Treatment of stable angina

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Severe atherosclerotic narrowing of one or more coronary arteries is responsible for myocardial ischemia and angina pectoris in most patients with stable angina pectoris. The coronary arteries of patients with stable angina also contain many nonobstructive plaques, which are prone to fissures or rupture resulting in presentation of acute coronary syndromes (unstable angina, myocardial infarction, sudden ischemic death). In addition to symptomatic relief of symptoms and an increase in angina-free walking time with antianginal drugs or revascularization procedures, the recent emphasis of treatment has been to reduce adverse clinical outcomes (coronary death and myocardial infarction). The role of smoking cessation, aspirin, treatment of elevated lipids, and treatment of high blood pressure in all patients and of β-blockers and angiotensin-converting enzyme inhibitors in patients with diminished systolic left ventricular systolic function in reducing adverse outcomes has been well established. What is unknown, however, is whether any anti-anginal drugs (β-blockers, long-acting nitrates, calcium channel blockers) effect adverse outcomes in patients with stable angina pectoris. Recent trials evaluated the usefulness of suppression of ambulatory ischemia in patients with stable angina pectoris, but it remains to be established whether suppression of ambulatory myocardial ischemia with antianginal agents or revascularization therapy is superior to pharmacologic therapy targeting symptom relief. Patients who have refractory angina despite optimal medical treatment and are not candidates for revascularization procedures may be candidates for newer techniques of transmyocardial revascularization, enhanced external counterpulsation, spinal cord stimulation, or sympathectomy. The usefulness of these techniques, however, needs to be confirmed in large randomized clinical trials. Curr Opin Cardiol 1999, 14:349–358

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Abbreviations

CAD	coronary artery disease
LV	left ventricular
MI	myocardial infarction

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The knowledge of the pathophysiology and natural history of stable angina has important treatment implications and is briefly reviewed in this article.

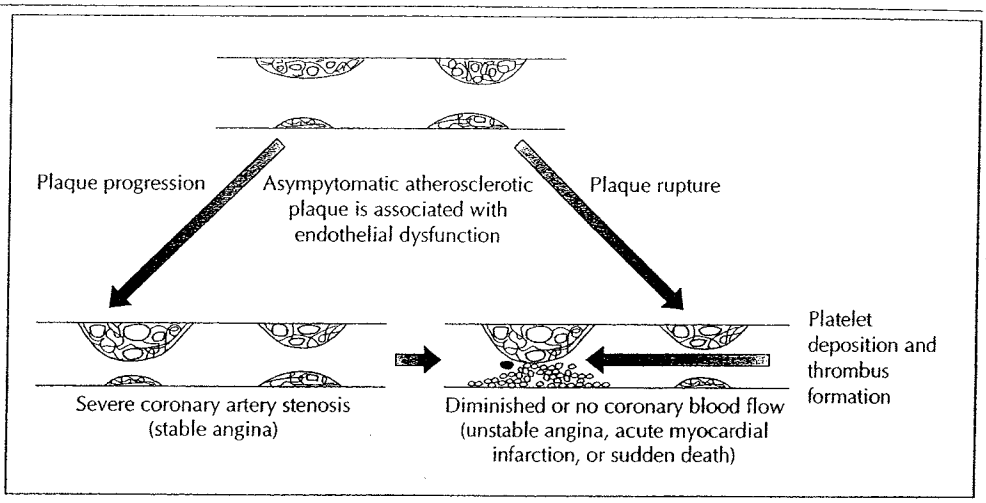
Pathophysiology

Patients with stable angina pectoris experience a predictable pressure or a choking sensation in the chest and adjacent areas or shortness of breath (angina equivalent) in association with physical or emotional stress. Prompt relief of symptoms in these patients is usually achieved with rest or sublingual nitroglycerin. The prerequisite for developing angina pectoris is a hemodynamically significantly diseased coronary arterial bed that produces myocardial ischemia and angina pectoris. Symptoms are caused by left ventricular (LV) dysfunction because of an inability of coronary blood flow to meet increased myocardial oxygen demand [1–3]. In addition, endothelial dysfunction also produces myocardial ischemia by paradoxical constriction of epicardial stenotic atherosclerotic coronary arteries during exertion or emotional stress [4,5]. Severe stenotic narrowing (usually more than 70%) of one or more coronary arteries is invariably responsible for myocardial ischemia and anginal pain in patients with stable angina pectoris. These severe lesions, however, are usually not responsible for acute ischemic syndromes (unstable angina, myocardial infarction (MI) or sudden ischemia death). The coronary arteries of patients with stable angina, and those with severe stenotic lesions, have nonobstructive atherosclerotic plaques that are prone to surface erosion or fissures with super-added platelet deposition and thrombosis, leading to the clinical manifestation of acute ischemic syndromes (Fig. 1) [6••]. Myocardial ischemia without anginal pain (silent myocardial ischemia) is a more frequent manifestation of coronary artery disease (CAD) in patients with stable angina pectoris [7–9]; however, repeated bouts of ischemia in the absence of an intervening MI do not lead to deterioration of systolic LV function [10•].

Some patients with stable angina also experience angina at rest or nocturnal angina, which is rapidly relieved with nitroglycerin and is presumably secondary to changes in coronary arterial tone caused by endothelial dysfunction [11]. Also, in certain pathophysiologic states, such as thyrotoxicosis, hypertension, severe anemia, aortic stenosis, and supraventricular tachycardia, patients with stable angina may experience angina at lower levels of physical activity or even at rest because of an increase in myocardial oxygen consumption [1–3,6••,12]. Rarely patients with stable angina pectoris have nonocclusive coronary disease [1].

Figure 1. Representation of asymptomatic coronary lesions and progression of lesions in patients with stable angina pectoris and in patients presenting with acute coronary syndromes

(From Asirvatham *et al.* [6••]; with permission.)



Natural history and prognosis

The annual death rate of patients with stable angina is 1.6% to 3.2% [13,14]. The most important determinants of prognosis are underlying LV systolic function at rest, comorbid conditions, and the severity and extent of CAD [14]. Previous studies show that the long-term prognosis for patients with stable angina pectoris and good LV function, despite severe CAD, is similar with medical treatment compared with surgical revascularization procedures [6••,16–18]. In these studies, only anti-anginal therapy was used in the medical treatment arm and pharmacologic agents known to reduce adverse outcomes were not used [6••,12]. Therefore, the outcomes of patients with stable angina might be better than currently recognized.

Treatment

The goals of treatment in stable angina are as follows: 1) to prolong life and reduce the incidence of acute coronary syndromes (unstable angina, MI), and 2) to decrease the frequency and severity of angina symptoms and increase angina-free exercise duration (functional capacity). Recent emphasis of treatment has been on reducing the frequency and severity of ambulatory myocardial ischemic episodes [9,19–21], but the usefulness of this approach needs to be confirmed in larger clinical trials. Once the diagnosis of stable angina is made, comorbid conditions that could aggravate angina must be sought and treated [6••,12]. In all patients, lifestyle modifications, especially smoking cessation, and risk factor modification must be stressed [6••,12].

Treatment aimed at prolonging life and preventing myocardial infarction and other acute ischemic syndromes

Cigarette smoking cessation

Cigarette smoking cessation reduces the risk of coronary heart disease mortality by 50% in 1 year, and after 5 to 10 years, reduces the coronary mortality risk to that of nonsmokers [22,23]. In a longitudinal study of patients with CAD aged 65 to 57 years, the mortality rate per 1,000 person-years was reduced by 52% (28.4% vs 49.7%) in ex-smokers compared with current smokers over a 4.5 year period, for an absolute risk reduction of 21.3% [22,23]. Transdermal nicotine and the newer agent Zyban (bupropion; Glaxo Wellcome, Research Triangle Park, NC) have been shown to be safe and superior to placebo in kicking the smoking habit.

Aspirin

Recently aspirin was approved by the US Food and Drug Administration on the basis of the published Swedish Angina Pectoris Aspirin Trial (SAPAT) and the totality of the data showing beneficial effects of aspirin in patients with acute MI and unstable angina [24–26]. Investigators for this trial enrolled 2,035 patients and randomized them to treatment with sotalol plus placebo or sotalol plus low-dose (80 mg) daily aspirin, and followed the patients for a median of 50 months [26]. Daily use of aspirin reduced the incidence of sudden death and acute MI by 34%, with an absolute reduction of 12 sudden deaths for every 1,000 patients treated during a 50-month period. The relative reduction in secondary endpoints (vascular events, vascular death, all cause mortality, stroke) ranged from 22% to 32%. There was no difference in major bleeding episodes, including hemorrhagic strokes in the aspirin and placebo groups.

Sotalol is not approved for use in patients with stable angina pectoris in the United States. Sotalol is a β-blocker but, in addition to beta blocking properties, this agent has type III antiarrhythmic activities that prolong the QT interval and is associated with 1% to 4% incidence of torsades de pointes [26]. The reduction in mortality with

aspirin might have been greater if no β-blocker or another β-blocker that does not cause torsades de pointes had been used in the Swedish study.

In another smaller study, the risk of a first MI in men with stable angina was reduced by 8.7% when patients were treated with aspirin [27]. The current recommended dose of aspirin is 80 mg to 320 mg in patients with stable angina pectoris, provided that patients are not intolerant to aspirin therapy [6••].

Ticlopidine and clopidogrel

No available data suggest that ticlopidine and clopidogrel improve prognosis in patients with stable angina pectoris. For patients who are allergic or intolerant to aspirin, clopidogrel may be an alternative [6••].

Statins for dyslipidemia

In the Scandinavian Simvastatin Survival Study (4S) trial, 4,444 patients with either a previous MI or stable angina pectoris and an elevated total and low-density lipoprotein cholesterol were randomized to either simvastatin or placebo [28]. After a mean follow-up of 5.4 years, simvastatin therapy was shown to provide a 38% reduction in low-density lipoprotein levels, a 30% reduction in all cause mortality, a 42% reduction in coronary events, and a 37% reduction in the need for revascularization procedures. The mortality reduction in the simvastatin group became apparent at 1 year of follow up. The 6-year probability of survival for placebo and simvastatin groups were 87.6% and 91.3%, respectively. In this study, a reduction in mortality in the simvastatin group was observed both in men and women and in those younger and older than 65 years.

Although trials with other HMG-CoA reductase inhibitors (statins) have not been performed specifically in patients with stable angina pectoris, a reduction in mortality, stroke rates, and cardiovascular morbidity in post-MI patients and in asymptomatic patients with elevated low-density lipoprotein levels suggests that this group of drugs is effective in reducing coronary morbidity and mortality in patients with established CAD [6••,29]. In a recent study presented by Dr. B. Pitt on behalf of AVERT investigators at the annual American Heart Association Meeting in Dallas in November 1998, treatment with atorvastatin (Lipitor; Parke-Davis, Ann Arbor, MI) reduced adverse outcomes compared with balloon angioplasty in patients with stable CAD. The results of this study remain to be confirmed in a larger trial. Lipid lowering therapy with HMG-CoA reductase inhibitors is, therefore, recommended for patients with stable angina pectoris and low-density lipoprotein levels greater than 125 to 130 mg/dL.

The role of other lipid lowering agents (nicotinic acid, fibrates) in reducing adverse outcomes in patients with stable angina needs to be studied [6••]. A recent trial in patients with low high-density lipoprotein levels and CAD showed a beneficial effect of gemfibrozil therapy (Veterans Administration HDL Intervention Trial [HIT]; Rubins, on behalf of the HIT investigators, Paper presented at the annual American College of Cardiology Meeting, New Orleans, 1999).

Treatment of hypertension

Patients with angina and hypertension need to have their blood pressure controlled below 140 mm Hg systolic and 90 mm Hg diastolic [30]. No specific trials of different antihypertensive agents in patients with stable angina and co-existing hypertension are available. A meta-analysis of nine major trials (n = 15,559) of antihypertensive treatment of elderly patients (> 59 years) showed a 12% reduction in all cause mortality, a 30% reduction in stroke, and a 25% reduction in CAD mortality [30]. In most of these trials, a regimen of diuretics and β-blockers and add-on therapy to lower blood pressure was used. In a recent trial of hypertensive patients, long-acting calcium channel blockers reduced coronary morbidity and stroke rate by 42% [30]. The totality of available data suggests that blood pressure must be adequately controlled in patients with stable angina and hypertension to favorably influence the outcome.

Hormonal replacement therapy

In postmenopausal women, estrogen replacement therapy has been associated with the reduced risk of CAD and mortality [31–33]. No outcome trials have been performed of women with stable angina pectoris who received estrogen replacement therapy. Large randomized studies are needed to address the role of hormonal replacement therapy in reducing adverse outcomes in patients with stable angina pectoris.

Revascularization procedures

Twenty-year follow-up in the VA Cooperative Study of coronary artery bypass surgery for stable angina showed that the probability of remaining free of MI and of being alive without MI were significantly higher with initial antianginal therapy, 57% versus 41% (P = 0.02) and 18% versus 11% (P = 0.00031), respectively [34••]. This small trial of 686 patients indicates that initial bypass surgery did not improve survival of low risk patients (those with good LV function) and did not reduce overall risk of MI. Furthermore, despite an early survival benefit [34••,35] of up to a decade with surgery in high-risk patients (impaired LV function), long-term survival rates were comparable in both treatment groups [34••]. In total, twice as many bypass procedures were performed in the group assigned to

surgery without any long-term survival or symptomatic benefit [34••].

A comparative double-blind study of balloon angioplasty and medical treatment in patients with stable angina pectoris and anterior descending CAD showed similar outcome for survival and MI in the two groups [36•]. The results of angioplasty were not superior to medical therapy in the second randomized intervention treatment of angina (RITA-2) trial [37].

Aggressive medical treatment incorporating lipid lowering therapy in stable patients with CAD was recently shown to be associated with better outcome compared to balloon angioplasty (Pitt, Paper presented at the annual American Heart Association Meeting, Dallas, 1998).

A review of data shows that revascularization with coronary artery bypass graft surgery or balloon angioplasty to achieve a reduction in adverse outcomes is not superior to medical therapy [6••,12,34••,37]. The only exception is patients with left main CAD, who were excluded from the randomized trials; these patients are candidates for coronary bypass surgery [15,16]. Revascularization strategy was recently shown to be superior to pharmacologic treatment targeting angina relief or myocardial ischemia, but the revascularization mortality in this study was only 1.2% [9,38,39]. National reported average mortality is 3.2% (range, 1%–12%), thus large trials are needed to address the issue of whether revascularization strategy is superior to strategies targeting angina relief or reduction of ambulatory ischemia [21]. Based on available data, one should consider initial medical therapy in all patients with stable angina pectoris.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors improve outcome in patients with reduced LV function [40,41] and are therefore indicated in patients with this reduced function who have stable angina pectoris. Angiotensin-converting enzyme inhibitors improve endothelial function [42,43], but whether these agents influence outcome in patients with stable angina pectoris who have good LV function remains unknown [44,45].

Antianginal drugs

Outcome studies with any of the antianginal drugs (β-blockers, nitrates, and calcium channel blockers) have not been performed in patients with stable angina [6••]. Recent trials have shown that β-blockers (bisoprolol and metoprolol long-acting/controlled-release) reduce mortality in patients with ischemic cardiomyopathy (Second Cardiac Insufficiency Bisoprolol Trial [CIBIS II] Investigators, Paper presented at the annual European College of Cardiology Meeting, Geneva, 1998, and Hjalmarsson, on behalf of Metoprolol Interventional Trial in Heart Failure [MERIT-HF], Paper presented at the annual American College of Cardiology Meeting, New Orleans, 1999). Also, β-blockers reduce mortality and morbidity in post-MI patients [46–48]. In a recent study of mildly symptomatic patients with stable angina pectoris who had evidence of exercise and ambulatory ischemia, treatment with atenolol reduced the composite endpoint of death, MI, hospitalization for unstable angina, and a need for revascularization procedures compared with placebo [20].

Diabetes mellitus

Patients with diabetes mellitus have increased risk of cardiovascular morbidity, especially after percutaneous transluminal coronary angioplasty. In this group of patients, the revascularization procedure of coronary artery bypass grafting has been shown to be superior to balloon angioplasty [6••,49]. Patients with diabetes and angina pectoris also need to have their blood pressure reduced to 120/80 mm Hg [30].

Antioxidants

In the Cambridge Heart Antioxidant Study (CHAOS), 800 mg of vitamin E was shown to reduce adverse outcomes [50]; however, in another study, α tocopherol and β-carotene had no effect on survival or prognosis in patients with stable angina [51].

Treatment aimed at decreasing the frequency and severity of anginal symptoms and myocardial ischemia

Three groups of drugs are available to achieve the goal of decreasing the frequency and severity of anginal symptoms and myocardial ischemia: long-acting nitrates, β-blockers, and calcium channel blockers. In addition, nicorandil is used in Japan and several European countries to treat angina pectoris. The efficacy of these agents has been well established [2,3,6••,12], and only a few recent studies have evaluated monotherapy with these agents. Most of the studies, published in the last 2 years, have evaluated the usefulness of combination therapy; these studies are briefly reviewed in this paper. Newer agents not approved for clinical use in the United States are also discussed.

Nitrates

Nitrates are nitric oxide donors and predominantly reduce myocardial oxygen demand by reducing venous return. These agents also dilate stenotic coronary lesions and favor subendocardial blood blow to the ischemic areas [52,53]. Older studies of nitrates were based on smaller sample size of a single agent to placebo in a select group of patients known to be nitrate responders [53]. Many of these older studies showed an initial favorable response with formulation or dosage regimens known to produce tolerance and were no more effective

than placebo [53–57]. Recent studies have required documentation of improved exercise performance. Based on the published data, it can be concluded that none of the nitrate regimens provide continuous 24-hour antianginal prophylaxis [58]. Dosing schedules that prevent tolerance and improve exercise performance for 8 to 12 hours after the morning dose [56–62] are shown in Table 1. Adjunct therapies to avoid nitrate tolerance have produced conflicting results in patients with stable angina and are not currently recommended [58].

β-Blockers

β-Blockers reduce myocardial oxygen demand by reducing heart rate, myocardial contractility, and exercise-induced increase in systolic blood pressure. These agents also increase coronary blood flow by increasing the diastolic filling period [47]. Previous studies have shown that monotherapy with β-blockers reduces angina frequency and improves exercise performance and evidence of exercise-induced myocardial ischemia and ambulatory ischemia in patients with stable angina [2,3,6••,47,63] These agents are the most effective anti-ischemic agents, and reduced exercise and ambulatory ischemia in these studies to a greater extent than other antianginal agents [20,48]. With regard to treatment for stable angina pectoris, nonselective and cardioselective agents improve exercise performance and reduce exercise-induced ST segment depression to a similar extent [2–4,47].

In a recent crossover study of three doses of carvedilol (12.5 mg, 25 mg, and 50 mg) given twice daily in 122 patients with stable angina, carvedilol at doses of 25 mg and 50 mg was shown to be superior to placebo [64]. The increase in time to angina, however, although statistically significant, was only 21 seconds and 29 seconds, and an increase in time to 1 mm ST segment depression was only 12 seconds and 22 seconds after the 25- and 50-mg doses compared with placebo [64]. These results with a vasodilator β-blocker do not appear to be superior to published data with nonvasodilating β-blockers [23,47].

Table 1. Interval therapy for effort angina using nitrate dosage schedules designed to avoid tolerance

Preparation	Dose
Isosorbide dinitrate	30 mg at 7 h and 13 h*
Isosorbide mononitrate	20 mg in the morning and second dose 7 h later
Isosorbide mononitrate (extended release)	120–240 mg/d†
Transdermal nitrate patches	7.5–10 mg/12 h; patches removed after 12 h
Phasic release nitroglycerine (glyceryl trinitrate patch)	15 mg; most released in first 12 h

*Efficacy of second dose not established; no data for other doses.
†Data from Thadani [53] and Thadani and Lipicky [57].
Adapted from Thadani *et al.* [52]; with permission.

Another study compared baseline placebo treatment with 25 mg and 50 mg of carvedilol and with 50 mg and 100 mg of metoprolol twice daily in 368 patients with stable angina [65]. Both drugs showed good antianginal and anti-ischemic efficacy, whereas improvement in time to 1 mm ST depression increased more with carvedilol compared with metoprolol. There was no parallel placebo group used in this study; placebo monotherapy has been shown to increase exercise duration and time to ischemia in this group of patients [2,3].

Reduction in exercise-induced myocardial ischemia [66], ambulatory myocardial ischemia [21,66–68], and ischemic LV dysfunction induced by mental stress [69] has also been documented with β-blocker therapy. Bisoprolol increased heart rate variability, suppressed ambulatory ischemia, and exerted beneficial effects on adverse outcome in another study [70•].

Calcium channel blockers

Calcium channel blockers act mainly by vasodilating the coronary arteries and by reducing peripheral vascular resistance. The nondihydropyridine agents verapamil and diltiazem, and the T-channel calcium channel blocker mibefradil inhibit sinoatrial and atrioventricular nodes and thus also reduce myocardial oxygen demand [71,72].

Despite the recent controversy with calcium channel blockers [73], recent studies with the long-acting dihydropyridine and nondihydropyridine groups of calcium channel blockers have shown that these agents are safe and effective in patients with ischemic heart disease [66,67,73–76]. Previously published data, which have been recently reviewed, showed that monotherapy with amlodipine, diltiazem, and verapamil increased exercise tolerance and time to 1-mm ST segment depression [76,77,78•,79,80]. Both nifedipine gastrointestinal therapeutic system and atenolol were effective in protecting mental-induced wall motion abnormalities [69]. Amlodipine at a dose of 10 mg was shown to be superior to 40 mg of slow-release isosorbide dinitrate twice daily in patients with stable angina [81]; however, physicians must recognize that the slow-release isosorbide dinitrate dosage regimen used has not been shown to be superior to placebo [56]. In a large study, verapamil monotherapy was shown to be superior to amlodipine [79]. Anti-ischemic effects of amlodipine, diltiazem, and verapamil have been reported in several trials [73,76,78•,79,80].

Mibefradil

Mibefradil was shown to be superior to placebo with regards to anti-anginal and anti-ischemic effects [76], but soon after its introduction, the drug was withdrawn because mibefradil and its metabolites affect the activity of cytochrome P450 (CYP) 3A4, which is an enzyme

responsible for the metabolism of many drugs, including those that prolong QT interval [6••].

Combination therapy

Optimum antianginal therapy with a single anti-anginal agent is often as effective as combination therapy with two or three agents [2,3,6••,12,82–88]. Published data show that maximal triple therapy is not superior to combination therapy with two agents [12,84–87].

In patients who are receiving β-blockers but are still symptomatic, the addition of amlodipine improved exercise performance and reduced evidence of myocardial ischemia [89]. This combination was as effective as monotherapy with verapamil in another study [79]. The combination of atenolol plus amlodipine was as effective as combination of atenolol plus diltiazem in another study [90], but the latter combination was associated with more severe adverse outcomes [90]. Similarly, the combination of β-blocker therapy and long-acting nitrates, especially mononitrates and nitroglycerin patches, has been shown to be effective in patients who remain symptomatic despite β-blocker therapy [56,57]. Patients who remain symptomatic despite treatment with long-acting nitrates improved their exercise performance by adding mibefradil to nitrates compared with nitrates plus placebo [91].

Adverse effects of antianginal therapy

The adverse effects of antiangial therapy have been extensively reviewed in a recent publication and are not discussed in this article [6••].

Lipid lowering agents

Improvement of myocardial ischemia during ambulatory monitoring has been described in several studies and this topic has been recently reviewed [92•]. Both the number of ischemic episodes and duration of ischemic episodes decrease with lipid lowering therapy with pravastatin [93] and lovastatin [94]. Whether these agents also improve exercise performance is not well studied.

Angiotensin-converting enzyme inhibitors

Conflicting results have been published with angiotensin-converting enzyme inhibitors in patients with stable angina pectoris [42–44,95]. Definitive trials are needed to evaluate the usefulness of these agents as anti-ischemic or antianginal agents during long-term treatment in patients with stable angina pectoris [6••].

Revascularization procedures

Both coronary artery bypass graft surgery and balloon angioplasty are effective in reducing angina frequency and exercise-induced ischemia [15–17,21,39]. In a recent study, percutaneous transluminal coronary angioplasty was associated with greater improvement in exercise tolerance compared with medical treatment [36•]. However, percutaneous transluminal coronary angioplasty was associated with worse morbid outcomes compared to medical treatment in another study (Pitt, Paper presented at the annual American Heart Association Meeting, Dallas, 1998). Revascularization procedures do not improve outcome compared with medical therapy [36•,37] and should be reserved for patients who do not respond to medical therapy or for those who experience intolerable effects from medical therapy.

Hormone replacement therapy

Therapy with estrogen replacement has produced conflicting results [96,97•]. In a recent study, reported beneficial antianginal and anti-ischemic effects of estrogen in women with stable angina pectoris could not be confirmed [97•]. Acute administration of testosterone compared with placebo has been shown to increase time to ischemia and total exercise duration in patients

Table 2. Antianginal treatment options in patients with and without concomitant disease

Concomitant disease	Long-acting nitrates	β-Blockers	Calcium antagonists	
			Long acting DHP	Non-DHP*
None	+++	+++	++	+++
Hypertension	+	+++	++	+++
Recent MI	+++	+++	++	+†
Reduced LV function	+++	+++	0	0
SVT	+	+++	0	+++
COPD	+++	0	+++	+++
PVD	++	++	+++	+++
Type 1 (insulin-dependent) diabetes mellitus	+++	+	+++	+++
Type 2 (non-insulin-dependent) diabetes mellitus	+++	++	+++	+++
Sinus bradycardia < 50 beats/min or AV block > first degree	+++	0	+++	0

*Verapamil and diltiazem. †Diltiazem in non-Q wave MI without congestive heart failure. AV, atrioventricular; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; LV, left ventricular; MI, myocardial infarction; PVD, peripheral vascular disease; SVT, supraventricular tachycardia; +++, very effective and desirable; ++, moderately effective and desirable; +, effective but less desirable; 0, should be avoided.
Adapted from Asirvatham *et al.* [6••]; with permission. Data from Thadani and Chohan [3], Asirvatham *et al.* [6••], and Task Force of the European Society of Cardiology [88].

Table 3. Proposed treatment for patients with stable angina pectoris

All patients	Daily aspirin (acetysalicyclic acid), smoking cessation, lipid level modification, and adequate blood pressure control
LM or three-vessel CAD with decreased LV function (EF < 50%)	Coronary artery bypass surgery if feasible; ACE inhibitor and a β-blocker when EF < 40%
One-, two-, or three-vessel disease with normal LV function	Drug treatment, PTCA, or coronary artery bypass surgery if symptoms are not controlled with drug treatment
Refractory angina, very poor LV function, or not candidate for revascularization	Consider bepridil, heart transplant, experimental transmyocardial revascularization, or transthoracic sympathetic denervation

ACE, angiotensin-converting enzyme; CAD, coronary artery disease; EF, ejection fraction; LM, left main coronary artery; LV, left ventricular; PTCA, percutaneous transluminal angioplasty.
Adapted from Asirvatham *et al.* [6••]; with permission.

with stable angina pectoris [98,99]; however, the role of long-term therapy with testosterone remains to be established.

Newer agents

Nicorandil is used as an antianginal agent in Japan and several European countries; however, the results of earlier positive studies [100] have not been confirmed in recent trials [101,102]. Ranolozine is a metabolic modulator [103] and was reported to exert antianginal effects [104], but in a large placebo controlled study, ranolozine was not superior to placebo treatment [105]. Trimetazidine is a metabolic modulator, and in acute studies of improved exercise duration, was effective as add-on therapy [106]. Placebo-controlled studies are needed to confirm these results. Sarpogrelate, a serotonin blocker, was used in 11 patients with stable angina pectoris and good collaterals. This drug improved exercise capacity in these patients but had no effect in patients without collaterals [107]. No placebo group was studied. D- and L-arginine enhance endothelial function but have no effect on stress-induced myocardial ischemia [108].

Treatment of patients with refractory angina

Bepridil

Bepridil is a calcium channel blocker, but this agent prolongs the QT interval and can produce torsades de pointes [6••,12]. Bepridil is a very effective anti-anginal agent but should only be used in patients who remain symptomatic despite maximum medical therapy and are not candidates for revascularization procedures.

Laser revascularization

Recent trials have shown that transmyocardial laser revascularization can improve angina class, but this procedure is associated with higher initial surgical morbidity and mortality [109,110]. Also, in a recent study, many of the patients who were considered refractory to medical therapy could be stabilized on optimal medical therapy [111•]. Thus, this treatment should be reserved for patients who are not candidates for revascularization procedures and remain symptomatic despite optimal medical therapy [111•].

The newer technique of transcutaneous laser myocardial revascularization is being investigated, and initial data indicate that this procedure might be associated with a lower morbidity and mortality compared with transmyocardial laser revascularization. Results of double-blind studies have not been adequately evaluated.

Enhanced external counterpulsation

Several recent studies have shown the usefulness of enhanced external counterpulsation in improving exercise performance, time to ischemia, and reduction of myocardial ischemia in patients with Canadian cardiovascular class II and III stable angina pectoris [112,113,114•,115•]. These trials are small, and larger trials are needed to establish the routine use of enhanced external counterpulsation in a broader population of patients with stable angina pectoris. In a multicenter study presented at the 1997 annual meeting of the American Heart Association, enhanced external counterpulsation therapy increased time to ischemia and total exercise duration compared with inactive counterpulsation therapy.

Spinal cord stimulation

In a randomized study in 100 patients with severe stable angina, spinal cord stimulation was equally effective in improving anginal symptoms and reducing myocardial ischemia during exercise compared with coronary artery bypass surgery [115•].

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation has been shown effective in patients who are refractory to antianginal therapy and are not candidates for bypass surgery [116].

Guidelines for choosing appropriate drug combination therapy for stable angina

Guidelines for choosing appropriate drug combination therapy for stable angina was recently reviewed [6••]. The choice of initial therapy should depend on the presence or absence of concomitant disease (Table 2).

Proposed treatment of patients with stable angina pectoris

Table 3, which has been modified from a recent publication [6••], outlines preference of therapeutic strategies in patients with stable angina.

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Papers of particular interest, published within the two year of review have been highlighted as:

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- •• Of outstanding interest

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This review focuses on the management of patients with stable angina, with emphasis of choosing appropriate therapy by considering comorbid conditions and adverse effects of therapy.

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