STRAIGHT TO THE POINT

Coronary artery disease: Part 2. Treatment

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INTRODUCTION

- Effective treatment of coronary artery disease (CAD) requires patient education, risk factor modification, medical therapy, and, as indicated, coronary revascularization.
- The American College of Cardiology and American Heart Association have developed and promoted a treatment mnemonic for the 10 most important elements in the management of stable angina[1]:

Aspirin and antianginal agents
Beta blocker and blood pressure
Cholesterol and cigarettes
Diet and diabetes
Education and exercise

[1] *ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Stable Angina). J Am Coll Cardiol 1999;33:2092-2196.* An outstanding compilation of evidence relevant to the management of CAD.

RISK FACTOR MODIFICATION

- Smoking: The overall adverse effects disappear within 3 years of cessation. Thrombogenic effects disappear more rapidly.
- Lipids: Aggressive treatment of hyperlipidemia with statins reverses atherogenesis, prevents cardiovascular events, and saves lives in patients with CAD (discussed later).
- Hypertension: Treatment of hypertension reduces the risk of coronary events (especially when angiotensin-converting enzyme inhibitors [ACEIs] are used—discussed later) and reverses left ventricular (LV) hypertrophy.
- Diabetes mellitus: The benefit of glucose control in preventing coronary events has not been conclusively demonstrated.[2]
- Exercise and weight loss: Benefits are possible, but a reduced incidence of coronary artery events has not been proved in a trial.

Smoking cessation: Observational studies suggest that the risk of myocardial infarction (MI) decreases rapidly over several months. Patients who continue to smoke after MI have a 22% to 47% increase in the risk of death compared with those who quit.

Patients should be counseled to follow the AHA Step I and II diets as indicated. LDL-cholesterol levels should be aggressively lowered to less than 2.59 mmol/L (>100 mg/dL).

[2] *UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-853 [erratum published in Lancet 1999;354:602].* Intensive treatment of type 2 diabetes reduced the risk of MI by a nonsignificant 16% (attributable risk reduction [ARR]=3/1,000 patient-years; $P > 0.05$).

MEDICATIONS

Antiplatelet agents

- Aspirin should be given to all patients with known or suspected CAD, unless contraindicated. The standard dose is 80 to 325 mg a day (table 1). The use of

Table 1 *Agents for coronary artery disease*

Type of drug (trade name)	Dosage forms, mg*	Usual dosage, mg	Adverse effects and comments
Antiplatelet agents			
Aspirin	81/325	81-325 qd	Gastritis, peptic ulcer, GI bleeding
Coated aspirin	81/325	81-325 qd	Less incidence of gastritis
Dipyridamole	25/50/75	75-100 qid	Hypotension
Clopidogrel (Plavix)	75	75 qd	
Ticlopidine (Ticlid)	250	250 bid	Diarrhea, nausea and vomiting, GI pain, severe neutropenia in 1% of patients (check complete blood cell count every 2 wk for 12 wk)
β-Blockers			
Propranolol HCl	10/20/40/60/80	10-80 qid	Short acting
Atenolol	25/50/100	25-200 qd	Cardioselective, least CNS effect
Metoprolol tartrate	50/100	50-200 bid	Cardioselective
Nadolol (Corgard)	20/40/80/160	40-320 qd	Not cardioselective
Pindolol (Visken)	5/10	5-10 bid	Partial agonist
Calcium channel blockers			
Nifedipine	10/20	10-40 tid	Pedal edema, reflex tachycardia
Nifedipine long-acting (Procardia XL)	30/60/90	30-90 qd	May be safer than nifedipine (see text) START
Diltiazem	30/60/90/120	30-90 qid	Bradycardia, heart block
Diltiazem CD (extended release)	120/180/240/300	120-300 qd	
Verapamil HCl	40/80/120	80-120 tid	Bradycardia, heart block, CHF
Verapamil HCl sustained release	120/180/240	180 qd-180 bid	
Isradipine (DynaCirc)	2.5/5	2.5-5 bid	Pedal edema, reflex tachycardia
Amlodipine (Norvasc)	2.5/5/10	2.5-10 qd	Pedal edema
Nitrate			
Nitroglycerin	0.3/0.4/0.6	1-2 tabs sublingually prn	Headache, hypotension for all nitroglycerin preparations
Isosorbide dinitrate	5/10/20/30/40	1-40 qid	Should be given at 9 AM, 1 PM, and 5 PM
Isosorbide dinitrate sustained-release	40	40-80 bid	
Isosorbide mononitrate	20	20 bid	
Nitroglycerin patch	5, 10, 20, or 30 cm^2	1 patch qd	Patches should be removed in the evening to prevent tolerance
Nitroglycerin ointment 2%		2.5-5.1 cm (1-2 in) tid	

GI = gastrointestinal; HCl = hydrochloride; CNS = central nervous system.
*Dosage abbreviations: qd = daily; bid = twice a day; tid = 3 times a day; qid = 4 times a day; prn = as needed.

low-dose aspirin is associated with a 33% reduction in the incidence of adverse coronary events.[3]

- Dipyridamole exhibits antithrombotic properties and vasodilatory effects on coronary resistance vessels. The latter can actually decrease perfusion by stenotic vessels. Thus, dypridamole should not be used as an antiplatelet agent.[1]
- Ticlopidine (Ticlid) is a thienopyridine derivative that inhibits platelet aggregation but may cause severe neutropenia.
- Clopidogrel bisulfate (Plavix) exerts a stronger antiplatelet effect than ticlopidine. In comparison with aspirin, clopidogrel was slightly more effective in preventing adverse outcomes in patients with cardiovascular disease.[4] It is most useful in patients who cannot tolerate the gastric effects of aspirin.

β-Blockers

- β-Blockers are first-line agents for the treatment of CAD. They are the only antianginal agents that prevent cardiovascular events (aspirin and ACEIs are not antianginal agents; calcium antagonists and nitrates do not prevent cardiovascular events). Long-term treatment up to 4 years has reduced mortality from 12.2% to 9.7% in survivors of myocardial infarctions (MIs).[5]
- These drugs are just as effective in anginal control and, contrary to popular opinion, better tolerated than calcium antagonists.[6]
- They also have proven ability to prevent silent ischemia in patients with CAD and to prevent sudden death and infarction in patients who have had MI.
- β-Blockers may be used in diabetic patients but should be used with caution in patients taking insulin (they blunt the response to hypoglycemia).

[3] *Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106.*

[4] *Caprie Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-1339.* Clopidogrel reduced the combined incidence of ischemic stroke, MI, or vascular death from 5.8% to 5.3% (relative risk [RR]=9%, ARR=0.5%). Because of its expense, clopidogrel is not considered a first-line agent for the treatment of stable angina.

[5] *Freemantle N, Cleland J, Young P, Mason J, Harrison J. β Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318:1730-1737.* The greatest benefits were noted with metoprolol tartrate, propranolol hydrochloride, and timolol maleate.

[6] *Heidenreich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. JAMA 1999;281:1927-1936.*
All types of β-blockers appear to be effective as antianginal agents. Partial agonists (eg, pindolol) can theoretically prevent exercise-induced tachycardia without causing resting bradycardia.

- Even cardioselective β-blockers can cause bronchospasm at antianginal doses. Asthma is a relative contraindication.
- Absolute contraindications to the use of β-blockers include severe bradycardia, high-degree atrioventricular block, sick sinus syndrome, and unstable heart failure.[1]

Nitrates

- Nitrates are effective in the treatment of symptoms but have not been proved to prevent adverse events. They are equally as effective as β-blockers in reducing anginal symptoms.[6]
- Nitrates provide additional antianginal effects in combination with β-blockers and calcium antagonists.[7]
- The sublingual form is appropriate to treat or prevent exertional chest pain and may be the treatment of choice in patients with rare symptoms. As prophylaxis, it may be taken immediately before exertional activity.
- Long-term use of nitrates is effective in patients with more frequent symptoms, but staggered dosing is required to prevent tolerance. Isosorbide dinitrate should be taken at 9 AM, 1 PM, and 5 PM. Nitrate patches should be taken off in the evening to provide a "drug holiday."

[7] *Akhras F, Jackson G. Efficacy of nifedipine and isosorbide mononitrate in combination with atenolol in stable angina. Lancet 1991;338:1036-1039.* When taking atenolol alone, patients could exercise 440 seconds; on a regimen of atenolol plus nifedipine, 451 seconds; and on a regimen of atenolol plus mononitrate, 486 seconds ($P < 0.01$).

Nitrate-β-blocker collaboration: Through preload reduction, nitrates can reduce the wall stress that may be induced by excessive rate control in β-blockade. β-Blockers can reduce reflex tachycardia that may be induced by nitrates.

Calcium antagonists

- Calcium antagonists are effective in reducing symptoms alone or in combination with β-blockers and nitrates.
- They are especially useful in patients with diabetes, asthma, or chronic obstructive pulmonary disease who may not tolerate β-blockers.
- They have no proven benefit in preventing adverse outcomes.
- Diltiazem and verapamil slow the heart rate and are a logical choice when no β-blocker is prescribed. They may be used alone or with nitrates.
- Amlodipine is a better choice to combine with β-blockers because it does not slow the heart rate.
- Short-acting nifedipine may increase cardiovascular mortality in some patient groups. Diltiazem may increase cardiovascular mortality in patients with LV dysfunction following MI.
- In the International Multicenter Angina Exercise (IMAGE) trial, combination therapy with metoprolol tartrate and nifedipine was superior to using either drug alone.[8]

Note: Amlodipine (Norvasc) is a once-a-day calcium antagonist that does not substantially affect heart rate or myocardial contractility, so it may be used in combination with β-blockers. Short-acting nifedipine is not an adequate substitute because of concerns about its safety in patients with CAD (although these doubts were raised by post-hoc analyses of trials intended to address other issues).

[8] *Savonitto S, Ardissiono D, Egstrup K, et al. Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris: results of the International Multicenter Angina Exercise (IMAGE) Study. J Am Coll Cardiol 1996;27:311-316.* Metoprolol alone increased exercise time to 1-mm ST segment depression by 70 seconds, nifedipine alone by 43 seconds, and both together by 108 seconds.

HMG-CoA reductase inhibitors

- The HMG-CoA reductase inhibitors (statins) have proven ability to prevent adverse outcomes and should be used to lower low-density-lipoprotein (LDL) levels to less than 2.59 mmol/L (<100 mg/dL). Their mechanism of action includes stabilization of existing coronary artery plaques.
- In a trial of more than 4,400 patients with known CAD and high LDL levels (mean, 4.91 mmol/L [190 mg/dL]), simvastatin lowered overall mortality from 11.5% to 8.2% in 5 years.[9] The relative risk of coronary events was reduced by 42%.
- In a trial of patients with known CAD and moderately elevated LDL-cholesterol levels (mean, 3.88 mmol/L [150 mg/dL]), pravastatin prevented

[9] *Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-1389.* Simvastatin lowered LDL-cholesterol levels by 38% and raised high-density-lipoprotein levels by 8%.

about 2 coronary deaths and 4 coronary events for every 100 patients treated for 6 years.[10]

- Gemfibrozil and nicotinic acid have both been shown to decrease the incidence of coronary events and may be suitable alternatives to statins in patients with low high-density-lipoprotein (HDL) and high triglyceride levels.

[10] *The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-1357.*

The recommendation to set the LDL target level at 2.59 mmol/L (100 mg/dL) is based on the high risk of events in patients with CAD. The target has not actually been tested in a randomized trial.

ACEIs

- The ACEIs are growing in importance as agents of prevention. They should be used in diabetic patients and those with hypertension who have CAD.
- In the Heart Outcomes Prevention Evaluation (HOPE) trial, a regimen of ramipril, 10 mg per day, reduced the incidence of cardiovascular events in patients older than 55 years with known CAD or diabetes plus another CAD risk factor. About 2 strokes and 2 cardiovascular deaths were prevented in every 100 treated patients.[11]

[11] *Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-153 [errata published in N Engl J Med 2000;342:748 and 1376].* Average follow-up was 3.5 years. Benefit appeared to be equal in patients with and without diabetes.

A SUGGESTED STRATEGY FOR MEDICAL TREATMENT OF STABLE ANGINA

- Aggressively pursue smoking cessation and lifestyle change.
- Immediately start a regimen of coated aspirin at 80 to 325 mg a day.
- A regimen of atenolol, 25 to 50 mg a day (or metoprolol, 25 mg twice a day), should be started and the dosage titrated upward to a resting heart rate of 55 to 60 beats per minute and the prevention of exertional symptoms. Prophylactic sublingual nitroglycerin can be used, if indicated.
- Add amlodipine, 5 to 10 mg a day, if the patient is still symptomatic after adequate doses of atenolol. Consider the use of isosorbide dinitrate, 20 to 40 mg 3 times a day, if angina persists or if the use of a β-blocker is contraindicated.
- Begin a statin drug if the LDL level is greater than 2.59 mmol/L (>100 mg/dL) with the patient on a diet.
- Consider an ACEI if the patient has diabetes or hypertension.
- Refer the patient for catheterization if medical management fails or the patient has high-risk features.

Some medications (aspirin and ACEIs) prevent events but not symptoms; others (nitrates and calcium antagonists) reduce symptoms but not events; and others (β-blockers) achieve both objectives.

Triple therapy with β-blockers, nitrates, and calcium blockers probably adds little to double therapy.

INDICATIONS FOR REFERRAL TO A CARDIOLOGIST

- For diagnostic or prognostic purposes
- Conventional medical therapy has failed
- Complicating conditions, such as valvular disease or heart failure, are present
- Evidence of high-risk features (see below)
- Patients with refractory angina who are ineligible for procedures

REVASCULARIZATION

- Revascularization should be considered in patients in whom medical management has failed or who have high-risk features.
- Exercise stress testing can identify patients at high risk for adverse outcomes.

Although revascularization procedures have been studied extensively, most studies were performed before the extensive use of stents and modern medical therapy. The use of these modalities would likely improve the outcomes of all revascularized patients.

Revascularization should be considered in these patients, even if symptoms are acceptably controlled.

- The Duke treadmill score[12] is a useful way to stratify cases of possible CAD (table 2).
- Note in table 2 the excellent prognosis for patients with low scores.
- Patients at intermediate or high risk should be further risk stratified with additional studies (see right column).
- The choices for revascularization include percutaneous transluminal coronary angioplasty (PTCA), with or without stenting, and coronary artery bypass grafting (CABG).

[12] *Mark DB, Shaw L, Harrell FE, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 1991;325:849-853.*

The Duke treadmill test score = [exercise time in minutes] − [5 × ST segment depression in millimeters] − [4 × angina index]. The angina index = 0 if no angina occurs during exercise stress test, 1 if angina occurs, and 2 if angina is the reason for stopping the test.

Additional high risk features
- LV dysfunction
- Increased lung uptake or extensive distribution of ischemia on exercise nuclear scan
- Fall in ejection fraction during exercise echocardiography or gated pool scan

Table 2 *Survival based on Duke treadmill test scores**

Score	Patients, %	4-year survival, %	Annual mortality, %
≥5	62	99	0.25
−10 to 4	34	95	1.25
≤−10	4	79	5.00

*From Mark et al. [12]

CABG versus medical management

- Three large trials were conducted in the 1970s: Coronary Artery Surgery Study (CASS), European Coronary Surgery Study (ECSS), and the Veterans Administration Cooperative Study (VA study).
- Table 3 shows the outcomes demonstrated by a meta-analysis of these studies.[13]
- For patients without a proximal left anterior descending artery (LAD) lesion, surgery improved survival only in those with left main or 3-vessel disease.
- For patients with a proximal LAD lesion, surgery improved survival in those with 2- or 3-vessel disease.

[13] *Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994;344:563-570 [erratum published in Lancet 1994;344:1446].*

Overall mortality at 5, 7, and 10 years following medical treatment is 15.8%, 21.7%, and 30.5%, respectively; and following surgical treatment, 10.2%, 15.8%, and 26.4%, respectively.

PTCA versus medical management

- In the ACME trial, patients with 1-vessel disease and exercise-induced ischemia who were randomly allocated to PTCA were more likely (64%) to be free of angina than medically managed patients (46%).[14]
- In the second Randomised Intervention Treatment of Angina (RITA-2) trial, patients with 1 to 3 diseased vessels who were randomly allocated to PTCA were slightly more likely to be free of antianginal agents than medical patients at 1 year (20% vs 7%); however, PTCA patients were significantly more likely to experience the primary outcome of death or definite MI (6.3% vs 3.0%).[15]

[14] *Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. N Engl J Med 1992;326:10-16.*

[15] *RITA-2 trial participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. Lancet 1997;350:461-468.* Patients undergoing PTCA had a higher risk of MI due to transient enzyme elevations that occurred at the time of the procedure.

Neither the ACME nor the RITA-2 investigators employed stenting, which has been shown to reduce the incidence of recurrent stenosis following PTCA.

Revascularization versus medical management

- In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, patients with CAD well controlled with medications but who had documented silent ischemia were randomly allocated to revascularization (CABG or PTCA at physician's discretion) or medical management.[16]
- Revascularized patients had lower mortality (1.1% vs 5.5%), especially within the subgroup with proximal left anterior descending lesions (3.3% vs 13.3%).
- The Medicine, Angioplasty or Surgery Study (MASS) compared medical management, PTCA, and CABG in a 3-arm trial of patients with solitary severe

[16] *Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037-2043.* Many of these patients had high-risk features. The average degree of ST segment depression during exercise stress testing was 2.4 mm.

Table 3 *5-Year mortality: CABG vs medical management*

Disease	Medical therapy, %	Surgery, %
Left main	36.5	15.5*
3 vessel	17.6	11.0*
2 vessel	11.7	10.0†
1 vessel	9.9	5.6†
Abnormal LV function	25.2	16.6‡

*$P < 0.01$
†Not significant (P not given).
‡$P < 0.05$.

proximal LAD lesions.[17] At 3 years, mortality rates were similar in all groups, but revascularized patients were more likely to be free of angina (CABG, 98%; PTCA, 82%; medical, 32%).

[17] *Hueb WA, Bellotti G, de Oliveira SA, et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. J Am Coll Cardiol 1995;26:1600-1605.* The MASS trial subjects appeared to be at lower risk than ACIP trial patients. The event rates in all 3 arms were low.

PTCA versus CABG

- Studies typically included only the subset of patients with lesions amenable to angioplasty and did not include stenting.
- In the largest of these, the Bypass Angioplasty Revascularization Investigation (BARI) trial, a diverse group of patients with multivessel disease were randomly assigned to CABG or PTCA.[18] All subjects had lesions amenable to PTCA. The study showed a survival benefit that was entirely confined to the subset of patients with diabetes (table 4).
- In patients without diabetes, outcomes were identical between those undergoing CABG and those undergoing PTCA whether or not patients had 3-vessel disease, proximal LAD disease, or LV dysfunction.

[18] *The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. J Am Coll Cardiol 2000;35:1122-1129.* All subsets of diabetic patients derived equal benefit from CABG, even those with mild symptoms, normal LV function, double-vessel disease, or no LAD lesions. In nondiabetic patients, mortality was equal across all subgroups, but patients undergoing CABG had a lower rate of subsequent revascularization (13% vs 60%).

Table 4 *BARI trial mortality rates at 7 years*

Subset	CABG, %	PTCA, %
Total	15.6	19.1*
Diabetic patients	23.6	44.3†
Nondiabetic patients	13.6	13.2‡

*$P = 0.04$
†$P < 0.001$.
‡Not significant (P not given).

SUMMARY AND CONCLUSIONS

Many trials have demonstrated a benefit of revascularization in the control of symptoms and survival for specific subsets of patients. In patients with lesions amenable to angioplasty, the survival advantage of CABG over PTCA may be confined to the subset with diabetes.

Acceptable revascularization strategies

- CABG in patients with significant left main CAD
- CABG or PTCA in nondiabetic patients with significant 3-vessel disease or 2-vessel disease and proximal LAD stenosis
- CABG in diabetic patients with 2- or 3-vessel disease requiring revascularization[19]
- CABG or PTCA in patients with 1- or 2-vessel disease with a large area of myocardium at risk.
- CABG or PTCA in patients in whom medication fails to control symptoms

[19] *King SB, Kosinski AS, Guyton RA, Lembo NJ, Weintraub WS. Eight-year mortality in the Emory Angioplasty Versus Surgery Trial (EAST). J Am Coll Cardiol 2000;35:1116-1121.* The investigators in the much smaller EAST also compared PTCA with CABG. The outcomes were essentially the same in both arms. There were trends favoring surgery in patients with LAD stenoses and in patients with diabetes, but they were not statistically significant in these relatively small subgroups (only 59 patients with diabetes were enrolled).

The choice between CABG and PTCA often depends on the anatomy of the lesions requiring revascularization and local experience of the interventional cardiologists and cardiovascular surgeons. Lesions that are not amenable to angioplasty will naturally require surgery.