Treatment of stable angina pectoris: focus on the role of calcium antagonists and ACE inhibitors

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Introduction

Coronary artery disease (CAD) is the most common type of heart disease that is typically initially manifested by angina. Like many high-income countries during the last century, low- and middle-income countries are witnessing an alarming increase in the rates of CAD, and this change is accelerating [1].

Stable angina pectoris is the result of myocardial ischaemia caused by an imbalance between myocardial blood supply and oxygen demand. Typically, it is characterised by exertional pain that is relieved by rest or nitrates.

The treatment goals of angina pectoris are improvement in quality of life, by limiting the number and severity of attacks, protection against future lethal events, and measures to lower the burden of risk factors to slow disease progression. This requires lifestyle modification as well as medical treatment [2].

Prevalence

Globally, CAD is the leading cause of death and is predicted to remain so for the next 20 years [3]. Each year, approximately 3.8 million men and 3.4 million women die from CAD worldwide [4]. In 2020, it is estimated that this disease will be responsible for a total of 11.1 million deaths globally [3]. Unlike other manifestations of coronary artery disease, angina does not appear to be declining in incidence [5]. The Health Survey for England (2006) found that about 8% of men and 3% of women aged between 55 and 64 years, and 14% of men and 8% of women aged between 65 and 74 years have had angina. Prevalence is higher in men than in women, and increases progressively with age. Being diagnosed with angina can have a significant impact on a person's quality of life, which deteriorates gradually in proportion to the severity of symptoms [6]. Thus, stable angina pectoris remains an important clinical issue with profound effects on the quality of life and long-term prognosis of patients.

Prognosis of angina pectoris

People with angina pectoris are two to five times more likely to develop other manifestations of coronary heart disease (CHD) than people who do not have angina. Clinical trials in people with stable angina pectoris have tended to recruit participants who were not considered to be in need of coronary revascularisation. Prognosis is better in these people, with an annual mortality rate of 1-2% and an annual rate of non-fatal MI of 2-3% [7]. Features that indicate a poorer prognosis include more severe symptoms,

male sex, abnormal resting ECG, previous myocardial infarction (MI), left ventricular dysfunction, easily provoked or widespread coronary ischaemia on stress testing, and significant stenosis of all three major coronary arteries or the left main coronary artery. Control of these risk factors is crucial to manage the secondary prevention of ischaemic cardiac events.

Calcium antagonists

Calcium antagonists (CAs) reduce angina by inhibiting inward calcium currents through the cell membrane in many tissues, including the myocardium, cardiac conduction tissues, and vascular smooth muscle cells in both coronary arteries and peripheral vessels. Intracellular calcium deprivation relaxes smooth muscle cells, causing vasodilation in the peripheral and coronary beds and increased coronary blood flow. The less selective, non-dihydropyridine (non-DHP) CA, verapamil and diltiazem, also slow sinoatrial (SA) and atrioventricular (AV) nodal conductions to reduce heart rate and depress contractility under physiological conditions. All CAs are effective vasodilators. The subclasses of CAs are listed in Table 1.

Table 1. Subclasses of calcium antagonists.

Type	Properties	Drugs
Dihydropyridines (DHPs)	Peripheral and coronary vasodilators, negative inotropic action	Amlodipine, nifedipine, felodipine, isradipine, nicardipine, nisoldipine
Non-dihydropyridines (non-DHPs)		
Phenylalkylamine	Additional negative chronotropic and inotropic actions	Verapamil
Benzothiazepine	Additional negative chronotropic and inotropic actions	Diltiazem

Type	Properties	Drugs
Mixed sodium and CA	Non-selective, blocking delayed rectifier K^+ current and fast Na^+ current. Also inhomogeneous electrical effects, prolonged QT interval, and linked to torsade de pointes.	Bepridil
Antihistamine	Used for migraine prophylaxis, peripheral vascular disease, vertigo, but not for angina.	Flunarizine

Dihydropyridines (DHPs) lower BP and myocardial wall tension to reduce myocardial oxygen consumption. A rise in coronary blood flow further contributes to correcting myocardial oxygen imbalance. These drugs lower the frequency of angina, lower the need for nitrates, increase treadmill walking time, and improve ischaemic ST-segment changes on exercise testing and electrocardiographic monitoring [8].

The antianginal effects of CAs have been proved in many studies and are considered to be comparable to those achieved by beta-blockade therapy. In addition, CAs have been extensively used for the management of hypertension. There have been limited data regarding the prognostic benefits of CAs in patients with stable angina pectoris. Furberg et al demonstrated that high doses of short-acting nifedipine results in increased mortality [9]. However, the ACTION study evaluated the prognostic role of CAs in patients with stable angina pectoris and concluded that long-term nifedipine (gastrointestinal therapeutic system) safely relieved angina and prolonged event-free survival in patients with stable angina pectoris and hypertension [10].

Calcium antagonists have been shown to be equally effective as beta-blockers in the management of stable angina [11]. ESC guidelines on stable coronary artery disease for the management of stable angina consider either a beta-blocker or a CA as appropriate first-line treatment [12]. The usual dose of calcium antagonists in common use for angina and their common side effects are summarised in Table 2.

Table 2. Duration of action, usual dose and common side effects of calcium antagonists.

Drug	Duration of action	Usual dose	Common side effects
Dihydropyridines (DHPs)			

Drug	Duration of action	Usual dose	Common side effects
Nifedipine, slow release	Long	30-180 mg/d	Hypotension, oedema, dizziness, flushing, nausea, constipation
Amlodipine	Long	5-20 mg (daily)	Headache, oedema
Felodipine, sustained release	Long	5-10 mg (daily)	Headache, oedema
Isradipine, sustained release	Medium	2.5-10 mg (twice a day)	Headache, fatigue
Nicardipine	Short	20-40 mg (3 times a day)	Headache, oedema, dizziness, flushing
Non-dihydropyridines (non-DHPs)			
Diltiazem, immediate release	Short	30-80 mg (4 times a day)	Hypotension, dizziness, flushing, bradycardia, oedema
Diltiazem, slow release	Long	120-320 (daily)	Hypotension, dizziness, flushing, bradycardia, oedema
Verapamil, immediate release	Short	80-160 mg (3 times a day)	Hypotension, negative inotropism, HF, bradycardia, oedema
Verapamil, slow release	Long	120-480 mg (daily)	Hypotension, negative inotropism, HF, bradycardia, oedema

Non-DHP drugs, such as verapamil and diltiazem, also reduce heart rate and contractility and decrease myocardial oxygen demand. Verapamil has comparable antianginal action to metoprolol and can be useful for the treatment of supraventricular arrhythmias and hypertension. However, verapamil should be avoided in patients taking beta-blockers owing to the risk of heart block, and in those with heart failure (HF) because of its negative inotropic effect. Diltiazem has a low adverse effect profile with a modest negative inotropic effect. Care should be taken when prescribing it in combination with a beta-blocker and in patients with left ventricular dysfunction.

DHPs such as amlodipine, felodipine and lercanidipine have greater vascular selectivity and minimal negative inotropic properties. They are therefore safer in patients with left ventricular dysfunction. Amlodipine is an effective once-daily antianginal drug that can be used in combination with a beta-blocker. Long-acting nifedipine is a proven antianginal drug and is most effective when used in conjunction with a beta-blocker. Short-acting CAs, particularly nifedipine, are not suitable for patients with stable angina pectoris because they cause reflex tachycardia which may exacerbate ischaemia and have been associated with an increased risk of cardiovascular events. They should therefore be avoided. Contraindications to nifedipine use include severe aortic stenosis, obstructive cardiomyopathy and heart failure.

If combining beta-blockers and calcium antagonists, it is appropriate to use a non-rate-limiting (DHP) calcium antagonist such as felodipine or amlodipine. Diltiazem may be used cautiously in combination with a beta-blocker when the heart rate remains above 60 beats per minute despite maximum tolerated doses of beta-blocker. Verapamil is not suitable in combination with beta-blockers because severe bradycardia and HF can occur.

Common side effects of CAs are headache, dizziness, flushing, and oedema due to vasodilation. In some patients, constipation also may occur. Interaction with other negative chronotropic or inotropic agents to produce bradycardia, heart block, or HF has been reported. For patients with severe systolic dysfunction, calcium antagonists can worsen and/or precipitate congestive heart failure. CAs may also suppress lower oesophageal sphincter contraction and worsen symptoms of gastroesophageal reflux disease. CAs inhibit the CYPA4 enzyme in the liver and, therefore, may raise levels of statins and many other drugs, something which may be overlooked [13]. Cimetidine and grapefruit juice may raise the effective level of CAs. In addition, magnesium supplements may also enhance the actions of CAs, particularly nifedipine.

Ace inhibitors

Angiotensin-converting enzyme (ACE) inhibitors lower total peripheral resistance by blocking the actions of ACE, the enzyme that converts angiotensin I to angiotensin II. There are three subclasses of ACE inhibitors: sulphhydryl group – captopril; decarboxylase group – enalapril, lisinopril; phosphonate group – fosinopril. Captopril and lisinopril are not prodrugs whilst the others are considered prodrugs. ACE inhibitors

were classified into two groups according to their ability to cross the blood-brain barrier. These determinations were made based primarily on experiments in rats. The two most common means of measuring ability to cross the blood-brain barrier were: 1) analysis of ground up, tissue-specific ACE activity after administration of ACE inhibitors orally or subcutaneously, and 2) tissue-specific imaging of a radio-labelled ACE inhibitor after administration of various ACE inhibitors (which compete for binding with the radio-labelled ACE inhibitor). After a review of the literature, captopril, fosinopril, lisinopril, perindopril, ramipril, and trandolapril were classified as crossing the blood-brain barrier, while benazepril, enalapril, moexapril, and quinapril were classified as not.

The HOPE study, which involved 9,297 high-risk patients with vascular disease or diabetes plus one other cardiovascular risk factor without a history of HF or left ventricular dysfunction, showed that ramipril was associated with significant reductions in all-cause mortality, MI and stroke in these patients. The findings of the HOPE study support the prescription of an ACE inhibitor for prevention of cardiovascular complications in all high-risk patients, which therefore includes those with stable angina [14].

The use of perindopril in the EUROPA study, involving 13,655 patients with stable coronary disease and no clinical evidence of HF, reduced the risk of cardiovascular death, MI or cardiac arrest. These situations are, of course, complementary to the classic indications that may also be present in patients with stable angina, notably following MI and in left ventricular dysfunction or HF. The results of the EUROPA study further demonstrated that these ACE inhibitors should be considered in all patients with CAD [15].

The PEACE trial, using trandolapril in 8,290 patients with no history of clinical HF or echocardiographic evidence of left ventricular systolic dysfunction, did not reveal any benefit on cardiovascular events although the event rate was unexpectedly low. This discrepancy may be due to the inclusion of a low-risk patient population in the PEACE trial. In high- and intermediate-risk patients, ACE inhibitors have a consistent benefit, as demonstrated by Deckers et al in their study [16].

A smaller trial (QUIET) of 1,750 patients with CHD and normal left ventricular function found that the ACE inhibitor quinapril did not significantly affect clinical outcomes or the progression of coronary atherosclerosis [17].

A meta-analysis of six randomised trials, including 33,500 patients with coronary artery disease and preserved left ventricular systolic function, showed that ACE inhibitors significantly reduced cardiovascular (relative risk [RR] 0.83, CI: 0.72 to 0.96, absolute risk reduction [ARR] 0.86%, p=0.01) and all-cause mortality (RR 0.87, CI: 0.81 to 0.94, ARR 1.06%, p=0.0003) [18].

Therefore, Danchin and colleagues searched the literature for comparable randomised controlled trials regarding ACE inhibitors in CAD. Seven trials met their selection criteria, and included a total of 33,960 patients followed up for a mean of 4.4 years. Treatment

with ACE inhibitors significantly decreased overall mortality, cardiovascular mortality, MI, stroke, and other endpoints [19]. ACE inhibitors have been shown to reduce morbidity and mortality in patients with left ventricular systolic dysfunction in the settings of chronic heart failure and MI and also in patients with diabetes mellitus that is accompanied by proteinuria or chronic kidney disease. For those with preserved left ventricular function, ACE inhibitors lower cardiovascular and all-cause mortality by 17% and 13%, respectively [20].

Contraindications to ACE inhibitors include pregnancy, a history of angioedema or anuric renal failure during previous exposure to an ACE inhibitor and severe hypotension. Hypotension may also occur when ACE inhibitors are combined with other vasodilators such as nitrates or beta-blockers especially with low ejection fraction. While the majority of patients with pre-existing renal insufficiency often tolerate ACE inhibitors well, a baseline serum creatinine >220 μmol/L (>2.5 mg/dL) should be considered a relative contraindication and requires close observation if an ACE inhibitor is initiated. The most common side effect of ACE inhibitors observed in clinical practice is a non-productive cough that occasionally requires discontinuation.

All patients with stable vascular disease are likely to derive some benefit from these drugs, to a degree approximately proportional to the level of baseline risk. Patients with stable angina pectoris who have diabetes, hypertension, proteinuria, or chronic renal disease or those with impaired left ventricular systolic function (left ventricular ejection fraction <40%) and all post-MI patients should also be treated with an ACE inhibitor.

Conclusion

Stable angina pectoris is typically provoked by exertion or emotional stress and relieved by rest or nitrate intake. Risk stratification and underlying pathophysiological mechanisms should be considered for the selection of treatment strategies. The treatment goals of angina pectoris are improvement in quality of life by limiting the symptoms, and protection against future cardiovascular events and long-term complications.

Calcium antagonists and beta-blockers remain first-line options for the treatment of angina to control symptoms. DHPs have minimal negative inotropic properties and they are safer in patients with ventricular dysfunction. They can be used in combination with beta-blockers. However, one should be aware that the combination of beta-blockers and verapamil is not recommended due to their more marked negative inotropic effects.

All patients with stable angina pectoris should be considered for treatment with ACE inhibitors. As recommended in current ESC guidelines (stable coronary artery disease), ACE inhibitors should be used due to their long-term positive effect on events in patients with stable angina pectoris, especially with co-existing hypertension, LVEF ≤40%, previous myocardial infarction, diabetes or CKD, who will gain relatively more benefit from these drugs, unless contraindicated.

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