

# 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,  $\beta$ -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,  $\beta$ -blockers, calcium channel blockers, ranolazine, refractory angina, prevention of heart disease, coronary artery bypass surgery, primordial prevention, statin drugs

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## 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.<sup>1</sup> 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.<sup>2</sup> Reasons for its near-universal neglect are complex and only partially appreciated, but remain unsolved despite widespread praise for its value.<sup>3</sup> 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,  $\beta$ -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.<sup>4,5</sup> 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<sup>1</sup>). 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 denitrication 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.<sup>6</sup> Similarly, NO activates platelet cGMP to reduce intraplatelet calcium concentrations, impairing platelet activation to a degree.<sup>7</sup> In effect, nitrates act as exogenous NO donors, in addition to raising endogenous production of NO.<sup>8</sup> 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.<sup>9,10</sup> Finally, nitroglycerin redistributes coronary blood flow from normally perfused areas of myocardium to ischemic zones.<sup>11,12</sup> 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.<sup>13</sup>

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).<sup>14</sup> 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.<sup>15</sup> Tolerance develops within 12–24 hours, which may be avoided with a nitrate-free period of about 8 hours each day.<sup>16,17</sup> Patients using patches must remember to remove them at night. Proposed mechanisms for tolerance<sup>18</sup> 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;<sup>19</sup> (2) impaired bioactivation of nitroglycerin resulting from limited availability of sulfhydryl groups;<sup>20</sup> (3) inhibition of

mitochondrial aldehyde dehydrogenase, which regulates biotransformation of nitrates to NO;<sup>21,22</sup> (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 I $\beta$ , an isoform of the predominant type cGKI $\alpha$ , much less efficient in activating the large-conductance Ca<sup>2+</sup>-dependent potassium channel (BK channel), which is responsible for vascular smooth muscle relaxation.<sup>23,24</sup>

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.<sup>5,25</sup> 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  $\beta$ -blocker, diltiazem, or verapamil is usually advised.<sup>5</sup> When used together with  $\beta$ -blockers or CCBs, anti-ischemic effects may be synergistic.<sup>5</sup> Nitrates and CCBs are effective in Prinzmetal's or vasospastic angina, whereas response to  $\beta$ -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.

### $\beta$ -blockers

Adrenergic receptors are a class of G-protein coupled receptors stimulated by the catecholamines, and those in the  $\beta$ -family have most effects mediated by adenylyl cyclase. Specific  $\beta_1$  effects include increased heart rate and contractility, increased

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

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

<sup>a</sup>Requires 8–10 h nitroglycerin free recovery period because of tolerance; <sup>b</sup>May exhibit tolerance in 7–8 h; <sup>c</sup>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.  $\beta_2$ -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.<sup>5</sup> 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  $\beta_1$  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.<sup>26</sup>

$\beta$ -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.<sup>27</sup> 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

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

<sup>a</sup>Drugs with partial agonist activity are not included; <sup>b</sup>Combined  $\alpha$ -blocking and  $\beta$ -blocking activities; <sup>c</sup>Combined  $\alpha$ -blocking,  $\beta_1$ -blocking, and  $\beta_2$ -blocking activities;

<sup>d</sup>Antiarrhythmic class I effect; <sup>e</sup>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  $\beta$ -blockers due to an unopposed  $\alpha$ -adrenergic effect. Patients with cocaine-induced coronary vasoconstriction may also react adversely when given  $\beta$ -blockers, with hypertension and seizures. Similarly, since  $\beta$ -adrenergic receptors may be up-regulated when patients are treated with  $\beta$ -blockers, these agents should not be abruptly discontinued, lest rebound vasoconstriction precipitate unstable angina or even MI.<sup>28,29</sup> Patients with asthma, claudication, or HF whose symptoms increase with  $\beta$ -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  $\beta$ -blockers. In these instances, a solution involving adjustments in exercise details, goals, and  $\beta$ -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.

DHPs lower BP and myocardial wall tension to reduce myocardial oxygen consumption. A rise in coronary blood

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.<sup>5,30-32</sup> Amlodipine, in particular, may have some independent action in relieving diastolic dysfunction other than a reduction in BP.<sup>33</sup>

CCBs find clinical use in patients who cannot tolerate  $\beta$ -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.<sup>34</sup> When DHPs are used in combination with  $\beta$ -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,  $\beta$ -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.<sup>35,36</sup> Verapamil acts chiefly through a negative inotropic action, with less associated reflex tachycardia;

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

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

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



**Table 4** CCBs used for ischemic heart disease

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

<sup>a</sup>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.

diltiazem has greater vasodilatory actions than verapamil. 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.<sup>35</sup> Use of non-DHPs after complex MIs should be avoided because of the possibility of HF as well.<sup>37,38</sup> 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  $\beta$ -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 CYP4A enzyme in the liver and, therefore, may raise levels of statins and many other drugs, which may be overlooked.<sup>39</sup> 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,  $\beta$ -blockers, and CCBs,  $\beta$ -blockers lowered the frequency of anginal attacks better than CCBs, not including amlodipine and felodipine.<sup>30</sup> The combination of  $\beta$ -blockers with nitrates is favored because they both lower myocardial oxygen demand and raise subendocardial blood flow through different mechanisms, whereas the  $\beta$ -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  $\beta$ -blockers (Table 5).  $\beta$ -blockers combined with DHP CCBs improve exercise duration more than either alone and

**Table 5** Cardiovascular effects of nitrates, CCBs, and  $\beta$ -blockers in angina

Variable	Nitrates	Calcium channel blockers	$\beta$ -blockers
Collateral blood flow	$\uparrow\uparrow$	$\uparrow\uparrow$	$\rightarrow$
Endomyocardial to epimyocardial flow	$\uparrow\uparrow$	$\uparrow$	$\uparrow$
Heart rate	$\uparrow$ (reflex)	$\uparrow\downarrow$ (reflex)	$\downarrow\downarrow$
Left ventricular wall tension	$\downarrow\downarrow$	$\downarrow$	$\uparrow\rightarrow$
Myocardial contractility	$\uparrow$ (reflex)	$\uparrow\downarrow\rightarrow$ (reflex)	$\downarrow\downarrow$
Cardiac work	$\downarrow\downarrow$	$\downarrow\downarrow$	$\downarrow\downarrow$

**Abbreviation:** CCBs, calcium channel blockers.

tolerance is acceptable,<sup>40</sup> but the combination of  $\beta$ -blockers with verapamil is still generally to be avoided. On the other hand, amlodipine along with  $\beta$ -blockers is more effective than either one alone<sup>41</sup> 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.<sup>42</sup> About 5%–15% of patients are refractory to “triple therapy”.<sup>43</sup>

### 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.<sup>44</sup> Use is associated with improved myocardial function during ischemia-reperfusion,<sup>45,46</sup> protection of myocardium during ischemia,<sup>44,47</sup> 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,<sup>48</sup> 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,<sup>49</sup> 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.<sup>50</sup> A dose of 10–40 mg twice daily controls 70%–80% of stable chronic angina patients, with an effect maintained for about 12 hours.<sup>51</sup> 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 “ $I_f$  current,” an important pacemaking current in SA node cells, to slow the rate of diastolic depolarization and lower heart rate.<sup>52</sup> 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.<sup>53,54</sup> In noninferiority trials, ivabradine compared well to atenolol<sup>55</sup> or amlodipine.<sup>56</sup> The BEAUTIFUL trial<sup>57</sup> 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<sup>58</sup> 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  $\beta$ -blockers for additional antianginal effect or used in patients who cannot take  $\beta$ -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  $\leq 10\%$  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,<sup>59</sup> partially inhibiting  $\beta$ -oxidation of fats by decreasing activity of mitochondrial enzyme 3-KAT.<sup>60,61</sup> The drug raises myocardial glucose utilization, prevents a decrease

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<sup>62</sup> without changes in heart rate, negative inotropic, or vasodilator actions. Trimetazidine may be added to ongoing therapy with  $\beta$ -blockers, CCBs, and nitrates with safety. The TIGER study<sup>63</sup> confirmed the usefulness of this agent in elderly patients resistant to traditional anti-ischemic agents with effects mediated through hemodynamic changes. A Cochrane review<sup>64</sup> 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.<sup>65–67</sup>

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.<sup>68</sup> 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 sarcolemmal  $\text{Na}^+/\text{K}^+$ -ATPase and sarcoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase (transfers calcium from the cytosol to the sarcoplasmic reticulum lumen). The potential energy stored in the electrochemical  $\text{Na}^+$  gradient established by the former usually furnishes the power for calcium removal from the intracellular to extracellular space by the  $\text{Na}^+/\text{Ca}^{2+}$  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.<sup>69</sup>

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 sodium current 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.<sup>70–73</sup>

Intracellular sodium ( $\text{Na}^+$ ) 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.<sup>70,74–76</sup> 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.<sup>77–80</sup> 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 postischemic 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.<sup>81,82</sup> 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.<sup>83–86</sup> 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.<sup>75,76,87</sup> 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,<sup>88</sup> 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 proarrhythmogenic 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.<sup>74</sup>

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.<sup>89</sup> 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.<sup>39,90</sup>
- Since verapamil inhibits P-glycoprotein in doses of  $\geq 360$  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<sub>c</sub> 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.<sup>91–93</sup>

Early ranolazine trials confirmed a significant prolongation in exercise duration to angina and to ST-segment depression (1 mm) in angina patients.<sup>94,95</sup> In the first of the 4 major clinical studies, the MARISA trial<sup>96</sup> 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<sup>97</sup> 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,<sup>98</sup> 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.<sup>99,100</sup> 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<sup>101</sup> 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,<sup>102,103</sup> 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 bolus followed by oral therapy or placebo. Ranolazine did not affect the composite of cardiovascular death, MI, or recurrent ischemia.<sup>102</sup> However, further analysis revealed a reduction in angina and improvement in exercise duration with an acceptable safety profile. The study also suggested an antiarrhythmic effect, and a small reduction in  $\text{Hb}_{\text{A1c}}$  was observed in diabetics. Confirming

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).<sup>104</sup> 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.<sup>105</sup>

### 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 multimechanistic), enhanced external counterpulsation (EECP) to raise myocardial perfusion, and angiogenesis through extracorporeal cardiac shock wave therapy (noninvasive), transmyocardial laser revascularization (invasive), or 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).<sup>106</sup>

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.<sup>107,108</sup> The simultaneous presystolic decompression in the cuffs reduces afterload so that the ejection fraction (EF) improves,<sup>109</sup> whereas the work of the heart diminishes.<sup>110</sup> 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<sup>111</sup> and reduced levels of inflammatory cytokines have also been identified.<sup>112</sup> It is believed that vasoactive moieties, including NO, vascular endothelial growth factor, and endothelin play a part in producing these effects.<sup>113</sup> The MULTicenter STudy of Enhanced External CounterPulsation (MUST-EECP) trial<sup>114</sup> 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<sup>115</sup> 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.<sup>116</sup> Approximately 62% of patients treated with EECP maintain benefits for 1 year, whereas 29% of patients sustain improvement for 24 months,<sup>117</sup> some even as much as 5 years.<sup>118</sup> Whether endurance of EECP effect is related to an increase in number and colony-forming capacity of circulating endothelial progenitor cells is unknown.<sup>119</sup>

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<sup>5</sup> (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.<sup>120–124</sup>

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.<sup>125–131</sup> SCS raises release of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid, lowering the amount of 2 excitatory amino acids, glutamate and aspartate, which in turn suppresses processing

of the nociceptive A $\delta$  and C nerve fibers. In addition, SCS also raises  $\beta$ -endorphin release, lowering pain perception.<sup>132</sup> Recent data, however, show that additional mechanisms also account for the effects of SCS, including sympatholytic activity under stress conditions<sup>133</sup> and changes in cerebral blood flow.<sup>134</sup> 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,<sup>135–140</sup> 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.<sup>141,142</sup> Recently, a 52% (range, 33%–65%) reduction in sympathetic activity was documented during SCS activity during heart rate variability recordings.<sup>143</sup>

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.<sup>144</sup> In the ESBY study,<sup>145</sup> 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 CABG 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.<sup>146</sup>

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%).<sup>139</sup> 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.<sup>147</sup> The typical SCS treatment consists of three 1-hour stimulations daily. The ACC/AHA guideline grade assigned is class IIb, LOE: B.<sup>5</sup> 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.<sup>148,149</sup>

Low-energy, electrohydraulic shock wave therapy is an additional option to induce neovascularization.<sup>150–152</sup> 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 therapy<sup>43,153,154</sup> 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)<sup>155</sup> 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 paper<sup>156</sup> identifying hypertension, hypercholesterolemia, and arrhythmias as risk factors, but also referring to smoking. A seminal paper that followed<sup>157</sup> 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.<sup>158</sup> 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.<sup>159</sup> 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.<sup>160</sup> 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 treated 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,<sup>161,162</sup> 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.<sup>163</sup> 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.<sup>164</sup>

### 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.<sup>160</sup> 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.<sup>165</sup> 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.<sup>166</sup> 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.<sup>167</sup> 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.<sup>168–179</sup> 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.<sup>180</sup> Pediatric data, pathological reports from the military, and other epidemiological studies suggest the typical incubation period may be on the order of  $2.0\text{--}3.3 \pm 1.8$  decades. Under ideal circumstances, lifestyle modifications should be optimized during this period.<sup>181</sup>

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.<sup>182</sup> 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<sup>183</sup> 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.<sup>184</sup> Shortly thereafter, the 2010 update of heart disease and stroke statistics<sup>185</sup> 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,<sup>186</sup> defining and setting 2020 impact goals for cardiovascular health promotion and disease reduction.

This unique document<sup>186</sup> 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<sup>a,166</sup>

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

<sup>a</sup>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.



lifestyles in a population that did not permit risk factors to develop, associated with ideal cardiovascular health, was called primordial prevention. This term was coined in 1978 by Strasser<sup>187</sup> to mean intervention that stopped the appearance of risk factors in a population. The same theme was featured at the Third International Heart Health Conference held in Singapore in 1998.

In addition, the 2020 goals statement,<sup>186</sup> 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.<sup>188</sup> 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”.<sup>186</sup> 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/m<sup>2</sup>.
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<sup>189</sup> 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.<sup>186</sup> 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;<sup>190</sup> 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,<sup>191,192</sup> 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<sup>193</sup> revised the full 2002 ACC/AHA Chronic Angina Guidelines,<sup>5</sup> 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,<sup>194</sup> guidelines written specifically for women,<sup>195</sup> guidelines for secondary prevention generally,<sup>196</sup> and European guidelines for prevention of heart disease.<sup>197–200</sup> Related guidelines of interest include those for

**Table 7** Selected recommendations from the ACC/AHA updated guidelines on risk reduction in patients with angina

Risk factor	Recommendations	COR/LOE <sup>a</sup>	Comments (not part of the guidelines)
Smoking	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.	I (B)	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.
Hypertension	BP should be kept <140/90 mmHg, or <130/90 mmHg in DM or CKD.	I (A)	Evidence at the ACC 2010 sessions raised doubts about the wisdom of tight BP control in DM. <sup>205,206</sup>
	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.	I (B)	New Joint National Conference 8 Guidelines for hypertension are expected late in 2011.
	For patients with established CHD, use $\beta$ blockers or ACE inhibitors first, then other agents.	I (C)	When a prior AMI has not occurred, ACE/ARB use is quite discretionary – see below.
Dyslipidemia	When baseline LDL $\geq$ 100 mg/dL, begin drugs with lifestyle measures.	I (A)	Intensify therapy to reach 30%–40% reduction in high-risk patients, or <70 mg/dL.
	Daily exercise, weight control, low-saturated fat diet <7%, reduce dietary TFA, and cholesterol intake <200 mg/d.	I (B)	The less dietary TFA, the better.
	If TG = 200–499 mg/dL, non-HDL should be <130 mg/dL.		
	Add plant stanols 2 g/d and/or soluble fiber >10 g/d.	IIa (A)	A somewhat greater intake may improve results, with maximum reduction of about 9% from each maneuver.
	Lowering LDL < 70 mg/dL or using high-dose statins is reasonable.	IIa (A)	Aggressive LDL lowering is being favored in many different clinical situations, but still leaves unacceptable residual risk.
	If baseline LDL is 70–100 mg/dL, lowering LDL to < 70 mg/dL is reasonable.	IIa (B)	
	When TG are 200–499 mg/dL, lowering non-HDL < 100 mg/dL is reasonable.	IIa (B)	Although LDL remains the official primary target, non-HDL better incorporates the atherogenicity of other particles.
	Niacin or fibrates can be used to lower non-HDL after LDL therapy is begun.	IIa (B)	
	Omega-3 fish oil, 1 g/d is reasonable. Greater amounts (>2.5/d) are needed for elevated TG levels.	IIb (B)	1 g fish oil means the sum of EPA + DHA, not total marine oil. Most people consume too little, even from supplements. More usually offers better protection against SCD. Omega-3 fats are pleiotropic.
Weight control	TG > 500 mg/dL should be addressed first to avoid pancreatitis with fibrates or niacin.	I (C)	
	Keep BMI between 18.5–24.0 kg/m <sup>2</sup> . Aim for a 10% reduction first. Be persistent and measure waist circumference. If it is $\geq$ 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.	I (B)	Sustained weight control, since there is no truly effective pharmacologic therapy, is most difficult to achieve without surgery, but it is fundamental to risk reduction.
Physical activity	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.	I (B)	
	Resistance training 2 d/wk may be reasonable.	IIb (C)	3 days of strength training 45–60 min each session is usually the eventual goal if medically appropriate.

(Continued)

**Table 7** (Continued)

Risk factor	Recommendations	COR/LOE <sup>a</sup>	Comments (not part of the guidelines)
Diabetes	Keep HbA <sub>1c</sub> levels “near normal”.  Reduction of other risk factors (weight, physical activity, dyslipidemia, and BP should be vigorously pursued as recommended).	I (B)	ACCORD and other studies have recently modified views on the merits of very tight control. <sup>39,207,208</sup> HbA <sub>1c</sub> guidelines from the ADA remain intact presently.
β blockers	Begin and continue indefinitely in all patients with prior AMI, ACS, or LV dysfunction with or without HF symptoms unless contraindicated.	I (A)	See discussion above concerning β blockers.
Antiplatelet agents	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.	I (A) I (B)	Use in primary prevention is controversial. Genetic variation in responsiveness is now of clinical importance. Use of PPIs with clopidogrel is debated, and there is an FDA warning.
RAA system blockers	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 >2.5 mg/dL in men, >2 mg/dL in women, or K <sup>+</sup> > 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.	I (A) I (B)	For patients who have not sustained an AMI, use of ACEI or ARB in angina patients is not established.
Vaccination	Influenza vaccination-recommended annually.	I (B)	

**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.

<sup>a</sup>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, risk ≥ benefit, 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<sup>+</sup>, serum potassium level.

unstable angina/NSTEMI,<sup>173,201,202</sup> exercise testing<sup>203</sup> and the ACC/AHA/SCAI updates on PCI.<sup>204</sup>

## 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.<sup>185</sup> 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,<sup>209</sup> 25% are in patients with chronic stable angina, and approximately half are in patients above 65 years of age.<sup>210</sup> 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.<sup>211</sup>

## 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.<sup>4</sup> 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 anti-anginal 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.<sup>212</sup>

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.<sup>213</sup> 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 were 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 angina-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,<sup>214–216</sup> although now of less concern than when the issue was initially evaluated.<sup>217–219</sup>

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<sup>4</sup>

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

**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.

COURAGE trial.<sup>102,103</sup> 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.<sup>220</sup> 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,<sup>221</sup> 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<sup>1</sup> 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  $\mu\text{m}$ , 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.<sup>222</sup> 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<sup>223</sup> 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,<sup>224</sup> 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.<sup>225</sup> 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.<sup>226</sup> An additional specified subset analysis of COURAGE confirmed the original findings in the elderly.<sup>227</sup> Other commentaries followed with supporters and opponents about the validity of the COURAGE trial.<sup>228–231</sup> 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.<sup>228</sup> 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.<sup>231</sup> A release of the details in COURAGE revealed the extraordinary efficiency and aggressive nurse case management used, with most medications supplied without cost.<sup>232</sup> 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.<sup>233</sup> 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.<sup>229</sup> It is estimated that one-third of PCIs now performed would be COURAGE-eligible to forego the procedure and follow OMT.<sup>230</sup> 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.<sup>232</sup> 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.<sup>234</sup>



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,<sup>235</sup> 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.<sup>236</sup>

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<sup>237,238</sup> – worsens prognosis, the extent of stenosis may correlate with mortality,<sup>239</sup> and revascularization through PCI or CABG increases survival,<sup>240</sup> then PCI should be more effective in trials such as COURAGE.<sup>241</sup> 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.<sup>241</sup>

Indeed, cardiac risk and prognosis of patients with CAD are generally related to the burden of atherosclerosis as it is customarily tallied.<sup>5</sup> The survival rates of patients with CAD (Table 9) follow both severity and location of lesions.<sup>242</sup> 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.<sup>243,244</sup>

**Table 9** Extent of CAD in nonresistance vessels, 5-year survival rate (%), and prognostic weight (0–100), based upon medical therapy only<sup>242</sup>

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

**Abbreviations:** CAD, coronary artery disease; LAD, Left anterior descending.

### 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.<sup>245</sup> 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<sup>5</sup>

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

**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.<sup>246</sup> 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 one by the Agency for Healthcare Research and Quality<sup>247</sup> and a recent narrative.<sup>248</sup>

## 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

- Kones R. Recent advances in the management of chronic stable angina I. Approach to the patient, diagnosis, pathophysiology, risk stratification, and gender disparities. *Vasc Health Risk Manag*. 2010;6:635–656.
- van Dam RM, Willett WC. Unmet potential for cardiovascular disease prevention in the United States. *Circulation*. 2009;120:1171–1173.
- Grundy SM. Prevention of atherosclerotic cardiovascular disease: why are the benefits of lifestyle therapies neglected? *Dialogues Cardiovasc Med*. 2005;11:73–86.
- Fox K, Garcia MA, Ardissino D, et al; for Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology; ESC Committee for Practice Guidelines (CPG). Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J*. 2006;27:1341–1381.
- Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina – summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol*. 2003;41:159–168.
- O'Rourke ST. Nitro vasodilators: pharmacology and use in the treatment of myocardial ischemia. *Am J Pharm Educ*. 2002;66:177–180.
- Lacoste LL, Theroux P, Lidon RM, et al. Antithrombotic properties of transdermal nitroglycerin in stable angina pectoris. *Am J Cardiol*. 1994;73(15):1058–1062.
- Gori T, Parker JD. Long-term therapy with organic nitrates. The pros and cons of nitric oxide replacement therapy. *J Am Coll Cardiol*. 2004;44:632–634.
- Schiffrin EL. Oxidative stress, nitric oxide synthase, and superoxide dismutase: a matter of imbalance underlies endothelial dysfunction in the human coronary circulation. *Hypertension*. 2008;51:31–32.
- Berges A, Nassauw LV, Timmermans JP, Vrints C. Role of nitric oxide during coronary endothelial dysfunction after myocardial infarction. *Euro J Pharmacol*. 2005;23:516(1):60–70.
- Bottcher M, Madsen MM, Randsbaek F, et al. Effect of oral nitroglycerin and cold stress on myocardial perfusion in areas subtended by stenosed and nonstenosed coronary arteries. *Am J Cardiol*. 2002;89:1019–1024.
- Tadamura E, Mamede M, Kubo S, et al. The effect of oral nitroglycerin on myocardial blood flow in various segments characterized by rest-redistribution thallium SPECT. *J Nucl Med*. 2003;44:745–751.
- Dumont L, LeLorier J, Stanley P, Chartrand C. Effect of nitroglycerin on regional myocardial blood flow following an experimental coronary spasm. *Angiology*. 1984;35(9):553–559.
- Abrams J. Nitroglycerin and long-acting nitrates in clinical practice. *Am J Med*. 1983;74:85–94.
- Thadani U. Nitrate tolerance, rebound, and their clinical relevance in stable angina pectoris, unstable angina, and heart failure. *Cardiovasc Drugs Ther*. 1997;10:735–742.
- Parker JO, Farrell B, Lahey KA, et al. Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. *N Engl J Med*. 1987;316:1440–1444.
- de Mols H, Glasser SP. Intermittent transdermal nitroglycerin therapy in the treatment of chronic stable angina. *J Am Coll Cardiol*. 1989;13:786–795.
- Daiber A, Mülsch A, Hink U, et al. The oxidative stress concept of nitrate tolerance and the antioxidant properties of hydralazine. *Am J Cardiol*. 2005;96(7B):25i–36i.
- Münzel T, Sayegh H, Freeman BA, Tarpey MM, Harrison DG. Evidence for enhanced vascular superoxide anion production in nitrate tolerance. A novel mechanism underlying tolerance and cross-tolerance. *J Clin Invest*. 1995;95(1):187–194.
- Jakschik B, Needleman P. Sulfhydryl reactivity of organic nitrates: biochemical basis for inhibition of glyceraldehyde-P dehydrogenase and monoamine oxidase. *Biochem Biophys Res Commun*. 1973;53:539–544.
- Daiber A, Oelze M, Wenzel P, et al. Nitrate tolerance as a model of vascular dysfunction: roles for mitochondrial aldehyde dehydrogenase and mitochondrial oxidative stress. *Pharmacol Rep*. 2009;61(1):33–48.
- Chen Z, Zhang J, Stamler JS. Identification of the enzymatic mechanism of nitroglycerin bioactivation. *Proc Natl Acad Sci U S A*. 2002;99:8306–8311.
- Knot HJ. Nitrate tolerance in hypertension: new insight into a century-old problem. *Circ Res*. 2003;93:799–801.

24. Gerzanich V, Ivanov A, Ivanova S, et al. Alternative splicing of cGMP-dependent protein kinase I in angiotensin-hypertension: novel mechanism for nitrate tolerance in vascular smooth muscle. *Circ Res*. 2003;93:805–812.
25. Cheitlin MD, Hutter AM Jr, Brindis RG, et al. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol*. 1999;33:273–282.
26. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). *Circulation*. 1994;90:762–768.
27. Freemantle N, Cleland J, Young P, et al.  $\beta$ -blockade after myocardial infarction: systematic review and meta regression analysis. *Br Med J*. 1999;318:1730–1737.
28. Miller RR, Olson HG, Amsterdam EA, et al. Propranolol withdrawal rebound phenomenon: exacerbation of coronary events after abrupt cessation of antianginal therapy. *N Engl J Med*. 1975;293:416–418.
29. Psaty BM, Koepsell TD, Wagner EH, et al. The relative risk of incident coronary heart disease associated with recently stopping the use of  $\beta$ -blockers. *JAMA*. 1990;263:1653–1657.
30. Heidenreich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. *JAMA*. 1999;281:1927–1936.
31. Nissen SE, Tuzcu EM, Libby P, et al; for the CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292:2217–2225.
32. Rice KR, Gervino E, Jarisch WR, Stone PH. Effects of nifedipine on myocardial perfusion during exercise in chronic stable angina. *Am J Cardiol*. 1990;65:1097–1101.
33. Tapp RJ, Sharp A, Stanton AV, et al; for the ASCOT Investigators. Differential effects of antihypertensive treatment on left ventricular diastolic function: an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Substudy. *J Am Coll Cardiol*. 2010;55:1875–1881.
34. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al; for the INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*. 2003;290:2805–2816.
35. Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet*. 2004;364:849–857.
36. Sierra C, Coca A. The ACTION study: nifedipine in patients with symptomatic stable angina and hypertension. *Expert Rev Cardiovasc Ther*. 2008;6(8):1055–1062.
37. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med*. 1996;335:1107–1114.
38. Goldstein RE, Bocuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation*. 1991;83:52–60.
39. Kones R. After cardiac surgery, how does nutrition fit in with risk factors? *J Parent Enteral Nutr*. 2010;34(2):163–167.
40. Leon MB, Rosing DR, Bonow RO, Epstein SE. Combination therapy with calcium-channel blockers and beta blockers for chronic stable angina pectoris. *Am J Cardiol*. 1985;55:69B–80B.
41. Waysbort J, Meshulam N, Brunner D. Isosorbide-5-mononitrate and atenolol in the treatment of stable exertional angina. *Cardiology*. 1991;79 Suppl 2:19–26.
42. Pepine CJ, Abrams J, Marks RG, et al. Characteristics of a contemporary population with angina pectoris. TIDES investigators. *Am J Cardiol*. 1994;74:226–231.
43. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. *Eur Heart J*. 2002;23:355–370.
44. Jahangir A, Terzic A, Shen WK. Potassium channel openers: therapeutic potential in cardiology and medicine. *Expert Opin Pharmacother*. 2001;2:1995–2010.
45. Zingman LV, Alekseev AE, Hodgson-Zingman DM, Terzic A. ATP-sensitive potassium channels: metabolic sensing and cardioprotection. *J Appl Physiol*. 2007;103(5):1888–1893.
46. Jahangir A, Terzic A. K(ATP) channel therapeutics at the bedside. *J Mol Cell Cardiol*. 2005;39:99–112.
47. John SA, Weiss JN, Xie LH, Ribalet B. Molecular mechanism for ATP-dependent closure for the K<sup>+</sup> channel Kir6.2. *J Physiol (Lond)*. 2003;552:23–34.
48. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet*. 2002;359:1269–1275.
49. Markham A, Plosker GL, Goa KL. Nicorandil: an updated review of its use in ischemic heart disease with emphasis on its cardioprotective effects. *Drugs*. 2000;60:955–974.
50. Ciampricotti R, Schotborgh CE, de Kam PJ, van Herwaarden RH. A comparison of nicorandil with isosorbide mononitrate in elderly patients with stable coronary heart disease: the SNAPE Study. *Amer Heart J*. 2000;139(5):939–943.
51. Simpson D, Wellington K. Nicorandil: a review of its use in the management of stable angina pectoris, including high-risk patients. *Drugs*. 2004;64:1941–1955.
52. Savelieva I, Cam AJ. I<sub>f</sub> inhibition with ivabradine: electrophysiological effects and safety. *Drug Saf*. 2008;31:95–107.
53. Borer JS, Fox K, Jaillon P, Lerebours G; for Ivabradine Investigators Group. Antianginal and antiischemic effects of ivabradine, an I<sub>f</sub> inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation*. 2003;107:817–823.
54. Lopez-Bescos L, Filipova S, Martos R. Long-term safety and efficacy of ivabradine in patients with chronic stable angina. *Cardiology*. 2007;108:387–396.
55. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K; for INITIATIVE Investigators. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J*. 2005;26:2529–2536.
56. Ruzyllo W, Tendera M, Ford I, Fox KM. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs*. 2007;67:393–405.
57. Fox K, Ford I, Steg PG, Tendera M, Ferrari R; for BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:807–816.
58. Tardif JC, Ponikowski P, Kahan T; for the ASSOCIATE Study Investigators. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4 month, randomized, placebo-controlled trial. *Eur Heart J*. 2009;30:540–548.
59. Marzilli M. Does timetazidine prevent myocardial injury after percutaneous coronary intervention? *Nat Clin Pract Cardiovasc Med*. 2008;5:16–17.
60. Stanley WC, Marzilli M. Metabolic therapy in the treatment of ischemia heart disease: the pharmacology of trimetazidine. *Fundam Clin Pharmacol*. 2003;17:133–145.
61. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res*. 2000;86:580–588.
62. Chazov EI, Lepakchin VK, Zharova EA, et al. Trimetazidine in angina combination therapy – the TACT study: trimetazidine versus conventional treatment in patients with stable angina pectoris in a randomized, placebo-controlled, multicenter study. *Am J Ther*. 2005;12:35–42.



63. Kolbel F, Bada V. Trimetazidine in geriatric patients with stable angina pectoris: the TIGER study. *Int J Clin Pract*. 2003;57:867–870.
64. Ciapponi A, Pizarro R, Harrison J. Trimetazidine for stable angina. *Cochrane Database of Systematic Reviews*. 2005;4:CD003614.
65. Tuunanen H, Engblom E, Naum A, et al. Trimetazidine, a metabolic modulator, has cardiac and extracardiac benefits in idiopathic dilated cardiomyopathy. *Circulation*. 2008;118:1250–1258.
66. Fragasso G, Pallosi A, Puccetti P, et al. A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. *J Am Coll Cardiol*. 2006;48:992–998.
67. Cera M, Salerno A, Fragasso G, et al. Beneficial electrophysiological effects of trimetazidine in patients with postischemic chronic heart failure. *J Cardiovasc Pharmacol Ther*. 2010;15(1):24–30.
68. Vicari RM, Chaitman B, Keefe D, et al; for Fasudil Study Group. Efficacy and safety of fasudil in patients with stable angina: a double-blind, placebo-controlled, phase 2 trial. *J Am Coll Cardiol*. 2005;46:1803–1811.
69. Barth AS, Tomaselli GF. Cardiac metabolism and arrhythmias. *Circ Arrhythm Electrophysiol*. 2009;3:327–335.
70. Belardinelli L, Antzelevitch C, Fraser H. Inhibition of late (sustained/persistent) sodium current: a potential drug target to reduce intracellular sodium dependent calcium overload and its detrimental effects on cardiomyocyte function. *Eur Heart J*. 2004;6:13–17.
71. Undrovinas AI, Belardinelli L, Undrovinas NA, et al. Ranolazine improves abnormal repolarization and contraction in left ventricular myocytes of dogs with heart failure by inhibiting late sodium current. *J Cardiovasc Electrophysiol*. 2006;17 Suppl 1:S169–S177.
72. Maltsev VA, Sabbah HN, Higgins RSD, Silverman N, Lesch M, Undrovinas AI. Novel, ultraslow inactivating sodium current in human ventricular cardiomyocytes. *Circulation*. 1998;98:2545–2552.
73. Pike MM, Kitakaze M, Marban E. Na-NMR measurement of intracellular sodium in intact perfused ferret hearts during ischemia and reperfusion. *Am J Physiol*. 1990;259:H1767–H1773.
74. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. *Circulation*. 2004;110:904–910.
75. Bers DM, Barry WH, Despa S. Intracellular Na<sup>+</sup> regulation in cardiac myocytes. *Cardiovasc Res*. 2003;57:897–912.
76. Murphy E, Cross H, Steenbergen C. Sodium regulation during ischemia versus reperfusion and its role in injury. *Circ Res*. 1999;84:1469–1470.
77. Kusuoka H, Marban E. Cellular mechanisms of myocardial stunning. *Annu Rev Physiol*. 1992;54:243–256.
78. Kusuoka H, Hurtado MCC, Marban E. Role of sodium/calcium exchange in the mechanism of stunning: protective effect of reperfusion with high sodium solution. *J Am Coll Cardiol*. 1993;21:240–248.
79. Imahashi K, Kusuoka H, Hashimoto K, Yoshioka J, Yamaguchi H, Nishimura T. Intracellular sodium accumulation during ischemia as the substrate for reperfusion injury. *Circ Res*. 1999;84:1401–1406.
80. Imahashi K, Mraiche F, Steenbergen C, Murphy E, Fliegel L. Overexpression of the Na<sup>+</sup>/H<sup>+</sup> exchanger and ischemia-reperfusion injury in the myocardium. *Am J Physiol Heart Circ Physiol*. 2007;292(5):H2237–H2247.
81. Taegtmeier H. Modulation of responses to myocardial ischemia: metabolic features of myocardial stunning, hibernation, and ischemic preconditioning. In: Dilsizian V, editor. *Myocardial Viability: A Clinical and Scientific Treatise*. Armonk, New York: Futura Publishing; 2000: 25–36.
82. Baker C, Rimoldi O, Camici P, et al. Repetitive myocardial stunning in pigs is associated with the increased expression of inducible and constitutive nitric oxide synthases. *Cardiovasc Res*. 1999;43(3):685–697.
83. Tani M, Neely JR. Role of intracellular Na<sup>+</sup> in Ca<sup>2+</sup> overload and depressed recovery of ventricular function of reperfused ischemic rat hearts. Possible involvement of H<sup>+</sup>-Na<sup>+</sup> and Na<sup>+</sup>-Ca<sup>2+</sup> exchange. *Circ Res*. 1989;65:1045–1056.
84. Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. *Heart*. 2006;92 Suppl 4:iv6–iv14.
85. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation*. 2006;113:2462–2472.
86. Wasserstrom JA, Sharma R, O'Toole MJ, et al. Ranolazine antagonizes the effects of increased late sodium current on intracellular calcium cycling in rat isolated intact heart. *J Pharmacol Exp Ther*. 2009;331(2):382–391.
87. Steenbergen C, Murphy E, Levy L, London RE. Elevation in cytosolic free calcium concentration early in myocardial ischemia in perfused rat heart. *Circ Res*. 1987;60:700–707.
88. Hayashida W, van Eyll C, Rousseau MF, Pouleur H. Effects of ranolazine on left ventricular regional diastolic function in patients with ischemic heart disease. *Cardiovasc Drugs Ther*. 1994;8:741–747.
89. Jerling M, Huan BH, Leung K, Chu N, Abdallah H, Hussein Z. Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem, or simvastatin during combined administration in healthy subjects. *J Clin Pharmacol*. 2005;45:422–433.
90. Ming EE, Davidson MH, Gandhi SK, et al. Concomitant use of statins and CYP3A4 inhibitors in administrative claims and electronic medical records databases. *J Clin Lipidol*. 2008;2:453–463.
91. Drew BJ, Ackerman MJ, Funk M, et al; for the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2010;55(9):934–947.
92. Sauer AJ, Moss AJ, McNitt S, et al. Long QT syndrome in adults. *J Am Coll Cardiol*. 2007;49:329–337.
93. Belardinelli L, Antzelevitch C, Vos MA. Assessing predictors of drug-induced torsade de pointes. *Trends Pharmacol Sci*. 2003;24:619–625.
94. Pepine CJ, Wolff AA. A controlled trial with a novel anti-ischemic agent, ranolazine, in chronic stable angina pectoris that is responsive to conventional anti-anginal agents. *Am J Cardiol*. 1999;84:46–50.
95. Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. *Am J Cardiol*. 2005;95:311–326.
96. Chaitman BR, Skettino SL, Parker JO, et al; for the MARISA Investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol*. 2004;43:1375–1382.
97. Chaitman BR, Pepine CJ, Parker JO, et al; for the CARISA Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA*. 2004;291:309–316.
98. Koren MJ, Crager MR, Sweeney M. Long-term safety of a novel antianginal agent in patients with severe chronic stable angina: the ranolazine open label experience (ROLE). *J Am Coll Cardiol*. 2007;49:1027–1034.
99. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106:793–800.
100. Alexander KP, Shaw LJ, Deling ER, Mark DB, Peterson ED. Value of exercise treadmill testing in women. *J Am Coll Cardiol*. 1998;32:1657–1664.
101. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine In Chronic Angina) trial. *J Am Coll Cardiol*. 2006;48:566–575.
102. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes. The MERLIN-TIMI 36 trial. *JAMA*. 2007;297(16):1775–1783.

103. Wilson SR, Scirica BM, Braunwald E, et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN – TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 trial. *J Am Coll Cardiol*. 2009;53(17):1510–1516.
104. Morrow DA, Scirica BM, Sabatine MS, et al. B-type natriuretic peptide and the effect of ranolazine in patients with non-ST-segment elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes 36) trial. *J Am Coll Cardiol*. 2010;55(12):1189–1196.
105. Califf RM, Shah SH, Newby LK. Biomarker bonanza. *J Am Coll Cardiol*. 2010;55:1197–1199.
106. Jax TW, Peters AJ, Khattab AA, Heintzen MP, Schoebel FC. Percutaneous coronary revascularization in patients with formerly “refractory angina pectoris in end-stage coronary artery disease” – Not “end-stage” after all. *BMC Cardiovasc Disord*. 2009;9:42. <http://www.biomedcentral.com/1471-2261/9/42>
107. Kones R. Mechanical circulatory assistance: present status. *NY State J Med*. 1974;74:516–531.
108. Michaels AD, Accad M, Ports TA, Grossman W. Left ventricular systolic unloading and augmentation of intracoronary pressure and Doppler flow during enhanced external counterpulsation. *Circulation*. 2002;106:1237–1242.
109. Arora RR, Lopes S, Saric M. Enhanced external counterpulsation improves systolic function by echocardiography in patients with coronary artery disease. *Heart Lung*. 2005;34:122–125.
110. Soran O. Treatment options for refractory angina pectoris: enhanced external counterpulsation therapy. *Curr Treat Options Cardiovasc Med*. 2009;11(1):54–60.
111. Bonetti PO, Barsness GW, Keelan PC, et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. *J Am Coll Cardiol*. 2003;41:1761–1768.
112. Casey DP, Conti CR, Nichols WW, Choi CY, Khuddus MA, Braith RW. Effect of enhanced external counterpulsation on inflammatory cytokines and adhesion molecules in patients with angina pectoris and angiographic coronary artery disease. *Am J Cardiol*. 2008;101(3):300–302.
113. Akhtar M, Wu GF, Du ZM, Zheng ZS, Michaels AD. Effect of external counterpulsation on plasma nitric oxide and endothelin-1 levels. *Am J Cardiol*. 2006;98:28–30.
114. Arora RR, Chou TM, Jain D, et al. The Multicenter Study of Enhanced External CounterPulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J Am Coll Cardiol*. 1999;33:1833–1840.
115. Michaels AD, Linnemeier G, Soran O, Kelsey SF, Kennard ED. Two-year outcomes after enhanced external counterpulsation for stable angina pectoris (from the International EECP Patient Registry [IEPR]). *Am J Cardiol*. 2004;93:461–464.
116. Lawson WE, Hui JC, Zheng ZS, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? *Cardiology*. 1996;87:271–275.
117. Erdling A, Bondesson S, Pettersson T, Edvinsson L. Enhanced external counterpulsation in treatment of refractory angina pectoris: two year outcome and baseline factors associated with treatment failure. *BMC Cardiovasc Disord*. 2008;8(1):39.
118. Lawson WE, Hui JC, Conn PF. Long term prognosis of patients with angina treated with enhanced external counterpulsation: five-year follow-up study. *Clin Cardiol*. 2000;23:254–258.
119. Barsheshet A, Hod H, Shechter M, et al. The effects of external counterpulsation therapy on circulating endothelial progenitor cells in patients with angina pectoris. *Cardiology*. 2008;110(3):160–166.
120. Braverman DL. Enhanced external counterpulsation: an innovative physical therapy for refractory angina. *Phys Med Rehabil*. 2009;1(3):268–276.
121. Cohn PF. EECP – new data on possible mechanisms of action. *Eur Heart J*. 2001;22:1363–1364.
122. Beaini Y, Morley C. EECP: a non-invasive therapy for refractory angina. *Practitioner*. 2009;253(1715):27–31.
123. Kumar A, Aronow WS, Vadnerkar A, et al. Effect of enhanced external counterpulsation on clinical symptoms, quality of life, 6-minute walking distance, and echocardiographic measurements of left ventricular systolic and diastolic function after 35 days of treatment and at 1-year follow up in 47 patients with chronic refractory angina pectoris. *Am J Ther*. 2009;16(2):116–118.
124. Campbell AR, Satran D, Zenovich AG, et al. Enhanced external counterpulsation improves systolic blood pressure in patients with refractory angina. *Am Heart J*. 2008;156(6):1217–1222.
125. Wu M, Komori N, Qin C, Farber JP, Linderth B, Foreman RD. Roles of peripheral terminals of transient receptor potential vanilloid-1 containing sensory fibers in spinal cord stimulation-induced peripheral vasodilation. *Brain Res*. 2007;1156:80–92.
126. Meyerson BA, Linderth B. Spinal cord stimulation: mechanisms of action in neuropathic and ischemic pain. In: Simpson BA, editor. *Electrical Stimulation and the Relief of Pain*. Vol 15. New York, NY: Elsevier Publishers; 2003:161–182.
127. Linderth B, Foreman RD. Mechanisms of spinal cord stimulation in painful syndromes: role of animal models. *Pain Med*. 2006;7:S14–S26.
128. Mannheimer C, Augustinsson LE, Carlsson CA, Manhem K, Wilhelmsson C. Epidural spinal electrical stimulation in severe angina pectoris. *Br Heart J*. 1988;59:56–61.
129. González-Darder JM, Canela P, González-Martínez V. High cervical spinal cord stimulation for unstable angina pectoris. *Stereotact Funct Neurosurg*. 1991;56:20–27.
130. Qin C, Farber JP, Linderth B, Shahid A, Foreman RD. Neuromodulation of thoracic intraspinal visceroreceptive transmission by electrical stimulation of spinal dorsal column and somatic afferents in rats. *J Pain*. 2008;9:71–78.
131. Linderth B, Meyerson B. Spinal cord stimulation: mechanisms of action. In: Burchiel K, editor. *Surgical Management of Pain*. New York, NY: Thieme Medical Publishers Inc; 2002:505–526.
132. Oldroyd KG, Harvey K, Gray CE, et al. Beta-endorphin release in patients after spontaneous and provoked acute myocardial ischaemia. *Br Heart J*. 1992;67:230–235.
133. Mannheimer C, Carlsson CA, Emanuelsson H, et al. The effects of transcutaneous electrical nerve stimulation in patients with severe angina pectoris. *Circulation*. 1985;527:11–16.
134. Haustvast RWM, Ter Horst GJ, de Jong BM, et al. Relative changes in regional cerebral blood flow during spinal cord stimulation in patients with refractory angina pectoris. *Eur J Neurosci*. 1997;9:1178–1183.
135. de Vries J, de Jongste MJL, Zijlstra F, et al. Long-term effects of electrical neurostimulation in patients with unstable angina. Refractory to conventional therapies. *Neuromodulation*. 2007;10:345–348.
136. Sanderson JE, Ibrahim B, Waterhouse D, et al. Spinal electrical stimulation for intractable angina – long-term clinical outcome and safety. *Eur Heart J*. 1994;15:810–814.
137. Andersen C, Enggard TP, Scherer C, et al. Spinal cord stimulation has a proven benefit on pain and quality of life in patients with angina pectoris when less invasive therapies have failed. *Neuromodulation*. 2006;9:314–319.
138. Eddicks S, Maier-Hauff K, Schenk M, et al. Thoracic spinal cord stimulation improves functional status and relieves symptoms in patients with refractory angina pectoris: the first placebo-controlled randomised study. *Heart*. 2007;93:585–590.
139. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20 year literature review. *J Neurosurg*. 2004;100:254–267.
140. Di Pede F, Lanza GA, Zuin G. Immediate and long-term clinical outcome after spinal cord stimulation for refractory stable angina pectoris. *Am J Cardiol*. 2003;91:951–955.
141. Chauhan A, Mullins PA, Thuraishingham G, et al. Effects of transcutaneous electrical nerve stimulation in coronary blood flow. *Circulation*. 1994;89:694–702.



142. Emanuelsson HC, Mannheimer F, Waagstein C, et al. Catecholamine metabolism during pacing-induced angina pectoris and the effect of transcutaneous electrical nerve stimulation. *Am Heart J.* 1987;114: 1360–1366.
143. Anselmino M, Ravera L, de Luca A, et al. Spinal cord stimulation and 30-minute heart rate variability in refractory angina patients. *Pacing Clin Electrophysiol.* 2009;32(1):37–42.
144. Hautvast RW, de Jongste MJ, Staal MJ, van Gilst WH, Lie KI. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. *Am Heart J.* 1998;136:1114–1120.
145. Mannheimer C, Eliasson T, Augustinsson LE. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris. The ESBY study. *Circulation.* 1998;97:1157–1163.
146. Erke O, Eliasson T, Norrsell H. Long-term effects of spinal cord stimulation and coronary artery bypass grafting on quality of life and survival in the ESBY study. *Eur Heart J.* 2002;23:1938–1945.
147. Eckert S, Dongas A, Güldner H, et al. Immediate and long-term clinical outcome after spinal cord stimulation for refractory stable angina pectoris in patients with chronic pacemaker- and ICD-treatment. *Eur Heart J.* 2006;27 Suppl 6:463S.
148. Taylor RS, de Vries J, Buchser E, de Jongste MJ. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. *BMC Cardiovasc Disord.* 2009;9:13.
149. Horvath KA. Transmyocardial laser revascularization. *J Card Surg.* 2008;23:266–276.
150. Uwatoku T, Ito K, Abe K, et al. Extracorporeal cardiac shock wave therapy improves left ventricular remodeling after acute myocardial infarction in pigs. *Coron Artery Dis.* 2007;18:397–404.
151. Fukumoto Y, Ito A, Uwatoku T, et al. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. *Coron Artery Dis.* 2006;17:63–70.
152. Khattab AA, Brodersen B, Schuermann-Kuchenbrandt D, et al. Extracorporeal cardiac shock wave therapy: first experience in the everyday practice for treatment of chronic refractory angina pectoris. *Int J Cardiol.* 2007;121:84–85.
153. Leschke M, Schoebel FC, Mecklenbeck W, et al. Long-term intermittent urokinase therapy in patients with end-stage coronary artery disease and refractory angina pectoris: a randomized dose-response trial. *J Am Coll Cardiol.* 1996;27:575–584.
154. Kim MC, Kini A, Sharma SK. Refractory angina pectoris: mechanism and therapeutic options. *J Am Coll Cardiol.* 2002;39(6):923–934.
155. The Framingham Heart Study site: <http://www.framinghamheartstudy.org>. Accessed Apr 2, 2010.
156. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J III. Factors of risk in the development of coronary heart disease – six-year follow-up experience: The Framingham Study. *Ann Intern Med.* 1961; 55:33–50.
157. Wilson PWF, D'Agostino R, Levy D, Belanger A, Silbershatz H, Kannel W. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837–1847.
158. Wilson P. Clustering of risk factors, obesity, and syndrome X. *Nutr Clin Care.* 1998;1 Suppl:44–50.
159. Brotman D, Walker E, Lauer MS, O'Brien RG. In search of fewer independent risk factors. *Arch Intern Med.* 2005;165:138–145.
160. Mayo W. The aims and ideals of the American Medical Association. Address given at: the 66th Annual Meeting of the National Education Association; 1928 Jul 1–6; Minneapolis. *Proc Natl Educ Assoc.* 1928;66:158–163.
161. Gonçalves I, Stenström K, Skog G, Mattsson S, Nitulescu M, Nilsson J. Short communication: dating Components of human atherosclerotic plaques. *Circ Res.* 2010;106:1174–1177.
162. Pasterkamp G, de Kleijn D. Cold war battle against hot atherosclerotic plaques. *Circ Res.* 2010;106:1017–1018.
163. Banks J, Marmot M, Oldfield Z, Smith JP. Disease and disadvantage in the United States and in England. *JAMA.* 2006;295:2037–2045.
164. Starfield B, Hyde J, Gervais J, Heath I. The concept of prevention: a good idea gone astray? *J Epidemiol Community Health.* 2008;62:580–583.
165. Kuller LH. Nutrition, lipids, and cardiovascular disease: clinical benefits without biochemical effects and biochemical effects without clinical benefits. *Curr Cardiovasc Risk Reports.* 2008;2:9–14.
166. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364: 937–952.
167. Hu G, Tuomilehto J, Silventoinen K, Sarti C, Männistö S, Jousilahti P. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Arch Intern Med.* 2007;167: 1420–1427.
168. Maruthur NM, Wang NY, Appel LJ. Lifestyle interventions reduce coronary heart disease risk: results from the PREMIER trial. *Circulation.* 2009;119:2026–2031.
169. Roger VL. Lifestyle and cardiovascular health: individual and societal choices [editorial]. *JAMA.* 2009;302(4):437–439.
170. Djoussé L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *JAMA.* 2009;302(4): 394–400.
171. Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. *JAMA.* 2009;302(4): 401–411.
172. Ford ES, Bergmann MM, Kröger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European prospective investigation into cancer and nutrition – potsdam study. *Arch Intern Med.* 2009;169(15):1355–1362.
173. Katz DL. Life and death, knowledge and power: why knowing what matters is not what's the matter. *Arch Intern Med.* 2009;169(15): 1362–1363.
174. Mozaffarian D, Kamineni A, Carnethon M, Djoussé L, Mukamal KJ, Siscovick D. Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. *Arch Intern Med.* 2009; 169:798–807.
175. Chiave SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and anti-hypertensive medications. *Circulation.* 2006;114:160–167.
176. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation.* 2010;121:750–758.
177. Patel NB, Balady GJ. The rewards of good behavior. *Circulation.* 2010;121:733–735.
178. Danaei G, Rimm EB, Oza S, Kulkarni SC, Murray C, Ezzati M. The promise of prevention: the effects of four preventable risk factors on national life expectancy and life expectancy disparities by race and county in the United States. *PLoS Med.* 2010;7(3):e1000248.
179. Phillips LS, Twombly JG. It's time to overcome clinical inertia. *Ann Intern Med.* 2008;148:783–785.
180. Rose G. Incubation period of coronary heart disease. *Int J Epidemiol.* 2005;34(2):242–244.
181. Labarthe DR. Preventing the risk to heart health, from womb to tomb. *CVD Prevention.* 1998;1:259–265.
182. Snyderman R, Dinan MA. Improving health by taking it personal. *JAMA.* 2010;303(4):363–364.
183. Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. *Arch Intern Med.* 2010;170(8):711–718.
184. Carnethon M, Whitsel LP, Franklin BA, et al; for the American Heart Association Advocacy Coordinating Committee; Council on Epidemiology and Prevention; Council on the Kidney in Cardiovascular Disease; and Council on Nutrition, Physical Activity and Metabolism. Worksites wellness programs for cardiovascular disease prevention: a policy statement from the American Heart Association. *Circulation.* 2009;120:1725–1741.
185. Lloyd-Jones D, Adams RJ, Brown TM, et al; for American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2010 update: a report from the American Heart Association. *Circulation.* 2010;121:e46–e215.

186. Lloyd-Jones D, Hong Y, Labarthe D, et al; for American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121: 586–613.
187. Strasser T. Reflections on cardiovascular diseases. *Interdisc Sci Rev*. 1978;3:225–230.
188. Rose G. Strategy of prevention: lesions from cardiovascular disease. *Br Med J (Clin Res Ed)*. 1981;282:1847–1851.
189. Johnson RK, Appel LJ, Brands M, et al; for the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2009;120:1011–1020.
190. Bethesda, National Heart, Lung, and Blood Institute. *Morbidity and Mortality: 2009 Chart Book on Cardiovascular, Lung, and Blood Diseases*: National Institutes of Health; 2009.
191. Capewell S, Ford ES, Croft JB, Critchley JA, Greenlund KJ, Labarthe DR. Cardiovascular risk factor trends and potential for reducing coronary heart disease mortality in the United States of America. *Bull World Health Organ*. 2010;88:120–130.
192. Department of Health and Human Services. *Healthy People 2010: Understanding and Improving Health and Objectives for Improving Health*. Washington, DC: Government Printing Office; 2000. Available at: [http://www.cdc.gov/nchs/healthy\\_people.htm](http://www.cdc.gov/nchs/healthy_people.htm). Accessed Apr 4, 2010.
193. Fraker TD Jr, Fihn SD; for 2002 Chronic Stable Angina Writing Committee. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *J Am Coll Cardiol*. 2007;50:2264–2274.
194. Redberg RF, Benjamin EJ, Bittner V, et al. ACCF/AHA 2009 performance measures for primary prevention of cardiovascular disease in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures for Primary Prevention of Cardiovascular Disease) developed in collaboration with the American Academy of Family Physicians; American Association of Cardiovascular and Pulmonary Rehabilitation; and Preventive Cardiovascular Nurses Association: Endorsed by the American College of Preventive Medicine, American College of Sports Medicine, and Society for Women's Health Research. *Circulation*. 2009;120:1296–1336, and *J Am Coll Cardiol*. 2009;54:1364–1405.
195. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481–1501.
196. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol*. 2006;47:2130–2139.
197. de BG, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease and prevention in clinical practice. *Atherosclerosis*. 2003;171:145–155.
198. JBS 2. Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*. 2005;91 Suppl 5:v1–v52.
199. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Eur Heart J*. 2007;28:2375–2414.
200. Bassand JP, Hamm CW, Ardissino D, et al; for The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007;28:1598–1660.
201. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction). *J Am Coll Cardiol*. 2007;50:e1–e157.
202. Crowe E, Lovibond K, Gray H, et al; for Guideline Development Group. Early management of unstable angina and non-ST elevation myocardial infarction: summary of NICE guidance. *BMJ*. 2010;340:c1134.
203. Gibbons RJ, Balady GJ, Beasley JW, et al; for ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol*. 1997;30(1): 260–311.
204. King SB, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the 2005 guideline update for percutaneous coronary intervention. American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *J Am Coll Cardiol*. 2008;51:172–209.
205. Cushman WC, Evans GW, Byington RP, et al; for the ACCORD study group. Effects of intensive blood pressure control in type 2 diabetes mellitus. *New Engl J Med*. 2010;362(17):1575–1585.
206. Nilsson PM. ACCORD and risk-factor control in type 2 diabetes. *New Engl J Med*. 2010;362(17):1628–1630.
207. Currie CJ, Peters JP, Tynan A, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *Lancet*. 2010;375(9713):481–489.
208. Balkau B, Simon D. Survival in people with type 2 diabetes as a function of HbA1c. *Lancet*. 2010;375(9713):438–440.
209. Feldman DN, Gade CL, Slotwimer AJ, et al. Comparison of outcomes of percutaneous coronary interventions in patients of three age groups (<60, 60 to 80, and >80 years) (from the New York State Angioplasty Registry). *Am J Cardiol*. 2006;98:1334–1339.
210. Kirtane AJ, Cohen DJ. When is better not good enough? Insights from the COURAGE economic study. *Circ Cardiovasc Qual Outcomes*. 2008;1:4–6.
211. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA*. 2008;300:1765–1773.
212. Kastritis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in non-acute coronary artery disease: a meta-analysis. *Circulation*. 2005;111:2906–2912.
213. Boden WE, O'Rourke RA, Teo KK, et al; for the COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356(15):1503–1516.
214. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;356:998–1008.
215. Garg S, Serruys PW. Drug-eluting stents: a reappraisal. *Heart*. 2010;96:489–493.
216. Bhatt DL. Controversies in non-ST-elevation acute coronary syndromes and percutaneous coronary interventions. *Cleve Clin J Med*. 2010;77:101–109.
217. Hilliard AA, From AM, Lennon RJ, et al. Percutaneous revascularization for stable coronary artery disease: temporal trends and impact of drug-eluting stents. *J Am Coll Cardiol Interv*. 2010;3:172–179.
218. Costa JR Jr, Sousa A, Moreira AC, et al. Incidence and predictors of very late ( $\geq 4$  years) major cardiac adverse events in the DESIRE (Drug-Eluting Stents in the Real World)-Late registry. *J Am Coll Cardiol Interv*. 2010;3:12–18.
219. Windecker S, Raber L. The DESIRE-Late registry: what is left to be desired? *J Am Coll Cardiol Interv*. 2010;3:19–21.
220. Newby LK, Peterson ED. Does ranolazine have a place in the treatment of acute coronary syndromes? *JAMA*. 2007;297(16):1823–1825.

221. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Eng J Med*. 2001;344(15):1117–1124.
222. Sdringola S, Loughin C, Boccalandro F, Gould KL. Mechanisms of progression and regression of coronary artery disease by PET related to treatment intensity and clinical events at long-term follow-up. *J Nucl Med*. 2006;47:59–67.
223. Hochman JS, Steg PG. Does preventive PCI work? *N Eng J Med*. 2007;356:1572–1574.
224. Peterson ED, Dai D, DeLong ER, et al; for NCDR Registry Participants. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol*. 2010;55:1923–1932.
225. Weintraub WS, Boden WE, Zhang Z, et al; for Department of Veterans Affairs Cooperative Studies Program No. 424 (COURAGE Trial) Investigators and Study Coordinators. Cost-effectiveness of percutaneous coronary intervention in optimally treated stable coronary patients. *Circ Cardiovasc Qual Outcomes*. 2008;1:12–20.
226. Weintraub WS, Spertus JA, Kolm P, et al; for the COURAGE Trial Research Group. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med*. 2008;359:677–687.
227. Davidson MH. Clinical significance of statin pleiotropic effects: hypotheses versus evidence. *Circulation*. 2005;111:2280–2281.
228. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283–1291.
229. Diamond GA, Kaul S. COURAGE under fire. On the management of stable coronary disease. *J Am Coll Cardiol*. 2007;50:1604–1609.
230. Peterson ED, Rumsfeld JS. Finding the courage to reconsider medical therapy for stable angina. *N Engl J Med*. 2008;359:751–753.
231. Kereiakes DJ, Teirstein PS, Sarembock IJ, et al. The truth and consequences of the COURAGE trial. *J Am Coll Cardiol*. 2007;50:1598–1603.
232. Maron DJ, Boden WE, O'Rourke RA, et al; for the COURAGE Trial Research Group. Intensive multifactorial intervention for stable coronary artery disease. Optimal medical therapy in the COURAGE trial. *J Amer Col Cardiol*. 2010;55(13):1348–1358.
233. O'Gara PT. The COURAGE trial: can we deliver on its promise? *J Am Coll Cardiol*. 2010;55(13):1359–1361.
234. Ciccone MM, Aquilino A, Cortese F, et al. Feasibility and effectiveness of a disease and care management model in the primary health care system for patients with heart failure and diabetes (Project Leonardo). *Vasc Health Risk Manag*. 2010;6:297–305.
235. Schömig A, Mehilli J, de Waha A, Seyfarth M, Pache J, Kastrati A. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2008;52:894–904.
236. O'Rourke RA. Optimal medical therapy is a proven option for chronic stable angina. *J Am Coll Cardiol*. 2008;52:905–907.
237. Marie PY, Danchin N, Durand JF, et al. Long-term prediction of major ischemic events by exercise thallium-201 single-photon emission computed tomography. Incremental prognostic value compared with clinical, exercise testing, catheterization and radionuclideangiographic data. *J Am Coll Cardiol*. 1995;26:879–886.
238. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation*. 2007;115:1769–1776.
239. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50:1161–1170.
240. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation*. 1997;95:2037–2043.
241. Kastritis DG, Meier B. Percutaneous coronary intervention for stable coronary artery disease. *J Am Coll Cardiol*. 2008;52:889–893.
242. Califf RM, Armstrong PW, Carver JR, et al. Task Force 5. Stratification of patients into high-, medium-, and low-risk subgroups for purposes of risk factor management. *J Am Coll Cardiol*. 1996;27:964–1047.
243. Bramlage P, Messer C, Bitterlich N, et al. The effect of optimal medical therapy on 1-year mortality after acute myocardial infarction. *Heart*. 2010;96:604–609.
244. Cavender MA, Alexander KP, Broderick S, et al. Long-term morbidity and mortality among medically managed patients with angina and multivessel coronary artery disease. *Am Heart J*. 2009;158(6):933–940.
245. Hannan EL, Racz MJ, Gold J, et al. Adherence of catheterization laboratory cardiologists to American College of Cardiology/American Heart Association guidelines for percutaneous coronary interventions and coronary artery bypass graft surgery: what happens in actual practice? *Circulation*. 2009;121:267–275.
246. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization. American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*. 2009;53:530–553.
247. Executive Summary. Comparative effectiveness of percutaneous coronary interventions and coronary artery bypass grafting for coronary artery disease. Agency for Healthcare Research and Quality Pub. No. 08-EHC002-1. 2007 Oct 15. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm). Accessed May 1, 2010.
248. King SB III, Marshall JJ, Tummala PE. Revascularization for coronary artery disease: stents versus bypass surgery. *Annu Rev Med*. 2010;61:199–213.

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