Current Medical Management of Chronic Stable Angina

Udho Thadani

J Cardiovasc Pharmacol Ther 2004; 9; S11
DOI: 10.1177/107424840400900103

J Cardiovasc Pharmacol Therapeut 9(Supplement 1):S11–S29, 2004

Current Medical Management of Chronic Stable Angina

Udho Thadani, MD, MRCP, FRCPC, FACC, FAHA

Severe atherosclerotic narrowing of one or more coronary arteries is responsible for myocardial ischemia and angina pectoris in most patients with stable angina. The coronary arteries of patients with stable angina also contain many more non-obstructive plaques, which are prone to rupture resulting in acute coronary syndrome (unstable angina, myocardial infarction, sudden ischemic death). Therefore, the medical management must use strategies which not only relieve symptoms and prolong angina free walking but also reduce the incidence of adverse clinical outcomes. Whether any of the approved antianginal drugs, nitrates, beta-blockers, and calcium channel blockers reduce the incidence of adverse clinical outcomes in patients with stable angina has not been studied to date. Published data shows that percutaneous coronary revascularization procedures and coronary bypass surgery are effective in relieving angina but these procedures do not reduce mortality or the incidence of myocardial infarction compared to anti-anginal drug therapy. From the available data, an initial trial of medical treatment with anti-anginal drugs and strategies to reduce adverse clinical outcomes (smoking cessation, daily aspirin, treatment of dyslipidemias and hypertension) is indicated in most patients with stable angina pectoris. The initial choice of drug will depend on the presence or absence of comorbid conditions. Patients who do not respond to medical therapy or do not wish to take anti-anginal drugs and whose life style is limited because of anginal symptoms should be offered percutaneous revascularization procedures with or without stent placement or coronary bypass surgery. New drug -coated stents hold promise but long-term data and large-scale trials assessing the continued long-term improvement in symptoms and reduction of adverse outcomes is needed before offering such devices to all patients with stable angina. Newer medical therapies such as metabolic modulators and sinus rate lowering drugs also hold promise but need further evaluation. Patients who have refractory angina despite optimal medical therapy and are not candidates for revascularization procedures may be candidates for some new techniques of enhanced external Counterpulsation, Spinal Cord Stimulation, sympathectomy or direct transmyocardial revascularization. The usefulness of these techniques, however, needs to be confirmed in large randomized trials.

Key Words: stable angina, pharmacologic treatment, metabolic modulators, coronary artery revascularization.

The term "chronic stable angina" refers to a predictable occurrence of pressure or choking sensation in the chest or adjacent areas or angina equivalents (breathlessness, fatigue, nausea or recurrent belching) caused by myocardial ischemia in association with physical activity or emotional stress, and prompt relief of symptoms with rest or sublingual nitroglycerin (1–3). By arbitrary definition symptoms are reproducible over a period of 3–6 months. However, many patients with stable angina experience angina at rest, which is rapidly relieved with sublingual nitroglycerin (4,5). Patients often complain of earlier onset of angina after a heavy meal (3,5) and may experience worsening of their symptoms with a diminished exercise threshold either through progression of underlying disease or through pathophysiologic states such as thyrotoxicosis, supraventricular tachycardia, aortic stenosis, uncontrolled hypertension or severe anemia (3,5–7).

Professor Emeritus of Medicine, Cardiovascular Section, University of Oklahoma Health Sciences Center, Consultant Cardiologist Oklahoma University, Medical Center and VA Medical Center, Oklahoma City, Oklahoma.

Reprint requests: Udho Thadani, MD, Professor Emeritus of Medicine, Oklahoma University Health Sciences Center, 920 Stanton L. Young Blvd., WP3010, Oklahoma City, OK 73104.

An imbalance between myocardial oxygen demand and supply is responsible for myocardial ischemia and anginal pain (6–9). In most patients with chronic stable angina, the underlying lesion responsible for reduced myocardial blood flow (oxygen supply) is severe atherosclerotic narrowing of one or more coronary arteries (3,9–11), which paradoxically constrict during exercise owing to endothelial dysfunction (12). In addition to severe atherosclerotic lesions, coronary arteries of patients with chronic stable angina contain many non-obstructive lesions (10). These lesions grow at variable rates and rupture unpredictably (Fig. 1) (13) and may remain silent or manifest as acute coronary syndromes (myocardial infarction, unstable angina or sudden ischemic death).

The annual death rate of patients with chronic stable angina is 1.6 to 3.2% (14). The principal determinants of prognosis are underlying left ventricular function, extent and severity of coronary artery disease, exercise duration or effort tolerance, and comorbid conditions (3,8,14–16). Patients can be risk stratified into low and high risk by evaluating their left ventricular function and functional capacity and for any evidence of ischemia during stress testing (3,14-18). Ability to complete stage III of Bruce protocol and normal left ventricular function denote a relatively good prognosis (3,15–19). Patients with an early positive stress test or those with a fall in systolic blood pressure during exercise and those showing left ventricular cavity dilatation during exercise can be further risk stratified by diagnostic coronary angiography to exclude or confirm the presence of significant left main disease or severe triple vessel disease (3,17–19). Patients with severe left main disease and those with severe three vessel disease may be candidates for coronary bypass surgery but the remainder (majority) of the patients can be managed with medical therapy or with percutaneous coronary interventions (3,9,19–23).

There are no data showing that either coronary bypass surgery or percutaneous coronary interventions or for that matter any of the approved anti-anginal drugs, except in some special situations, reduce mortality or the incidence of myocardial infarction in patients with stable angina pectois (3,5,9,13,20–25). Anti-anginal drugs and revascularization procedures are, however, quite effective in either abolishing or reducing the frequency of anginal symptoms (3,5,9,20–26). On the other hand, life style modifications and other pharmacologic therapy reduce the incidence of death and myocardial infarction but have little effect on symptoms (3,5,9,13). Therefore, it is imperative that physicians should have an open discussion with the patient and his or her family members regarding the myths, benefits, and adverse effects of various therapeutic options available to treat stable angina.

Strategies for Symptom Relief and for Increasing Angina-Free Walking Duration

Available strategies are: 1) to increase myocardial oxygen supply by a coronary revascularization procedure and 2) to reduce myocardial oxygen demand with pharmacotherapy.

Pharmacologic Treatment

In the United States three classes of anti-anginal drugs, organic nitrates, beta-blockers, and calcium channel blockers are approved by the Food and Drug Administration for the treatment of stable angina. In addition, in several European countries and in Asia, nicorandil and trimetazidine are widely used to treat patients with stable angina.

Nitrates, beta-blockers, and calcium channel blockers exert anti ischemic and anti-anginal effects via different mechanisms (Table 1) (13).

Nitrates

Nitrates are potent venodilators and reduce venous return and thus ventricular volumes and pressures with resultant decrease in wall stress. In addition, nitrates dilate stenotic coronary segments (12) and increase collateral blood flow to the ischemic myocardium.

Nitrates have an established role in the treatment of stable angina (26,27). Nitroglycerin administered sublingually increases exercise duration and relieves an established attack of angina. The major problem with nitrate therapy is that continuous or intermittent around the clock use leads to development of tolerance with loss of efficacy (28–33). The exact mechanism of tolerance development is unknown, although several have been proposed (30). The only practical way to avoid tolerance and maintain therapeutic efficacy is to provide either nitrate free or declining nitrate concentration at night in order to maintain therapeutic effects during the waking hours (30). Several nitrate formulations and dosing regimens permit avoidance of nitrate tolerance (Table 2) (3) but with these dosing regimens it is not possible to provide around the clock (24 hour) prophylaxis and the patient remains unprotected at night and in the early hours of the morning (30).

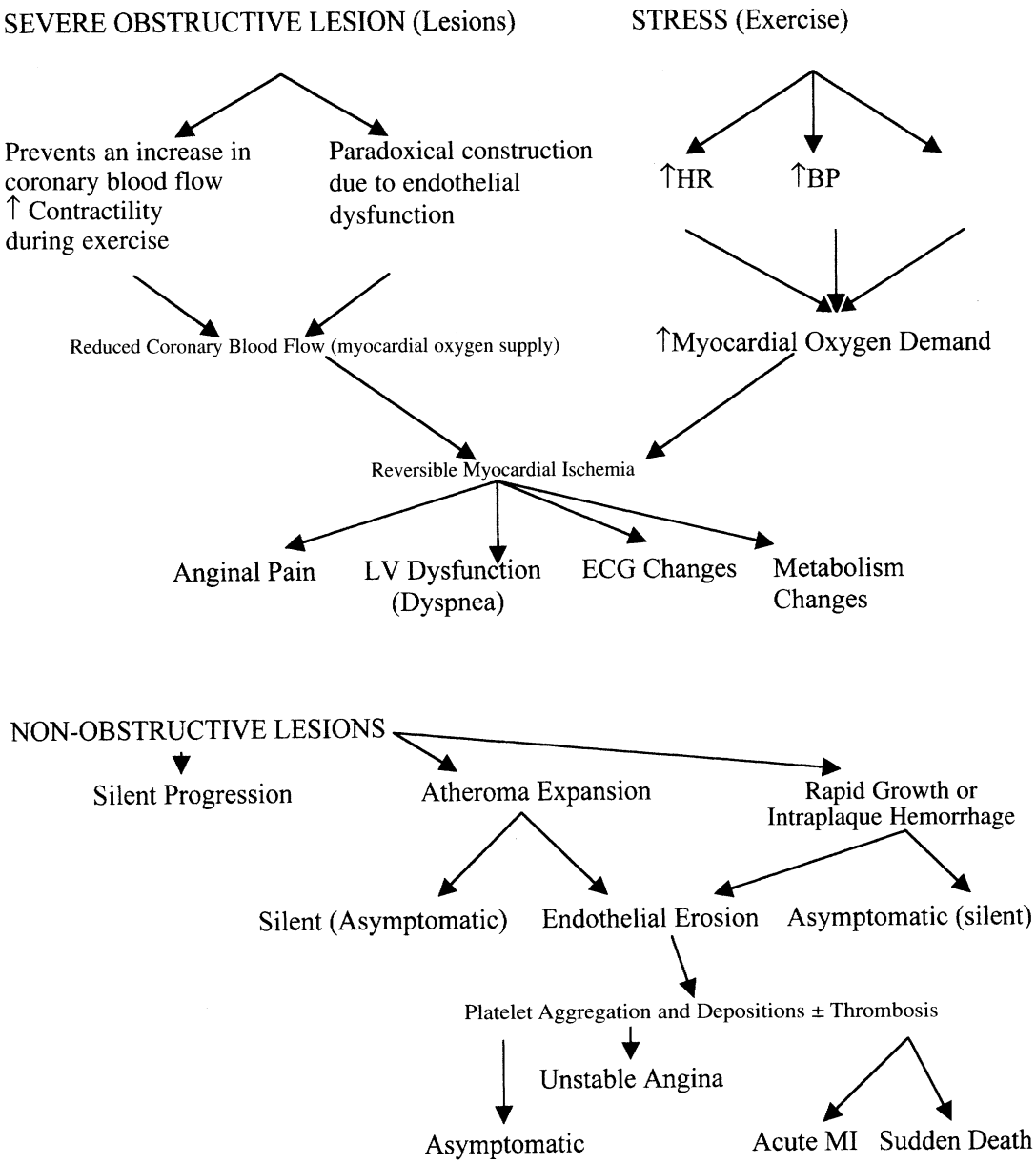

Fig. 1. Pathophysiologic mechanisms of adverse outcomes in stable angina. From Thadani (13).

Also, during intermittent therapy nitrate-induced headaches are common and can be severe necessitating discontinuation of treatment (5,30).

Very rarely, some patients experience nitrate induced syncope, and in these patients nitrate therapy is contraindicated (5,27).

Beta-Blockers

Beta-blockers are the most potent anti-ischemic agents and exert their anti-anginal effect by blocking β_1 receptors, resulting in lowering of heart rate, reduction of myocardial contractility and an attenuation of rise in systolic blood pressure during exercise (34–37). These effects translate into a reduction in myocardial oxygen demand. In addition, beta-blockers increase coronary blood flow during diastole by increasing the diastolic filling period (36). These beneficial effects are in part offset by an increase in wall stress due to ventricular dilation. However, the net effect is a marked reduction in myocardial oxygen demand (36).

In addition to β_1-blockade, some beta-blockers also have β_2 blocking and/or alpha blocking properties and

Table 1. Effects of Anti-anginal Drugs and Revascularization Procedures on Myocardial Oxygen Supply and Demand

	Myocardial Oxygen Demand	Myocardial Oxygen Supply
Nitrates	↓↓↓ (Reduced LV Volume and Wall Stress)	↑ (Dilation of stenotic lesion and increased collateral flow)
Beta Blockers	↓↓↓ (Reduction in HR, SBP and Contractility)	↑ (Increase in diastolic blood flow)
Non Dihydropyridine Calcium channel blockers	↓↓ (Reduction in HR, and PVR)	↑ (Coronary vasodilation)
Dihydropyridine Calcium channel blockers	↓↓ (Reduction in PVR)	↑↑ (Coronary vasodilation)
Coronary Bypass Surgery	No Effect	↑↑↑ (Increased blood flow)
Coronary Angioplasty and/or Stenting	No Effect	↑↑ (Increased blood flow)

LV = left ventricular; HR = heart rates; SBP = systolic blood pressure; PVR = peripheral vascular resistance; ↓ = decrease; ↑ = increase from Thadani (3).

Table 2. Recommended Preparations and Regimens of Nitrates for Chronic Stable Angina

Preparation	Dose	Comments
Nitroglycerin (sublingual)	0.3 to 0.4 mg PRN. Up to 4 tablets 5 min apart	For established attack of angina, or prophylactic prior to physical activity
Isosorbide-5-Mononitrate (Rapid Release)	20 mg in the morning and second dose 7 hours later	Total duration of effect 12–14 hours; no rebound angina during low nitrate periods
Isosorbide-5-Mononitrate (Sustained Release)	120–240 mg in the morning	Duration of effect 10–12 hours; no rebound angina; 30 and 60 mg doses ineffective
Transdermal Nitroglycerin Patches	7.5–10 mg/12 hour; patches removed at night	Duration of effect 10–12 hours; occasional rebound angina at night and poor exercise tolerance, predose zero hour effect
Phasic Release Nitroglycerin Patches	15 mg, most released in first 12 hours	
Isosorbide Dinitrate (Rapid Release)	30 mg bid at 0700 and second dose at 1300 hours	Effective for up to 6 hours after after 0700 dose; no data after 1300 hour dose.

*Other nitrate preparations or formulations and dosing regimens either ineffective or inadequate data; headaches may limit therapy; nitrate-induced syncope due to hypotension is rare but is a contraindication to nitrate therapy. Do not use concomitantly with Viagra. From Thadani (13).

/or intrinsic sympathomimetic activity and some are lipid soluble (lipophilic) while others are water-soluble (hydrophilic) (34–36). However, irrespective of these additional properties, all approved beta-blockers are equally effective in treating patients with stable angina (34–36). Cardioselective agents are preferred in patients with stable angina who also have reactive obstructive airway disease, diabetes mellitus, or peripheral arterial disease (5). For optimal therapy of stable angina with a beta-blocker one should use the maximum tolerated, recommended dose of beta-blockers as shown in Table 3 (3). Adequacy of beta-blockers must be assessed by evaluating their effects on exercise heart rates and not the resting heart rates (37).

In general, beta-blockers are well tolerated, but fatigue, erectile dysfunction, sleep disturbances, and vivid dreams may be troublesome adverse effects in some patients (5). Others are not candidates for treatment with beta-blockers due to underlying severe reactive pulmonary obstructive disease or severe peripheral vascular disease with resting leg pain or high degree AV block or resting sinus bradycardia. Nearly 10% to 15% of patients with stable angina do

Table 3. Beta-Blockers for Chronic Stable Angina*

Preparation	Dose	Comments
Atenolol	50–100 mg od	Cardioselective
Bisoprolol	5–10 mg od	Cardioselective
Metoprolol (Rapid Release)	50–100 mg bid or tid	Cardioselective
Metoprolol XL/CR	50–200 mg od	Cardioselective
Betaxolol	10–20 mg od	Cardioselective
Acebutolol	200–400 mg tid	Cardioselective with ISA
Propranolol (Rapid Release)	40–80 mg bid or tid	Non-cardioselective
Propranolol (Long Acting)	80–320 mg od	
Oxprenolol	40–80 mg tid	Non-cardioselective with ISA
Timolol	5–15 mg tid	Non-cardioselective
Nadolol	80–240 mg od	Non-cardioselective
Carvedilol	25–50 mg bid	Non-cardioselective with α blocking activity
Labetalol	100–200 mg tid	Non-cardioselective with vasodilation activity
Pindolol	2.5–7.5 mg tid	Non-cardioselective, with ISA
Celiprolol	400 mg od	Cardioselective with ISA and B_2 stimulation

*Contraindicated in asthma, severe chronic obstructive pulmonary disease, high grade AV block, peripheral vascular disease with rest leg pain; may cause fatigue, bronchospasm, central nervous system side effects, cold extremities, impotence, bradycardia, hypotension. From Thadani (3).

not benefit from beta-blocker therapy as assessed by objective exercise testing (5,34,35).

Calcium Channel Blockers

Calcium channel blockers are widely used to treat patients with stable angina and are as effective as beta-blockers or nitrates (3,9,26,38–45). They exert their anti-ischemic and anti-anginal effects mainly by vasodilation and reduction of afterload and an increase in coronary blood flow (3). In addition, non-dihydropyridine agents, verapamil and diltiazem, reduce heart rate and rate pressure product during exercise resulting in a decrease in myocardial oxygen demand. In vitro, all calcium channel blockers exert negative inotropic effects, but these effects are offset in part by their predominant afterload reducing effects (38).

If used appropriately and in adequate doses (38–45), Table 4 (3), all currently approved calcium channel blockers are effective anti-anginal agents, although anti-ischemic effects are more pronounced with rate lowering non-dihydropyridine agents, diltiazem and verapamil. Non-dihydropyridine calcium channel blockers should not be used as first line therapy in patients with left ventricular systolic dysfunction as they may worsen heart failure and increase mortality (3,5). In patients with high degree AV block, diltiazem and verapamil may induce complete AV block (5). Bepridil was shown to be superior to diltiazem (46) but in the USA this drug was approved only for the treatment of patients with stable angina who do not respond to other anti-anginal drugs, as bepridil can cause torsade de pointes. Recently marketing of this drug was discontinued due to limited use.

Combination Therapy

Many patients with stable angina remain symptomatic despite treatment with a single agent from a given class (beta-blocker or nitrates or calcium channel blocker). Combination therapy with two agents from a different class i.e. a beta-blocker plus nitrates, or a beta-blocker plus long-acting dihydropyridine calcium channel blocker, or non-dihydropyridine agent diltiazem are often effective in further reducing angina frequency and exerting additional anti-ischemic effects (3,9,40,44,47–53). Calcium channel blockers plus nitrates are widely used in clinical practice, but objective studies regarding the usefulness of this combination therapy has not been adequately studied in patients with stable angina (9). Combination of a beta-blocker with diltiazem, although effective, should be used with caution as it may lead to development of severe bradycardia and high-grade AV block in some patients (5).

Triple therapy with three different classes of drugs is widely used in clinical practice, but there is no objective data showing superiority of triple therapy in comparison to treatment with two agents from a different class (3,5,48,52,53). Triple therapy also increases the adverse effects (5).

Table 4. Calcium Antagonists for Chronic Stable Angina*

Preparation	Dose	Comments
Diltiazem (Rapid Release)	60–120 mg od	Contraindicated in > 1st degree AV block, LV systolic dysfunction
Diltiazem (Slow Release)	80–240 mg bid	
Diltiazem CD	120–420 mg od	240 to 360 mg most effective
Verapamil (Rapid Release)	80–120 mg tid	Contraindicated in > 1st degree AV block, LV systolic dysfunction Constipation a problem in elderly
Nifedipine Slow Release	30–120 mg od	Avoid in aortic stenosis
Amlodipine	5–10 mg od	Avoid in aortic stenosis
Nisoldopine CC/SR	20–40 mg od	Avoid in aortic stenosis
Felodipine	10–20 mg od	Avoid in aortic stenosis

LV = left ventricular. *Ankle edema incidence > with non-dihydropyridine agents. From Thadani (3).

Nicorandil

Nicorandil is a nitrate-moiety, nicotinamide ester adenosine triphosphate (ATP) potassium (K+) channel opener. In several European countries and in Japan, this agent is widely used to treat patients with stable angina (54). An earlier study reported antianginal and anti-ischemic effects (54); studies in the USA and Australia, however, failed to confirm the superiority of nicorandil over placebo (55,56). Nicorandil is not available for clinical use in North America.

Metabolic Modulators

The concept of a pharmacologic approach to treat myocardial ischemia and angina pectoris is a novel one. The heart is an aerobic organ that needs oxygen in order to oxidize substances that provide energy for contraction and other functions (57–61). Free fatty acids (FFAs), glucose and lactate are the primary myocardial fuels that provide ATP (57–61). Under normal conditions, when oxygen is freely available, FFA oxidation generates more ATP molecules overall than glucose oxidation (59,60). However, when oxygen supply to the myocardium is limited, glucose oxidation yields more ATP per oxygen molecule consumed than FFA oxidation and supports more work than FFA oxidation (59,60).

During stress, FFAs increase in concentration and suppress glucose oxidation via inhibition of pyruvate dehydrogenase (13,57–62). This leads to accumulation of lactic acid, ATP breakdown, Na^+ and Ca^+ overload, and reduced cardiac contractility (57–60).

Inhibition of FFA oxidation has been shown to limit lactate production and conserve oxygen, preserve high-energy phosphates and maintain contractility function (13,57–62). Inhibiting FFA oxidation results in increased glucose utilization, which may reduce myocardial oxygen supply needed to support a given level of cardiac work, so that at any given level of coronary flow, myocardial ischemia is less likely (59–64). These metabolic effects are devoid of hemodynamic effects.

Various strategies to inhibit FFA oxidation have been tired in patients with stable angina pectoris. Trimetazidine, a 3-ketocyl co-enzyme thiolase (3-KAT) inhibitor (65), is being used with increased frequency in several European and Asian countries to treat stable angina (65–79). When used as monotherapy or in combination with beta-blockers or calcium channel blockers trimetazidine increases angina-free exercise duration and reduces myocardial ischemia during exercise (66–78). In a recent double-blind parallel placebo controlled trial in 223 patients with stable angina on background treatment with atenolol (50 mg daily) trimetazidine, modified release (MR) 35 mg administered twice daily was compared to placebo (79). After eight weeks of therapy, data was reported in 180 of the 223 patients. After trimetazidine and placebo therapy, the mean changes from baseline for time to onset of 1 mm ST-segment depression were 48 vs 7 seconds, P = 005, time to onset of angina were 20 vs. 6 seconds, P = 0.09 and total exercise duration were 4 vs –11 seconds, P = 0.13, respectively (79). Adverse effects were similar in the two groups (79). Trimetazidine is not available in the USA for clinical use.

The partial fatty acid oxidation (pFox) inhibitor, ranolazine, was shown to exert anti-ischemic effects in rats (80). In earlier studies, smaller doses of standard (rapid release) formulation of ranolazine increased angina-free exercise duration and reduced angina frequency (81,82). In a subsequent, double-blind, randomized study, however, the same doses of standard formulation of ranolazine were not superior to placebo with regard to anti-anginal or anti-ischemic effects (83). In a subsequent study, larger doses of standard formulation of ranolazine administered twice daily increased exercise duration (84).

Monotherapy with the long-acting formulation of ranolazine with doses ranging from 500 mg–1500 mg twice daily, increased exercise duration and reduced exercise-induced ischemia and angina frequency during daily activities compared to placebo (85). This was a four-way period cross-over study and different doses of ranolazine and placebo were administered in a random manner. Patients were exposed to each dose for a period of two weeks. A dose-response relationship was observed with increases in total exercise duration of 22 to 48 seconds compared to placebo ($P < 0.005$). Time to onset of angina was prolonged by 25 to 60 seconds ($P = 0.005$), and time to 1 mm ST segment depression was prolonged by 22–66 seconds ($P < .001$) after ranolazine compared to placebo. Dizziness, constipation, nausea and asthenia were experienced with greater frequency during 1500 mg twice daily dosing.

In a subsequent double-blind parallel study effects of placebo or 750 mg or 1000 mg of sustained release ranolazine administered twice daily were evaluated over a 12-week period in patients with stable angina, who were symptomatic despite treatment with either a beta blocker or a calcium channel blocker (86). Patients had exercise induced angina and myocardial ischemia despite treatment with either 50 mg atenolol, or 180 mg of diltiazem in a once a day formulation or 5 mg of amlodipine once a day. No long acting nitrates were allowed. Patients were allowed to take sublingual nitroglycerin if needed. A total of 823 patients were randomized and at enrollment, 354 patients (45%) were taking atenolol, 256 (31.1%) amlodipine, and 213 (25.9%) diltiazem. Ranolazine reduced the mean angina attacks per week from 3.3 for placebo to 2.5 for 750 mg ($P = 0.006$) to 2.1 for 1000 mg ($P = < 0.001$). Total exercise duration after 12 weeks of therapy increased in both the placebo and active ranolazine groups (116 vs. 92 seconds) but compared to placebo increases were greater after both doses of ranolazine ($P < 0.01$). Compared to placebo time to onset of angina increased by 30 and 26 seconds and time to 1 mm ST-segment depression by 20 and 21 seconds respectively after 750 and 1000 mg twice-daily therapy with ranolazine. There were no changes in heart rate, and the average decrease in systolic blood pressure was less than 3 mmHg. The most common dose-related adverse effects were constipation, dizziness, nausea, and asthenia (≤ 7.3% in both ranolazine groups; ≤ 0.7% in the placebo group). Mortality was similar in ranolazine and placebo groups but 5 patients in the 1000 mg ranolazine group experienced syncope. Four of the patients were taking diltiazem and all five were taking an angiotensin converting enzyme inhibitor. There were no documented cases of ventricular arrhythmias or *torsade de pointes* reported in this study. Small dose-related increase in QTc intervals of less than 10m sec were observed but were not considered clinically relevant. Syncope observed in the 1000 mg dose group was a concern but the mechanism of syncope remains unknown at present (86).

At present, ranolazine is not approved by the FDA for clinical use. The data was recently presented to the FDA Cardiorenal Advisory Committee on 6th December 2003 and the consensus of the committee members was that ranolazine is an effective anti-anginal and anti-ischemic agent but more data regarding safety and efficacy during concomitant anti-anginal therapy are needed. The usefulness and safety of ranolazine plus long-acting nitrate therapy has not been studied.

At present, metabolic modulators hold great potential as anti-anginal and anti-ischemic drugs for treating patients with ischemic heart disease, as these agents are devoid of major circulatory, hemodynamic and pulmonary effects. Patients with contraindications to currently available antianginal drugs and those who remain symptomatic despite optimal antianginal therapy will be candidates for treatment with a metabolic modulator. This group of drugs also holds promise as monotherapy for patients with stable angina, provided they are devoid of serious adverse events.

Sinus-Node Blocking Agents

Sinus node blockers reduce heart rate by blocking I_f current in the sinus node. Zatebradine, exerted anti-anginal and anti-ischemic effects in some but not in other studies (87). When added to extended release nifedipine, zatebradine did not provide additional benefit (88). The drug induced visual side effects and was not further developed.

In a double-blind, placebo controlled study, ivabradine (2.5, 5, or 10 mg twice daily) produced dose-

dependent improvements in exercise tolerance and time to development of ischemia during exercise (89). The drug was effective and safe during 3 months of use (89). In another trial ivabradine was shown to be as effective as atenolol (unpublished data). Ivabradine is not yet available for clinical use but has a potential for use in patients with stable angina who are not candidates for beta-blocker treatment.

ACE Inhibitors

In earlier studies, ACE inhibitors exerted variable anti-ischemic effects (3,5). In a recent large placebo-controlled trial, Quinapril did not increase angina-free walking time or reduce exercise-induced or ambulatory ischemia (90).

Revascularization Procedures

Percutaneous interventions to dilate stenotic coronary arteries and coronary bypass surgery increase blood flow to the ischemic myocardium. Both modalities relieve angina and reduce or abolish exercise-induced ischemia (3,9). The treatment effects are obvious soon after the procedure, but neither procedure reduces mortality or the incidence of myocardial infarction compared to antianginal drug therapy (9,20–25,91–94).

Percutaneous Coronary Revascularization

Balloon dilation of stenotic coronary lesions with or without stent placement abolishes or reduces the frequency of anginal symptoms, increases angina-free walking duration and reduces exercise-induced ischemia (3,92–100). Compared to medical therapy, symptom relief is immediate and of greater magnitude, but restenosis of the dilated lesions occurs in 20% to 40% of patients necessitating a repeat procedure or bypass surgery (92–94). Restenosis rates are even higher in diabetic patients (92). Recently drug-coated stents were approved by the Food and Drug Administration. Initially it was claimed that drug coated stents have 0% restenosis, but recent reports suggest a restenosis rate of 8% to 11% (95–100). Subacute thrombosis, which may be fatal, remains a concern following stent placement, including drug-coated stents and has been reported in 0.5% to 1% of patients (100). Serious adverse outcomes at six months following drug-coated stents were reported in 9% compared to 14% following bare stents in the same institution (100).

The majority of patients who undergo PTCA/stenting are maintained on anti-anginal drugs and it is difficult to evaluate the true beneficial effects of PTCA/stenting in the absence of concomitant anti-anginal drug therapy.

In a recent study in CCS Class II angina, optimal medical therapy, which also included high doses of the lipid-lowering agent atorvastatin was more effective in reducing adverse clinical outcomes compared to PTCA/stenting, although, symptom relief initially occurred more often with PTCA/stenting (101).

Trials have shown that PTCA/stenting is equally effective compared to coronary bypass surgery with the exception that symptoms recur more often following PTCA/stenting and a repeat revascularization procedure is needed in 20% to 30% of patients (3,9,20–22,94).

PTCA/stenting does not reduce the incidence of death or myocardial infarction in patients with stable angina (9,92–94). On the contrary, the reported incidence of peri-procedural biochemical myocardial infarction is 4% to 7% (3,9).

Coronary Artery Bypass Surgery

Coronary artery bypass surgery is highly effective in relieving angina and myocardial ischemia. However, many patients subsequently develop obstructive lesions in the venous conduits necessitating further risky interventions (3,5,20–25). Arterial conduits are preferred as late occlusion in the arterial conduits occurs less frequently (102).

Coronary bypass surgery, although effective, is associated with 1% to 3% mortality and significant morbidity (3,5,9). Published randomized trials have failed to show that coronary bypass surgery either reduces mortality or the incidence of myocardial infarction compared to medical treatment or PTCA/stenting (3,5,13,20–25,92). Subgroup analysis of the published data has shown beneficial effects of coronary bypass surgery in patients with left main stenosis and in those with three-vessel disease in one study and three-vessel disease with diminished left ventricular function in another study (20–25). Therefore, it should be reserved for patients with left main stenosis or those with multivessel disease and reduced LV systolic function and for patients who do not respond adequately to pharmacologic therapy and or PTCA/stenting procedures.

Strategies to Reduce Serious Adverse Clinical Outcomes (Death, Myocardial Infarction)

Although anti-anginal strategy provides symptomatic relief, it does not reduce the incidence of serious adverse clinical outcomes (3,9,13), which occur frequently in patients with stable angina. These serious adverse clinical outcomes manifest as acute coronary syndromes including sudden death or myocardial infarction. They occur at random and are usually due to disruption of non-obstructive lesions. In order to reduce the occurrence of these adverse clinical outcomes, the following strategies must be used in addition to anti-anginal strategies.

Smoking Cessation

Smoking cessation is a must in all patients with stable angina because it reduces the risk of coronary disease mortality by 50% in one year. After 10–15 years, the coronary mortality risk reaches that of non-smokers (103). Stopping smoking not only reduces cardiovascular mortality and morbidity, it also has a positive effect on exercise performance in patients with stable angina (3,5).

Aspirin

Daily aspirin is recommended for all patients with stable angina, unless there is a definite contraindication such as an allergic reaction, or major gastrointestinal side effects (104–106). In patients with stable angina daily aspirin reduced cardiovascular mortality and morbidity with an absolute reduction of 12 additional deaths for every 1000 patients treated during a 15-month period (104). Other available data has uniformly shown beneficial effects of daily aspirin (81 mg to 321 mg) in patients with acute myocardial infarction and unstable angina (105,106). Thus, daily aspirin is an inexpensive and effective way to reduce adverse clinical outcomes in patients with stable angina irrespective of coronary artery disease severity and whether the patient has or has not undergone revascularization procedures.

Clopidogrel

Clopidogrel when used for up to 11 months reduced adverse clinical outcomes in patients with non-ST elevation acute coronary syndrome (107). In patients who do not tolerate aspirin, clopidogrel 75 mg daily may be substituted, but the effectiveness of this drug in patients with stable angina is unknown at present and is being evaluated in the large multicenter CHARISMA study.

Lipid Lowering Therapy

No specific trials with lipid lowering agents have been conducted primarily in patients with stable angina (3,9). However, in the Scandinavian simvastatin (4S) trial, many patients had a history of stable angina (108). In this large study, simvastatin reduced total mortality by 30%, cardiovascular mortality and morbidity by 42% and the need for revascularization procedures by 37%. This trial and other primary and secondary prevention trials especially with statins have clearly established the beneficial effects of lipid lowering therapy with statins in patients with coronary artery disease (109).

Current guidelines recommend fasting LDL cholesterol of less than 100 mg/dL in patients with stable angina due to coronary artery disease. However, this approach is questionable as in a recent large trial in 20,536 patients with a history of coronary heart disease, diabetes or major cardiovascular risk factors (British Heart Protection Trial), with fasting total cholesterol greater than 135 mg/dL, a fixed dose of simvastatin 40 mg resulted in a significant reduction in total mortality, vascular morbidity and mortality and need for revascularization procedures (110). The benefit of simvastatin was seen both in men and women and in elderly to a similar extent irrespective of baseline LDL levels, which in many patients were less than 100 mg/dL. Therefore, all patients with stable angina due to coronary artery disease should be treated with 40 mg simvastatin daily provided their total cholesterol level is above 135 mg/dL and there are no contraindications to statin therapy.

In men who have low fasting HDL levels of < 40 mg/dL and LDL levels less than 130 mg/dL, treatment with 600 mg twice a day gemfibrozil reduced cardiovascular mortality and morbidity (111). Nicotinic acid is an alternative in this group of patients, although definitive outcome trials have not been performed with this agent.

The combination of a statin plus a fibrate should be used with caution as the incidence of rhabdomyolysis increases and there are no outcome studies evaluating the beneficial effects of this combination therapy. Combination treatment of statins and nicotinic acid has not been adequately studied in patients with stable angina or coronary artery disease.

Omega 3 Fatty Acids

There are no published trials of Omega 3 fatty acid in stable agnina, but secondary prevention trials in post-myocardial infarction patients have shown a significant reduction in cardiovascular mortality and morbidity with Omega 3 fatty acids (112). What is not known, is whether Omega 3 fatty acids exert further additional benefits when added to aspirin and statins or are equally or more effective than these agents.

Moderate Alcohol Intake

There are no placebo-controlled studies showing beneficial effects of alcohol on cardiovascular morbidity and mortality in patients with stable angina. However, alcohol consumption in moderation (up to 2 glasses of wine per day) has been shown to reduce the incidence of myocardial infarction in observational studies. Therefore, patients with stable angina can consume alcohol in moderation (113).

Angiotensin Converting Enzyme Inhibitors

Routine use of ACE inhibitors is recommended by US and European guidelines on the basis of published data showing improvement in cardiovascular modality and morbidity in patients with coronary artery disease who have reduced left ventricular systolic function (ejection fraction < 40%) and in patients with stable CAD (20–24,114).

At present ACE I should be used in patients with stable angina who have reduced LV function EF < 40% (3,13,20–23,114–117). Patients with stable angina who have diabetes and proteinuria also should be treated with ACE I as these drugs slow the progression of chronic kidney disease (3). In other patients with stable angina, routine use may be justified on the basis of the recently published EUROPA Trial (118). However, in that trial left ventricular function was not routinely measured. The results of the recently completed PEACE trial (119) in patients with documented CAD and preserved LV function is eagerly awaited. Patients, who experience cough from ACE inhibitors, may be treated with an angiotensin receptor blocker.

Beta-Blockers

Beta-blockers are most effective anti-ischemic agents. These agents improve survival and reduce hospitalization in patients with reduced LV systolic function (EF < 40%) and in survivors of an acute myocardial infarction (120–124). Therefore, beta-blockers should be used as first line agents in patients with stable angina who have reduced LV function provided these patients are on background treatment of ACE I and also preferably digoxin. In mildly symptomatic patients with ischemia during daily activities, daily treatment with atenolol reduced composite end point of death, myocardial infarction, need for revascularization and worsening angina compared to medical therapy (124).

Anti-ischemic Versus Anti-anginal Versus Revascularization Strategy to Improve Clinical Outcomes in Patients with Stable Angina

In a pilot NIH sponsored study, revascularization strategy and anti-ischemic guided therapy were superior to anti-anginal guided therapy (125). However, the event rate was low and a large prospective study is needed before accepting the superiority of anti-ischemic strategy over anti-anginal guided strategy.

Nicorandil

In a large placebo controlled study (IONA Trial) nicorandil reduced the composite endpoint of death, myocardial infarction, worsening angina in patients with stable coronary artery disease (126). The drug is available in Europe for clinical use but not in the USA.

Treatment of Concomitant Hypertension

Many patients with stable angina have co-existing hypertension. Current evidence suggests that adequate control of blood pressure to levels below 140/90 mmHg in all hypertensives and below 130/85 mmHg in patients with diabetes reduces stroke rate by 40% to 52% and cardiovascular morbidity by 18% to 20% (127). Initial trial of a beta-blocker or a calcium blocker is justified as these agents exert anti-anginal effects in addition to lowering blood pressure. Additional therapy with a diuretic (chlorthalidone or hydrochlorothiazide) and other anti-hypertensive agents should be used to adequately control the blood pressure (128).

Management of Patients with Stable Angina with Comorbid Conditions

The presence or absence of comorbid conditions influences the selection of therapy. Preferred initial antianginal drug therapy is outlined in Table 5 (3).

Management of Patients with Refractory Stable Angina

In recent years, there has been an increase in the numbers of patients who continue to remain symptomatic despite optimal medical therapy with beta-blockers, calcium channel blockers and regimens and formulations of nitrates that do not produce tolerance (129,130). In addition, these patients either due to unsuitable anatomy or comorbid conditions are not candidates for a revascularization procedure. Many have had coronary bypass surgery several years previously and have developed progression of coronary artery disease in their native coronary arteries and occlusions of the bypass venous and or arterial conduits.

In some of these patients, percutaneous revascularization or a repeat bypass surgery is attempted but these procedures are associated with a significant morbidity and increased mortality (130).

For the patient with refractory angina, it is imperative to treat concomitant conditions, such as, anemia, thyrotoxicosis, arrhythmias, uncontrolled hypertension which are known to aggravate ischemia and anginal symptoms. Treatment of these disorders often relieves symptoms.

It is also worth trying to adjust anti-anginal treatment as treatment with two drugs from a different class are often superior to triple anti-anginal therapy (3,5,13,53). All patients with refractory angina must stop smoking and be treated with daily aspirin, lipid lowering agents, especially statins and ACE inhibitors as these medications reduce the incidence of serious adverse clinical outcomes such as death and myocardial infarction.

In recent years non-pharmacologic invasive procedures such as enhanced external counterpulsation (EECP) and transcutaneous nerve stimulation (TENS) and invasive procedures such as spinal-cord stimulation (SCS) and to a lesser extent transmyocardial laser revascularization (TMLR), are gaining popularity (129,130). The use of many of these treatment modalities in patients with disabling angina is not based on well-designed placebo or Sham controlled trials. This subject has been reviewed recently (129,130) and is briefly outlined here.

Enhanced External Counterpulsations (EECP)

EECP mimics the principles of intra-aortic balloon pump counter pulsation in that EECP augments coro-

Table 5. Antianginal Treatment Options in Patients With and Without Concomitant Disease

Concomitant Disease	Long-Acting Nitrates	β-blockers	Calcium Antagonists	
			Long-Acting DHP	Non-DHP[a]
None	+++	+++	++	+++
Hypertension	+	+++	++	+++
Recent MI	+++	+++	0	+[b]
Reduced LV function	+++	+++	0	0
SVT	+	+++	0	+++
Mild COPD	+++	+	+++	+++
Severe COPD, Asthma	+++	0	+++	+++
PVD	++	++	+++	++
Type 1 (insulin-dependent) diabetes mellitus	+++	+	+++	+++
Type 2 (non-insulin-dependent) diabetes mellitus	+++	++	+++	+++
Chronic renal disease	+++	++	+++	+++
Sinus bradycardia (50 beats/min or AV block > first degree	+++	0	+++	0

[a]Verapamil and diltiazem.

[b]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. From Thadani (3).

nary blood flow in diastole and facilitates left ventricular blood flow in systole. The EECP device currently marketed for clinical use consists of three paired pneumatic cuffs that are applied to lower extremities. The cuffs are sequentially inflated by applying 250 to 300 mmHg of external pressure during diastole. This increases venous return to the heart, with resultant increase in cardiac output. An increase in aortic cardiac output and pressure increases coronary blood flow in diastole. The cuffs are deflated simultaneously in systole reducing peripheral resistance to flow and thus providing left ventricular unloading and easier emptying in systole.

The exact mechanism by which EECP improves and maintains improvement in patients with stable angina remains unclear (130), although various mechanisms including an increase in collateral blood flow to the ischemic areas, improvement in diastolic filling, improvement in endothelial function (131–133) and neovascularization (angiogenesis) in the ischemic areas have been proposed but not proven (130).

Treatment requires one-hour sessions, five times a week for a total of 35 sessions and the treatment is expensive. There are no double-blind, Sham controlled studies of EECP in patients with refractory stable angina. Published data are from earlier uncontrolled studies and from recent registry data (130). The only Sham-controlled study was in patients with stable angina with Canadian Cardiovascular Society Classification (CCS) Class I to III in whom the active treatment group showed an increase in time to stress induced ischemia compared to Sham group (37 ± 11 seconds vs. –4 ± 12 seconds, $P = 0.05$), but there was no significant increase in total exercise duration (133). However, the active EECP group experienced a greater reduction in angina frequency, compared to the Sham treatment group. Only a selected group of patients were studied and many patients with uncontrolled hypertension, a history of severe peripheral vascular disease, patients on coumadin and those in atrial fibrillation or frequent ventricular percutaneous beats were excluded. Of the 133 randomized patients, only 115 completed the study; more patients in the active group (n = 14) than Sham group (n = 4) did not complete the study (130,133).

Subsequent to the approval of the EECP device for clinical use, EECP Registry was kept and in a report of 2289 consecutive patients enrolled in an EECP consortium, EECP was found to be safe and well tolerated with a 4.0% rate of adverse experiences (134). Angina class improved in 70% of patients with limiting CCS angina class III and IV; patients who were most impaired at baseline demonstrated the greater improvement.

The Registry data was updated in 2002 and showed similar results (135). It is unclear from the Registry data whether all patients were on optimal medical therapy and whether they were or were not candidates for revascularization. Sham (placebo)-controlled studies are needed prior to routine acceptance of EECP for treatment of refractory angina, as placebo effect with relief of symptoms is well described in patients with stable angina.

Neuromodulation (Spinal Cord Stimulation) and other Neurologically Based Therapies

Acupuncture, thoracic epidural anesthesia, stellate ganglion block, and sympathectomy have been tried in isolated reports for the management of refractory angina (143). No Sham-controlled studies have been published. Transcutaneous nerve stimulation (TENS) was shown to improve exercise tolerance, prolong time to pacing-induced ischemia and reduce sympathetic discharge (136–142). A possible placebo effect could not be excluded. For TENS, electrodes are applied to the chest, one in the dermatome with the highest intensity of projected or perceived pain and the other in the contralateral dermatome. The stimulus intensity is adjusted below the individual's pain threshold. TENS leads to high frequency stimulation of large non-nociceptive myelinated A fibers and inhibits the impulse through smaller nonmyelinated type C fibers, thereby reducing the activation of control pain receptors.

TENS units have been successfully used to treat refractory angina, but is not widely used because of local skin complications and lack of large, controlled trials.

Spinal Cord Stimulation (SCS)

Low voltage electric stimulation of the spinal cord inhibits the sensation of pain (143). The sensation of stimuli is perceived as paresthesia. The dorsal spine is opened and an electrode is placed at the level of the T_4 and T_5 vertebra; a lead is placed at T_1 and T_2 level. During the procedure, the field of paresthesia produced is noted in the awake patient and this should be in the area of referred pain. The stimulation device is connected to the lead and implanted under the skin in the abdomen or lower thorax. The current applied varies from 2 to 7 volts, at rates of 30 to 90 Hz and a pulse width of 210 to 450 _JEK. The device has a

simple control mechanism and the patient can turn the device on and off and can increase or decrease the amplitude of the current depending on the pain intensity. The mechanism by which pain is alleviated is either direct inhibition of secondary pathways carrying the pain stimuli or a reduction of myocardial ischemia.

Open clinical trials with SCS have shown a marked reduction in angina frequency, improvement in exercise tolerance and reduction in ischemic episodes (144–156). In a recent trial SCS was compared to coronary bypass surgery in patients with limiting angina CCS class III and IV (155). There was a similar reduction in angina frequency but a greater increase in exercise workload and reduction in exercise induced ischemia with coronary bypass surgery. However, mortality was higher in the coronary bypass group. A larger multicenter study is currently underway to evaluate the usefulness of SCS in patients with refractory angina. At present SCS is mostly used in Scandinavian countries.

Transmyocardial Laser Revascularization

It has been proposed that transmyocardial channels open after transmyocardial revascularization and may lead to angiogenesis (157–160). However, published data show that channels close with time and angiogenesis remains unproven. The most likely mechanism of action of TMLR is cardiac denervation (161). Surgical TMLR has been performed only in patients who are not candidates for revascularization and have viable but ischemic myocardium. Both CO_2 and homium: YAG lasers have been approved by the FDA Device Committee for clinical use in patients with refractory angina (162–169). To date, there are no Sham-controlled studies (130). In open trials, improvement in anginal symptoms but no improvement in 12-month mortality rates has been reported. Sham-controlled studies have not been performed, as thoracotomy is required (130). However, a placebo effect of the TMLR remains a strong possibility as recent Sham-controlled trials with percutaneous transmyocardial revascularization (PTMLR) have failed to confirm the beneficial effects of open label trials with PTMLR (170–172).

Newer Promising but Unproven Therapies: Metabolic Modulation

In animals, inhibitors of oxidative phosphorylation and substrate utilization from fatty acid and oxidation of glucose metabolism ameliorates experimental myocardial ischemia. Studies with trimetazidine and ranolazine have shown improvement in exercise tolerance, reduction in myocardial ischemia and frequency of angina in patients with stable angina who were still symptomatic despite background therapy with one of the conventional anti-anginal drugs such as a beta-blocker or a calcium channel blocker. Patients in these studies were however, not on optimum antianginal therapy with regards to dosage of the medications or combination therapy of different classes of anti-anginal drugs.

Metabolic modulators, as a class, nevertheless hold great promise for managing patients with refractory angina, as these agents are devoid of negative chronotropic or inotropic effects and do not significantly lower blood pressure at the doses used. Further placebo-controlled studies are needed to evaluate the efficacy and safety of these agents in patients with refractory angina despite optimal medical therapy.

Sinus Rate Lowering Agents

Ivabradine lowers sinus rates at rest and during exercise and in recent trials it reduced angina frequency and myocardial ischemia and increased exercise time to onset of angina in patients with stable angina. One can anticipate using this drug or drugs from a similar class in patients who are either not candidates for a beta-blocker or experience adverse events. Studies in patients with refractory angina are needed to better define the role of these agents in refractory angina.

Other Experimental Therapies

Angiogenic gene therapy to stimulate angiogenesis holds promise. Earlier uncontrolled studies have shown a beneficial effect on angina frequency and exercise duration (173–178). Double-blind studies are ongoing to evaluate the usefulness of gene therapy in patients with stable angina and in those refractory to medical therapy and not candidates for revascularization procedures.

Proposed Management of Chronic Stable Angina

The majority of the patients with stable angina can be managed medically. Recurrent and refractory angina following revascularization procedures in patients

Table 6. Proposed Treatment for Patients with Stable Angina Pectoris

All patients	Daily aspirin (acetylsalicylic acid), smoking cessation, treat dyslipidemia. Control of high blood pressure to levels ≤ 140/90 mm Hg, and to 120/80 mm Hg in diabetics.
LM or 3 vessel CAD with decreased LV function	Coronary artery bypass surgery if feasible; ACE inhibitor and beta-blockers when EF < 40%.
One vessel, 2 vessel or 3 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, EECP, TMLR, spinal cord stimulation, transthoracic sympathetic denervation or heart transplant.

CAD = coronary artery disease; EECP = External Enhanced Counter Pulsation; EF = ejection fraction; LM = left main coronary artery; LV = left ventricular; PTCA = percutaneous transluminal angioplasty; TMLR = transmyocardial laser revascularization. From Thadani (3).

with stable angina remains a concern (179). The emphasis of therapy must be in preventing serious adverse clinical outcomes in addition to therapy aimed at relief of symptoms. Patients with stable angina pectoris should be encouraged to exercise regularly. A recent study showed that exercise training and continued medical treatment was superior to percutaneous coronary angioplasty in patients with stable angina pectoris (180). The proposed therapeutic options are shown in Table 6 (3).

References

1. Heberden W. Some account of a disorder of the breast. Med Trans R Coll Phys 2:59, 1772
2. Thadani U. Medical therapy of stable angina pectoris. Cardiol Clin 9:73–88, 1991
3. Thadani U. Stable angina pectoris. In: Crawford MH, Dimarco JP, eds. Cardiology Mosby 6.1–6.14, 2001
4. Pepine CJ, Abrams J, Mark RA, et al. Characteristics of a contemporary population with angina pectoris. TIDES Investigators. Am J Cardiol 74:226–231, 1994
5. Asirvatham S, Sebastian C, Thadani U. Choosing the most appropriate treatment for stable angina: Safety considerations. Drug Saf 19:23–44, 1998
6. Braunwald E, Sobel B. Coronary blood flow and myocardial ischemia. In: Braunwal E, ed. Heart disease: A textbook of cardiovascular medicine. Philadelphia: WB Saunders, pp. 1191–1221, 1988
7. Thadani U, Olson EG, Hamilton SF. Pathophysiology of myocardial ischemia. In: Abrams J, Pepine CE, Thadani U eds. Medical therapy of ischemic heart disease. Nitrates, beta-blockers and calcium antagonists. Boston: Little Brown, pp. 1–36, 1992
8. Sarnoff SJ, Braunwald E, Welch GH, et al. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. Am J Physiol 132:148–156, 1958
9. Thadani U. Management of stable angina pectoris. Prog Cardiovasc Dis 14:349–358, 1999
10. Davies MJ, Thomas AC. Plaque fissuring: The cause of acute myocardial infarction, sudden ischemic death, and crescendo angina. Br Heart J 53:363–368, 1985
11. Thadani U, Chohan A. Chronic stable angina pectoris: Strategies for effective drug therapy. Postgrad Med 98:175–188, 1995
12. Gage JE, Jess DM, Murakami T, et al. Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: Reversibility by nitroglycerin. Circulation 73:865–871, 1986
13. Thadani U. The Pursuit of optimum outcomes in stable angina. Am J Cardiovasc Drugs (suppl 1), pp. 11-20, 2003
14. Hinton TC, Chaitman BR. The prognosis in stable and unstable angina. Cardiol Clin. 9:27-38, 1991
15. Myers J, Prakash M, Partington S, Atwood E. Exercise capacity and instability among men referred for exercise testing. N Eng J Med 346:793-780, 2002
16. Mark DB, Shaw L, Harrell GE, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary disease. N Eng J Med 325:849–853, 1991
17. Dagianti A, Penco M, Agati L, et al. Stress echocardiography: Comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. J Am Coll Cardiol 26:18–25, 1995
18. Wackers FJTH, Soufer R, Zaret BL. Nuclear cardiology. In: Braunwald E, ed. Heart disease: A textbook of cardiovascular medicine. Philadelphia: WB Saunders pp. 273–359, 1997
19. Thadani U. Management of patients with chronic stable angina at low risk for serious cardiac events. Am J Cardiol 79:24–30, 1997

20. Task Force of the European Society Cardiology: Management of stable angina pectoris: Recommendations of the Task Force of the European Society Cardiology. Eur Heart J 18:394–413, 1997
21. Canadian Cardiovascular Society 1997 Consensus Conference on the Evaluation and Management of Chronic Ischemic Heart Disease. Can J Cardiol 14(Suppl C):1c–23c, 1998
22. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA/ACP-ASIM Guideline update for the management of patients with chronic stable angina: summary and abstract. Circulation 107:143–158, 2003
23. Yusuf S, Zucker D, Peducci P, et al. Effect of coronary artery bypass graft surgery on survival: Overview of ten year results from randomized trials by the coronary artery bypass graft surgery trialists collaboration. Lancet 344:563–570, 1994
24. Peduzzi P, Kamina A, Detre K, for the VA Coronary Artery Bypass Surgery Cooperative Study Group. Twenty-two-year follow-up in the VA cooperative study of coronary artery bypass surgery for stable angina. Am J Cardiol 81:1393–1399, 1998
25. Hartigan PM, Giacomini JC, Folland ED, Parisi A, for VA Cooperative Studies Program ACME Investigators. Two- to three-year follow-up of patients with single-vessel coronary artery disease randomized to PTCA or medical therapy (results of a VA cooperative study). Am J Cardiol 82:1445–1450, 1998
26. Heidenreich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing β-blockers, calcium antagonists, and nitrates for stable angina. JAMA 281: 1927–1936, 1999
27. Thadani U, Opie LH. Nitrates. In: Opie LH, ed. Drugs for the heart, 4th ed. Philadelphia: WB Saunders, pp. 31–48, 1995
28. Thadani U, Lipicky RJ. Short and long acting oral nitrates for stable angina pectoris. Cardiovasc Drugs Ther 8:611–623, 1994
29. Thadani U, Lipicky RJ. Ointments and transdermal nitroglycerin patches for stable angina pectoris. Cardiovasc Drugs Ther 8:625–633, 1994
30. Thadani U. Nitrate tolerance, rebound and their clinical relevance in stable angina pectoris, unstable angina and heart failure. Cardiovasc Drugs Ther 10:735–742, 1996
31. Thadani U, Fung HL, Darke AL, Parker JO. Oral isosorbide dinitrate in angina pectoris: Comparison of duration of action and dose response relationship during acute and sustained therapy. Am J Cardiol 49:411–419, 1982
32. Parker JO, Van Koughnett KA, Fung HL. Transdermal isosorbide dinitrate in angina pectoris. Am J Coll Cardiol 54:8–13, 1984
33. De Mots H, Glasser SP. Intermittent transdermal nitroglycerin therapy in the treatment of chronic stable angina. J Am Coll Cordiol 13:786–792, 1989
34. Thadani U, Sharma B, Meeran MD, et al. Comparison of adrenergic beta-receptor antagonists in angina pectoris. BMJ 1:138–142, 1973
35. Thadani U, Davidson C, Simpleton W, Taylor SH. Comparison of the immediate effects of five beta adrenoceptor blocking drugs with different ancillary properties in angina pectoris. N Engl J Med 300:750–755, 1979
36. Opie LH, Sonnenblick EH, Frishman W, Thadani U. Beta blocking agents. In: Opie LH, ed. Drugs for the heart. Philadelphia: WB Saunders pp. 1–27, 1995
37. Thadani U. Assessment of 'optimal' beta-blockade in treating patients with angina pectoris. Acta Med Scand 694(Suppl):179–187, 1985
38. Opie LH. Calcium channel antagonists in the treatment of coronary artery disease: Fundamental pharmacological properties relevant to clinical use. Prog Cardiovasc Dis 38:273–290, 1996
39. Thadani U. Selective L-Type, and non-selective calcium channel blockers for stable angina pectoris (editorial). Am Heart J 144:8–10, 2002
40. Dargie HJ, Ford I, Fox KM, on behalf of the TIBET Study Group. Effects of ischemia and treatment with atenolol, nifedipine SR and their combination on outcomes in patient with chronic stable angina. Eur Heart J 17:104–112, 1996
41. Thadani U, Glasser S, Bittar N, et al. Dose-response evaluation of once-daily therapy with a new formulation of diltiazem for stable angina pectoris. Am J Cardiol 74:9–17, 1994
42. Rehnquist N, Hjemdahl P, Billing E, et al. Effect of metoprolol versus verapamil in patients with stable angina pectoris. The angina prognosis study in Stockholm (APSIS). Eur Heart J 17:76–81, 1996
43. Pepine CJ, Faich G, Makuch R. Verapamil use in patients with cardiovascular disease: An overview of randomized trials. Clin Cardiol 21:633–641, 1998
44. Frishman W, Glasser S, Stone P, et al. Comparison of controlled onset, extended release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. Am J Cardiol 83:507–514, 1999
45. Shapiro W, Dibianco R, Thadani U. Comparative efficacy of 200, 300, and 400 mg of bepridil for chronic, stable angina pectoris. Am J Cardiol 55:36C–42C, 1985
46. Singh BN. Comparative efficacy and safety of bepridil and diltiazem in chronic stable angina pectoris refractory to diltiazem. The bepridil Collaborative Study Group. Am J Cardiol 68:306–312, 1991
47. Frishman WH, Crawford MW, Dibianco R, et al. Combination propranolol-bepridil therapy in stable angina pectoris. Am J Cardiol 55:43C–49C, 1985
48. Thadani U. Combination therapy. Am Coll Cardiol Curr J Rev 6:24–25, 1997
49. Dunselman P, van Kempen L, Bouwens L, et al. Value of the addition of amlodipine to atenolol in patients with angina pectoris despite adequate beta blockade. Am J Cardiol 81:128–132, 1998
50. Knight C, Fox K. Amlodipine versus diltiazem as additional antianginal treatment to atenolol. Am J Cardiol 81:133–136, 1998
51. Strauss WE, Parisi AF. Combined use of calcium channel and beta blockers for the treatment of stable angina, rationale, efficacy and adverse events. Ann Intern Med 109:570–575, 1988
52. Akhras F, Jackson A. Efficacy of nifedipine and isosorbide mononitrate in combination with atenolol in stable angina. Lancet 338:1036–1039, 1991

53. Tolins M, Weir EK, Chesler E, Pierpont GL. Maximal drug therapy is not necessarily optimal in chronic angina pectoris. Am Coll Cardiol 4:1051–1057, 1984
54. Meany JB, Richardson P, Camm AJ, et al. Exercise capacity after single and twice-daily doses of nicorandil in chronic stable angina pectoris. Am J Cardiol 63:66J–70J, 1989
55. Thadani U, Strauss W, Glasser SP, et al. Evaulation of antianginal and anti-ischemic efficacy of nicorandil: Results of a multicenter study. J Am Coll Cardiol 23:276A, 1994
56. Rajarathan R, Brieger D, Hawkins R, Friedman S. An evaluation of anti-ischemic efficacy during therapy with nicorandil in patients with stable angina pectoris. Am J Cardiol 83:1120–1124, 1999
57. Opie LH, King LM. Glucose and glycogen utilization in myocardial ischemia-changes in metabolism and consequences for the myocyle. Mol Cell Biochem 180:3–26, 1998
58. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischemic conditions. Cardiovasc Res 33:243–257, 1997
59. Taegtmeyer H. Energy substrate metabolism as target for pharmacotherapy in ischemic and repurfused heart muscle. Heart and Metabolism 1:5–9, 1998
60. Lopaschuk GD. Optimizing cardiac energy metabolism: A new approach to treating ischemic heart disease. Eur Heart J Supplement 1(Suppl O):O32–O39, 1999
61. Schwartz GG, Greyson C, Wisneski JA, Garcia J. Inhibition of fatty acid metabolism alters myocardial high energy phosphates in vivo. Am J Physiol 267:H224–H231, 1994
62. Meehan AG, Higgins AJ. Oleate plus oxfenicine improves functional recovery assessed via an intraventricular balloon, in ischemic reperfused rat hearts. Ann NY Acad Sci 723:343–344, 1994
63. Lopaschuk GD, Kozak R. Trimetazidine inhibits fatty acid oxidation in the heart. J Mol Cell Cardiol 30:A112, 1998
64. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normaxic, ischemic, and reperfused ischemic rate hearts. Circulation 93:135–142, 1996
65. Kantor PF, Lucien A, Kozak R, et al. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain ketoacyle coenzyme A thiolase. Circ Res 86:580–588, 2000
66. Mehrotra TN, Bassadone ET. Trimetazidine in the treatment of angina pectoris. Br J Clin Prac 21:553–554, 1967
67. Brodbin P, O'Conner CA. Trimetazidine in the treatment of angina pectoris. Br J Clin Prac 22:395–396, 1968
68. Sellier P. The effects of trimetazidine on ergometric parameters in exercise-induces angina. Controlled multicenter double blind versus placebo study. Arch Mal Coeur Vaiss 79:1331–1336, 1986
69. Sellier P, Audouin P, Payen B, Duong TC, Ourbak P. Ergometric effects of a single administration of trimetazidine. Presse Med 15:1771–1774, 1986
70. Passerson J. Effectiveness of trimetazidine in stable effort angina due to chronic coronary insufficiency. A double-blind versus placebo study. Presse Med 15:1775–1778, 1986
71. Gallet M. Clinical effectiveness of trimetazidine in stable effort angina. A double-blind versus placebo-controlled study. Presse Med 15:1779–1782, 1986
72. Detry JM, Sellier P, Pennaforte S, et al. Trimetazidine: A new concept in the treatment of angina. Br J Clin Pharmacol 37:279–288, 1994
73. Dalla-Volta S, Maraglino G, Della-Valentinea P, Viena P, Desideri A. Comparison of trimetazidine with nefedipine in effort angina: A double-blind crossover study. Cardiovasc Drugs Ther 4(Suppl 4):853–859, 1990
74. Levy S, Manchanda SC, Krishnaswani S. Combination treatment with trimetazidine and diltiazem in stable angina pectoris. Heart 76:353–357, 1997
75. Michaelides AP, Vyssoulis GP, Bonoris PB. Beneficial effects of trimetazidine in men with stable angina under beta-blocker treatment. Curr Therapeut Res 46:1179–1190, 1989
76. Michalides AP, Spiropoulos K, Dimopoulos K, et al. Antianginal efficacy of the combination of trimetazidine-propranolol compared with isosorbide dinitrate-propranolol in patients with stable angina. Clin Drug Invest 13:8–14, 1997
77. Chierchia SL, Fragasso G. Protective effects of trimetazidine on ischemic myocardial dysfunction. Eur Heart J Supplement 1(Suppl O):O24–O27, 1999
78. Szwed H, Sadowski Z, Elikowski W, et al. Combination treatment in stable effort angina using trimetazidine and metoprolol. Eur Heart J 22:2267–2274, 2001
79. Sellier P, Brounstet JP. Assessment of anti-ischemic and antianginal effect at trough plasma concentration and safety of trimetazidine MR 35 mg in patients with stable angina pectoris. A multicenter, double blind, placebo controlled study. Am J Cardiovasc Drugs 3(s):361–369, 2003
80. Aaker A, McCormack JG, Hirai T, et al. Effects of ranolazine on the exercise capacity of rats with chronic heart failure induced by myocardial infarction. J Cardiovasc Pharmacol 28(3):353–362, 1996
81. Jain D, Dasgupta P, Hughes LO, et al. Ranolazine (RS-43285): A preliminary study of a new anti-anginal agent with selective effect on ischemic myocardium. Eur J Clin Pharmacol 38(2):111–114, 1990
82. Cocco G, Rousseau MF, Bouvy T, et al. Effects of a new metabolic modulator, ranolazine, on exercise tolerance in angina pectoris patients treated with beta-blocker or diltiazem. J Cardiovasc Pharmacol 20(1):131–138, 1992
83. Thadani U, Ezekowitz M, Fenney L, et al. Double-blind efficacy and safety study of a novel anti-ischemic agnet, ranolazine, versus placebo in patients with chronic stable angina pectoris; Ranolazine Study Group. Circulation 30(2):726–734, 1994
84. 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 84(1):46–50, 1999
85. Chaitman BR, Skettino SL, Parker JO, for the monotherapy assessment of ranolazine in stable angina (MARISA)

Investigators. Anti-ischemic and long term survival during ranolazine monotherapy in patients with severe chronic stable angina. J Am Coll Cardiol 43:1375–1382, 2004
86. Chaitman BR, Pepine J, Parker JO, for the CLARISA Study Group. Effects of ranolazine with atenolol, amlodipine or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. JAMA 291:309–316, 2004
87. Glasser SP, Michie DD, Thadani U, et al. For the zatebradine investigators. Effects of zatebradine (ULFS/USCL), a sinus node inhibitor, on heart rate and exercise duration in chronic stable angina. Am J Cardiol 79:1401–1404, 1997
88. Frishman WH, Pepine CJ, Weiss RJ, Baiker WM. Addition of zatebradine, a direct sinus node inhibitor, provides no greater exercise tolerance benefit in patients with angina taking extended-release nifedipine: Results of a multicenter, randomized double-blind, placebo-controlled, parallel-group study. The Zatebradine Study Group. J Am Coll Cardiol 26(2):305–312, 1995
89. Borer JS, Fox K, Jaillon P, et al for the Ivabradine Investigators group. Anti-anginal and anti-ischemic effects of Ivabradine, an If inhibitor, in stable angina. Circulation 107:817–824, 2003
90. Pepine CJ, Rouleau JL, Annis K, et al. Effect of angiotensin converting enzyme inhibitor on transient ischemia: The Quinapril anti-ischemia and symptoms of angina reduction. (QUASAR) trial. J Am Coll Cordiol 42:2043–2059, 2003
91. Chaitman BR, Rosen AD, Williams DO, et al. Myocardial infarction and cardiac mortality in the bypass angioplasty revascularization investigation (BARI) randomized trial. Circulation 96:2162–2170, 1997
92. Mathew V, Gersh BJ, Williams BA, et al. Outcomes in patients with diabetes mellitus undergoing percutaneous coronary intervention in the current era: A report from the prevention of restenosis with Tranilast and its outcomes (PRESTO) trial. Circulation 103:476–480, 2004
93. Henderson RA, et al. For the randomized intervention treatment of angina trial participants. Seven-year outcome in the RIATA –2 trial. Coronary angioplasty versus medical therapy. J Am Coll Cardiology 42:1167–1170, 2003
94. King SR III. Dilate or defer? View of a skeptic. J Am Coll Cardiol 42:1171–1172, 2003
95. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with standard stent for coronary revascularization. N Engl J Med 346: 1773–1780, 2002
96. Mosses JW, Leon MB, Pompa JJ, et al. Sirolimus-eluting stents versus standard stents in patients with a native coronary artery. N Engl J Med 349:1315–1324, 2003
97. Shofer J, Schluter M, Gershlick AH, et al. For the E-SIRUS sirolimus-eluting stents for the treatment of patients with long atherosclerotic lesions in small coronary arteries: Double-blind, randomized controlled trial. (E-SIRUS). Lancet 362:1093–1099, 2003
98. Ellis S, Stone W, Pompa JJ, et al. The TAXUS IV study: Final angiographic results 108(Suppl IV):IV–532, 2003
99. Le Mos PM, Serruys PW, Vandomburg RJ, et al. Unrestricted utilization or sirolimus-eluting stents compared with conventional bare stents implantation in the "real world" the rapamycin eluting stents evaluated at Rotterdam Cardiology Hospital (Research) Registry. Circulation 109:190–195, 2004
100. Faxon DP. Bringing reality to drug-coated stents. Circulation 109:140–142, 2004
101. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. N Engl J Med 341:70–76, 1999
102. Muneretto C, Bisleri G, Negri A, et al. Total arterial myocardial revascularization with composite grafts improves results of coronary surgery in elderly: A prospective randomized comparison with conventional coronary artery bypass surgery. Circulation 108:1129–1133, 2003
103. Doll R, Peto R. Mortality in relation to smoking: 20-year observations on British doctors. BMJ 2:1526–2536, 1976
104. SAPAT (Swedish Angina Pectoris Aspirin Trial) Group, Juul-Moller S, Edvardson N, Jahnmatz B, et al. Double blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. Lancet 340:1421–1425, 1992
105. Food and Drug Administration. Acetylsalicyclic acid and the heart. JAMA 270:2669, 1993
106. Fuster V, Dyken ML, Vokonas PS, Hennekens C. Aspirin as a therapeutic agent in cardiovascular disease. Circulation 87:659–675, 1993
107. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 345:494–502, 2001
108. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease, the Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383–1389, 1994
109. Vaughan CJ, Gotto AM, Basson CT. The evolving role of statins in the management of artherosclerosis. J Am Coll Cardiol 35:1–10, 2000
110. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in high risk individuals. A randomized placebo controlled trial. Lancet 36:7–22, 2003
111. Rubins HB, Robins S, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 341:410–418, 1999
112. Din JN, Newby DE, Flapan AD. Omega 3 fatty acids and cardiovascular disease-fishing for a natural treatment. BMJ 3:30–35, 2004
113. Imhof A, Koenig W. Alcohol inflammation and coronary heart disease. Addiction Biology 8:271–277, 2003
114. Pepine C. Rationale for ACE inhibition as anti-ischemic therapy. Eur Heart J 19:G34–G40, 1998
115. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 527:669–677, 1992
116. The SOLVD investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med 325:293–302, 1991

117. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramapril, on cardiovascular events in high-risk patients. N Engl J Med 342:145–153, 2000
118. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease. Investigators. Efficacy of perindopril in reduction of cardiovascular events among patietns with stable coronary artery disease: randomized, double-blind, placebo controlled, multicenter trial (The EUROPA study) Lancet 2003 (Sept 1) published on-line.
119. Pfeffer MA, et al for the PEACE Investigators. The continuation of the prevention of events with angiotensin-converting enzyme inhibition (PEACE) trial. Am Heart J p. 142, 2001
120. Hjalmarson A. Effects of beta blockade on sudden cardiac death during acute myocardial infarction and the post infarction period. Am J Cardiol 80(9B):35J–39J, 1997
121. MERIT–HF Study Group. Effect of metoprolol Cx/xL in chronic heart failure. Metoprolol Cx/CL, randomized international trial in congestive heart failure (MERIT HF) Lancet 353:2001–2007, 1999
122. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Jeart Failure Study Group. N Engl J Med 33:1349–1355, 1996
123. CIBIS II Investigators. The cardiac insufficiency bisoprolol study (CIBIS II) A randomized trial. Lancet 353:9–13, 1999
124. Pepine CJ, Cohn PF, Deedwania P, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life: The atenolol silent ischemia study (ASIST). Circulation 90:762–768, 1994
125. Davis R, Goldberg A, Forman S, Pepine C, 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 95:2037–2043, 1997
126. The IONA study group. Effect of nicorandil on coronary events in patients with stable angina: The impact of nicorandil in angina (IONA) randomized trial. Lancet 35S: 1265–1279, 2003
127. Seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure (JNCVII). Hypertension 43(1):1–3, 2004
128. ALLHAT officers and coordinators for the ALLHAT collaborative group. Major outcomes in high risk hypertensive patients. Randomized angiotensin-converting enzyme inhibitor, calcium channel blocker vs. diuretic. The antihypertensive and lipid lowering treatment to prevent hart attack trial (ALLHAT). JAMA 288:2981–2987, 2002
129. Kim MC, Kini A, Sharma SK. Refractory angina pectoris. J Am Coll Cardiol 39:923–934, 2002
130. Thadani U. Patient with disabling angina not amenable to revascularization procedures in acute coronary syndromes: A comparison to Braunwald's heart disease. P. Theroux Ed. Saunders pp. 535–552, 2003
131. Lawson WE, Hui JC, Zheng ZS, et al. Improved exercise tolerance following enhanced external counterpulsation: Cardiac or peripheral effect? Cardiology 87:271–275, 1996
132. Masuda D, Nohara R, Hirai T, et al. Enhanced external counterpulsation improved myocardial perfusion and coronary flow reserve in patients with chronic stable angina; evaluation by (13) N-ammonia positron emission tomography. Eur Heart J 22(16):1451–1458, 2001
133. Schecter M, Matotzky P, Feinberg S, et al. Enhanced counter pulsation therapy improves endothelial function in patients with refractory angina pectoris. J Am Coll Cardiol 42:2090–2095, 2003
134. Arora R, Chou T, 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 33:1833–1840, 1999
135. Lawson WE, Hui JC, Cohn PF. Long-term prognosis of patients with angina tratment with enhanced external counterpulsation: Five-year follow-up study. Clin Cardiol 23:254–258, 2000
136. Barsness G, Feldman AM, Holmes DR, et al. The International EECP Patient Registry (IEPR): Design, methods, baseline characteristics, and acute results. Clin Cardiol 24:435–442, 2001
137. Bueno EA, Mamtani R, Frishman WH. Alternative approaches to the medical management of angina pectoris. Acupuncture, electrical nerve stimulation, and spinal cord stimulation. Heart Disease 3:236–241, 2001
138. Chester M, Hammond C, Leach A. Transcutaneous electrical stimulation in severe angina pectoris. Eur Heart J 3:297–302, 1982
139. Mannheimer C, Carlsson CA, Emanuelson H, et al. The effects of transcutaneous electric stimulation in patients with severe angina pectoris. Circulation 71:308–316, 1985
140. Mannheimer C, Carlsson CA, Vedin A, Wilhelmsson C. Transcutaneous electrical nerve stimulation (TENS) in angina pectoris. Pain 26:291–300, 1986
141. Mannheimer C, Emanuelsson H, Waagstein F, Wilhemsson C. Influence of naloxone on the effects of high frequency transcutaneous electrical nerve stimulation in angina pectoris induced by atrial pacing. Br Heart J 62:36–42, 1989
142. Magarian GJ, Leikam B, Palac R. Transcutaneous electrical nerve stimulation (TENS) for treatment of severe angina pectoris refractory to maximal medical and surgical management—a case report.. Angiology 41:408–411, 1990
143. Murphy DF, Giles KE. Dorsal column stimulation for pain relief from intractable angina pectoris. Pain 28:365–368, 1987
144. Mannheimer C, Augustinsson LE, Carlsson CA, et al. Epidural spinal electrical stimulation in severe angina pectoris. Br Heart J 49:46–61, 1988
145. Sanderson JE, Brooksby P, Waterhouse D, et al. Epidural spinal electrical stimulation for severe angina: A study of its effects on symptoms, exercise tolerance and degree of ischaemia. Eur Heart J 13:628–633, 1992
146. Harke H, Ladleif HU, Rethage B, Grosser KD. Epidural spinal cord stimulation in therapy-resistant angina pectoris. Anaesthesist 42:557–563, 1993

147. Mannheimer C, Augustinsson LE, Eliasson T. Spinal cord stimulation in severe angina pectoris. Reduced ischemia and increased quality of life. Lakartidningen 91:3257–3261, 1994
148. Jacques L, Napoleon MS, Gagnon RM, et al. Epidural stimulation in the treatment of refractory angina. Annales de Chirurgie 48:764–767, 1994
149. Hautvast RW, DeJongste MJ, Staal MJ, et al. Spinal cord stimulation in chronic intractable angina pectoris: A randomized, controlled efficacy study. Am Heart J 137:1114–1120, 1998
150. Hautvast RWM, Brower J, DeJonste MJL, Lie KI. Effect of spinal cord stimulation on heart rate variability and myocardial ischemia in patients with chronic intractable angina pectoris: A prospective ambulatory electrocardiographic study. Clin Cardiol 21:33–38, 1998
151. Greco S, Auriti A, Fiume D, et al. Spinal cord stimulation for the treatment of refractory angina pectoris: A two-year follow up. Pacing Clin Electrophysiol 22:26–32, 1999
152. Norrsell H, Eliasson T, Augustinsson LE, Mannheimer C. Spinal cord stimulation in angina pectoris—what is the current situation? Lakartidningen 96:14302,1435–1437, 1999
153. Barolat G, Sharan AD. Future trends in spinal cord stimulation. 22:279–284, 2000
154. Latif OA, Nedeljkovic SS, Stevenson LW. Spinal cord stimulation for chronic intractable angina pectoris: A unified theory on its mechanism. Clin Cardiol 24:533–541, 2001
155. Mannheimer C, Eliasson T, Augustinsson LE, et al. Electrical stimulation versus coronary artery bypass surgery is severe angina pectoris: The ESBY study. Circulation 37:1157–1163, 1998
156. Murray S, Collins PD, James MA. Neurostimulation treatment for angina pectoris. Heart 83:217–220, 2000
157. Wearn JT, Mettier SR, Klumpp TG, et al. The nature of the vascular communications between the coronary arteries and the chambers of the heart. Am Heart J 9:143–164, 1933
158. Okada M, Ikuta H, Shimizu K, et al. Alternative method of myocardial revascularization by laser: Experimental and clinical study. Kobe J Med Sci 32:151–161, 1986
159. Horvath KA, Cohn LH, Cooley DA, et al. Transmyocardial laser revascularization: Results of a multicenter trial with transmyocardial laser revascularization used as sole therapy for end-stage coronary artery disease. J Thorac Cardiovasc Surg 113:645–654, 1997
160. Cherian SM, Bobryshev YV, Liang H, et al. Ultrastructural and immunohistochemical analysis of early myocardial changes following transmyocardial laser revascularization. J Car Surg 15:341–346, 2000
161. Al-Sheikh T, Allen KB, Straka SP, et al. Cardiac sympathetic denervation after transmyocardial laser revascularization. Circulation 100:135–140, 1999
162. Lange RA, Hillis LD. Transmyocardial laser revascularization. N Engl J Med 341:1074–1076, 1999
163. Burns SM, Sharples LD, Tait S, Cain N, Wallwork J, Schofield PM, et al. The transmyocardial laser revascularization international registry report. Eur Heart J 20:31–37, 1999
164. Horvath KA, Aranki SF, Cohn LH, et al. Sustained angina relief 5 years after transmyocardial laser revascularization with a CO_2 laser. Circulation 18:104(Suppl 1)1-4, 2001
165. Schofield PM, Sharples LD, Caine N, et al. Transmyocardial laser revascularization in patients with refractory angina: A randomized controlled trial. Lancet 353:519–524, 1999
166. Frazier OH, March RJ, Horvath KA. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. N Engl J Med 341:1021–1028, 1999
167. Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. N Engl J Med 341:1029–1036, 1999
168. Burkoff D, Schmidt S, Schulman SP, et al. The Angina Treatments-Lasers and Normal Therapies In Comparison Investigators (ATLANTIC). Transmyocardial laser revascularization compared with continued medical therapy for treatment of refractory angina pectoris: A prospective randomized trial. Lancet 354:885–890, 1999
169. Hughes GC, Landolfo KP, Lowe JE, Coleman RB, Donovan CL. Perioperative morbidity after transmyocardial laser revascularization: Incidence and risk factors for adverse events. J Am Coll Cardiol 33:1021–1026, 1999
170. Leon MB, Bain DS, Moses JW, et al. Direct laser myocardial revascularization with BiosenseTM LV electromechanical mapping in patients with refractory myocardial ischemia. Final results of a blind randomized clinical trial. JACC 38:595–596, 2001
171. Oesterle SN, Sanborn TA, Ali N, et al. Percutaneous transmyocardial laser revascularization for severe angina: The Potential Class Improvement From Intramyocardial Channels (PACIFIC) randomized trial. Lancet 356:1705–1710, 2000
172. Stone GSW, Teirstein PS, Rubenstein R, et al. A prospective, multicenter, randomized trial of percutaneous laser revascularization in patients with non-recanalizable ostial occlusions. J Am Coll Cardiol 39:1581–1587, 2002
173. Henry TD, Annex, BH, Azrin MA, et al. Final results of the VIVA trial of rhVEGF for human therapeutic angiogenesis. Circulation 100(suppl):I-476, 1999
174. Simons M, Annex BH, Laham RJ, et al. Pharmacologist treatment of coronary artery disease with recombinant fibroblast growth factor-2 (rFGF-2): Double-blind, randomized controlled clinical trial. Circulation 2002, in press.
175. Ware JA. Too many vessels? Not enough? The wrong kind? The VEGF debate continues. Nature Med 7:425–429, 2001
176. Henry TD, Rocha-Singh K, Isner JM, et al. Intracoronary administration of recombinant human vascular endothelial growth factor to patients with coronary artery disease. Am Heart J 142:972–980, 2001
177. Epstein SE, Kornowski R, Fuchs S, Dvorak HF. Angiogenesis therapy. Amidst the hype, the reflected potential for serious side effects. Circulation 104:115–119, 2001
178. Grines CL, Watkins MW, Helmer G, et al. Angiogenic gene therapy (AGENT) trial in patients with stable angina pectoris. Circulation 105:1291–1297, 2002
179. Thadani U. Recurrent and refractory angina following revascularization procedures in patients with stable angina. Editorial. Coronary Artery Disease 15(Suppl 1):S1–S4, 2004
180. Hambrecht R, Walther C, Mobius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease. Circulation 109:1371–1378, 2004