	\$44.28
Nitro-Bid	6	6	0.78%	\$75.26	\$12.54
Nitrolingual Pumpspray	7	7	0.91%	\$1,494.03	\$213.43
Nitro-Dur	1	2	0.26%	\$850.45	\$425.23
Isosorbide dinitrate ER	1	1	0.13%	\$57.28	\$57.28
Class Total:	605	771	100%	\$19,433.12	\$25.21

Recommendations

All generic products in this managed category, with the exception of isosorbide dinitrate SL tablet, are listed as preferred on the Department of Vermont Health Access (DVHA) preferred drug list (PDL). No changes to the current DVHA approval criteria for nitrates/nitrites (see below) are proposed.

Dilatrate-SR[®], Imdur[®]:

- The patient has had a side effect, allergy, or treatment failure to at least two of the following medications: isosorbide dinitrate ER tablet, isosorbide mononitrate ER tablet, nitroglycerin ER capsule or Nitro-time[®]. If a product has an AB rated generic, one trial must be the generic formulation.

Ismo[®], Isordil[®], Monoket[®], Isosorbide dinitrate SL tablet:

- The patient has had a side effect, allergy, or treatment failure to at least two of the following medications: isosorbide dinitrate tablet or isosorbide mononitrate tablet. If a product has an AB rated generic, one trial must be the generic formulation.

Nitro-Dur[®]:

- The patient has had a side effect, allergy, or treatment failure to Nitrek[®] or generic nitroglycerin transdermal patches.

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