Management of Angina

SALIENT CLINICAL FEATURES

Angina is a pain in the chest or adjacent areas caused by severe, but temporary, lack of blood (ischemia) to a segment of heart muscle, hence the term myocardial ischemia. For stable angina, the most important feature is the causation of pain by a particular exertional activity and relief within minutes of cessation of the precipitating activity.

Angina may be classified as

- Stable angina.
- Unstable angina.
- Variant angina (Prinzmetal’s), coronary artery spasm (CAS).

The pain of angina must be differentiated from commonly occurring

- Gastroesophageal reflux and motility disorders.
- Musculoskeletal disorders, particularly costochondritis that causes tenderness without swelling of the second to fourth left costochondral junctions and may occur concomitantly with coronary artery disease.

It is necessary to document the presence or absence of diabetes and cigarette smoking, which markedly increases risk, and asthma, which contraindicates the use of beta-blocking drugs.

Physical examination should exclude secondary factors that may precipitate angina:

- Anemia and hypertension.
- Aortic stenosis, severe valvular disease, and hypertrophic cardiomyopathy.
- Arrhythmias.

Relevant baseline investigations include resting and stress electrocardiogram (ECG), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, as well as hemoglobin, glucose serum creatinine, and estimated glomerular filtration rate (GFR).

Pathophysiologic Implications

Three determinants play major roles in the pathogenesis of myocardial ischemia to cause stable or unstable angina:

- Atheromatous lesions are mainly concentric with stable angina and eccentric with unstable angina and cause >70% coronary stenosis.
- Myocardial oxygen demand is increased.
- Catecholamines are released in response to exertional and emotional stress or other activity. Catecholamines cause an increase in heart rate, velocity, and force of myocardial contraction.
that increase oxygen demand and ischemia. Increased heart rate decreases the diastolic interval during which coronary artery perfusion occurs. Ischemia further stimulates catecholamine release, thereby perpetuating the vicious circle.

Catecholamine release initiates and perpetuates a dynamic process. Thus, beta-blocking agents play a key role in the management of patients with myocardial ischemia manifested by anginal pain or silent ischemia. The pathophysiology of unstable angina is more complex and is dealt with later in this chapter.

**TREATMENT OF STABLE ANGINA**

It is crucial to control known risk factors for coronary artery disease strictly:

- Cigarette smoking must be curtailed; weight and stress must be addressed.
- Hypertension must be controlled with an appropriate drug; goal blood pressure (BP): systolic < 135 mmHg.
- Hyperlipidemia must be brought to goal levels: LDL < 2.5 mmol/L (100 mg/dL) and for high-risk patients < 60 mg/dL (1.6 mmol/L); HDL > 1.0 mmol/L (39 mg/dL).
- Diabetes must be treated aggressively.

**Beta-Adrenoceptor Blocking Agents**

All cardiologists now agree that beta-blockers are standard first-line therapy for stable and unstable angina. In the first edition of this book in 1984, I constructed a table that compared beta-blockers, nitrates, and calcium antagonists and indicated the rationale for beta-blockers as first-line treatment; this table has remained unaltered (Table 10-1).

Many patients with left ventricular (LV) dysfunction and borderline and class II–III heart failure (HF) were deprived of beta-blocker therapy from 1970 to 1999. These drugs were believed to be contraindicated in HF. However, beta-blockers continue to surprise us (1). Randomized controlled trials (RCTs) have proved solidly that these drugs decrease mortality and morbidity in patients with all grades of HF (see Chapter 12), and at present

<table>
<thead>
<tr>
<th>Effect on</th>
<th>Beta-blocker</th>
<th>Calcium antagonist</th>
<th>Oral nitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↑↓</td>
<td>—</td>
</tr>
<tr>
<td>Drastolic filling of coronary arteries</td>
<td>↑</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↓↓</td>
<td>↓↓</td>
<td>—</td>
</tr>
<tr>
<td>Rate pressure product (RPP)</td>
<td>↓↓</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>Relief of angina</td>
<td>Yes</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Blood flow (subendocardial ischemic area)</td>
<td>↑</td>
<td>↓</td>
<td>Variable</td>
</tr>
<tr>
<td>First-line treatment for angina pectoris</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prevention of recurrent ventricular fibrillation</td>
<td>Proven</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prevention of cardiac death</td>
<td>Proven</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prevention of pain from coronary artery spasm</td>
<td>No</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Prevention of death in patient with coronary artery spasm</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*a*RPP variable decrease on exercise, but not significant at rest or on maximal exercise.

*b*Distal to organic obstruction.

↓, decrease; ↑, increase; —, no significant change.

---

### Table 10-1

**Beta-Blocker: First-Line Oral Drug Treatment in Angina Pectoris**

<table>
<thead>
<tr>
<th>Effect on</th>
<th>Beta-blocker</th>
<th>Calcium antagonist</th>
<th>Oral nitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↑↓</td>
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</tr>
<tr>
<td>Drastolic filling of coronary arteries</td>
<td>↑</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↓↓</td>
<td>↓↓</td>
<td>—</td>
</tr>
<tr>
<td>Rate pressure product (RPP)</td>
<td>↓↓</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>Relief of angina</td>
<td>Yes</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Blood flow (subendocardial ischemic area)</td>
<td>↑</td>
<td>↓</td>
<td>Variable</td>
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<td>No</td>
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<td>Proven</td>
<td>No</td>
<td>No</td>
</tr>
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<td>No</td>
<td>Yes</td>
<td>Variable</td>
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<td>Prevention of death in patient with coronary artery spasm</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*a*RPP variable decrease on exercise, but not significant at rest or on maximal exercise.

*b*Distal to organic obstruction.

↓, decrease; ↑, increase; —, no significant change.
they are strongly recommended in patients with angina and HF or LV dysfunction. Calcium antagonists and nitrates cannot reduce mortality or morbidity in these patients and are relegated to second-line therapy. Therefore, virtually all patients with angina should receive a beta-blocker, preferably bisoprolol, metoprolol, or carvedilol, at a cardio-protective dosage (see the later discussion of cardioprotective dose).

These 3 of the 12 available beta-blockers are chosen because they have been shown to decrease mortality in patients with coronary heart disease (see Chapter 1). Atenolol, a water-soluble drug, is frequently used worldwide for angina and hypertension. The water-soluble, non-lipid-soluble beta-blockers atenolol and nadolol have not been shown in RCTs to decrease mortality in patients after myocardial infarction (MI) (2).

- It is important to reemphasize that only the cardioselective, lipid-soluble beta-blockers metoprolol, timolol (3), and propranolol (in nonsmokers) and, recently, carvedilol (4) have been shown in RCTs to decrease mortality in post-MI patients. Beta-blockers have important subtle clinical differences (2).

- It remains probable that beta 1 and beta 2 effects are needed to render further cardio-protection (see Chapter 1).

Beta-blockers significantly reduce the number of episodes of angina in more than 75% of patients. Beta-blockers may prevent up to 25% of deaths in patients with angina (3), but reduction in mortality has not been documented in RCTs of patients with angina. Only a few small trials have been conducted, and with poor methodology. With the current use of aspirin, statins, and angiotensin-converting enzyme (ACE) inhibitors as routine therapy in patients with angina, it will take a huge number (>7000) of patients to mount a sound RCT, and such a trial is not planned. Patients receiving a beta-blocking agent have the advantage of pretreatment before a subsequent severe ischemic episode (3,4).

Atenolol has been shown to reduce the number of ischemic episodes on Holter monitoring (5). In a study by Laukkanen and associates (6), silent ischemia detected on exercise test in middle-aged men with coronary risk factors but no prior coronary heart disease was associated with increased coronary events and mortality. The study provides strong support of silent ischemia as a marker of adverse outcome in presumably healthy middle-aged men with one or more risk factors (7).

Observations have established that silent ischemia is common and is easily provoked by daily stressful activities (8,9). Patients with angina may have more silent than painful episodes (10,11). Beta-blockers, nitrates, and calcium antagonists have been shown to abolish silent ischemic episodes (12), but beta-adrenergic blockers are superior. Atenolol and bisoprolol are more effective than nifedipine, especially in reducing the morning surge of silent ischemia (13,14). Suggested steps in how to treat chronic stable angina pectoris are outlined in Figure 10-1.

The salutary effects of beta-adrenoceptor blockade are illustrated in Figure 1-1. These beneficial effects in myocardial ischemia result from

- A decrease in myocardial oxygen demand as a result of a decrease in heart rate.
- A decrease in the velocity and force of myocardial contraction.
- A fall in cardiac output and blood pressure; thus the rate pressure product (heart rate × systolic blood pressure) is reduced.
- Improvement in blood supply caused by a decrease in heart rate, which lengthens the diastolic interval. Because the coronary arteries fill during diastole, coronary perfusion improves.
- Blocking of exercise-induced catecholamine vasoconstriction at sites of coronary stenosis where atheroma could impair the relaxing effects of the endothelium.
A shift of blood from the epicardium to the subendocardial ischemic area (see Table 10-1).
- Decreased conduction through the atrioventricular (AV) node resulting in slowing of the ventricular response in atrial fibrillation or other supraventricular arrhythmias that may occur in patients with myocardial ischemia.
- Decrease in phase four diastolic depolarization producing suppression of ventricular arrhythmias, especially those induced by catecholamines and/or ischemia.
- Increase in ventricular fibrillation (VF) threshold reduces the incidence of VF and sudden deaths that could, at some stage, occur in patients with angina (see Chapter 1 for other mechanisms).

**Cardioprotection and Dosage of Beta-Blocker**

Table 1-4 gives dosages of beta-blockers. The dose of **metoprolol** is 100–300 mg, that of **propranolol** in nonsmokers is 160–240 mg, and that of **timolol** is 10–20 mg daily (3,4), because these doses have been shown to be effective in preventing sudden death and decreasing total cardiac deaths in well-designed clinical trials (3,15), albeit in patients after MI. The salutary effect of smaller doses is unknown, and larger doses are likely to be nonprotective (see Chapter 1) (3).
The dose of beta-blocker is kept within the cardioprotective range, to maintain a resting heart rate of 52–60 beats/min bearing in mind that no patient should be allowed to have significant adverse effects from medication. If side effects occur, the dose is reduced, and a nitrate or calcium antagonist is added. If the maximum cardioprotective dose is used and angina is not controlled, the dose of beta-blocker can be increased, but adverse effects may limit the increase. Some patients do better on an average dose of beta-blocker plus a nitrate or calcium antagonist. Trial and error are necessary in many patients. See Chapter 1 for the choice of a beta-blocker.

**CONTRAINDICATIONS TO BETA-BLOCKERS**

Contraindications to the use of a beta-blocking drug are

- Asthma.
- Severe chronic obstructive pulmonary disease.
- Severe HF (decompensated class IV). These agents have been approved for cautious use in patients with compensated class IV HF.
- Bradyarrhythmias (second- or third-degree AV block).
- Brittle insulin-dependent diabetes and patients prone to hypoglycemia. Beta-blockers are strongly indicated, however, in other diabetic patients because these patients are at high risk of coronary events, and calcium antagonists have been shown in an RCT to increase mortality (see the discussion of the United Kingdom Prospective Diabetes Study Group in Chapter 1).

An algorithm for the management of stable angina is depicted in Figure 10-1.

**Calcium Antagonists**

These agents are used as second-line therapy when beta-blockers are genuinely contraindicated. Several trials have shown that verapamil is as effective as beta-blockers in the control of angina, but this agent does not prolong life. Verapamil is a more effective antianginal agent than diltiazem or dihydropyridines (DHPs) and is considered a first choice, but the drug must be used with caution and must not be combined with a beta-blocker.

**Contraindications** to the use of verapamil and diltiazem include

- HF, suspected LV dysfunction, and ejection fraction (EF) < 40%, because verapamil has a strongly negative inotropic action and diltiazem is moderately so.
- Sinus or AV node disease.
- Bradycardia.

Amlodipine (Norvasc) has a less negative inotropic effect than other DHPs, but in the Prospective Randomized Amlodipene Survival Evaluation (PRAISE) study, although amlodipine use was generally safe in patients with HF, it caused an increased incidence of pulmonary edema in patients with EF < 30%. The drug is not recommended if the EF is <35% and should not be combined with a beta-blocker if the EF is <40%.

**Combination of Beta-Blockers and Calcium Antagonists**

Amlodipine has minimal negative inotropic effects and can be combined with a beta-blocker in patients with EF > 35%. Although beta-blockers may be used in patients with EF < 30%, the combination of a beta-blocker with diltiazem or dihydropyridine should be avoided in patients with EF < 40%.
Verapamil (17,18) and, to a lesser extent, diltiazem (18), when added to a beta-blocker, may cause conduction disturbances or HF, and the verapamil combination is considered unsafe. The hemodynamic, electrophysiologic, and pharmacokinetic effects, adverse effects, and relative effectiveness of calcium antagonists are given in Tables 5-2 and 5-3 and are discussed in Chapter 5.

**Nitrates**

<table>
<thead>
<tr>
<th>Drug name:</th>
<th>Nitroglycerin: glycercyl trinitrate</th>
</tr>
</thead>
</table>
| Supplied: | Sublingual nitroglycerin: 0.15, 0.3, 0.6 mg  
Sublingual glycercyl trinitrate: 300, 500, 600 mg (UK)  
Spray (Nitrolingual): 0.4-mg metered dose, 200 doses/vial |
| Dosage: | See text |

**Dosage**

Start with 0.15 or 0.3 mg as a test dose with the patient sitting. The drug will not be as effective if the patient is lying down; if the patient is standing, dizziness or presyncope may occur. Thereafter, prescribe 0.3 µg nitroglycerin or 300 µg glycercyl trinitrate. If the systolic blood pressure in routine follow-up is more than 130 mmHg, then it is safe to give 0.4 mg.

The patient must be instructed that nitroglycerin tablets are to be kept in their dark, light-protected bottles; they may be rendered useless after 6 mo, or even earlier, if they are not protected from light. Patients should be advised to have at least two bottles available. These two bottles must contain approx 1 mo supply and no cotton wool, to ensure rapid availability in emergencies. At the end of each month, the containers should be emptied and the supply replenished from a third stock bottle. Patients may take one tablet before precipitating activities. If pain occurs and is not relieved by two tablets, the patient should immediately go to an emergency department. A third tablet can be taken before leaving for the hospital.

**Oral Nitroglycerin Tablets**

For Nitrong SR 2.6 mg, the dosage is 1 tablet at 7 AM and 2 PM daily. This will allow a 12-h nitrate-free interval to maintain the efficacy of the drug. The maximum dose 6.25 mg tab may cause bothersome headaches. Table 10-2 gives some of the available nitrate preparations.

**Action**

Nitrate bind to “nitrate receptors” in the vascular smooth muscle wall that activate guanylate cyclase and thereby stimulate the generation of cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle and thus dilation of veins and, to a lesser extent, arteries. The reason that venous dilation is greater than arterial is unknown. The result is marked dilation of the venous bed and therefore reduction in preload and a minimal decrease in afterload. A modest variable dilation of coronary arteries occurs. Nitrate have a direct effect on the compliance of the left ventricle and cause a downward shift in pressure-volume relationship.

The nonmononitrate are rapidly metabolized in the liver. The large first-pass inactivation of orally administered nitrate causes poor bioavailability to vascular receptors. Transdermal, buccal mononitrate or intravenous (IV) preparations partially overcome this problem.
Table 10-2
Nitrates

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name or available asa</th>
<th>Supplied and dosageb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Nitroglycerin</td>
<td>0.15, 0.3, 0.4, 0.6 mg (USA)</td>
</tr>
<tr>
<td>Nitrostat</td>
<td>0.3, 0.6 mg (C)</td>
<td></td>
</tr>
<tr>
<td>Nitrodefi</td>
<td>600 µg (C)</td>
<td></td>
</tr>
<tr>
<td>Nitrolingual spray</td>
<td>Metered dose of 0.4 mg</td>
<td></td>
</tr>
<tr>
<td>Glyceryl trinitrate (UK)</td>
<td>Glyceryl trinitrate (GTN)</td>
<td>300, 500, 600 µg</td>
</tr>
<tr>
<td>Coro-nitro spray</td>
<td>400 µg/metered dose</td>
<td></td>
</tr>
<tr>
<td>Nitrolingual spray oral</td>
<td>400 µg/metered dose</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin oral tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrogard (USA)</td>
<td>1, 2, 3 mg</td>
<td></td>
</tr>
<tr>
<td>Susadrin (USA)</td>
<td>1, 2, 3 mg</td>
<td></td>
</tr>
<tr>
<td>Nitrogard SR (C)</td>
<td>1, 2, 3 mg</td>
<td></td>
</tr>
<tr>
<td>Suscard (UK)</td>
<td>1, 2, 3, 5 mg</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate oral, tablets</td>
<td></td>
<td>10, 20, 30, 40 mg (USA)</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>10, 20, 30 mg (UK)</td>
<td></td>
</tr>
<tr>
<td>Isordil</td>
<td>10, 30 mg (C)</td>
<td></td>
</tr>
<tr>
<td>Cedocard 10, Cedocard 20</td>
<td>10, 20 mg (UK)</td>
<td></td>
</tr>
<tr>
<td>Cedocard Retard</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>Isordil Tembids</td>
<td>40 mg capsules</td>
<td></td>
</tr>
<tr>
<td>Sorbitrate</td>
<td>10, 20 mg (USA, UK)</td>
<td></td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>Elantan 20</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>Elantan 40</td>
<td>40 mg</td>
<td></td>
</tr>
<tr>
<td>Ismo</td>
<td>20 mg b.i.d., 7 h apart</td>
<td></td>
</tr>
<tr>
<td>Imdur</td>
<td>60–120 mg once daily</td>
<td></td>
</tr>
</tbody>
</table>

aSeveral other trade names are available.
bFor dosage see text.
cC, Canada.

**CUTANEOUS NITROGLYCERINS**

Long-acting or slow-release cutaneous nitroglycerin preparations are available.

Transderm-Nitro: 0.2, 0.4, 0.6 mg released/h
Nitro-Dur II: 0.2, 0.4, 0.6 mg released/h

The advantage of a cutaneous preparation is that the active drug reaches the target organs before it is inactivated by the liver. A therapeutic effect can be anticipated in 30–60 min and will last 4–6 h with the paste and about 20 h with long-acting preparations. Transdermal preparations should not be applied to the distal parts of the extremities or to the precordium where defibrillator paddles or chest leads may be placed. (Rare explosive events have been reported when contact was made with defibrillator paddles.) Cutaneous preparations are useful during dental work or minor or major surgery in patients with ischemic heart disease or hypertension. It is important, however, to ensure that such...
patients have tried the preparation and that the systolic blood pressure does not fall to <110 mmHg, because premedication and anesthetics can cause a further decrease in blood pressure. An attempt should be made by the physician to restrict the continuous use of transdermal preparations to up to 3 d and then 12 h daily allowing at least a 10-h nitrate-free interval. The patient should be weaned from the drug slowly, to avoid rebound.

**Nitrate Tolerance**

- It is well established that nitrate tolerance commonly occurs after several weeks of continuous nitrate use. Continuous infusion of nitroglycerin can result in tolerance within 24 h (19,20).
- All long-acting nitrate preparations—transdermal, isosorbide dinitrate (ISDN) regular strength, or sustained-release isosorbide-5-mononitrate (ISDN 5. MN)—have shown complete attenuation of antiischemic effects after 1–2 wk of continuous daily use (21).
- A nitrate-free interval limits the development of nitrate tolerance. When 20 mg ISDN was given at 8 AM and 1 PM for 8 d, leaving a nitrate-free interval during the night, no alteration of the antiischemic effect of the drug occurred (22). However, 15 d of continuous therapy with long-acting ISDN caused a 35–60% alteration of both ST segment and the EF response to exercise (23). The vasodilator effect of transdermal nitroglycerin in HF is maintained with intermittent treatment, whereas tolerance develops with continuous therapy (24).
- Veins and arteries are important sites of nitrate biotransformation. Organic nitrates are converted by intracellular sulfhydryl (SH) groups to nitric oxide and sulfhydryl-containing compounds. Vascular tolerance to nitrates is believed to result from a relative depletion of SH groups in vascular smooth muscle cells. A nitrate-free interval is necessary to allow intracellular generation of an adequate supply of SH groups and to restore vascular responsiveness.
- A nitrate-free interval of 10–12 h is necessary to prevent nitrate tolerance. Suggested steps include the following: ISDN 15–40 mg given at 7 AM, 12 noon, and 5 PM daily, or sustained-release one tablet 8 AM daily; Nitrong SR 7 AM and 2 PM daily; Ismo 20 mg twice daily 7 h apart; Imdur 30–120 mg once daily. Transdermal preparations should be used for about 12 h daily.

**Drug name:** Isosorbide dinitrate  
**Trade names:** Coronex, Isordil, Iso-Bid, Sorbitrate (UK)  
**Supplied:** Isordil: 5-, 10-, 20-, and 30-mg tablets; 40-mg capsules; 10 mL ampules for IV use (1 mg/mL)  
**Dosage:** 30 mg 7 AM, 1 PM daily; see text

**Dosage**

**IV:** 2–7 mg/h, polyethylene apparatus.  
**Sublingual:** 5 mg before activities known to precipitate angina. Do not use the sublingual preparation instead of nitroglycerin for the relief of pain because the onset of action is delayed for 3–5 min.  
**Oral:** 10–30 mg three times daily; if possible ¼ h before meals or on an empty stomach. Maintenance: 30 mg at 7 and 11 AM and 4 PM; allow a 12-h nitrate-free interval to prevent tolerance. The 10-mg dose is ineffective.

**Drug name:** Isosorbide mononitrate  
**Trade names:** Imdur, Elantan, Ismo (UK)  
**Dosage:** Initial 30 mg, then 60–120 mg once each AM; max. 240 mg if tolerated  
**Dosage advice:** Halve the dose for 1 wk if headache occurs with oral nitrate
The 5-mononitrate of isosorbide achieves consistent plasma nitrate levels, but tolerance quickly develops. The drug does not undergo hepatic degradation. It is excreted by the kidneys, unchanged and partially as an inactive compound. Activity lasts for 12 h and thus nitrate tolerance is avoided.

**Caution:** Gradually discontinue long-term nitrate therapy to avoid the rare occurrence of rebound increase in angina. Cover the nitrate-free interval with a beta-blocker or, if these drugs are contraindicated, administer a calcium antagonist.

**Intravenous Nitroglycerin**

IV nitroglycerin is of proven value in the management of unstable angina. Onset of action is within 1.5 min, with a duration of about 9 min.

- Low doses predominantly dilate the venous capacitance vessels and therefore decrease preload. The drug reduces LV dimensions and LV wall tension, thereby reducing myocardial oxygen consumption. The drug can also cause an increased myocardial oxygen consumption because of a reflex increase in the heart rate.
- Higher doses cause systemic arteriolar dilation and reduction in afterload.
- In rare instances when the patient does not respond and seems to be doing worse, the physician should entertain the possibility that the nitroglycerin has caused a shunting of blood from the ischemic to the nonischemic zone.

**Indications**

These include

- Refractory or unstable angina, chest pain, or acute coronary insufficiency. In this setting, continuous IV nitroglycerin is necessary without consideration of tolerance. The dose is titrated to control pain but with careful monitoring of BP.
- CAS.
- Pulmonary edema resulting from LV failure.
- Intraoperative arterial hypertension, especially during cardiac surgery (not routine), and in patients with Prinzmetal’s angina and organic obstruction who are undergoing bypass surgery.
- To reduce the size of MI (not proved to be effective). A modest decrease in mortality rate was observed in one study of patients with acute MI.

**Contraindications to Intravenous Nitrate or High-Dose Therapy**

- Hypovolemia.
- Increased intracranial pressure.
- Cardiac tamponade and constructive pericarditis.
- Obstructive cardiomyopathy, severe aortic stenosis, or mitral stenosis.
- Right ventricular infarction. (Decrease in preload may cause clinical and hemodynamic deterioration in categories 3, 4, and 5.)
- Glaucoma: closed-angle glaucoma or severe uncontrolled glaucoma.

**Warnings**

- IV nitroglycerin is a potent vasodilator, and hemodynamic monitoring is usually necessary.
  - The systolic blood pressure should not drop by >20 mmHg; reduce the dose if the systolic blood pressure is <100 mmHg.
  - A diastolic blood pressure of >60 mmHg is necessary for adequate coronary artery perfusion.
The pulmonary wedge pressure should be maintained at 15–18 mmHg in patients with acute MI.

As much as 80% of the nitroglycerin may bind to the polyvinyl chloride infusion set. If such an apparatus is used, the infusion should be slowed down after 2 h because the binding sites in the tubing become saturated. Special polyethylene tubing sets should therefore be used.

Use an infusion pump to ensure titrated dose response (Table 10-3). IMED infusion pumps are not compatible with the new non-polyvinyl chloride administration sets; however, new pump systems are being developed.

Wean the patient from the drug slowly.

Methemoglobinemia may occur after extended, continuous, high doses at levels greater than 7 µg/kg/min; cyanosis with normal arterial blood gases and methemoglobin levels > 1.5 g/dL confirm the diagnosis. Hypoxemia may result from increased venous admixture.

Interactions with heparin or tissue plasminogen activator may occur.

**Aspirin**

All patients with stable angina should be administered a chewable or plain aspirin, enteric coated, 75–325 mg daily (24). Aspirin is a potent antiplatelet agent and has been shown to improve survival and to prevent infarction in patients with unstable angina or after MI. A 75-mg dose has been shown to be effective and causes less gastrointestinal bleeding than the commonly prescribed 325-mg dose. An 81-mg enteric-coated aspirin tablet is available.

<table>
<thead>
<tr>
<th>Dose (µg/min)</th>
<th>Infusion rate (mL/h)</th>
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<td>5</td>
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<td>120</td>
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<td>250</td>
<td>150</td>
</tr>
</tbody>
</table>

*Increase by 5 µg/min every 5 min until relief of chest pain; decrease rate if systolic blood pressure < 100 mmHg or falls to 20 mmHg below the baseline, or diastolic blood pressure < 65 mmHg.*
Aspirin inhibits cyclooxygenase and the subsequent suppression of thromboxane A₂, the key moderator of irreversible platelet aggregation. A prospective study (24) of 2035 patients with stable angina showed that 75 mg aspirin added to sotalol produced a 34% decrease in primary outcome events of MI and sudden death (p = 0.003).

If aspirin use is contraindicated, clopidogrel is advisable. Clopidogrel has been shown to have favorable effects on cardiovascular events, equal to those of aspirin, but 75–160 mg coated aspirin is safer.

**MANAGEMENT OF UNSTABLE ANGINA**

More than half a million individuals are discharged from hospitals in the United States with a proven diagnosis of unstable angina.

Figure 10-2 gives acute coronary syndrome terminology. The pathophysiology of unstable angina has been clarified. In most cases, plaques are asymmetric, with irregular borders and a narrow neck. Rupture of the plaque with overlying thrombus is a common finding on angioscopy (25). In addition, an inflammatory process, probably activated by microorganisms such as *Chlamydia pneumoniae*, appears to play a role in atheroma and plaque formation. There is a strong association between C-reactive protein (CRP) and coronary events. Lipid-rich plaques have a predilection for rupture. Silent ischemia is frequently observed in patients with unstable angina, and the prognosis seems to be worse in this subset (26,27).

- The **order sheet** should indicate the **diagnosis**, rule out acute MI, and have the following suggested orders:

  **Investigations**

  - Serial ECGs.
  - Troponin T or troponin I, 6- and 12-h to exclude non-ST elevation MI (NSTEMI) assist with risk stratification; measurement of creatine kinase, myocardial bound (CK-MB) isoenzyme levels, every 6 h for 24 h.
Diagnosis and Risk Stratification

Unstable angina, unlike NSTEMI, is a heterogeneous entity and exhibits marked variations in risk for coronary events such that patients admitted with a diagnosis of unstable angina may have no significant or mild coronary artery disease (CAD), and in others severe disease is present. Table 10-4 indicates the likelihood of significant CAD in patients with symptoms suggestive of unstable angina, and Table 10-5 gives the probable short-term risk of death or nonfatal MI.

Medications

- Relief of pain: give morphine sulfate 2–5 mg IV and every 30 min if required, to a maximum dose of 15 mg/h for 3 h. (Caution should be exercised in patients with severe pulmonary disease.) If morphine is still required after 3–4 h, this indicates that there may be progression of ischemia, which will require an increase in beta-blockers, IV nitroglycerin, or earlier coronary arteriography.
• Sedative: give oxazepam 15 mg (or equivalent) at bedtime.

• A stool softener is prescribed.

**Specific Cardiac Medications**

Figure 10-3 gives an algorithm for the management of unstable angina.

1. **IV nitrates** (if unavailable, use transdermal nitrate plus oral nitrates in high doses). Reduce the dose if the systolic blood pressure is <100 mmHg. A nitrate-free interval may place the patient at risk. It is advisable to continue IV nitroglycerin and titrate the dose upward to pain relief. Failure to gain complete pain relief with IV nitroglycerin, a beta-blocker, and diltiazem, if there is no contraindication to the last combination, should prompt consideration of coronary angiography and interventional therapy.

2. **Must add unless contraindicated: beta-blocker** in sufficient doses (e.g., metoprolol 50–100 mg every 8 h). Hold the dose if the systolic blood pressure is <95 mmHg or the heart rate is <45 per min or give IV beta-blockers for one or two doses followed by oral doses (see Chapter 1 for doses).
If pain is not completely controlled, add

3. Calcium antagonist: preferably **amlodipine** 5 mg, if no contraindication to combination with beta-blocker (LV dysfunction, EF < 35%, systolic BP < 120 mmHg). Monitor the BP carefully, because calcium antagonists may cause severe hypotension, especially if used concomitantly with IV nitroglycerin, and diltiazem may cause severe bradycardia or sinus arrest in patients with sick sinus syndrome, and a combination with a beta-blocker may be hazardous.

4. Diltiazem plus nitrates should be started at the time of admission if:
   - Beta-blockers are contraindicated, in the following situation:
     - CAS is strongly suspected: the patient gives a clear history of chronic resting angina; or transient ST segment elevation is present during pain. Severe obstructive atherosclerotic coronary artery disease is very common, whereas CAS in its pure form is very rare. Thus, in patients with new-onset resting angina not proved to result from CAS, beta-blocker therapy is strongly indicated.

**NEWER ANTIANGINAL AGENTS**

Ranolazine and nicorandil are discussed in the Controversies section at the end of this chapter.

**ASPIRIN**

A timely Veterans Administration Study using 324 mg aspirin in patients with unstable angina resulted in a 50% reduction in mortality rate and nonfatal MIs (28). In another randomized study, aspirin was shown to reduce the cardiac mortality rate by 50% in patients with unstable angina (29). A Swedish study using 75 mg aspirin in patients with stable angina showed a 34% reduction in MI and death.

All patients should receive aspirin 160–325 mg daily if there is no contraindication. Aspirin should be avoided in patients with variant angina because the drug may precipitate episodes of angina.

**CLOPIDOGREL**

Clopidogrel 600 mg loading dose is given in some hospitals on presentation as soon as the diagnosis of probable NSTEMI/unstable angina is made and is given at the same time as chewable aspirin 75–100 mg. In other hospitals clopidogrel is given 600 mg <2 h before percutaneous coronary intervention (PCI). (See Chapters 11, 19, and 22 for further discussion regarding clopidogrel administration.)

**HEPARIN**

Paul Wood has observed that heparin reduces the incidence of MI in patients with acute coronary insufficiency; Telford and Wilson (30) showed heparin to be effective in the intermediate coronary syndrome. In most patients with unstable angina, a combination of nitrates with a beta-blocker and/or calcium antagonist with aspirin or heparin is advisable (2,31). Heparin is often used in place of aspirin or added to aspirin (32). The study by Theroux and colleagues (32) showed no significant differences among the three treatment arms with respect to fatal or nonfatal infarction. A clinical study by Holdright and associates (33) showed that combined therapy with heparin and aspirin compared with aspirin alone made no difference in the development of MI, death, or transient myocardial ischemia. A further study by Theroux and colleagues (34) showed heparin to be superior to aspirin in preventing infarction during the acute phase of unstable angina; MI occurred in 0.8% of heparin-treated patients and in 3.7% of aspirin-treated patients ($F < 0.05$).
LOW-MOLECULAR-WEIGHT HEPARIN

Several RCTs have shown that LMWH is as effective as standard heparin and is easier to administer. The need for measurement of the prothrombin time is not required, and the incidence of thrombocytopenia appears to be lower. Because this agent can be used at home, it has the potential for cost savings.

The Enoxparin in Unstable Angina and Non Q Wave Myocardial Infarction (ESSENCE) study (35) randomized 3171 patients with unstable angina or non-Q-wave MI. Patients received IV dose-adjusted regular heparin plus aspirin 100-160 mg or subcutaneous enoxaparin 1 mg/kg 12 hourly plus aspirin. At 14 d, the risk of death, MI, or recurrent angina was significantly lower in patients assigned to enoxaparin than in those receiving regular heparin (16.6% versus 19.8%; \( p = 0.019 \)). This improvement in events was maintained at 30 d. The 30-d incidence of major bleeding complications was 7% in the regular heparin group and 6.5% in the enoxaparin group. (See Chapters 11 and 22 for results of recent RCTS and comparison with fondaparinux.)

**Dosage:** Enoxaparin: 1 mg/kg every 12 h subcutaneously.

- Patients 75 yr and older should receive 0.75 mg/kg once daily dosing with a caution to assess creatinine clearance; if the estimated GFR is < 50 mL/min, the dose should be given once daily and avoided if estimated GFR is < 30 mL/min.
- Patients with estimated GFR 30–40 mL/h should receive half the standard dose given above once daily. LMWH is not advisable if the GFR is < 30 mL/min.
- Patients should not be switched from LMWH to UF heparin or vice versa.

STATINS

- It is imperative to maintain the LDL cholesterol level at < 60 mg/dL (1.6 mmol/L) in patients with unstable angina.
- A level of 60 mg (1.6 mmol/L) or less is now preferred (see ASTEROID trial in Chapter 22).

Thus, the use of a high-dose statin (e.g., atorvastatin 60–80 mg or rosuvastatin 20–40 mg daily) should be commenced in most patients during the hospital stay with monitoring of lipid levels in the subsequent weeks. Simvastatin and pravastatin have been shown in several RCTs to cause a decrease in cardiac mortality, a reduction in nonfatal and fatal MI, and angiographic regression of atheroma in patients with ischemic heart disease. Some of the salutary effects of statin therapy may result from modification of endothelial cell dysfunction; this modification occurs within days of therapy. Statins decrease elevated CRP levels, with reduction of CAD. Thus, it is advisable to initiate potent statin therapy when the patient is admitted for acute coronary syndrome (ACS) (see the RCT, PROVE IT-TIMI in Chapter 22).

PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR BLOCKERS

Several RCTs have studied glycoprotein IIb/IIIa receptor blockers in unstable angina. Abciximab (ReoPro) has proved to be effective in clinical trials. The drug is indicated in patients undergoing coronary angioplasty and in those with unstable angina not responding to conventional medical therapy when angioplasty is planned within 24 h (see below).

Tirofiban (Aggrastat) plus aspirin was compared in a clinical study with aspirin plus heparin in patients with unstable angina (36); at 30 d, the frequency of the composite end point with addition of readmission for unstable angina was similar in the two groups: 15.9% in the tirofiban group versus 17.1% in the heparin group \( (p = 0.34) \). A study of 1915 patients randomly assigned in a double-blind manner to receive tirofiban, heparin,
or tirofiban plus heparin was stopped prematurely for the group receiving tirofiban alone because of excess mortality at 7 d (37). There were fewer events at 7 d among patients who received tirofiban plus heparin and aspirin than in those who received heparin and aspirin (4.9% versus 17.9%, \( p = 0.004 \)). The incidence at 30 d was 18.5% versus 22.3% (\( p = 0.03 \)), and at 6 mo it was 27.7% versus 32.1% (\( p = 0.02 \)). The incidence of death or MI at 6 mo was 12.3% in the tirofiban plus heparin and aspirin group compared with 15.3% of the heparin-aspirin group (\( p = 0.06 \)). The results were not significant at 6 mo. Although platelet glycoprotein IIb/IIIa receptor blockers are expensive, the cost effectiveness of abciximab (ReoPro) and eptifibatide (Integrilin) in reducing mortality during PCI is favorable.

These agents are strongly recommended in patients at high risk of periprocedural complications, particularly, diabetes. Interventional therapy is necessary in virtually all patients at high risk. Abciximab is effective given as a bolus 10–60 min before the procedure; a pre-treatment regimen offers no clear advantages, but the 12-h postprocedural infusion is necessary for a significant prevention of events. The European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPIRIT) trial results indicate that eptifibatide administered to patients undergoing nonurgent percutaneous transluminal coronary angioplasty (PTCA) with stent caused a 40% reduction in death or MI at 48 h after the procedure.

Eptifibatide, lamifiban, and tirofiban have been tested in randomized trials with mixed results. Some trials have not shown beneficial effects, and caution is required: Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT) II, eptifibatide (\( p = 0.063 \) and 0.220); Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE), tirofiban (\( p = 0.052 \)). In the Platelet IIb/IIIa Underpinning the Receptor for Suppression of Unstable Ischemia Trial (PURSUIT), eptifibatide-treated patients who underwent PCI within 72 h showed benefit (\( p = 0.01 \)), but no benefit at 30 d in those without PCI (\( p = NS \)). Lamifiban (Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network [PARAGON]) showed no significant effect on the incidence of death or MI at 30 d (see Chapters 11, 19, and 22 for TACTICS and other RCTs).

ANTIINFLAMMATORY AND ANTIINFECTIVE THERAPY

The atheromatous plaque, whatever the causative factor, is exceedingly inflammatory in unstable angina, and reactivation of the process and plaque rupture may trigger new thrombus.

There is a large body of evidence indicating a role for Helicobacter pylori and C. pneumoniae. Mounting evidence exists implicating C. pneumoniae. Particularly high titers of antibodies have been observed in patients with unstable angina, as well as the presence of elementary bodies, DNA, and antigens in the atherosclerotic arterial wall (38).

In a study of 200 patients with unstable angina and non-Q-wave MI, treatment with roxithromycin administered for 30 d reduced the 6-mo mortality rate from MI from 4% to 0%, and the rate of death, MI, or recurrent ischemia from 9% to 2% (39). A larger secondary prevention trial using azithromycin for 6 mo showed no benefit.

Cannon and colleagues enrolled 4162 patients who had had an coronary syndrome event within the prior 10 d and assessed the efficacy of gatifloxacin, a bactericidal antibiotic known to be effective against C. pneumoniae, in a double-blind RCT trial (40). Patients were given 400 mg of gatifloxacin daily during an initial 2-wk course of therapy that began 2 wk after randomization, followed by a 10-d course every month for the duration of the trial (mean duration, 2 yr), or placebo.
The primary end point was a composite of death from all causes, MI, documented unstable angina requiring rehospitalization, revascularization, and stroke.

The rates of primary end-point events at 2 yr were 23.7% in the gatifloxacin group and 25.1% in the placebo group (hazard ratio, 0.95; 95% confidence interval, 0.84–1.08; \( p = 0.41 \)). No benefit was observed in subjects with elevated titers to \( C.\ pneumoniae \) or CRP (40).

Importantly, the inflammation observed in atheromatous plaques is probably a non-specific inflammatory response to endothelial injury. This process, which occurs within the media, is nature’s modulation, designed to protect and stabilize the injured area of the arterial wall (41).

**VARIANT ANGINA (PRINZMETAL’S)**

**Clues to Diagnosis**

- Pain usually occurs at rest (often during sleep between midnight and 8 AM).
- The ECG shows ST-segment elevation during pain.
- Patients have a poor response to beta-blockers alone or a worsening of pain.
- CAS can be provoked by the use of IV ergonovine (with IV nitroglycerin drip on standby; nifedipine may be necessary to reverse spasm, which should be precipitated only in the cardiac laboratory). The test is not necessary, however, to initiate therapy.
- A few patients have ST-segment depression, and it is impossible to separate them from patients with angina from ischemic heart disease with fixed obstruction, except by a history of variable threshold or by an ergonovine test.
- Variable threshold angina may exist.

A subset of patients with variant angina may have significant obstructive coronary artery disease with spasm at the site of the plaque (Prinzmetal’s) and may demonstrate any or all of the aforementioned features.

**Investigations**

Coronary arteriography should be considered in all patients.

**Treatment**

- Patients should stop smoking.
- Nitroglycerin tablets are taken sublingually.
- Among calcium antagonists, DHPs, verapamil, and diltiazem are equally effective (41).
- It may be necessary to combine both a calcium antagonist and ISDN or isosorbide 5-mononitrate. Occasionally, the patient may respond to nitrates only, but at high doses.
- Beta-blockers provide no benefit, but combined with nitrates they are not as harmful as some would have us believe. Importantly, a review of all trials using beta-blocker monotherapy for CAS indicates neither benefit nor exacerbation (42). Chronic resting angina is usually the result of CAS. New-onset resting angina must be considered as unstable angina, and in this large subset of patients, beta-blocker therapy (42) combined with nitrates remains routine (42).
- Avoid aspirin because the drug can precipitate spasm in patients with variant angina (43).

Unfortunately, patients with variant angina, even when the syndrome is completely controlled by calcium antagonists, have died or have had MIs (42). Although calcium antagonists are efficient in controlling the pain of variant angina, they do not prevent death. Nitrates are much less effective and also do not appear to improve survival. Cardiac surgery is indicated in patients with significant atheromatous coronary artery obstruction.
INTERVENTIONAL THERAPY

1. Seven RCTs of coronary artery bypass grafting (CABG) versus medical therapy were conducted during the 1970s and 1980s. CABG significantly decreased mortality at 5 and 7 yr. However, medical therapy did not include optimal treatment with beta-blockers, aspirin, statins to maintain LDL < 2 mmol/L (<79 mg/dL) \((44)\), and ramipril, the last agent proved in the Heart Outcomes Prevention Evaluation (HOPE) trial \((45)\).

2. Medical therapy versus PCI was assessed by the Randomized Intervention Treatment of Angina (RITA)-2 \((46)\) and showed no difference in death and MI. In the small Atorvastatin Versus Revascularization Treatment (AVERT) trial \((44)\), stents were used in 30% of lesions, and aggressive medical therapy with atorvastatin maintained LDL < 77 mg/dL. The ischemic event rate was 13% versus 21% in the PCI-treated group.

3. CABG versus PTCA in patients with multivessel disease and normal LV function was assessed in seven RCTs including the Arterial Revascularization Therapies (ARTS) study \((47)\), which showed no significant difference in mortality or MI. These were relatively low-risk patients, however, with normal LV function and mainly two-vessel disease (68% in ARTS). The ARTS study \((47)\) compared stents with CABG; 16.8% of the stent group required a second revascularization, with a 73.8% event-free survival, 79% angina-free survival, and 21% free of anginal medication, versus, 3.5%, 87.8%, 90%, and 41.5%, respectively.

**Diabetes:** Niles and colleagues \((48)\) analyzed a large regional contemporary database of patients with diabetes; 736 had PCI and 5030 had CABG. The 5-yr mortality was significantly increased after initial PCI, and this finding supports the conclusion in the Bypass Angioplasty Revascularization Investigation (BARI) trial \((49)\). Spencer King’s editorial \((50)\) reads: “Overall, the vote is in, and the winner has been declared. Surgery with at least one internal mammary artery graft [emphasis added] is superior to angioplasty in diabetics with multivessel disease” and normal EF (52%). Diabetics, if selected for PCI, should have normal LV function, two-vessel disease, absence of proximal left anterior descending (LAD) coronary artery disease, and suitable lesions from a technical standpoint.

CABG is recommended for patients with

- Triple-vessel disease, most patients with left main coronary artery, and particularly if LV dysfunction is present.
- Diabetes with two-vessel disease with a proximal LAD coronary artery suitable for internal mammary grafting (see earlier).
- Diabetes with lesions and LV dysfunction.
- PCI is recommended for patients with single-vessel and two-vessel disease, selected three-vessel disease, normal LV function, and suitable anatomy for the procedure. Diabetic patients with normal LV function who have single- and two-vessel disease in the absence of proximal LAD coronary artery disease may be suitable and selected on an individual basis.

**Stable angina:** Coronary angiograms with a view to revascularization are indicated in patients with the following: bothersome symptoms affecting lifestyle; ischemia despite optimization of medical therapy with a beta-blocker, nitrate, long-acting DHP (e.g., amlodipine), and statin to goal LDL < 2 mmol/L (80 mg/dL), and ACE inhibitor; patients with high-risk noninvasive test results and left ventricular dysfunction: EF 25–35%.

**Unstable angina:** Coronary angiograms are needed in patients at high risk (see Tables 10-5 and 10-6).
Table 10-5

Short-Term Risk of Death or Nonfatal MI in Patients with Unstable Angina

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Low risk</th>
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</thead>
<tbody>
<tr>
<td><strong>At least one of the following features must be present:</strong></td>
<td>No high risk feature, but must have any of the following:</td>
<td>No high or intermediate risk feature, but may have any of the following features:</td>
</tr>
<tr>
<td>• Prolonged ongoing (≥20 min) rest pain</td>
<td>• Prolonged (&gt;20 min) rest angina, now resolved, with moderate or high likelihood of CAD</td>
<td>• Increased angina frequency, severity, or duration</td>
</tr>
<tr>
<td>• Pulmonary edema, most likely related to ischemia</td>
<td>• Rest angina (&gt;20 min or relieved with rest or sublingual nitroglycerin)</td>
<td>• Angina provided at a lower threshold</td>
</tr>
<tr>
<td>• Angina at rest with dynamic ST-segment changes ≥ 1 mm</td>
<td>• Nocturnal angina</td>
<td>• New-onset angina with onset 2 wk to 2 mo prior to presentation</td>
</tr>
<tr>
<td>• Angina with new or worsening MR murmur</td>
<td>• Angina with dynamic T-wave changes</td>
<td>• Normal or unchanged ECG</td>
</tr>
<tr>
<td>• Angina with S3 or new and/or worsening rates</td>
<td>• New-onset CCSC III or IV angina in the past 2 wk with moderate or high likelihood of CAD</td>
<td></td>
</tr>
<tr>
<td>• Angina with hypotension</td>
<td>• Pathologic Q waves or resting ST-segment depression ≤ 1 mm in multiple lead groups (anterior, inferior, lateral)</td>
<td></td>
</tr>
<tr>
<td>• Age &gt; 65 yr</td>
<td>• Age &gt; 65 yr</td>
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</table>

Abbreviations: CAD, coronary artery disease; CCSC, Canadian Cardiovascular Society class; MI, myocardial infarction; MR, mitral regurgitation.

From Cannon CP. Management of Acute Coronary Syndromes, 2nd ed. Humana Press, Tototwa, NJ, p. 186; with permission.

In TACTICS-TIMI 18 trial (51), early invasive strategy was beneficial only in patients with elevated troponin T levels (i.e., NSTEMI) and not in unstable angina patients with no elevation of troponins (see TACTICS in Chapter 22). The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study (52) suggests that clopidogrel plus aspirin has beneficial effects in patients with non-ST elevation acute coronary syndrome, but the benefit was small and was partially offset by an increased risk of bleeding necessitating transfusion (6 of every 1000 treated). Caution is also required because the drug can rarely cause thrombotic thrombocytopenic purpura and neutropenia. The 8-mo benefits in patients after PCI resulted in a 31% reduction in cardiovascular death or MI in the PCI-CURE study (53) (see Chapter 22 for the ACUITY trial).

CONTROVERSIES

1. **Does Clopidogrel plus Aspirin Have Any Value?**

   The CHARISMA trial (54) randomized 15,603 patients with either clinically evident CVD or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75–162 mg/d) or placebo plus low-dose aspirin. At 28 months clopidogrel plus aspirin was
not significantly more effective than aspirin alone in reducing CVD outcomes. However, it is established that after PCI and stenting clopidogrel plus aspirin significantly reduces CVD outcomes and clopidogrel should not be discontinued prematurely.

2. Are Newer Agents More Useful than Beta-Blockers?

Ranolazine is a new second-line antianginal agent. The drug acts as a selective inhibitor of the late sodium current, which acts to reduce intracellular calcium in myocytes, thereby reducing the tension or stiffness of the myocardium that occurs during ischemia or HF. The drug may be combined with beta-blockers and ACE inhibitors because the drug does not cause a reduction in heart rate or BP and has no significant effects on myocardial contractility.

In small RCTs the drug reportedly reduced the number of anginal attacks per week and caused a modest improvement in treadmill exercise duration.

- Large-scale RCTs are required to establish this agent as an effective and safe antianginal agent. The drug, causes
- A prolongation of the QT interval, and syncope has been reported.
- Significant interaction occurs with potent CYP3A inhibitors including the antianginal agent diltiazem.

Nicorandil is a nicotinamide nitrate that acts as a potassium channel activator but also has a nitrate-like action. The drug reportedly causes modest dilation of large coronary arteries and reduces preload and afterload. Indications: prophylaxis and treatment of angina. The drug is used sparingly in the United Kingdom but extensively in Japan.

The drug has shown low efficacy in small RCTs and is not used in the United States and Canada. Avoid in patients with hypovolemia; low systolic blood pressure, cardiogenic shock; acute pulmonary edema; and acute MI with acute LV failure and low filling pres-
sures. There are several drawbacks: oral ulceration, myalgia, and rash; at high dosage, reduction in blood pressure and/or increase in heart rate; angioedema, hepatic dysfunction, and anal ulceration; headache, flushing; nausea, vomiting, dizziness, weakness also reported.

It seems unlikely that nicorandil or ranolazine would fill a role for the effective management of stable angina; use in unstable angina remains controversial.

REFERENCES
14. von Arnim T, for the TIBBS investigators. Medical treatment to reduce total ischemic burden: Total Ischemic Burden Bisoprolol Study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. J Am Coll Cardiol 1995;25:231.


SUGGESTED READING


