Recent advances in the management of chronic stable angina II. Anti-ischemic therapy, options for refractory angina, risk factor reduction, and revascularization

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Abstract: The objectives in treating angina are relief of pain and prevention of disease progression through risk reduction. Mechanisms, indications, clinical forms, doses, and side effects of the traditional antianginal agents – nitrates, β-blockers, and calcium channel blockers – are reviewed. A number of patients have contraindications or remain unrelieved from anginal discomfort with these drugs. Among newer alternatives, ranolazine, recently approved in the United States, indirectly prevents the intracellular calcium overload involved in cardiac ischemia and is a welcome addition to available treatments. None, however, are disease-modifying agents. Two options for refractory angina, enhanced external counterpulsation and spinal cord stimulation (SCS), are presented in detail. They are both well-studied and are effective means of treating at least some patients with this perplexing form of angina. Traditional modifiable risk factors for coronary artery disease (CAD) – smoking, hypertension, dyslipidemia, diabetes, and obesity – account for most of the population-attributable risk. Individual therapy of high-risk patients differs from population-wide efforts to prevent risk factors from appearing or reducing their severity, in order to lower the national burden of disease. Current American College of Cardiology/American Heart Association guidelines to lower risk in patients with chronic angina are reviewed. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed that in patients with stable angina, optimal medical therapy alone and percutaneous coronary intervention (PCI) with medical therapy were equal in preventing myocardial infarction and death. The integration of COURAGE results into current practice is discussed. For patients who are unstable, with very high risk, with left main coronary artery lesions, in whom medical therapy fails, and in those with acute coronary syndromes, PCI is indicated. Asymptomatic patients with CAD and those with stable angina may defer intervention without additional risk to see if they will improve on optimum medical therapy. For many patients, coronary artery bypass surgery offers the best opportunity for relieving angina, reducing the need for additional revascularization procedures and improving survival. Optimal medical therapy, percutaneous coronary intervention, and surgery are not competing therapies, but are complementary and form a continuum, each filling an important evidence-based need in modern comprehensive management.

Keywords: coronary artery disease, ischemic heart disease, myocardial oxygen balance, cardiovascular risk reduction, acute coronary syndrome, COURAGE study, percutaneous coronary intervention, revascularization, nitrates, β-blockers, calcium channel blockers, ranolazine, refractory angina, prevention of heart disease, coronary artery bypass surgery, primordial prevention, statin drugs
**Introduction**

The goals in treating patients with chronic stable angina are (1) to relieve symptoms, (2) to prevent progression of the atherosclerotic process and reduce risk of myocardial infarction (MI) or sudden cardiac death, and (3) to control complicating factors which trigger or worsen ischemia. In the first of this 2 part series, the definition, clinical types of angina, differential diagnosis, risk stratification, and prognostication using exercise testing and imaging were addressed, with mention of gender disparities. In this second part, anti-ischemic therapy, newer agents, risk reduction, and revascularization are discussed.

Although sometimes difficult, the practitioner should impress upon the patient that no pill or surgical procedure will completely reverse the problem, but lifestyle changes will influence the course of the disease in the most fundamental way and are preferred. Lifestyle therapy is efficacious, widely available, innocuous, and an inexpensive form of management of angina and coronary artery disease (CAD), but is underused and unsupported. Ample proven potential for reducing cardiovascular risk has not been realized. Reasons for its near-universal neglect are complex and only partially appreciated, but remain unsolved despite widespread praise for its value. The disconnection occurs between the oratory and effective implementation of lifestyle changes by patients – from counseling and contract to behavior change. The complete physician will use the first available opportunity to enlist the patient as a partner in initiating and continuing all lifestyle changes that will contribute to risk factor reduction and a training effect of exercise.

**Antianginal therapy**

Anti-ischemic therapy includes the use of 3 traditional antianginal agents: nitrates, β-blockers, and calcium channel blockers (CCBs). Traditional agents lower anginal symptoms and prolong exercise duration and/or time to ST-segment depression on the electrocardiogram (ECG). Frequently a combination of these drugs is necessary for symptom control. However, none of these drugs have been shown to be disease modifying – their use does not change the risk of MI, sudden cardiac death, or all-cause mortality. Their mechanism of action is the reduction of myocardial oxygen demand (heart rate, afterload, and preload) so that the threshold producing anginal symptoms is not reached (see Part I of this series). In practice, this translates to lowering rate-pressure product and/or producing systemic venodilation, thereby lowering left ventricular end-diastolic pressure (LV-EDP) and volume and reducing myocardial wall tension. In turn, this permits greater flow in the epicardial coronary arteries and improves myocardial oxygen delivery. Relative advantages of each agent with respect to cardiac physiology and patient comorbidities permit partial customization of therapy.

**Nitrates**

Nitroglycerin, in clinical use since 1878, causes dilation of epicardial coronary arteries, even when they are partially stenosed, by relaxing arterial smooth muscle. Nitroglycerin does not release nitric oxide (NO) directly, as compared with sodium nitroprusside. The organic nitrates react with intracellular sulfhydryl groups (eg, from methionine or cysteine) and enzymes to produce NO or the intermediate S-nitrosothiol, which is reduced to NO. Thus, nitrates are prodrugs that undergo enzymatic denitrification within the vascular wall, most significantly by mitochondrial aldehyde dehydrogenase. NO then activates smooth muscle guanylyl cyclase, raising cyclic guanosine monophosphate (cGMP) levels to inhibit calcium entry into the muscle cell and relax muscle filaments. NO also acts to inhibit potassium channels, hyperpolarizing muscle membranes, and activating light chain phosphatase, both of which effect relaxation, and may account for a significant proportion of vasodilation. Similarly, NO activates platelet GMP to reduce intraplatelet calcium concentrations, impairing platelet activation to a degree. In effect, nitrates act as exogenous NO donors, in addition to raising endogenous production of NO. Although the predominant effect of nitrates is to reduce preload, ie, produce venodilation, with greater activity in the venous than arterial beds, at higher doses its direct effect upon arteries is more pronounced, with a greater reduction in blood pressure (BP) and afterload. The net result is a reduction in myocardial oxygen consumption, but an overall increase in exercise capacity in patients with CAD as well, permitting a greater total workload before angina is triggered. In addition, NO improves endothelial function, which contributes to vasodilation and optimizes vascular reactivity. Finally, nitroglycerin redistributes coronary blood flow from normally perfused areas of myocardium to ischemic zones. A reduction in ventricular diastolic pressure and an increase in collateral blood flow play a part in this phenomenon, favoring subendocardial perfusion relative to the subepicardial. In an experimental model of coronary vasospasm, the observed rise in blood flow to the ischemic myocardium produced by nitroglycerin was not accompanied by diminished perfusion in normal myocardium.

Sublingual nitroglycerin is readily absorbed through mucous membranes, and its effect is prompt (1–3 minutes),
reliable, and more effective than other forms, such as sprays, ointments, transdermal patches, and sustained release preparations. It should be offered to all patients with angina unless there are contraindications. Duration is on the order of 30 minutes. Patients should use nitroglycerin prophylactically about 5 minutes prior to any stress or activity that is known to produce angina, as well as for acute events. Side effects include cerebral vasodilation and headache, postural hypotension, dizziness, and rarely, syncope in hypovolemic patients. If angina is unrelieved after using up to 3 sublingual tablets or sprays, patients should be instructed to go the emergency department promptly for further care. Nitroglycerin is adsorbed by plastic containers and deteriorates with exposure to light, humidity, and ambient air. Even when stored in small brown glass containers seemingly tightly sealed, potency may be lost over time, so regular replacement is prudent.

Long-acting nitrates in common use include an ointment, patches, isosorbide dinitrate and its metabolite, isosorbide mononitrate (Table 1).14 None is as effective as the sublingual form, and higher doses of oral forms are necessary because of first-pass metabolism by hepatic glutathione reductases. Isosorbide mononitrate is the exception. These agents effectively extend the duration of action of sublingual nitroglycerin, but since response is less predictable, individual titration is advised. Although they are convenient in once-daily doses, none provide full 24-hour protection.15 Tolerance develops within 12–24 hours, which may be avoided with a nitrate-free period of about 8 hours each day.16,17 Patients using patches must remember to remove them at night. Proposed mechanisms for tolerance18 include (1) overproduction of superoxide and/or peroxynitrite-free radicals which inactivate NO, preventing vasodilation to both endogenous and exogenous NO and raising responsiveness to vasoconstrictors;19 (2) impaired bioactivation of nitroglycerin resulting from limited availability of sulfhydryl groups;20 (3) inhibition of mitochondrial aldehyde dehydrogenase, which regulates biotransformation of nitrates to NO;21,22 (4) expansion of plasma volume, with or without (5) additional release or enhanced sensitivity to catecholamines, angiotensin II, or other vasoconstrictors; (6) upregulation of cGMP-dependent kinase type Iβ, an isoform of the predominant type cGKIα, much less efficient in activating the large-conductance Ca2+-dependent potassium channel (BK channel), which is responsible for vascular smooth muscle relaxation.23,24

cGMP-dependent phosphodiesterase inhibitors (type 5 or PDE5), such as sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®), must not be used with nitrates within the same 24-hour period because of the risk of severe hypotension.5,25 cGMP is degraded by phosphodiesterase, but cGMP levels are raised by nitrates. Together with PDE5 inhibition of the degrading enzyme, undue elevations of cGMP can lead to hypotension and lower coronary perfusion. Other contraindications to nitrate use include obstructive hypertrophic cardiomyopathy, severe aortic stenosis, constrictive pericarditis, mitral stenosis, or closed-angle glaucoma.

Reflex tachycardia may develop when using nitrates, and for this reason, combination with a β-blocker, diltiazem, or verapamil is usually advised.1 When used together with β-blockers or CCBs, anti-ischemic effects may be synergistic.1 Nitrates and CCBs are effective in Prinzmetal’s or vasospastic angina, whereas response to β-blockers is variable or unlikely. Aspirin may worsen ischemic attacks in this variant. The forms, doses, onset, and duration of clinical nitrates are summarized in Table 1.

![Table 1](https://www.dovepress.com/)

**Table 1** Common forms of nitrates used as anti-ischemic agents in angina

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Usual dose (daily unless mentioned)</th>
<th>Onset of action, min</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Sublingual</td>
<td>0.3–0.6 mg up to 1.5 mg as needed, up to 3 tabs</td>
<td>2–5</td>
<td>10–30 min</td>
</tr>
<tr>
<td></td>
<td>Spray/mist/aerosol</td>
<td>0.4 mg, 1–2 sprays prn as needed, up to 3 doses 5 min apart</td>
<td>2–5</td>
<td>10–30 min</td>
</tr>
<tr>
<td></td>
<td>Ointment 2%</td>
<td>7.5–40 mg, 6 × 6 in or 15 × 15 cm</td>
<td>20–60</td>
<td>3–8 h</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>0.2–0.8 mg/h q24 h; remove at night for 12 h</td>
<td>&gt;60</td>
<td>8–12 h</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>5–200 µg/min (used in ACS) titrated to symptom relief, headache, or hypertension</td>
<td>1–2</td>
<td>While infusing</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Oral</td>
<td>5–80 mg, 2–3 times daily</td>
<td>30–60</td>
<td>4–6 h</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Oral</td>
<td>20 mg twice daily, 7–8 h apart</td>
<td>30–60</td>
<td>6–8 h</td>
</tr>
<tr>
<td>Isosorbide mononitrate SR</td>
<td>Oral</td>
<td>30–240 mg daily, given once daily</td>
<td>30–60</td>
<td>12–18 h</td>
</tr>
</tbody>
</table>

*Requires 8–10 h nitroglycerin free recovery period because of tolerance; May exhibit tolerance in 7–8 h; Also available in sublingual form.

**Abbreviations:** q24 h, every 24 hours; ACS, acute coronary syndrome; SR, sustained release.
automaticity and conduction velocity, release of renin from juxtaglomerular cells, and lipolysis. $\beta_1\text{-adrenergic}$ receptor stimulation relaxes smooth muscle in the bronchi and elsewhere, dilates peripheral, coronary, and carotid arteries, and promotes glycogenolysis and gluconeogenesis, among other actions. All $\beta$-blockers are effective against anginal pain because they lower heart rate, BP, and contractility, thereby reducing myocardial oxygen demand. As such, guidelines indicate that they should be used as first-line therapy in patients without prior MI (class I, level of evidence [LOE]: B) and when a previous MI has been sustained (class I, LOE: A) unless contraindications exist. In addition, because of their negative chronotropic effect, $\beta$-blockers prolong diastole, raising coronary artery blood flow and myocardial perfusion. They lower heart rate at rest and limit rises in heart rate during exercise, keeping myocardial oxygen demand below the threshold at which angina occurs. Most antianginal effects of $\beta$-blockers result from $\beta$-inhibition. When used alone, there is some evidence that $\beta$-blockers may be more effective than long-acting nitrates or CCBs in reducing ischemic episodes when they are mild.

$\beta$-blocker dosages are titrated to a resting heart rate of 55–60 bpm and an exercise heart rate response $<75\%$ of the rate that precipitates ischemia. In patients with severe angina, target heart rates of $<50$ bpm are sometimes used provided no symptoms result and atrioventricular (AV) block does not occur. Some $\beta$-blockers are partial agonists with some intrinsic sympathomimetic activity, which blunts secondary preventive benefits, and are not used. Some newer $\beta$-blockers, such as labetalol, carvedilol, and bucindolol, also have partial $\alpha_1$-adrenergic blocking effects, causing vasodilation. Others have antiarrhythmic class effects—propranolol, metoprolol, and carvedilol a class I effect (sodium-channel blockade), and sotalol a class III effect (potassium channel blockade). Further, carvedilol and its metabolites have antioxidant, antiproliferative properties, which inhibit apoptosis. Most $\beta$-blockers are well absorbed. $\beta$-Blockers that are lipid-soluble, such as propranolol and metoprolol, have shorter half-lives because they are metabolized by the liver. Hydrophilic $\beta$-blockers, on the other hand, such as atenolol and nadolol, are eliminated renally and have longer half-lives. Timolol is among the most potent of the $\beta$-blockers; labetalol is the weakest. The clinician should be familiar with the differences between $\beta$-blockers, including duration of action, although as far as anti-ischemic efficacy is concerned, equipotent doses produce similar effects. In larger doses, predominantly $\beta_1$-blockers may lose some specificity and inhibit $\beta_2$-receptors. Pertinent clinical information is summarized in Table 2.

### Adverse reactions of $\beta$-blockers

Absolute contraindications to $\beta$-blockers are severe or advanced bradycardia, conduction system disease (sinus node dysfunction and/or high-grade AV block), asthma, peripheral vascular disease (PAD) with rest ischemia, depression, and overt heart failure (HF). Less marked or controlled versions of the same phenomena are relative contraindications. These include a PR interval $>0.24$ seconds, systolic BP $<100$ mm Hg, Raynaud’s phenomenon, and pregnancy. Rises in triglycerides (TGs) and lower levels of high-density lipoprotein (HDL) cholesterol have been reported with $\beta$-blockers. Fatigue, mild depression, and lack of motivation are usually dismissed, but upon careful questioning, these are more common barriers to patient adherence than appreciated. Similarly, the cause of impotence is difficult to identify in men with angina, but an association with $\beta$-blockers is well described. $\beta$-blockers may blunt the tachycardic response to hypoglycemia in diabetics, and worsening of hypoglycemia in

### Table 2 $\beta$-Adrenergic blockers used to treat angina

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Dose time to peak action after oral intake, h</th>
<th>Elimination half-life, h</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>$\beta_1$</td>
<td>2–4</td>
<td>6–9</td>
<td>50–200 mg/d</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>$\beta_1$</td>
<td>2–4</td>
<td>9–12</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Esmolol, IV</td>
<td>$\beta_1$</td>
<td>2–5 min</td>
<td>9 min</td>
<td>50–300 $\mu$g/kg/min</td>
</tr>
<tr>
<td>Metoprolol$^{4+}$</td>
<td>$\beta_1$</td>
<td>1–2</td>
<td>3–6</td>
<td>50–200 mg twice daily</td>
</tr>
<tr>
<td>Propranolol$^4$</td>
<td>None</td>
<td>1–2</td>
<td>14–24</td>
<td>40–80 mg/d</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>3–4</td>
<td>3–5</td>
<td>80–120 mg twice daily</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>1–2</td>
<td>4–5</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td>Carvedilol$^{4,6}$</td>
<td>None</td>
<td>1.0–1.5</td>
<td>7–10</td>
<td>3.125–25 mg twice daily</td>
</tr>
<tr>
<td>Labetalol$^6$</td>
<td>None</td>
<td>2–4</td>
<td>3–6</td>
<td>200–600 mg twice daily</td>
</tr>
</tbody>
</table>

*Drugs with partial agonist activity are not included; $^4$Combined $\alpha$-blocking and $\beta$-blocking activities; $^6$Combined $\alpha$-blocking, $\beta_1$-blocking, and $\beta_2$-blocking activities.

*pAntiarhythmic class I effect; $^4$An extended release formulation may be begun at 100 mg daily.

**Abbreviation:** IV, intravenous.
diabetics on oral agents or insulin has been reported. As a rule of thumb, cardioselective agents are preferred in asthmatics, diabetics, and patients with PAD, simply because there is less interference with bronchodilation, peripheral arterial dilation, and glycogenolysis. As mentioned, Prinzmetal’s angina may worsen with β-blockers due to an unopposed α-adrenergic effect. Patients with cocaine-induced coronary vasconstriction may also react adversely when given β-blockers, with hypertension and seizures. Similarly, since β-adrenergic receptors may be up-regulated when patients are treated with β-blockers, these agents should not be abruptly discontinued, lest rebound vasconstriction precipitate unstable angina or even MI.28,29 Patients with asthma, claudication, or HF whose symptoms increase with β-blockers should be reevaluated for possible substitution with CCBs and appropriately monitored. Sleep disturbances with nightmares and cold extremities may also be limiting. On occasion, athletes, exercise enthusiasts, and those in cardiac rehabilitation programs may object to limitations in heart rate and exercise capacity while using β-blockers. In these instances, a solution involving adjustments in exercise details, goals, and β-blocker dose or type can usually be negotiated.

Calcium Channel Blockers

CCBs bind to and inhibit L-type calcium channels, reducing calcium influx into cells. Intracellular calcium deprivation relaxes smooth muscle cells, causing vasodilation in the peripheral and coronary beds and increased coronary blood flow. The less selective, nondihydropyridine (DHP) CCBs, verapamil and diltiazem, also slow sinoatrial (SA) and AV nodal conductions to lower heart rate and depress contractility under physiological conditions. All the CCBs are effective coronary vasodilators. The 2 major subdivisions of CCBs are listed in Table 3.

<table>
<thead>
<tr>
<th>Type</th>
<th>Properties</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridines (DHP)</td>
<td>Peripheral and coronary vasodilators, negative inotropic action</td>
<td>Amlodipine, nifedipine, felodipine, isradipine, nicardipine, nisoldipine</td>
</tr>
<tr>
<td>Nonhydropyridines (non-DHP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylalkylamine</td>
<td>Additional negative chronotropic and inotropic actions</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Benzoazepine</td>
<td>Additional negative chronotropic and inotropic actions</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Mixed sodium and CCB</td>
<td>Nonselective, blocking delayed rectifier K⁺ current and fast Na⁺ current. Also inhomogeneous electrical effects, prolonged QT interval, and linked to torsade de pointes. Not in current use</td>
<td>Bepridil</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>Used for migraine prophylaxis, PAD, vertigo, but not for angina.</td>
<td>Flunarizine</td>
</tr>
</tbody>
</table>

**Table 3** CCBs are classified chemically, which reflects their properties

Abbreviations: CCBs, calcium channel blockers; PAD, peripheral vascular disease.

flow further contributes to correct myocardial oxygen imbalance. These drugs lower the frequency of angina, reduce the need for nitrates, extend treadmill walking time, and improve ischemic ST-segment changes on exercise testing and electrocardiographic monitoring.5,30-32 Amlodipine, in particular, may have some independent action in relieving diastolic dysfunction other than a reduction in BP.35

CCBs find clinical use in patients who cannot tolerate β-blockers, when they are ineffective, and in combination for additive anti-ischemic effects. The CCBs in common use for angina are summarized in Table 4. Although they are effective antianginal agents, they do not modify the natural progression of the disease. The large International Verapamil-Trandolapril Study (INVEST) trial reported a reduction in number of patients with angina from about 65%–25% using verapamil as compared with atenolol, with no difference in mortality over a 2-year period.34 When DHPs are used in combination with β-blockers, reflex tachycardia from the CCB is blunted. Long-acting DHPs are preferred. If clinically needed, verapamil or diltiazem may be used with caution to lower heart rate or slow AV conduction further when ventricular function is preserved. In patients with stable angina and hypertension, β-blockers in combination with amlodipine and long-acting nifedipine, nicardipine, isradipine, or felodipine offer an advantage. Of all agents available, the greatest clinical experience has been with amlodipine and felodipine.

Short-acting nifedipine has been linked to an increase in MI and should be avoided in unstable angina or acute coronary syndromes (ACS). The A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) study showed that long-acting nifedipine (gastrointestinal therapeutic system) safely relieved angina and prolonged event-free survival in patients with stable angina and hypertension.35,36 Verapamil acts chiefly through a negative inotropic action, with less associated reflex tachycardia;
Both verapamil and diltiazem are contraindicated in patients with uncompensated HF because of their negative inotropic effects; amlodipine and felodipine appear safe when LV dysfunction is compensated. Use of non-DPHs after complex MIs should be avoided because of the possibility of HF as well. DHPs, particularly nifedipine, are effective in managing Prinzmetal’s variant angina along with long-acting nitrates.

Although CCBs are effective anti-ischemic agents, in patients with unstable angina/ST segment elevation myocardial infarction (STEMI), they do not improve mortality. Diltiazem and verapamil are contraindicated in patients with STEMI accompanied by systolic LV dysfunction and HF. Immediate release forms of DHP CCBs are contraindicated in STEMI because reflex tachycardia increases myocardial oxygen demand and hypotension potentially lowers coronary perfusion pressure. Also, they should not be used in unstable angina/STEMI without a β-blocker.

Common side effects of headache, dizziness, flushing, and edema are due to vasodilation. Interaction with other negative chronotropic or inotropic agents to produce bradycardia, heart block, or HF has been reported. CCBs may also suppress lower esophageal sphincter contraction and worsen symptoms of gastroesophageal reflux disease. CCBs inhibit the CYP A4 enzyme in the liver and, therefore, may raise levels of statins and many other drugs, which may be overlooked. Cimetidine and grapefruit juice may raise the effective level of CCBs. Since magnesium is a calcium antagonist, magnesium supplements may enhance the actions of CCBs, particularly nifedipine.

### Summary
A comparison of the relative physiological effects of the 3 traditional anti-ischemic agents is summarized in Table 5.

Although efficacious, traditional anti-ischemic agents do not produce relief in all patients, and individual variation in responsiveness is well known. In a meta-analysis of all 3 types of agents, nitrates, β-blockers, and CCBs, β-blockers lowered the frequency of anginal attacks better than CCBs, not including amlodipine and felodipine. The combination of β-blockers with nitrates is favored because they both lower myocardial oxygen demand and raise subendocardial blood flow through different mechanisms, whereas the β-blockers prevent potential reflex tachycardia from nitrate-induced hypotension, and nitrates modify any potential rise in LV-EDP or preload from negative inotropic actions of the β-blockers (Table 5). β-blockers combined with DHP CCBs improve exercise duration more than either alone and

### Table 4 CCBs used for ischemic heart disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of action</th>
<th>Usual dose</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dihydropyridines (DHP)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine, slow release</td>
<td>Long</td>
<td>30–180 mg/d</td>
<td>Hypotension, edema, dizziness, flushing, nausea, constipation</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Long*</td>
<td>5–20 mg qd</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Felodipine, SR</td>
<td>Long</td>
<td>5–10 mg qd</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Isradipine, SR</td>
<td>Medium</td>
<td>2.5–10 mg bid</td>
<td>Headache, fatigue</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Short</td>
<td>20–40 mg tid</td>
<td>Headache, edema, dizziness, flushing</td>
</tr>
<tr>
<td><strong>Nonhydropyridines (non-DHP)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem, immediate release</td>
<td>Short</td>
<td>30–80 mg qd</td>
<td>Hypotension, dizziness, flushing, bradycardia, edema</td>
</tr>
<tr>
<td>Diltiazem, slow release</td>
<td>Long</td>
<td>120–320 qd</td>
<td>Hypotension, dizziness, flushing, bradycardia, edema</td>
</tr>
<tr>
<td>Verapamil, immediate release</td>
<td>Short</td>
<td>80–160 mg tid</td>
<td>Hypotension, negative inotropism, HF, bradycardia, edema</td>
</tr>
<tr>
<td>Verapamil, slow release</td>
<td>Long</td>
<td>120–480 mg qd</td>
<td>Hypotension, negative inotropism, heart failure, bradycardia, edema</td>
</tr>
</tbody>
</table>

*Has the longest half life of the CCBs of 35–50 h.

**Abbreviations:** CCBs, calcium channel blockers; SR, sustained release; tid, 3 times a day; qid, 4 times a day; qd, daily; HF, heart failure.
tolerance is acceptable, but the combination of β-blockers with verapamil is still generally to be avoided. On the other hand, amlodipine along with β-blockers is more effective than either one alone since coronary blood flow increases with a fall in BP from amlodipine, but the CCB lowers heart rate and contractility, providing 4 near-orthogonal ways to improve myocardial oxygen balance. Hard data on the use of all 3 classes of agents together are lacking. In 1 analysis, use of all 3 traditional agents still resulted in an average residual of 2 attacks of angina per week among participants. About 5%–15% of patients are refractory to “triple therapy”.

Newer, nontraditional anti-ischemic agents

Nicorandil is structurally a nicotinamide derivative with a nitrate moiety and a dual mechanism of action. First, it increases potassium ion conductance by opening adenosine triphosphate (ATP)-sensitive potassium channels, in turn activating the enzyme guanylate cyclase. Second, nicorandil shares the smooth muscle-relaxing property of nitrates to vasodilate, lowering preload through venodilation. The drug also reduces afterload and promotes expression of endothelial NO synthase. Use is associated with improved myocardial function during ischemia-reperfusion, protection of myocardium during ischemia, shortened action potential duration, and prevention of intracellular calcium toxicity, of importance in modulating ischemic cell damage and death. In the Impact Of Nicorandil in Angina (IONA) study of 5,126 patients with angina, nicorandil produced a significant 17% reduction in hospitalization for chest pain, MI, and CAD death. The drug also prolongs time to the onset of angina and ischemic ECG changes, extends exercise duration, and reverses ischemia-related impairment in regional wall motion. In the multicenter, randomized SNAPE trial comparing it to isosorbide mononitrate, nicorandil was found to be both safe and efficacious in treating angina. A dose of 10–40 mg twice daily controls 70%–80% of stable chronic angina patients, with an effect maintained for about 12 hours. This drug is not yet approved for use in the United States, but it is available in other countries.

Ivabradine is a prototype of specific bradycardic agents and the only one in use and under current clinical investigation. These compounds selectively inhibit the inward sodium–potassium “I, current,” an important pacemaking current in SA node cells, to slow the rate of diastolic depolarization and lower heart rate. Ivabradine does not affect contractility, AV nodal conduction, nor alter hemodynamics.

Phase II studies confirmed the bradycardic effect of ivabradine at rest and during exercise, as well as antianginal efficacy. In noninferiority trials, ivabradine compared well to atenolol or amlodipine. The BEAUTIFUL trial found that in patients with CAD, LV dysfunction, and heart rates >70 bpm, ivabradine was able to lower the risk of acute myocardial infarction (AMI) and need for revascularization by one-third, even when therapy was considered optimal. In the overall study, population without higher heart rates, the reduction in heart rate induced by the agent (average, 6 bpm) did not result in a significant reduction of the primary composite end point (cardiovascular death, hospital admission for AMI, and admission for HF). The ASSOCIATE trial found that ivabradine titrated to a dose of 7.5 mg twice daily after 4 months, increased total exercise duration in concert with reductions in rate-pressure product at rest and at the peak of exercise, in patients taking atenolol 50 mg daily. Ivabradine is another well-tolerated agent in practitioners’ toolkits that may be added to nitrates and β-blockers for additional antianginal effect or used in patients who cannot take β-blockers. It is not yet approved in the United States. About 15% of patients experience a curious brightness in the visual fields because the drug also blocks a retinal current with similar characteristics. This side effect is transient and reversible, but in 1% of patients, ivabradine has to be discontinued. Other adverse reactions, including conduction abnormalities, occur in ≤10% of the cases. Ivabradine should not be used with CYP3A4 inhibitors or in patients with sinus node dysfunction.

Trimetazidine, a member of the class of “3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors,” is a metabolic modulator that improves myocardial energetics at several levels, partially inhibiting β-oxidation of fats by decreasing activity of mitochondrial enzyme 3-KAT. The drug raises myocardial glucose utilization, prevents a decrease

Table 5 Cardiovascular effects of nitrates, CCBs, and β-blockers in angina

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nitrates</th>
<th>Calcium channel blockers</th>
<th>β-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collateral blood flow</td>
<td>↑↑</td>
<td>↑↑</td>
<td>→</td>
</tr>
<tr>
<td>Endomyocardial to epimyocardial flow</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑ (reflex)</td>
<td>↓ (reflex)</td>
<td>↓↓</td>
</tr>
<tr>
<td>Left ventricular wall tension</td>
<td>↓↓</td>
<td>↓</td>
<td>↑→</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>↑ (reflex)</td>
<td>↑→ (reflex)</td>
<td>↓↓</td>
</tr>
<tr>
<td>Cardiac work</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
</tbody>
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Abbreviation: CCBs, calcium channel blockers.

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in ATP and phosphocreatine levels in response to hypoxia or ischemia, preserves ionic pump function, minimizes free radical production, and protects against intracellular calcium overload and acidosis. It raises coronary flow reserve, lowers frequency of anginal episodes, improves exercise performance, and spares the use of nitrates without changes in heart rate, negative inotropic, or vasodilator actions. Trimetazidine may be added to ongoing therapy with β-blockers, CCBs, and nitrates with safety. The TIGER study confirmed the usefulness of this agent in elderly patients resistant to traditional anti-ischemic agents with effects mediated through hemodynamic changes. A Cochrane review of 1,378 patients found that the drug was extremely well tolerated and agreed with the above-mentioned findings. Multiple intracellular metabolic and electrophysiological benefits have created an interest for possible use in HF and idiopathic dilated cardiomyopathy.

Rho kinase, or “ROCK”, is an important intracellular enzyme which phosphorylates proteins to affect a number of cellular functions, among them phosphorylation of myosin, resulting in smooth muscle contraction and vasoconstriction. Fasudil is a rho-kinase inhibitor that has been used to prevent vasospasm, especially in the pulmonary and cerebral arterial beds, in addition to inhibiting production of vascular endothelial growth factor. A phase II, multicenter, double-blind trial found that the agent prolonged the time to ST-segment depression on exercise testing, improved exercise duration, and significantly reduced the number of anginal attacks. The drug is effective and safe in patients with stable angina who are already being treated with traditional agents.

Ranolazine, which first attracted clinical attention in the 1980s, is the newest antianginal agent to receive approval from the US Food and Drug Administration in nearly 30 years, presently for use in patients uncontrolled by traditional agents. It is an important, welcome, and needed addition to the armamentarium of clinical cardiologists who manage patients with angina.

Normally, mitochondrial production of ATP provides the energy for the function of both sarcoplasmic Na+/K+-ATPase and sarcoplasmic reticulum Ca2+-ATPase (transfers calcium from the cytosol to the sarcoplasmic reticulum lumen). The potential energy stored in the electrochemical Na+ gradient established by the former usually furnishes the power for calcium removal from the intracellular to extracellular space by the Na+/Ca2+ exchanger (NCX). Ischemia impairs ATP synthesis, and since maintenance of ionic gradients is energy-intensive, ATPase function falls, limiting removal of intracellular sodium. Hence ischemia eventually causes intracellular sodium overload, followed by intracellular calcium accumulation via reverse-mode NCX1-activity, further mitochondrial inhibition, and extracellular potassium accumulation.

Sodium enters the myocyte rapidly during the initial depolarization or upstroke of the cardiac action potential, but it may be followed by a late inward cardiac action potential that persists significantly throughout the ensuing action potential when the myocyte is diseased. This late sodium current was initially ascribed to failure of fast sodium channels to close, but evidence indicates there are separate late sodium channel(s). Normally, late sodium inward current is small, about 1% of the total inward sodium flux. Ischemia (and HF) increases the late inward sodium current, which becomes a much larger proportion of the total sodium entering the cell.

Intracellular sodium (Na+) overload, through the reverse NCX mechanism mentioned above, leads to excess level of intracellular calcium and continued exposure of actin and myosin to calcium, causing a tonic contracture in isolated fibers, but diastolic stiffness in the intact heart. This extra contractile work wastes energy and compresses the vascular space during diastole, reducing myocardial oxygen supply even more. The rise in intracellular sodium concentration causes electrical instability, promoting arrhythmias. Intracellular sodium overload and the subsequent rise in intracellular calcium play a large role in myocardial stunning and reperfusion injury. Stunned myocardium has suffered transient ischemia with LV dysfunction, but perfusion is preserved at rest, and myocytes remain viable. There may be a 50% reduction in ATP content in stunned myocardium, which can require days to fully replete, as recovery occurs in postsischemic contractile dysfunction. Although ischemic episodes may be multiple or prolonged, the severity of metabolic impairment remains insufficient to result in irreversible cell injury, muscle loss, or disrupt cell membrane integrity. Subsequent reperfusion, however, may cause myofibrillar damage. Even though reversible, stunned myocardium may be less responsive to inotropic drugs and may lead to severe hemodynamic changes, even cardiogenic shock.

Ranolazine is a piperazine derivative that inhibits the late sodium channels, not only lowering total inward sodium flux but also the subsequent intracellular calcium overload. At therapeutic concentrations, fast inward sodium current is unchanged, and reduction of late inward sodium current is confined to ischemic or failing myocytes. By blunting the amount of excess sodium entering the cell, the total intracellular sodium concentration is restricted, thereby limiting the...
ischemia-associated calcium overload, the lethal component of events. The drug interrupts the positive feedback loop that perpetuates myocardial ischemia, sodium influx, loss of potassium, voltage gradient perturbations, and myocardial dysfunction. By preventing intracellular sodium overload, calcium accumulation is thwarted, diastolic muscle relaxation is normalized, and myocardial oxygen balance and myocardial blood perfusion are preserved. Improvement in the dual changes in intracellular sodium and calcium promotes electrical stability, minimizing the proarhythrogenic effects of ischemia. Ranolazine also reduces the late inward calcium current, the inward \( \text{Na}^+ / \text{Ca}^{2+} \) exchange current, and the outward repolarizing, delayed rectifier potassium current. Ion channel changes induced by ranolazine resemble those of amiodarone.

Peak plasma levels occur 4–6 hours after an oral dose, with 50%–55% bioavailability. Ranolazine is cleared by the hepatic enzymes CYP3A4 (70%–85%) and CYP2D6 (10%–15%) and is also a substrate of P-glycoprotein, a widely expressed membrane transporter protein. P-glycoprotein inhibitors, such as cyclosporine, reduce the dose of ranolazine needed to produce a given response. As a result of these pharmacokinetic properties, there are a number of clinical drug interactions of importance:

- Ketoconazole significantly raises ranolazine levels up to 4.5-fold, as would other CYP3A4 inhibitors, potentially increasing such side effects as dizziness, headache, and nausea. This applies to clarithromycin, ritonavir, nefazodone, rifampin, rifabutin, rifapentin, barbiturates, carbamazepine, phenytoin, St John's wort, grapefruit juice, and many other CYP3A4 interactants.
- Diltiazem, due to mild CYP3A4 inhibition, may raise ranolazine levels 1.5-fold.
- Paroxetine may raise plasma ranolazine concentrations by a factor of 1.2 because of CYP2D6 inhibition.
- Ranolazine may nearly double levels of simvastatin since it is a mild inhibitor of both CYP3A4 and CYP2D6. Simultaneous administration of CYP3A4 inhibitors together with some statins remains a clinical concern.
- Since verapamil inhibits P-glycoprotein in doses of \( \geq 360 \text{ mg/d} \), this CCB may raise ranolazine levels up to 3-fold.
- Digoxin levels may rise 1.4–1.6-fold because of P-glycoprotein competition by ranolazine.
- Ranolazine may prolong the rate-corrected QT interval, about 6 msec at a dose of 2 g/d. This would affect patients with congenital long QT syndrome or who take drugs that prolong the QT interval including class Ia (eg, quinidine) or class III (eg, dofetilide, sotalol, amiodarone) antiarrhythmic agents, erythromycin, amitriptyline, some antipsychotic agents (eg, thioridazine, ziprasidone), and others.

The clinical trials mentioned below eliminated participants who were taking such drugs, so data concerning the significance and extent of these interactions are lacking. Drug-induced prolongation of QT intervals is an important determinant of potentially lethal arrhythmias in both outpatient and inpatient settings.

Early ranolazine trials confirmed a significant prolongation in exercise duration to angina and to ST-segment depression (1 mm) in angina patients. In the first of the 4 major clinical studies, the MARISA trial used a crossover design, which probed the effects of 3 doses of ranolazine in 191 stable angina patients previously responsive to nitrates, \( \beta \)-blockers, and/or CCBs. Total exercise duration and time to onset of angina and to 1-mm ST-segment depression were all increased. A maximal dose of 1,000 mg twice daily was established as effective and safe. The CARISA trial confirmed similar effectiveness of ranolazine in 823 patients who continued to have effort angina despite use of atenolol, diltiazem, or amlodipine. In the Ranolazine Open Label Experience (ROLE) extension program, about 900 patients who participated in the MARISA or CARISA trials enrolled in an additional study to evaluate any ranolazine effect upon survival. Data did not reflect any deviation from the historical annual mortality of 4%–13% from counterparts not receiving the drug. After approximately 2 years of monitoring, 23% of patients discontinued ranolazine because of dizziness (12%) or constipation (11%). The Efficacy of Ranolazine In Chronic Angina (ERICA) trial showed ranolazine was useful when combined with nitrates and amlodipine in patients who had already been taking maximal doses of conventional anti-ischemic agents.

In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Segment Elevation Acute Coronary Syndromes 36 (MERLIN-TIMI 36) trial, 6,560 patients with CAD who were enrolled in the MERLIN study of non-ST-segment elevation ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous ACS were randomized to either ranolazine in an intravenous 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the efficiency of ranolazine to relieve ventricular wall stress by lowering myocardial sodium and calcium overload, these same investigators recently reported efficacy in a high-risk subgroup of STEMI patients with elevated concentrations of B-type natriuretic peptide (BNP). Such patients with high levels of BNP and the N-terminal portion of BNP prohormone, resulting from, and proportional to, the volume of myocardium that is ischemic, stiff, and dysfunctional, are at high risk for adverse cardiovascular events. Although preliminary, these data extend our information and unite a potent new agent with a specific application of this biomarker to improve patient outcomes.

**Options for refractory angina**

Refractory angina refers to patients who have continued angina, usually Canadian Cardiovascular Society (CCS) class III/IV, and objective evidence of ischemia despite optimum medical therapy, but who are not candidates for revascularization. In the United States, as many as 1.7 million patients are believed to have refractory angina, usually in the setting of advanced heart disease. Patients have a bleak future, with an annual rate of non-fatal MI of 3.2% and annual mortality of 1.8%. Treatment options for refractory angina are limited and include spinal cord stimulation (SCS) (invasive and multicellular), enhanced external counterpulsation (EECP) to raise myocardial perfusion, and angiogenesis through extracorporeal cardiac shock wave therapy (noninvasive), transmyocardial laser revascularization (invasive), and stem cell/gene therapy (invasive and preclinical). After intensive reevaluation, some patients with refractory angina have eventually been treated successfully with percutaneous coronary intervention (PCI).

EECP consists of the application of 3 pairs of pneumatic cuffs placed on the lower extremities at the levels of the calves and lower and upper thighs. Cuff inflation and deflation are synchronized with the ECG. At the onset of diastole, the cuffs are sequentially inflated from the calves proximally to the lower and upper thighs. Before the onset of systole, all cuffs are simultaneously deflated. The pressure created during inflation increases venous return and diastolic blood flow in the coronary arteries and other vascular beds in a manner similar to intra-aortic balloon counterpulsation. The simultaneous presystolic decompression in the cuffs reduces afterload so that the ejection fraction (EF) improves, whereas the work of the heart diminishes. Nonrandomized smaller studies reported improvements in perfusion imaging, angina classification, increased exercise tolerance, and longer time to ST-segment depression during stress testing after EECP use in patients. Improved endothelial function and reduced levels of inflammatory cytokines have also been identified. It is believed that vasoactive moieties, including NO, vascular endothelial growth factor, and endothelin play a part in producing these effects.

The MUlticenter Study of Enhanced External CounterPulsation (MUST-EECP) trial was a multicenter, randomized study that found a 15% rise in the time to the onset of 1-mm ST-depression, together with 25% fewer anginal episodes per week after EECP therapy. The International EECP Registry reported a reduction in angina episodes, lowering of angina class, reduction in use of nitrates, with 41% of registrants remaining angina-free during a 2-year period following treatment. EECP may also lower peripheral vascular resistance or mimic a training effect that has been likened to the effect of physical exercise. Approximately 62% of patients treated with EECP maintain benefits for 1 year, whereas 29% of patients sustain improvement for 24 months, some even as much as 5 years. Whether endurance of EECP effect is related to an increase in number and colony-forming capacity of circulating endothelial progenitor cells is unknown.

A typical course of EECP includes 35 1–2 hour sessions over 7 weeks. The American College of Cardiology/American Heart Association (ACC/AHA) guideline assignment is Class IIb, LOE: B** (see Table 7 caption for key).

In conclusion, EECP provides a noninvasive, effective alternative for treatment of refractory angina, capable of improving ventricular function, systolic BP, coronary perfusion, myocardial oxygen balance, and exercise tolerance. The treatment lowers the number of anginal episodes and spares nitrate use in an impressive proportion of patients, which may endure for years.

SCS involves implantation of an epidural electrode between levels C7 and T1 by puncturing the epidural space at T6-7. Generally, the stimulation electrode is connected to an external portable stimulator for a trial period. After angina frequency and intensity have been significantly reduced, the stimulation wire is connected to an implanted stimulator in the left abdomen. A magnetic hand-held control device turns the unit on and off and adjusts stimulation intensity within programmed parameters.

Originally, it was thought that stimulating large afferent fibers in the dorsal columns simply blocked impulses from the nociceptive afferent nerves carrying cardiac pain signals, according to the gate control hypothesis. SCS raises release of the inhibitory neurotransmitter γ-aminobutyric acid, lowering the amount of 2 excitatory amino acids, glutamate and aspartate, which in turn suppresses processing.
of the nociceptive Aδ and C nerve fibers. In addition, SCS also raises β-endorphin release, lowering pain perception.132 Recent data, however, show that additional mechanisms also account for the effects of SCS, including sympatholytic activity under stress conditions133 and changes in cerebral blood flow.134 Although there is little question that SCS improves time to ST-segment depression, total exercise time, anginal class, quality of life (QoL), and reduces the number of hospitalizations and outpatient visits,135–140 a purported increase in myocardial perfusion remains unsettled. SCS lowers catecholamine levels, and inhibition of tonic sympathetic tone may dilate coronary microvasculature, increasing myocardial perfusion, lowering the rate-pressure product and hence myocardial oxygen consumption.141,142 Recently, a 52% (range, 33%–65%) reduction in sympathetic activity was documented during SCS activity during heart rate variability recordings.143

Randomized clinical trials using SCS have reported a 39% increase in time to onset of ST depression and 19% prolongation in treadmill time, together with a 41% fall in number of anginal episodes and 48% decrease in nitrate use.144 In the ESBY study,145 104 patients with severe angina and increased surgical risk – expected to benefit with only symptomatic relief from surgery – were randomized to either SCS or coronary artery bypass surgery (CABG). SCS was as effective as SCS in lowering number of anginal attacks but with far less mortality and stroke. After 5 years, both survival and QoL were about equal in both groups.146

Complications from SCS include lead migration (13.2%), lead breakage (9.1%), and infection, either at the epidural site or at the abdominal pouch (3.4%).139 Fortunately, the chest pain of AMI is not concealed by SCS. There is no interference with pacemakers as long as strict bipolar right ventricular sensing is used. Use in patients with ICDs is possible, although only case studies are available.147 The typical SCS treatment consists of three 1-hour stimulations daily. The ACC/AHA guideline grade assigned is class IIb, LOE: B.3 In conclusion, SCS is a safe and effective procedure for refractory angina, considered a possible substitute for revascularization and is comparable to percutaneous myocardial laser revascularization, another option to treat refractory angina.148,149

Low-energy, electrohydraulic shock wave therapy is an additional option to induce neovascularization.150–152 A longitudinal acoustic wave is applied to the heart to create a so-called “cavitation effect” producing membrane drag and shear stresses. Hyperpolarization, ras activation, nonenzymatic upregulation of NO synthesis, and vascular endothelial growth factor and its tyrosine kinase receptor flt-1 are believed to be mediators of an eventual anti-ischemic effect. The technique has been used in the treatment of hind limb ischemia, resistant stress fracture, chronic plantar fasciitis, and wound healing after vein harvesting in coronary bypass surgery to induce angiogenesis.

Other treatments for refractory angina not discussed are intermittent urokinase therapy43,153,154 and heart transplantation.

Risk factor reduction and prevention
After relief of pain, involving a reduction in the frequency, number, and intensity of anginal attacks and restoration of the patient’s QoL, the second major goal in therapy of angina is risk factor reduction, to slow the progression of atherosclerosis, and hopefully forestall deadlier ischemic syndromes, such as AMI and sudden cardiac death. The importance of a systematic, comprehensive, and monitored program using available guidelines as a reference base cannot be overemphasized.

Risk factors and prevention – epidemiological notes
The Framingham Heart Study (FHS)55 began in 1948, with the announced intention of identifying the common factors that contributed to the development of cardiovascular disease. The legendary contributions of the founding investigators fundamentally changed the practice of cardiology and shaped future-related research activities. Their work established the basis for the common source epidemic of CAD humans now face. The term “risk factor” was first used by Dr Thomas Royle “Roy” Dawber, Director of the FHS from 1949–1960, in a landmark 1961 paper56 identifying hypertension, hypercholesterolemia, and arrhythmias as risk factors, but also referring to smoking. A seminal paper that followed57 used risk factors for prediction, beginning a new era in preventive cardiology.

Although Hippocrates regarded epidemics as diseases “visited upon” a population, as opposed to endemics that “reside within” a population, our present epidemic of CAD is actually imposed upon us by our own doing. Clearly this is an epidemic, occurring rapidly in numbers exceeding normal expectancy and arising from common sources, namely, inordinate rises in similar risk factors that are widely prevalent.

A risk factor is a quantifiable, “independent” variable, statistically associated with a specific disease, which predicts patient risk and hence relates to prevalence in a population. Once risk factors are identified, their predictive ability is assessed and defined. Implications for different approaches to
prevention and optimal treatment are then typically explored. Risk factors tend to occur together or cluster, and when they do their effects are not simply additive, but generally amplify each other. As a result, patients with 2 or more risk factors may increase their risk of CAD 4-fold, and those with 3 risk factors may face a risk 8-fold to 20-fold greater than those with no risk factors. Moreover, traditional major risk factors for CAD are not truly independent in the mathematical sense. If a risk factor retains its statistical association with an outcome after other risk factors are included in a model, it is considered independent. Independence depends upon the other variables included in the model, and inclusion of one may negate the independence of another. Independent risk factors may not be causes; causal factors may not be independent risk factors, and biomarkers used to judge efficacy of different treatments may not be risk factors. Thus, risk factors for CAD may have an astonishingly complex relationship with one another and with the many biochemicals, receptors, and markers involved in the pathophysiology of the disease.

The goal of medicine is to prevent disease, relieve suffering, and prolong life. Prevention has several meanings. Usually when primary care physicians refer to prevention, they mean vaccinations, screening tests to detect early pathology, and agents they prescribe to lower risk. Their contribution is clinical, individual, and disease-based. Often causal risk factors become surrogates for disease and are treated as diseases themselves. To epidemiologists, prevention means postponing or limiting the development of disease. Cardiologists speak of primary prevention to prevent or postpone CAD in people without the diagnosis and secondary prevention to avert recurrence of cardiac events in patients already diagnosed with heart disease. The interventional approach in high-risk individuals may produce abbreviated results because subsequent adherence to lifestyle counseling and prescription drugs is poor, and without risk factor reduction, the disease progresses after PCI or CABG. When risk factors, such as LDL or hyperglycemia, are ranked rather than the person or the disease, neither the cause nor the total outcome is addressed. The cause of the “risk factor” elevation may lie in overconsumption of calories and lack of exercise, and the outcome may be influenced by much more than the “risk factor” because it is only a surrogate for the outcome.

Prevention may also mean what the patient can do personally to avoid disease, owned lifestyle changes that may be extremely effective when continued over a prolonged period of time. Such prevention through lifestyle does not allow risk factors to develop in the first place and is more fundamental and complete than primary prevention. Since the incubation period of CAD is long, extending over decades, and begins much earlier than believed, all personal preventive measures are best begun as early as medically appropriate and be consistently applied over years. Furthermore, when atherosclerotic plaque is detected, its components have already been there for about 10 years, turnover within the lesion is slow, and quick improvement or regression in response to preventive therapies at that stage should not be routinely expected. Lifestyle measures have the advantage of reducing several risk factors simultaneously whenever they begin. Unfortunately, to many people “prevention” evokes images of endless, exhausting exercise and intolerable food deprivation, and in part this attitude contributes to the relative poor health of Americans. Lifestyle therapy is unpopular for 2 major reasons: (1) it requires time from physicians and is nonreimbursable and (2) it requires sustained mental and physical effort from patients who want a magic pill for an immediate cure, in part so that unhealthy habits may continue. Both these obstacles are nonmedical and may be reversed with specific, targeted public health policies. In view of the above, it is unlikely that without a major population-wide effort that includes dietary and other lifestyle changes, as well as major social and environmental adjustments, including food industry practices, the current progression of obesity, diabetes, and CAD will be stopped.

### Traditional risk factors and public health potential

Traditional risk factors include the nonmodifiable: age, gender, family history; and the modifiable: use of tobacco, hypertension, dyslipidemia, and diabetes mellitus. Obesity is not considered in some discussions because effects are substantially mediated by its consequences, namely diabetes, hypertension, and dyslipidemia. As a clinical entity, it obviously cannot be ignored. Other risk factors of major interest include C-reactive protein and chronic renal disease, although there are many others. In general, there is greater value in evaluating and monitoring long-term risk and its consequences in vivo rather than short-term risk using surrogates. Otherwise, as is now recognized after lowering LDL with pharmacological agents, significant residual risk will remain unaddressed.

INTERHEART, an international study, showed that although 80% of global cardiovascular disease is found in nonwealthy countries, the risk factors are the same everywhere and apply to men and women of all ages. Their striking finding was that 9 risk factors accounted for 90% of the risk in men and 94% in women. Since all 9 are modifiable, these percentages may be construed as possible upper ceilings on
the extent to which AMI can be prevented. It is instructive to note the population attributable risks and odds ratios for various risk factors found to account for AMI in these data (Table 6).

In the United States, of 3 risk factors – hypertension, diabetes, or dyslipidemia – about 45% of the adult population has 1 of them, 13% have 2 of the 3, and 3% has all 3 diseases. An additional 15% have 1 or more of these conditions that remain undiagnosed. To reap maximum benefits from following a lifestyle that optimizes risk factor reduction, “good behavior” must be applied with sufficient intensity to achieve a target reduction in a respective risk factor and be consistently maintained over a relatively long period of time. Interestingly, these are the same intensity and volume factors described in many physical systems, such as thermodynamics. The incubation period of atherosclerosis and CAD, according to the Seven Countries Study, is at least 10 years. Pediatric data, pathological reports from the military, and other epidemiological studies suggest the typical incubation period may be on the order of 2.0–3.3 ± 1.8 decades. Under ideal circumstances, lifestyle modifications should be optimized during this period.

Remarkably, meaningful improvements may occur much sooner when positive changes occur. Patients need to be reeducated and understand that transient improvements over a few days will not cure, but that life-long changes will produce control. Motivating for personal involvement and commitment, emphasizing individual responsibility for health, and shifting away from the disease-reactive model of care, add another dimension to health delivery and is workable. Pointing out that modest change in health behavior can delay aging by 12 years, accompanied by a 25% reduction in risk of death, such as reported by the UK Health and Lifestyle Survey is powerful material when presented to patients. Other advantages of the lifestyle method of management include enhanced personal joy, increased productivity, and the absence of adverse drug reactions or procedural complications.

### Primordial prevention to improve cardiovascular health

Recently, the AHA has reemphasized the profound potential effects of healthier personal habits and behavior patterns upon heart disease. The AHA issued a policy statement setting forth structural aspects of effective worksite wellness programs, outlining the benefits of patient education, smoking cessation, early detection and screening, weight control, nutrition, physical activity, stress management, and the environmental and social changes likely to promote cardiovascular health. Shortly thereafter, the 2010 update of heart disease and stroke statistics summarized national progress and failures with respect to cardiovascular risk factors. High rates of tobacco use, adult and pediatric obesity, and hypertension (at 34%) remained significant problems. An AHA special report followed, defining and setting 2020 impact goals for cardiovascular health promotion and disease reduction.

This unique document combined (1) a needed focus on the essence of the public health problem, (2) a blueprint and practical plan for the future, (3) a public message, with metrics and goals in language the public can easily grasp and use, (4) a guide to clinicians, and (5) a summary of the evidence-based recommendations. The AHA defined ideal cardiovascular health as not only the absence of cardiovascular disease but also following a healthy lifestyle together with a normal body mass index (BMI), cholesterol level, BP, and fasting glucose without treatment. In this review, the concepts discussed above were clearly set forth in the context of population-based personal ownership and commitment in affecting habit change. Personal heart-healthy

### Table 6 Relative contributions of risk factors to risk of AMI in the INTERHEART study

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>Population attributable risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>2.87 (for current vs never)</td>
<td>35.7% (for current and former vs never)</td>
</tr>
<tr>
<td>Raised ApoB/ApoA1 ratio</td>
<td>3.25 (for top vs lowest quintile)</td>
<td>49.2% (for top 4 quintiles vs lowest quintile)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.91</td>
<td>17.9%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.37</td>
<td>9.9%</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>1.12 (for top vs lowest tertile)</td>
<td>20.1% (for top 2 tertiles vs lowest tertile)</td>
</tr>
<tr>
<td>(for middle vs lowest tertile)</td>
<td>1.62</td>
<td>49.2% (for top 4 quintiles vs lowest quintile)</td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td>2.67</td>
<td>32.5%</td>
</tr>
<tr>
<td>Daily consumption of fruits and vegetables</td>
<td>0.70</td>
<td>13.7% (for lack of daily consumption)</td>
</tr>
<tr>
<td>Regular alcohol consumption</td>
<td>0.91</td>
<td>6.7%</td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>0.86</td>
<td>12.2%</td>
</tr>
</tbody>
</table>

All risk factors were significantly related to AMI ($P < 0.0001$ for all risk factors and $P = 0.03$ for alcohol).

**Abbreviation:** AMI, acute myocardial infarction.
vascular health in the population into poor, intermediate, or high-risk individuals unidentified and considerable amounts of unaddressed residual risk in those who are treated. In addition, the 2020 goals statement, recognizing the early beginnings of risk factors leading to CAD, stressed the need for prevention, over years, prior to the development of subclinical atherosclerosis and at all levels of risk. The difference between population-wide prevention and individual intensive treatment of high-risk patients was made clear. For the first time, optimal health was defined by a venerable medical organization as more than the absence of disease, and indeed a desirable goal, attainable through lifestyle modification. Reversing dyslipidemia and hypertension with medications does lower cardiovascular risk, the authors said, but does not restore risk to equal the absence of risk enjoyed by individuals who never had elevations in the first place. In other words, drug-induced reversal of risk factors, although necessary and the essential fabric of current therapy, does not equal elimination of risk factors through lifestyle, and it is in fact excluded from the definition of “ideal cardiovascular health”. This view not only reflects the pleiotropic action of lifestyle elements upon multiple risk factors but also the limitations of risk stratification and treatment, which leave some high-risk individuals unidentified and considerable amounts of unaddressed residual risk in those who are treated.

The AHA report simplified classification of cardiovascular health in the population into poor, intermediate, or ideal depending upon how patients satisfied new criteria, consisting of 7 targets:

1. Never having smoked or quitting over a year ago.
2. Keeping BMI < 25 kg/m².
3. Exercising at moderate intensity ≥150 minutes (or 75 minutes at vigorous intensity) each week.
4. Eating a “healthy diet”: adhering to 4 of 5 important dietary components.
   a. sodium intake <1.5 g/d;
   b. sugar-sweetened beverage intake <36 oz weekly;
   c. ≥4.5 cups of fruits and vegetables/d;
   d. ≥three 1 oz servings of fiber-rich whole grains/d;
   e. ≥two 3.5 oz servings of oily fish/week.
5. Maintaining total cholesterol <200 mg/dL.
6. Keeping BP < 120/80 mm Hg.
7. Keep fasting blood glucose <100 mg/dL.

The 7 targets included specifics regarding intake of dietary refined sugar from another closely-timed statement and defined a new limit on salt consumption, relating a comparatively small amount of salt to raised risk for cardiovascular disease.

Other dietary considerations were not overlooked. The importance of minimizing dietary trans and saturated fat, avoiding processed foods, especially meats, emphasizing a plant-based diet with inclusion of legumes, nuts and seeds, raising fiber intake through vegetable sources, and the general benefits of the DASH diet were included. The AHA also noted that only 5% of Americans presently satisfy these criteria, a sobering statistic. Those who do can expect to live 40 additional years without a cardiac event or stroke. Fulfillment of the new goals is projected to improve the cardiovascular health of Americans ≥20% by year 2020 and lower AMI and stroke deaths by an equal measure. The AHA achieved its 2010 goal of lowering heart and stroke deaths earlier than expected by a margin of 25%. In the United States, mortality from CAD has steadily declined over the past 40 years; hospital morbidity has remained unchanged due to age-shifting, and CAD prevalence rose with greater numbers of patients diagnosed and surviving. Most recently, hospitalization rates for AMI fell 23.4% from 2002–2007 for patients over 65 years of age, although, as discussed above, all indicators suggest that rising obesity rates and diabetes may handily reverse such gains. Not surprisingly, all contributory risk factors found significant in the INTERHEART study are included as targets in the AHA criteria, except for psychosocial factors, which cannot be easily quantified for use in this context. Finally, the 7 targets are expressed in simple language, without unnecessary complexities, an essential feature for success.

Management of risk factors in patients

In the individual patient with angina, major modifiable risk factors need to be addressed and optimized. A 2007 ACC/AHA Chronic Angina Focused Guideline Update revised the full 2002 ACC/AHA Chronic Angina Guidelines, using recent evidence that was considered compelling. Clinicians should heed the recommendations made as a basis for treatment (Table 7). Risk reduction in patients with chronic stable angina is similar, although certainly not identical to, the risk management in primary prevention, guidelines written specifically for women, guidelines for secondary prevention generally, and European guidelines for prevention of heart disease. Related guidelines of interest include those for...
### Table 7  Selected recommendations from the ACC/AHA updated guidelines on risk reduction in patients with angina

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Recommendations</th>
<th>COR/LOE</th>
<th>Comments (not part of the guidelines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Smoking must be stopped immediately, and second-hand smoke should be avoided. Pharmacotherapy with nicotine and other approved agents should be used along with referral to special programs. Use a stepwise strategy: Ask, Advise, Assess, Assist, and Arrange.</td>
<td>I (B)</td>
<td>Smoking is a potent and pernicious risk factor. Cessation may lower risk by 60% in 3 y, with half of that manifested within the first 3–6 months.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>BP should be kept &lt;140/90 mmHg, or &lt;130/80 mmHg in DM or CKD. Lifestyle modifications: weight control, physical activity, low alcohol, sodium intake, high consumption of fresh fruits and vegetables and low-fat dairy products – an improved “DASH diet” is advised. For patients with established CHD, use β blockers or ACE inhibitors first, then other agents.</td>
<td>I (A)</td>
<td>Evidence at the ACC 2010 sessions raised doubts about the wisdom of tight BP control in DM.205,206 New Joint National Conference 8 Guidelines for hypertension are expected late in 2011.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>When baseline LDL ≥100 mg/dL, begin drugs with lifestyle measures. Daily exercise, weight control, low-saturated fat diet &lt;7%, reduce dietary TFA, and cholesterol intake &lt;200 mg/d. If TG = 200–499 mg/dL, non-HDL should be &lt;130 mg/dL. Add plant stanols 2 g/d and/or soluble fiber &gt;10 g/d. Lowering LDL &lt;70 mg/dL or using high-dose statins is reasonable. If baseline LDL is 70–100 mg/dL, lowering LDL to &lt;70 mg/dL is reasonable. When TG are 200–499 mg/dL, lowering non-HDL &lt;100 mg/dL is reasonable. Niacin or fibrates can be used to lower non-HDL after LDL therapy is begun. Omega-3 fish oil, 1 g/d is reasonable. Greater amounts (&gt;2.5/d) are needed for elevated TG levels.</td>
<td>I (A)</td>
<td>Intensify therapy to reach 30%–40% reduction in high-risk patients, or &lt;70 mg/dL. The less dietary TFA, the better.</td>
</tr>
<tr>
<td></td>
<td>TG &gt;500 mg/dL should be addressed first to avoid pancreatitis with fibrates or niacin.</td>
<td>I (C)</td>
<td>A somewhat greater intake may improve results, with maximum reduction of about 9% from each maneuver.</td>
</tr>
<tr>
<td>Weight control</td>
<td>Keep BMI between 18.5–24.0 kg/m². Aim for a 10% reduction first. Be persistent and measure waist circumference. If it is ≥40” (102 cm) in men or 35” (89 cm) in women, consider MetS, especially in men with waists 37–40” (94–102 cm) with genetic insulin resistance.</td>
<td>I (B)</td>
<td>Aggressive LDL lowering is being favored in many different clinical situations, but still leaves unacceptable residual risk.</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Recommend 30–60 min of moderate-intensity aerobic activity, 7 d/wk, a minimum of 5 d/wk, supplemented by an increase in daily activities. An activity history should be recorded, and an exercise test is performed to guide the exercise prescription. CR programs should be recommended for at-risk patients such as recent ACS or revascularization, or HF. Resistance training 2 d/wk may be reasonable.</td>
<td>I (B)</td>
<td>Although LDL remains the official primary target, non-HDL better incorporates the atherogenicity of other particles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iib (C)</td>
<td>3 days of strength training 45–60 min each session is usually the eventual goal if medically appropriate.</td>
</tr>
</tbody>
</table>

(Continued)
### Table 7 (Continued)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Recommendations</th>
<th>COR/LOE</th>
<th>Comments (not part of the guidelines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Keep HbA1c levels “near normal”</td>
<td>I (B)</td>
<td>ACCORD and other studies have recently modified views on the merits of very tight control. HbA1c guidelines from the ADA remain intact presently.</td>
</tr>
<tr>
<td></td>
<td>Reduction of other risk factors (weight, physical activity, dyslipidemia, and BP should be vigorously pursued as recommended).</td>
<td>I (B)</td>
<td>See discussion above concerning β blockers.</td>
</tr>
<tr>
<td>β blockers</td>
<td>Begin and continue indefinitely in all patients with prior AMI, ACS, or LV dysfunction with or without HF symptoms unless contraindicated.</td>
<td>I (A)</td>
<td>Use in primary prevention is controversial.</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>72–162 mg aspirin should be used in all patients and be continued indefinitely unless contraindicated. Use with warfarin, and clopidogrel may increase bleeding and should be monitored.</td>
<td>I (B)</td>
<td>Genetic variation in responsiveness is now of clinical importance. Use of PPis with clopidogrel is debated, and there is an FDA warning.</td>
</tr>
<tr>
<td>RAA system blockers</td>
<td>ACEI should be used in all patients with LVEF ≤ 40% in all patients and in those with HTN, DM, or CKD. ARB should be used for those with HTN with indications but who cannot tolerate ACEI, have HF, or are post-MI with LVEF ≤ 40%. Aldosterone blockers should be used in post-MI patients without creatinine &gt; 2.5 mg/dL in men, &gt; 2 mg/dL in women, or K+ &gt; 5 mEq/L, who are receiving adequate doses of an ACEI and a β-blocker, have LVEF ≤ 40%, and have either DM or HF. ACEI for patients who are not low risk, ie, normal LVEF and in whom risk factors are controlled and revascularization has been performed.</td>
<td>I (A)</td>
<td>For patients who have not sustained an AMI, use of ACEI or ARB in angina patients is not established.</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Influenza vaccination—recommended annually.</td>
<td>I (B)</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** There are 5 treatments that are considered class I (A), ie, should be done in all patients. There are no lifestyle recommendations that are I (A), and specific diet changes are not addressed. Currently available data concerning diet and lifestyle do not permit such classifications, but are potent therapies. 

COR, classifications of recommendations is as follows: class I, benefit > > > risk, and treatment should be done; class IIa, benefit > > risk, and it is reasonable; class IIb, benefit ≥ risk, and it may be considered; class III, benefit ≤ risk, and the treatment should not be done since it is not helpful and may harm. Class III items have been omitted. LOE, level of evidence, an estimate of certainty of treatment effect, is as follows: level A, useful in different subpopulations, with general consistency of direction and magnitude of effect; level B, only 2 to 3 subpopulations or risk strata have been evaluated; level C, limited, with 1 to 2 subpopulations evaluated. Classification as levels B or C does not imply ineffectiveness or weakness of the recommendation, simply that clinical trials have not been performed.

**Abbreviations:** ACC, American College of Cardiology; AHA, American Heart Association; COR, classifications of recommendations; LOE, level of evidence; BP, blood pressure; DM, diabetes mellitus; CKD, chronic renal disease; CHD, coronary heart disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LDL, low-density lipoprotein; TFA, trans fatty acids; TG, triglycerides; HDL, high-density lipoprotein; BMI, body mass index; SCD, sudden cardiac death; CR, supervised cardiac rehabilitation programs; ACS, acute coronary syndrome; HF, heart failure; ADA, American Diabetes Association; AMI, acute myocardial infarction; PPis, proton pump inhibitors; FDA, Food and Drug Administration; RAA, renin-angiotensin-aldosterone; ACEI, angiotensin-converting enzyme inhibitor; LVEF, left ventricular ejection fraction; HTN, hypertension; MI, myocardial infarction; K+, serum potassium level.

Unstable angina/NSTEMI, exercise testing and the ACC/AHA/SCAI updates on PCI.

Revascularization

Revascularization is a mechanical treatment for flow-limiting coronary obstructive lesions in order to relieve myocardial ischemia. In 2006, about 1,313,000 PCI procedures and 448,000 CABG surgeries were performed in the United States. Many cardiologists, surgeons, and indeed, patients believe that for angina and ACS, revascularization with PCI or CABG—when appropriate—are the preferred treatments. There is little question that in high-risk ACS patients a routine invasive strategy produces the best outcomes, but thresholds have been unclear for some patients with chronic angina. About 85% of the PCIs performed are elective, 25% are in patients with chronic stable angina, and approximately half are in patients above 65 years of age. Although no hard data are available, estimates of those who are asymptomatic range from 12% to 25%. In 2004, only 44% of elderly patients underwent a noninvasive study prior to referral for PCI, currently part of evidence-based guidelines. PCI

The ACC/AHA guidelines for managing patients with chronic stable angina recommend PCI in high-risk patients as determined by noninvasive testing or for patients in whom
optimal medical treatment has failed. Accordingly, there are essentially 2 indications: either for relief of pain and disability or to prolong or save lives (Table 8).

Although several small trials prior to 2004 did confirm that PCI improved chest pain frequency and short-term exercise tolerance in patients with chronic angina, they failed to show that PCI either improved survival or prevented subsequent MI. In addition, there was significant persistence of angina and only minor reduction in the number of antianginal medications after the procedure. A meta-analysis of 11 randomized studies involving 2,950 patients with stable CAD treated with PCI showed no improvement in mortality, MI, or need for further revascularization, compared with medical management.

The COURAGE trial compared outcomes in patients with chronic angina treated with PCI together with optimal medical therapy (OMT), the PCI group, and patients treated with OMT alone, the OMT group. The primary outcome was all-cause mortality or nonfatal MI during a follow-up period of 2.5–7.0 years (median, 4.6 years). The study enrolled 2,287 patients with entry criteria of (1) stenosis of at least 70% in at least 1 proximal epicardial coronary artery, and objective evidence of myocardial ischemia (substantial changes in ST-segment depression or T-wave inversion on the resting ECG or inducible ischemia with either exercise or pharmacologic vasodilator stress) or (2) at least 1 coronary stenosis of at least 80% and classic angina without provocative testing. Exclusion criteria included an overtly positive stress test, CCS class IV angina, refractory HF or EF < 30%, revascularization within the prior 6 months, or coronary anatomy that precluded successful PCI. Patients who underwent PCI received aspirin and clopidogrel. Medical therapy consisted of long-acting metoprolol, isosorbide mononitrate, and amlodipine in various combinations, with either losartan or lisinopril for secondary prevention. Therapy to lower LDL to 60–85 mg/dL (1.55–2.20 mmol/L) with simvastatin and/or ezetimibe was followed by attempts to raise HDL > 40 mg/dL (1.03 mmol/L) and lower TG < 150 mg/dL (1.69 mmol/L) with exercise, niacin, and/or fibrates. Finally, in patients undergoing PCI, the goals were primary lesion revascularization, then total revascularization if possible. Angiographic success was defined as normal coronary blood flow and <50% stenosis in the luminal diameter after balloon angioplasty and <20% after stent implantation. Clinical success was angiographic success plus the absence of an in-hospital MI, emergency CABG, or death.

The study found that the PCI group and the OMT group did not differ significantly as far as the composite end point of death, MI, stroke, and hospitalization for ACS or for MI. Mortality for the 2 groups was 7.6% and 8.3%, respectively. Additional revascularization for angina refractory to OMT or for worsening ischemia on noninvasive testing was necessary in 21.1% of patients in the PCI group and in 32.6% in the OMT group. In other words, about one-third of the OMT group crossed over. Moreover, in subgroups with multivessel disease (67% of patients), with previous MI or diabetes, the primary end point was no different between treatment groups. Although there was an increase in angi-na-free status in patients undergoing PCI at 1 and 3 years, at 4.6 years the percentage of angina-free patients was 74% in the PCI group and 72% in the OMT group. In summary, the COURAGE trial found that PCI with OMT was not superior to OMT alone in preventing MI or death in symptomatic or asymptomatic patients with chronic angina and similar inclusion and exclusion criteria. In patients who have left main coronary artery lesions, who are unstable, or in whom OMT has failed, PCI would of course be preferred.

Limitations in COURAGE trial include a preponderance of men (85%) and insufficient numbers of patients with EFs between 30% and 50%. Since drug-eluting stents (DES) were unapproved until the final 6 months of the study, most stents were bare-metal (BMS). DES might have lowered the rate of repeat revascularization, which is found in about 25% of BMS placements. At the same time, however, use of DES would have introduced the possibility of associated late stent thromboses, although now of less concern than when the issue was initially evaluated.

It should be noted that ranolazine was not used in the COURAGE trial as part of the anti-ischemic protocol. In the MERLIN-TIMI 36 trial discussed above, a number of patients enrolled had chronic angina resembling those in the

Table 8 ACC/AHA recommendations for PCI in patients with chronic stable angina

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-vessel or 3-vessel disease with significant proximal LAD lesions, with anatomy enabling catheter-based therapy and normal LVF; diabetes under treatment excluded.</td>
<td>I (B)</td>
<td></td>
</tr>
<tr>
<td>1-vessel or 2-vessel disease without significant proximal LAD lesions, with high risk on noninvasive testing and a large area of viable myocardium.</td>
<td>I (B)</td>
<td></td>
</tr>
<tr>
<td>Prior PCI with either recurrence of stenosis or high risk on noninvasive testing.</td>
<td>II (C)</td>
<td></td>
</tr>
<tr>
<td>Failure of optimum medical therapy and with acceptable risk for revascularization procedure.</td>
<td>II (B)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; PCI, percutaneous coronary intervention; LOE, level of evidence; LAD, left anterior descending coronary artery; LVF, left ventricular function.
Based upon MERLIN-TIMI 36 trial, it is likely that ranolazine not only has a place in OMT for stable angina but also possibly for chest pain associated with ACS as well. Just as ranolazine does not change the natural history of chronic stable angina, it does not prevent MI or death in ACS. In the COURAGE study, a subset of patients continued to have angina despite OMT with PCI. Similarly, a number of patients experienced angina 1 year after PCI or CABG, indicating a need for additional therapies.

Although the COURAGE trial was regarded as practice-changing and a basis for recommending OMT as initial therapy for stable angina, the greater significance of the findings are that lifestyle changes and OMT have been underestimated and are more powerful than previously believed. The COURAGE trial also indicates that in stable patients, deferring intervention while under OMT is a viable approach, which does not significantly raise risk. Further, COURAGE data are consistent with current views about the pathogenesis of stable angina and ACS (see part I of these articles for a brief discussion of the pathology).

CAD is a diffuse disease, and OMT is a systemic therapy to prevent widespread atherosclerosis, and, when aggressive, is believed to stabilize plaques wherever they are. When fixed obstructive lesions can be visualized in epicardial vessels and coronary flow is restored, angina may be relieved. In contrast, ACS is caused by coronary thrombosis resulting from rupture of unstable, vulnerable plaque with thin fibrous caps, especially <65 µm, infiltrated by macrophages, with large necrotic cores, containing relatively less collagen matrix and smooth muscle. Not prone to expand toward the lumen, they are generally nonflow-limiting, and pathologically, may occur at areas other than significant stenoses, in lesions that may not be visualized on angiography. In fact, some data show risk for MI is unrelated to severity of stenoses. Therefore, opening discrete stenoses using PCI, a focal rather than diffuse therapy, would not be expected to affect vulnerable plaques that might rupture and cause future MI or deadly events. PCI adequately clears amenable fixed coronary obstructions but does not lower the burden of diffuse histological coronary atherosclerosis or the molecular pathogenesis. Reciprocally, aggressive lipid lowering with statins is more effective in reducing cardiac events than it is in causing regression of tight stenoses. Presently, it is not clinically possible to reliably locate or predict rupture in vulnerable plaques. Obviously, there is much to be learned.

An editorial accompanying COURAGE noted that the overall 4.6-year rate of MI was about 19% and mortality was 8% in both study groups. The 2.8% periprocedural MI was higher than anticipated, but included patients with prior PCI and multiple lesions that were dilated. In general, PCI is associated with a 1.27% risk of mortality, ranging from 0.65% in elective PCI to 4.81% in STEMI patients, about 2%–5% periprocedural MI, and <1% emergent CABG for a complication.

Post-COURAGE analysis suggested that adding PCI to OMT would not be cost-effective. A QoL analysis found that the improvement in QoL from adding PCI to OMT was too small to be clinically important and that PCI was not always necessary for the relief of symptoms. An additional specified subset analysis of COURAGE confirmed the original findings in the elderly. Other commentaries followed with supporters and opponents about the validity of the COURAGE trial. Is it realistic that a patient with angina and 80% obstruction in 2 of 3 coronary arteries be medically treated rather than stented? A nuclear-imaging substudy using SPECT suggested that patients with moderate to severe ischemia benefited more through PCI than OMT. Design flaws, use of BMS rather than DES, suboptimal PCI, and unrealistically good medical care not representative of actual patient services were also cited in the failure of PCI to outperform OMT. A release of the details in COURAGE revealed the extraordinary efficiency and aggressive nurse case management used, with most medications supplied without cost. Organization, function, and funding of most medical practices are simply not able to deliver the intensity of medical therapy afforded to the participants in the COURAGE trial. For this reason, the reproducibility of COURAGE results in the general population is unknown. Preventive care only works if it is done, and adherence to multiple drugs, lifestyle changes, and scheduled tests, given the documented poor history of patients thus far with respect to risk reduction pharmacy and behavioral improvements, are an unrealistic expectation.

In the midst of a strong defense of the COURAGE trial, there has been mention of excessive numbers of PCI procedures that may not be evidence-based. It is estimated that one-third of PCIs now performed would be COURAGE-eligible to forego the procedure and follow OMT. If this occurred, great attention to adherence to OMT would be necessary, using a case management system similar to the one used in the COURAGE trial. Issuing prescriptions using the current paradigm of patient care would be insufficient. Care management systems are feasible and effective when used with high-risk cardiovascular patients. They improve health behaviors and adherence to prescribed medications and monitoring, with projected lower rates of hospitalizations and overall cost.
A meta-analysis of 17 randomized trials comparing PCI and medical therapy in patients with angina but not ACS found a 20% reduction in odds ratio for all-cause death in a PCI group,\textsuperscript{230} prompting a call for a new clinical trial with greater power than COURAGE, but simultaneously recommending more aggressive medical therapy for patients with chronic angina.\textsuperscript{236}

In summary, OMT and PCI are complementary therapies with somewhat overlapping but specific indications, which are not mutually exclusive.

**CAD epicardial lesion burden, prognosis, and COURAGE**

Some authors reason that since ischemia – obstructive lesions as detected by perfusion imaging\textsuperscript{237,238} – worsens prognosis, the extent of stenosis may correlate with mortality;\textsuperscript{239} and revascularization through PCI or CABG increases survival,\textsuperscript{240} then PCI should be more effective in trials such as COURAGE.\textsuperscript{241}

A relatively short follow-up in relation to the long incubation period and slow regression of atherosclerosis, limited numbers of patients in studies, and unnecessarily complex PCI techniques are cited as possible causes of the disparity.\textsuperscript{241}

Indeed, cardiac risk and prognosis of patients with CAD are generally related to the burden of atherosclerosis as it is customarily tallied.\textsuperscript{5} The survival rates of patients with CAD (Table 9) follow both severity and location of lesions.\textsuperscript{242} In the years since these data were gathered, medical therapy has advanced significantly and is reflected in improved survival, but the relationship between severity of obstructions and prognosis remains valid.\textsuperscript{243,244}

### Table 9

<table>
<thead>
<tr>
<th>Extent of CAD</th>
<th>5-year survival (%)</th>
<th>Prognostic weight (0–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-vessel disease, 75%</td>
<td>93</td>
<td>23</td>
</tr>
<tr>
<td>&gt;1-vessel disease, 50%–74%</td>
<td>93</td>
<td>23</td>
</tr>
<tr>
<td>1-vessel disease, ≥95%</td>
<td>91</td>
<td>32</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>88</td>
<td>37</td>
</tr>
<tr>
<td>2-vessel disease, both ≥95%</td>
<td>86</td>
<td>42</td>
</tr>
<tr>
<td>1-vessel disease, ≥95% proximal LAD</td>
<td>83</td>
<td>48</td>
</tr>
<tr>
<td>2-vessel disease, ≥95% LAD</td>
<td>83</td>
<td>48</td>
</tr>
<tr>
<td>2-vessel disease, ≥95% proximal LAD</td>
<td>79</td>
<td>56</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>79</td>
<td>56</td>
</tr>
<tr>
<td>3-vessel disease, ≥95% in at least 1</td>
<td>73</td>
<td>63</td>
</tr>
<tr>
<td>3-vessel disease, 75% proximal LAD</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>3-vessel disease, ≥95% proximal LAD</td>
<td>59</td>
<td>74</td>
</tr>
</tbody>
</table>

**CABG**

Classic recommendations for CABG surgery include patients with left main coronary lesions, symptomatic 3-vessel disease, critical (≥75%) stenoses in all 3 major coronary arteries and LVEF < 50%, diabetics with multivessel disease, and very complex lesions. Generally, CABG produces lower rates of repeat revascularization and longer survival times than PCI. The risks of CABG surgery include 1%–3% death, 5%–10% perioperative MI, 10%–20% vein graft failure (first year), and a low risk of perioperative stroke and cognitive dysfunction. About 75% of patients remain angina-free or free of cardiac events after 5 years. Selected guidelines for revascularization are summarized in Table 10.

How well do catheterization cardiologists follow ACC/AHA guidelines when recommending PCI or CABG? About 94% of patients in whom PCI was indicated (according to the guidelines) were recommended for PCI, but 93% of the patients who satisfied indications for either PCI or CABG were recommended for PCI.\textsuperscript{245} In those for whom the guidelines recommend CABG, 53% were recommended for CABG, and 34% were recommended for PCI. Finally, in patients for whom neither PCI nor CABG were indicated, 21% were recommended for PCI.

As a supplement to guidelines, appropriateness criteria for coronary revascularization were issued to help guide

### Table 10

**Selected ACC/AHA guidelines for revascularization with CABG**

<table>
<thead>
<tr>
<th>Recommendations for CABG</th>
<th>Class and level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant left main coronary disease.</td>
<td>I (A)</td>
</tr>
<tr>
<td>Triple-vessel disease; survival benefit is greater in patients with LVEF &lt; 50%.</td>
<td>I (A)</td>
</tr>
<tr>
<td>Double-vessel disease with significant proximal LAD disease and either LVEF &lt; 50% or demonstrable ischemic on noninvasive testing.</td>
<td>I (A)</td>
</tr>
<tr>
<td>1- or 2-vessel disease without significant proximal LAD lesions, with high risk on noninvasive testing and a large area of viable myocardium.</td>
<td>I (B)</td>
</tr>
<tr>
<td>1- or 2-vessel disease without significant proximal LAD lesions who have survived SCD or sustained VT.</td>
<td>I (C)</td>
</tr>
<tr>
<td>Failure of optimum medical therapy and with acceptable risk for a revascularization procedure.</td>
<td>I (B)</td>
</tr>
<tr>
<td>1- or 2-vessel disease without significant proximal LAD Lesions, but with a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing.</td>
<td>Ia (B)</td>
</tr>
<tr>
<td>Single vessel disease with significant proximal LAD disease.</td>
<td>Ia (B)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACC/AHA, American College of Cardiology/American Heart Association; CABG, coronary artery bypass surgery; LAD, Left anterior descending; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death; VT, ventricular tachycardia.
clinicians with input from 6 medical societies.\textsuperscript{246} The appropriateness criteria drew from at least 5 individual guidelines concerning imaging, exercise testing, and specific therapies, but it also blended the experience of experts into the text. The technical panel composed of cardiologists, surgeons, interventionalists, radiologists, internists, and health-services researchers rated some 180 clinical scenarios for appropriateness in performing revascularization in this project. Most of the categories considered appropriate are listed in Tables 8 and 10. Other noteworthy reviews concerning effectiveness of PCI and CABG for CAD include

**Conclusion**

Advances in the understanding of ischemic heart disease and improved technology during the last decade have been striking. These have occurred in the areas of epidemiology, risk assessment, pharmacological risk factor reduction, mechanisms of disease, early detection, imaging, interventional cardiology, electrophysiology and devices, and surgery.

Cardiovascular disease is the leading cause of death in the United States, yet it is a preventable disease. The current epidemic of obesity threatens to reverse recent advances in controlling this foe. For this reason, bold proposals and calls for implementation of population-wide lifestyle and environmental changes are being made.

In the individual patient, the clinician has a broader spectrum of potent tools than ever before at his or her disposal to prevent and manage chronic stable angina. Applied in an evidence-based manner, current therapies permit patients to live pain-free, participate in physical and social activities, and enjoy a fuller, longer life.

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**References**


