Medical management of angina: treatment of associated conditions and the role of antiplatelet drugs

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In spite of enormous improvements in technology and skills in percutaneous revascularisation over the last two decades, medical treatment remains a very important modality of management for angina and atherosclerotic heart disease. The goals of medical treatment are relief of symptoms, prevention of further progression of atherosclerotic heart disease and reduction in the incidence of acute coronary syndrome and mortality. Treatment of associated conditions causing or precipitating angina, management of coexistent risk factors and prescription of antiplatelet drugs to prevent further cardiovascular events are very important aspects of medical treatment.

Topic(s):

Ischemic Heart Disease and Acute Cardiac Care;

Abbreviations

ACE: angiotensin-converting enzyme

ARB: angiotensin receptor blocker

AVR: aortic valve replacement

BP: blood pressure

CAD: coronary artery disease

CCS: Canadian Cardiovascular Society

EMA: European Medicines Agency
LDL-C: LDL cholesterol

LVEDP: left ventricular end-diastolic pressure

MI: myocardial infarction

NSTEMI: non-ST-elevation myocardial infarction

PVD: peripheral vascular disease

SA: sino-atrial

TAVI: transcatheter aortic valve implantation

Introduction

Coronary artery disease is a leading cause of morbidity and mortality in Europe. It can present in several ways including chronic stable angina and acute coronary syndrome. Angina pectoris is traditionally defined as a clinical syndrome of chest discomfort precipitated by physical exertion or emotional stress which increases myocardial oxygen demand and is relieved by rest or nitrate.

Angina can be treated in several ways including medical treatment as well as percutaneous and surgical revascularisation. This article will concentrate on medical treatment of angina in the setting of stable coronary artery disease with special reference to treatment of associated conditions and the role of antiplatelet drugs.

Medical management of angina generally consists of

1. treatment of associated conditions that can precipitate angina, e.g., anaemia, occult thyrotoxicosis, tachycardia, etc.
2. treatment of risk factors such as hypertension, dyslipidaemia, diabetes mellitus (DM) to reduce further progression of atherosclerotic disease.
3. additional disease-modifying drugs for event prevention and mortality reduction, such as aspirin, ACE inhibitors and beta-blockers.
4. medications to prevent episodes of angina

- Beta-blocker
- Ca channel blocker
- Nitrate
- Other pharmacologic agents such as ranolazine, nicorandil, ivabradine and trimetazidine

5. treatment of special forms of angina

- Microvascular dysfunction
- Vasospastic angina

Treatment of associated conditions

Although angina is predominantly caused by atherosclerotic coronary artery disease, there are certain other cardiac and non-cardiac conditions that can cause/precipitate angina (Table 1). Some of these conditions can themselves cause angina in the presence of normal coronary arteries and some of them can precipitate or aggravate angina in patients with stable coronary artery disease. Awareness of these associated conditions, conscious effort to look for them and treatment if needed are important for the management of angina.

Table 1. Conditions (other than atherosclerotic coronary artery disease) causing/exaggerating angina.

Cardiac	Non-cardiac
• Aortic stenosis	• Anaemia • Hypoxaemia • Hyperviscosity

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Tachycardia
- Microvascular disease
- Polycythaemia
- Sickle cell disease
- Sympathomimetic toxicity (cocaine use)
- Hypertension
- Thyrotoxicosis
- Hyperthermia
- Anxiety

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Hypertrophic cardiomyopathy

Patients with hypertrophic cardiomyopathy may have coexistent coronary artery disease but chest pain is also quite common in the absence of atherosclerotic coronary artery disease. Chest pain occurs possibly due to myocardial 02 demand/supply mismatch because of microvascular dysfunction, increased LV wall stress and left ventricular outflow tract (LVOT) obstruction. Compression of epicardial and intramural coronary arteries during systole is common but usually of no clinical significance [2]. The treatment goal of symptomatic patients with LVOT obstruction is to reduce LVOT gradient either with drugs (beta-blocker, disopyramide or calcium channel blocker such as verapamil and diltiazem) or invasive procedures such as ventricular septal myectomy or alcohol septal ablation if the LVOT gradient is more than 50 mmHg. In the absence of LVOT gradient, angina is usually managed with beta-blockers, calcium channel blockers or cautious use of nitrates.

Aortic valve disease

Angina can occur in aortic stenosis with or without coexistent coronary artery disease. In patients without coexistent coronary artery disease, increased myocardial oxygen demand due to increased LV muscle mass, elevated LV systolic pressure and prolonged ejection time and decreased blood supply due to elevated LVEDP and hence reduced coronary perfusion pressure (aortic-LV pressure gradient in diastole) cause angina. [3]. Symptomatic patients are usually

candidates for aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI). Medical therapy has very little to offer.

Angina can occur in severe aortic regurgitation (AR); nocturnal angina is more common when the heart rate slows and diastolic blood pressure falls significantly. Symptomatic AR is treated by AVR. Nitrates are not helpful (as in coronary artery disease) but are probably worth trying.

Anaemia can precipitate angina in a patient with known coronary artery disease. Severe anaemia itself can cause angina in the presence of normal coronary arteries. Anaemia should be investigated and appropriately treated, which may obviate the need for a further increase in antianginals.

Hypoxaemia of any cause can precipitate angina in patients with obstructive coronary artery disease. Treatment of the clinical condition with improvement in oxygenation will help in preventing angina.

An episode of arrhythmia causing a fast ventricular rate can trigger angina by increasing myocardial oxygen demand as well as reducing diastolic time. Management to reduce episodes of arrhythmia will help to reduce angina.

Severe uncontrolled hypertension can precipitate angina by causing increased LV wall stress and hence increased oxygen demand and reduced subendocardial perfusion. Control of the blood pressure with appropriate antihypertensive agents will help in preventing angina.

Thyrotoxicosis

Some patients with thyrotoxicosis experience angina-like chest tightness. In patients with known coronary artery disease, an increase in cardiac output and contractility increases myocardial oxygen demand and may precipitate angina. Angina responds well to beta-blockers as it also does to the restoration of euthyroid state.

Cocaine-related chest pain

Cocaine is one of the commonly used illicit drugs and is associated with several cardiovascular complications including angina pectoris, myocardial infarction, LV dysfunction and

aortic dissection. Cocaine can cause myocardial ischaemia/infarction by several mechanisms. Cocaine increases myocardial oxygen demand by increasing heart rate, blood pressure and cardiac contractility through its sympathomimetic activity. It can also cause marked coronary artery vasoconstriction as well as induce a prothrombotic state by increasing plasminogen activator inhibitors and stimulating platelet activation and aggregation.

Patients presenting with cocaine-associated chest pain, unstable angina or MI should be treated as usual for possible ACS or ACS with some modifications. These recommendations are based on case series, observational studies, cardiac catheterisation findings and animal studies. In patients with cocaine-associated chest pain, intravenous benzodiazepines help chest pain and have beneficial haemodynamic effects. Beta-blockers should not be used in the acute setting in view of the chance of increasing coronary spasm. The benefit of a drug-coated stent should be weighed against the possible non-compliance of dual antiplatelet therapy.

Cessation of cocaine use is probably the best secondary prevention strategy. Aggressive risk factor control should be pursued when there is definite evidence of MI or atherosclerosis. Long-term use of a beta-blocker is probably beneficial in patients with MI and LV dysfunction who stopped cocaine use but, in patients with continued use of cocaine, beta-blocker use should be considered only in patients with the strongest indications and on a case-by-case basis [4].

Treatment of risk factors and lifestyle modification

Dyslipidaemia should be managed according to the recent guidelines. Established coronary artery disease patients are considered a very high-risk group for future cardiovascular events and hence they should be on statins irrespective of cholesterol level. The target should be LDL cholesterol below 1.8 mmol/L (70 mg/dL) or a >50% reduction in LDL-C when the target cannot be achieved. In most patients, statin monotherapy is enough. In a meta-analysis of 170,000

participants in 26 randomised trials, statins showed a 20% reduction in CAD death and a 10% reduction in all-cause mortality with every 1.0 mmol/L reduction in cholesterol [5].

Other medications, such as fibrates, bile acid sequestrants, niacin, and ezetimibe, can cause a decrease in cholesterol but there is no significant evidence that they change clinical outcome. PCSK9 inhibitors, a new group of drugs, decrease LDL-C by up to 60%, either as monotherapy or in combination with statins, and there is some preliminary evidence that they may reduce cardiovascular events.

Hypertension is an important risk factor for coronary artery disease. In patients with stable coronary artery disease, blood pressure should be reduced to systolic <140 and diastolic <90. A meta-analysis of clinical trials of mild to moderate hypertension showed that treatment with antihypertensives reduced CAD events and MI by a statistically significant 16% [6].

Overweight and obesity have been shown to be consistently associated with increased cardiovascular events and all-cause mortality. There are few clinical trial data on the effect of weight loss, specifically on the cardiovascular event rate, although the Swedish Obese Subjects (SOS) trial showed that weight loss from 20 to 32% at one year with bariatric surgery decreased mortality by 24% [7], and a recent meta-analysis showed that patients who were treated with bariatric surgery had fewer cardiovascular events when compared to non-surgical controls [8].

It is recommended that people who are overweight or obese should try to achieve a healthy weight in order to reduce BP, dyslipidaemia and the chance of developing type 2 DM and hence reduce overall cardiovascular risk [8]. Diet, physical exercise and behaviour modifications are the mainstay of therapy, but in some individuals medical therapy or bariatric surgery may be helpful.

Diabetic patients are at significantly higher risk for coronary artery disease. Though intensive glycaemic control is associated with a favourable impact on microvascular complications, the effect on macrovascular complications including coronary artery disease is uncertain. Recent guidelines recommend an individualised approach with a more liberal HbA1c target in elderly, frail patients, those with

existing cardiovascular disease and those with a long duration of diabetes. A target of HbA1c of <7.0% (53 mmol/mol) is recommended to reduce CVD risk and microvascular complications for the majority of non-pregnant individuals with either type 1 or type 2 DM. Weight reduction, undertaking regular physical activity, blood pressure control and lipid management are very important for all diabetic patients with coronary artery disease. In diabetic patients with existing cardiovascular disease, treatment with a sodium-glucose co-transporter-2 (SGLT-2) inhibitor reduced CVD and total mortality as well as heart failure hospitalisation. SGLT-2 inhibitors should be considered early in this group of patients [9].

Patients with chronic kidney disease are at higher risk of cardiovascular events. Extra care should be taken to address risk factors and achieve BP and lipid management targets.

Smoking is a strong risk factor for coronary artery disease. Quitting smoking is one of the most effective preventive measures and is associated with a reduction in mortality of 36% after MI [10]. Smoking status (including passive smoking) of all patients with coronary artery disease should be assessed, and all smokers should be strongly advised to stop smoking and should be offered cessation assistance. In addition to smoking cessation advice, encouragement and motivational interventions, nicotine replacement therapy, bupropion or varenicline should be offered to help patients quit smoking. All forms of nicotine replacement therapy (NRT) (chewing gum, transdermal nicotine patches, nasal spray, inhaler, sublingual tablets) are effective and safe in coronary artery disease. NRT and bupropion help 80% more people to quit compared to placebo. Bupropion carries a small risk of seizure (1 in 1,000).

Varenicline, a partial nicotine receptor agonist, increases the chance of quitting smoking by twofold compared to placebo. The main side effect is nausea which usually settles over time.

Electronic cigarettes (e-cigarettes) have been designed for the users to inhale nicotine without the harmful effects of smoking. They deliver nicotine by heating and vaporising a solution of it. Data from observational studies and a randomised trial show that the efficacy of e-cigarettes is similar to NRT patches or inhalers in terms of smoking

cessation [8]. An independent review of Public Health England found that e-cigarettes are 95% safer than smoking [11]. The long-term health effects of e-cigarettes are not known and there is a need for further research.

Depression is a common comorbidity in people with stable coronary artery disease as well as in those recovering from MI. Many observational studies have shown a correlation between depression and cardiovascular events. Stable coronary artery disease patients who also had depression as a comorbidity had more frequent angina and a lower quality of life compared to those without depression [12,13]. A meta-analysis of 21 studies in healthy populations found an 81% greater incidence of MI or fatal ischaemic heart disease (IHD) in patients with depression over a follow-up period of 10.8 years [14]. Despite the correlation, there is no significant evidence to suggest that treatment with counselling or antidepressants reduces cardiovascular events. The safety and efficacy of sertraline, citalopram and mirtazapine in treating depression have been demonstrated in stable coronary artery disease patients as well as in ACS and post-MI patients. In a trial involving 2,481 patients with depression or low social support after MI, cognitive behavioural therapy, supplemented by a selective serotonin uptake inhibitor (SSRI) when needed, improved depression compared to the usual care but did not improve event-free survival after a mean follow-up of 24 months [15]. A subgroup analysis, however, showed a significant decrease in death and MI in patients treated with SSRI [15].

Patients with stable coronary artery disease suffer from a high level of psychosocial stress. Stress management interventions can reduce stress and anxiety but there is no evidence that they reduce cardiovascular risk.

A healthy diet reduces cardiovascular risk. A large study showed that the Mediterranean diet supplemented with extra virgin olive oil or nuts reduced major cardiovascular events in subjects at high risk for coronary artery disease without previous cardiovascular disease [16].

Regular physical activity is associated with a reduction in cardiovascular morbidity and mortality in established coronary artery disease patients. Regular moderate to vigorous

intensity aerobic exercise for 30 minutes at least three times a week is recommended for all patients with stable coronary artery disease.

Some adaptation in lifestyle may be helpful for preventing angina and improving quality of life in chronic stable angina patients. One needs to avoid or modify strenuous activities if they constantly and repeatedly produce angina. Isometric exercises such as weightlifting are not advisable. One should avoid sudden bursts of activity, particularly after a long period of rest/inactivity, after meals or in cold weather. The threshold for angina is lower after arising and hence morning chores should be paced appropriately. Prophylactic use of a short-acting nitrate several minutes before engaging in strenuous activity may prevent angina. The majority of chronic stable angina patients can continue to take part in satisfactory sexual activity with some precautions (e.g., starting more than two hours after a meal and using a short-acting nitrate 15 minutes before).

Additional disease-modifying drugs for event prevention and mortality reduction

Antiplatelets

As platelet activation and aggregation are thought to be the key elements in thrombotic response to a ruptured plaque, it seems logical that antiplatelet agents will reduce the incidence of acute coronary syndromes in patients with established coronary artery disease.

In a collaborative meta-analysis of 287 studies of high-risk patients with acute or previous vascular disease or some other predisposing condition (involving 135,000 patients when antiplatelet therapy was compared to control and 77,000 patients when different antiplatelet regimens were compared), antiplatelet agents reduced the combined outcome of any serious vascular event by about one quarter, non-fatal myocardial infarction by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth, with no apparent adverse effect on other deaths. This reduction of vascular

events was also valid in the subset of stable coronary artery disease patients (p=0.0005). Aspirin was used as antiplatelet agent in the vast majority of these trials [17].

In six randomised trials of 9,853 patients, aspirin therapy was associated with a significant 21% reduction in the risk of cardiovascular events (non-fatal MI, non-fatal stroke, and cardiovascular death), a 26% reduction in the risk of non-fatal MI, a 25% reduction in the risk of stroke, and a 13% reduction in the risk of all-cause mortality [18].

The most widely used antiplatelet agent is aspirin: it produces its antithrombotic effect by irreversibly acetylating and inhibiting platelet cycloxygenase-1, an enzyme necessary for thromboxane A2 which causes platelet activation. Aspirin doses of 75-150 mg daily are at least as effective as higher daily doses and are associated with lower risk of bleeding. The effects of doses lower than 75 mg daily are less certain.

The other common antiplatelet agents are clopidogrel, prasugrel and ticagrelor. They all act as antagonist to platelet ADP receptor P2Y12 inhibiting platelet aggregation. Of these three antiplatelet agents, only clopidogrel has been tried in stable coronary artery disease. The CAPRIE trial showed an overall benefit of clopidogrel over aspirin in reducing cardiovascular events in patients with previous MI, stroke or peripheral vascular disease. The benefit of clopidogrel over aspirin was small and was driven by the peripheral vascular disease group. Prasugrel and ticagrelor can cause greater platelet inhibition and are associated with greater reduction of cardiovascular events compared to clopidogrel in acute coronary syndrome patients when used with aspirin, but there are no clinical studies evaluating the effect of prasugrel and ticagrelor in stable coronary artery disease.

Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor has been accepted as a standard practice in acute coronary syndrome for up to one year after the event, as well as in post PCI. However, in the CHARISMA study dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease and patients at risk of atherothrombotic disease did not show any benefit over aspirin only, although post hoc analysis showed that a subgroup of patients with previous MI/stroke/PVD actually had some benefit over aspirin alone. Dual antiplatelet therapy with

vorapaxar, an antagonist to platelet-activated thrombin generation, showed a reduced number of major cardiovascular events in patients with stable coronary artery disease, particularly in patients with a history of MI over a period of 2.5 years, though the rate of moderate to severe bleeding including intracranial bleeding increased [19]. Combined platelet therapy may be beneficial in a high-risk group of patients but cannot be recommended to all stable CAD patients at this stage.

The response to antiplatelet therapy may vary from person to person and this is probably even more true in the case of clopidogrel. Clopidogrel is converted to its active metabolite by cytochrome P450 enzymes, mainly by CYP2C19, and genetic variants of CYP2C19 have been identified which can cause a suboptimal antiplatelet effect as evidenced by platelet aggregation assays and higher ischaemic event rates after ACS and PCI. However, there are no data to suggest that this is also applicable to stable coronary artery disease and there is no recommendation to perform genetic testing in patients with stable CAD.

All patients with stable coronary artery disease should be on aspirin. Clopidogrel is an alternative if there is an allergy to aspirin. Dual antiplatelet therapy may be beneficial in some high-risk patients but cannot be recommended for all stable CAD patients.

Conclusion

In spite of the widespread use of percutaneous and surgical revascularisation, medical treatment of angina remains an important modality for the management of coronary artery disease (Table 2).

In addition to symptom control with antianginal drugs, medical treatment also involves the identification and treatment of associated conditions, risk factor reduction and lifestyle modification. Antiplatelet drugs are hugely important in all stages of coronary artery disease, including stable CAD, to prevent further cardiovascular events.

Table 2. Medical management of angina.

Angina relief	Prevention of further atherosclerosis & CV event prevention
• **Treat associated conditions if any (e.g., anaemia)** • Short-acting nitrate plus ◦ Beta-blocker/rate-lowering CCB ◦ (Beta-blocker if history of MI or LV dysfunction) ◦ Consider CCB-DHP if low heart rate/intolerance/contraindications ◦ Consider beta-blocker + DHP-CCB if still symptomatic • Add second-line drugs if still symptomatic or contraindications/intolerance to first-line drugs ◦ Long-acting nitrate ◦ Ivabradine ◦ Nicorandil ◦ Ranolazine ◦ Trimetazidine	• **Control of risk factors** • **Lifestyle modification and adaptation** • **Antiplatelet (aspirin)** • Statin • ACEI/ARB if LV dysfunction, diabetes, high BP, and CKD, consider ACEI for all stable CAD patients • Beta-blocker if post MI or LV dysfunction

Only headings in bold have been described in detail in this article. ACEI: ACE inhibitor; ARB: angiotensin receptor blocker; CV: cardiovascular; CCB: calcium channel blocker; CKD: chronic kidney disease; DHP: dihydropyridine

Adapted from Montalescot G e al, 2013 ESC guidelines on the management of stable coronary artery disease, with permission from Oxford University Press [20].

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The author has no conflicts of interest to declare.