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DRUGS FOR STABLE ANGINA PECTORIS

Many nitrates, beta-blockers, and calcium-channel blockers have now been approved by the US Food and Drug Administration for treatment of stable angina pectoris. The table beginning on page 112 lists the individual drugs, their dosage, and their cost.

NITRATES — Nitrates are potent venous and arterial dilators. They decrease venous return and myocardial oxygen demand and increase collateral blood flow to ischemic areas. All nitrates can cause rapid development of tolerance, but a drug-free interval overnight can reverse the tolerance that develops during the day.

Nitroglycerin — Sublingual nitroglycerin is the drug of choice for an acute attack of angina. The therapeutic effect lasts for less than an hour, making it unsuitable for long-term prophylaxis, but in patients who have angina associated with physical activity, sublingual nitroglycerin taken five to ten minutes before the activity can prevent or delay an attack. A translingual spray is as effective as the sublingual tablets and has the same indications (Medical Letter, 28:59, 1986). Nitroglycerin is also available in an extended-release transmucosal tablet (Medical Letter, 29:39, 1987). The absorption of swallowed nitroglycerin is poor, and its effectiveness for long-term treatment has never been established.

Absorption of transdermal nitroglycerin from skin varies in different patients and at different sites of application. One to two inches of nitroglycerin ointment (2%) applied over an area of 36 square inches three or four times a day and removed for 10 to 12 hours during each 24-hour period is effective for short-term treatment of angina, but its long-term effectiveness has never been established. Continuous use of nitroglycerin patches causes rapid development of tolerance. Intermittent treatment with the patches — leaving them off for 10 to 12 hours overnight — prevents development of tolerance but may cause rebound nocturnal angina and decrease early-morning exercise capacity (Medical Letter, 31:65, 1989; Steering Committee, Am J Cardiol, 68:1263, 1991).

Isosorbide Dinitrate — Sublingual isosorbide dinitrate is slower in onset of action than sublingual nitroglycerin and less effective for treatment of acute angina. Its one-to-two-hour duration of action does make it suitable, however, for prevention of angina during physical exertion. Use of oral isosorbide dinitrate four times a day leads to tolerance, but taking it two or three times a day in the morning and afternoon can prevent tolerance (JO Parker et al, N Engl J Med, 316:1440, 1987). The long-term effectiveness of oral slow-release formulations of isosorbide dinitrate has not been established. In one trial, a 40-mg sustained-release formulation t.i.d. was not superior to placebo (RG Friedman et al, J Invasive Cardiol, 4:319, 1992).

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Isosorbide-5-Mononitrate – Isosorbide-5-mononitrate is the major active metabolite of isosorbide dinitrate. Unlike the dinitrate, it is nearly 100% bioavailable and has no active metabolites. Twice-daily treatment in the morning and afternoon does not produce tolerance or rebound nocturnal angina (JO Parker et al, *Am J Cardiol*, 72:871, 1993; U Thadani et al, *Ann Intern Med*, 120:353, 1994). A controlled-release form of isosorbide mononitrate (*Imdur*) was recently marketed in the USA; once-daily doses appear to be effective without producing tolerance (SG Chrysant et al, *Am J Cardiol*, 72:1249, 1993; Medical Letter, 36:13, 1994).

Adverse Effects – Nitrates are generally well tolerated. The most common adverse effect is headache, which occurs in 30% to 60% of patients taking long-acting nitrates. Occasionally, headaches may be severe and associated with nausea and prostration. Some patients develop symptomatic postural hypotension, and syncope can occur.

DRUGS FOR STABLE ANGINA PECTORIS

Drug	Dosage	Cost ¹
NITRATES		
Nitroglycerin		
sublingual tablets – <i>Nitrostat</i> (Parke-Davis)	0.3 to 0.6 mg PRN (up to 3 tablets)	\$ 6.18 ²
translingual spray – <i>Nitrolingual</i> (Rhône-Poulenc Rorer)	0.4 mg/spray (up to 3 sprays)	22.92 ³
transmucosal tablets – <i>Nitrogard</i> (Forest)	1 to 3 mg q5h 3x/day	29.45
oral extended-release	2.5 to 6.5 bid to qid	
average generic price (capsules)		4.03
<i>Nitroglyn</i> (Kenwood)		4.69
<i>Nitrong</i> (Rhône-Poulenc Rorer)		14.21
ointment – 2%	1" to 2" q4h for 12 to 14 hours/day	
average generic price		10.28 ⁴
<i>Nitro-Bid</i> (Marion-Merrell Dow)		6.25 ⁴
transdermal patches ⁵	one patch 12 to 14 hours/day	
average generic price		40.26 ⁶
<i>Deponit</i> (Schwarz)		45.13 ⁶
<i>Minitrans</i> (3M)		43.44 ⁷
<i>Nitrodisc</i> (Searle)		48.18 ⁶
<i>Nitro-Dur</i> (Key)		42.85 ⁶
<i>Transderm-Nitro</i> (Ciba)		50.08 ⁶
Isosorbide Dinitrate		
sublingual tablets – immediate release	2.5 to 10 mg q2-3h	
average generic price		3.60 ²
<i>Isordil</i> (Wyeth-Ayerst)		21.54 ²
<i>Sorbitrate</i> (Zeneca)		17.22 ²
oral tablets	30 mg bid or 20 mg tid in morning and afternoon	
average generic price		3.35
<i>Isordil Titrados</i>		28.15
<i>Sorbitrate</i>		22.52
extended-release tablets and capsules	40 to 80 mg once daily to tid	
average generic price		2.38
<i>Isordil Tembids</i>		14.81
<i>Dilatrate SR</i> (Reed & Carnrick)		13.85
Isosorbide-5-Mononitrate		
immediate release	20 mg in morning and afternoon, 7 hours apart	
<i>ISMO</i> (Wyeth-Ayerst)		39.49
<i>Monoket</i> (Schwarz)		31.59
extended-release	60 to 120 mg once daily	
<i>Imdur</i> (Schering/Key)		19.44

Drug	Dosage	Cost ¹
BETA-BLOCKERS		
Atenolol	50 to 100 mg once daily	
average generic price		\$ 19.63
<i>Tenormin</i> (Zeneca)		26.02
Metoprolol	50 to 200 mg bid	
average generic price		13.40
<i>Lopressor</i> (Geigy)		14.87
Nadolol	40 to 80 mg once daily	
average generic price		25.30
<i>Corgard</i> (Bristol)		30.03
Propranolol		
immediate release	80 to 320 mg divided bid, tid, or qid	
average generic price		5.51
<i>Inderal</i> (Wyeth-Ayerst)		32.14
extended release	80 to 160 mg once daily	
average generic price		21.80
<i>Inderal LA</i>		25.29
CALCIUM-CHANNEL BLOCKERS		
Dihydropyridines		
Amlodipine – <i>Norvasc</i> (Pfizer)	5 to 10 mg once daily	34.01
Nicardipine – <i>Cardene</i> (Syntex)	20 to 40 mg tid	36.64
Nifedipine		
immediate release	10 to 30 mg tid or qid	
average generic price		39.66
<i>Adalat</i> (Miles)		41.86
<i>Procardia</i> (Pfizer)		52.43
extended-release		
<i>Procardia XL</i>	30 to 90 mg once daily	35.54
Other Classes		
Diltiazem		
immediate release	30 to 120 mg tid or qid	
average generic price		32.17
<i>Cardizem</i> (Marion-Merrell Dow)		39.15
extended-release		
<i>Cardizem CD</i>	120 to 480 mg once daily	31.32
Verapamil	80 to 120 mg tid or qid	
average generic price		20.73
<i>Calan</i> (Searle)		41.36
<i>Isoptin</i> (Knoll)		39.81
Bepridil – <i>Vasacor</i> (McNeil)	200 to 400 mg once daily	70.10

1. Cost to the pharmacist for 30 days' treatment (unless otherwise noted) with lowest recommended dose based on wholesale price (AWP) listings in *Red Book* 1994 and November *Update*.
2. Cost of one bottle of 100 tablets.
3. One canister (14.49 grams) containing 200 0.4-mg metered doses.
4. Cost of one 60-gram tube. One inch of ointment contains 15 mg of nitroglycerin.
5. Nitroglycerin patches are available in sizes ranging from 0.1 mg/hour to 0.8 mg/hour (formerly 2.5 mg to 20 mg/24 hours).
6. Cost of 30 patches delivering 0.4 mg/hour.
7. Cost of 33 patches delivering 0.4 mg/hour.

BETA-ADRENERGIC BLOCKERS — Beta-blockers decrease myocardial oxygen demand by decreasing heart rate, contractility, and systolic blood pressure during exercise. By slowing the heart rate, they prolong diastolic filling, making more time available for coronary blood flow. Of all the available antianginal drugs, beta-blockers without intrinsic sympathomimetic activity (all except acebutolol, carteolol, penbutolol, and pindolol) are the most effective in decreasing myocardial ischemia (AA Quyyumi et al, *Br Heart J*, 57:505, 1987; PH Stone et al, *Circulation*, 82:1962, 1990). In post-infarction patients, controlled trials have shown that a beta-blocker can decrease the risk of another myocardial infarction and death (S Yusuf et al, *JAMA*, 260:2088, 1988).

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Adverse Effects – In general, beta-blockers are well tolerated. Because of their negative inotropic effects, they can precipitate or aggravate heart failure. Symptomatic bradycardia, hypotension, fatigue, depression, cold extremities, impotence, constipation, and vivid dreams can occur. In diabetic patients who develop hypoglycemia, beta-blockers can mask some of the symptoms and delay recovery. Even cardioselective beta-blockers can produce severe bronchospasm in patients with asthma or other reactive airway disease. Sudden withdrawal of a beta-blocker can exacerbate angina or lead to a myocardial infarction; gradual withdrawal over several days is recommended. Beta-blockers are contraindicated in patients with Raynaud's phenomenon and those with pain at rest due to peripheral vascular disease. Beta-blockers used concurrently with verapamil or diltiazem may have marked negative inotropic effects and may cause bradycardia and occasionally high-grade AV block.

CALCIUM-CHANNEL BLOCKERS – Calcium-channel blockers decrease myocardial oxygen demand and increase coronary blood flow. Verapamil and diltiazem also decrease exercise-induced increases in heart rate (D Acanfora et al, *G Ital Cardiol*, 23:451, 1993; U Thadani et al, *Am J Cardiol*, 74:9, 1994). All of the calcium-channel blockers currently available in the USA except diltiazem, verapamil, and bepridil are dihydropyridines.

Choice of Drugs – A calcium-channel blocker is the drug of choice for patients with both angina and hypertension who have contraindications to treatment with a beta-blocker. In patients with angina who also have episodes of supraventricular tachycardia, verapamil or diltiazem is effective for both, but the dihydropyridines are not and can aggravate the arrhythmia. Therapeutic doses of amlodipine generally do not have a negative inotropic effect (D Murdoch and RC Heel, *Drugs*, 41:478, 1991), and the drug has been used in small numbers of patients with depressed left ventricular function without aggravating heart failure (Medical Letter, 34:99, 1992), but adequate controlled trials in patients with heart failure are not available. Bepridil alone or added to other drugs may be more effective than other calcium-channel blockers for treatment of patients with refractory angina (BN Singh, *Am J Cardiol*, 68:306, 1991; Medical Letter, 33:53, 1991), but it can cause serious adverse effects.

Adverse Effects – In general, calcium-channel blockers are well tolerated; they can cause vasodilator effects such as headache, flushing, and dizziness. They can also precipitate heart failure in patients with compromised left ventricular function, particularly if verapamil or diltiazem is used with a beta-blocker. Verapamil and diltiazem are more likely to suppress cardiac contractility and slow cardiac conduction; the dihydropyridines are more potent vasodilators. Peripheral edema secondary to vasodilation occurs more often with dihydropyridines than with diltiazem or verapamil. Constipation is often a problem with verapamil, especially in the elderly. Bradycardia or high-degree AV block may develop with diltiazem or verapamil, especially if they are used with a beta-blocker. The dihydropyridines can induce angina due to reflex tachycardia secondary to vasodilatation; these effects are rare, however, with amlodipine or slow-release formulations of nifedipine. Concurrent use of a beta-blocker can decrease both the tachycardia and the angina. Bepridil prolongs the QT interval and can cause torsades de pointes, a serious ventricular arrhythmia, especially in patients with hypokalemia (P Coumel, *Am J Cardiol*, 69:75D, 1992).

CONCLUSION – Nitrates, beta-blockers, and calcium-channel blockers are all effective for treatment of angina pectoris. When the response to one type of drug is inadequate, a second and

sometimes a third may be added. Only beta-blockers after myocardial infarction have been shown to decrease mortality.

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