correcting supply/demand blood flow mismatch that is the cause of myocardial ischemia and angina pectoris (Table 8-5). Interestingly, these drugs principally control symptoms in chronic stable angina pectoris, but they do not reduce mortality risk as therapy with aspirin or statins does.

Nitrates in various forms have a long history of use in patients with symptomatic CAD and can be very effective in controlling exertion-related angina. Nitrates work by venodilating large-capacitance veins and thus shifting blood out of the heart, reducing preload and myocardial oxygen demand. Nitrates are also potent coronary vasodilators and can reverse coronary spasm, allowing for improved perfusion. Short-duration but quick-acting sublingual nitroglycerin has been a mainstay both for treatment of an anginal episode and for prophylaxis against angina in situations where it is likely to occur. Patients who respond well to nitrates are frequently treated with long-acting oral or topical preparations. Both methods can effectively prevent angina pectoris, but continued use can induce tolerance. There is a recognized need for patients to have a nitrate-free period of about 8 hours every day to prevent tolerance. This usually involves cessation of use during sleep. Intravenous nitroglycerin administered by continuous drip is reserved for patients with unstable angina or acute MI.

β-Blocker therapy is very effective at reducing the likelihood of exertion-related angina. β-Blockers bind to cell surface β-receptors and by so doing reduce heart rate, contractility, and blood pressure, all of which tip the balance in favor of reduced oxygen demand and less angina. The use of β-blockers can be limited by the degree of bradycardia they induce or by baseline atrioventricular (AV) conduction abnormalities. Patients with higher degrees of AV block, β-blockers can induce complete heart block. These drugs also vary in their β-receptor selectivity. Blockade of $\beta_2$-adrenergic receptors can lead to bronchospasm and vasoconstriction. Even selective $\beta_1$-adrenergic antagonists such as atenolol and metoprolol have some $\beta_2$ activity at higher doses. Intolerance of β-blockers can limit their use in patients with significant COPD or peripheral vascular disease. β-Blockers may also add to glucose intolerance and may affect lipids by increasing triglycerides or reducing HDL. In general, these effects do not preclude their use if they prove effective in controlling angina pectoris.

Calcium channel blocking drugs can decrease myocardial oxygen demand by causing arterial vasodilation, bradycardia, and decreased contractility. The magnitude of these effects varies according to the class of agent used. Dihydropyridines such as nifedipine and amlodipine cause arterial vasodilation leading to a blood pressure–lowering effect. In the dose ranges administered, they have no significant effect on contractility or heart rate. In contrast, verapamil, a phenylalkylamine, has significant effects on heart rate, AV conduction, and contractility. Benzothiazepine agents such as diltiazem manifest less vasodilation than dihydropyridines and less effect on contractility than phenylalkyamine drugs. The net effect of calcium channel blocking drugs is reduced myocardial oxygen demand and less angina pectoris. Diltiazem should be used with caution in patients who are also taking a β-blocker, because severe bradycardia or heart block can occur. Verapamil should not be co-administered with a β-blocker.

A newer class of antianginal drug is represented by ranolazine. This drug is a selective inhibitor of late sodium current and reduces sodium-induced calcium overload in myocytes. Although it has no effect on heart rate or blood pressure, ranolazine demonstrates antianginal properties. It is typically used when other medical therapy is insufficient in controlling angina.

### Revascularization Therapy for Chronic Stable Angina Pectoris

Revascularization therapy is an option to be considered when medical therapy is not sufficiently controlling symptoms leading to impaired lifestyle. It is also frequently pursued in the face of high-risk situations such as unstable angina, STEMI, heart failure complicated by angina, arrhythmias associated with angina, or

**TABLE 8-5** MEDICATIONS FOR ANGINA PECTORIS

| DRUG CLASS | EXAMPLES | ANTIANGINAL EFFECT | PHYSIOLOGIC SIDE EFFECTS | COMMENTS |
|---|---|---|---|---|
| Nitroglycerin | Sublingual<br>Topical<br>Intravenous<br>Oral | Decreased preload and afterload<br>Coronary vasodilation<br>Increased collateral blood flow | Headache<br>Flushing<br>Orthostasis | Tolerance develops with continuous use |
| β-Adrenergic blocking agents | Metoprolol<br>Atenolol<br>Propranolol<br>Nadolol | Decreased heart rate<br>Decreased blood pressure<br>Decreased contractility | Bradycardia<br>Hypotension<br>Bronchospasm<br>Depression | May worsen heart failure and AV conduction block; avoid in vasospastic angina |
| Calcium channel blocking agents (non-dihydropyridine) | Phenylalkylamine (verapamil)<br>Benzothiazepine (diltiazem) | Decreased heart rate<br>Decreased blood pressure<br>Decreased contractility<br>Coronary vasodilation | Bradycardia<br>Hypotension<br>Constipation with verapamil | May worsen heart failure and AV conduction |
| Calcium channel blocking agents | Dihydropyridine (nifedipine, amlodipine) | Decreased blood pressure<br>Coronary vasodilation | Hypotension, reflex tachycardia<br>Peripheral edema | Short-acting nifedipine is associated with increased risk for cardiovascular events. |
| Late sodium current blocking agents | Ranolazine | Inhibits cardiac late $I_{Na}$<br>Prevents calcium overload | Dizziness<br>Headache<br>Constipation<br>Nausea | No effects on blood pressure or heart rate<br>Modest QTc prolongation |

AV, Atrioventricular; $I_{Na}$, sodium current.