Clinical Medicine 2013, Vol 13, No 1: 63–70

Pharmacological treatment of chronic stable angina pectoris

Jason M Tarkin and Juan Carlos Kaski

ABSTRACT – Chronic stable angina is the most common manifestation of ischaemic heart disease in the developed world and is associated with impaired quality of life and increased mortality. The pathogenesis of stable angina is complex and often, albeit not always, involves flow-limiting epicardial coronary artery stenoses (atheromatous plaques) that reduce the ability of the coronary circulation to deliver appropriate blood supply to the myocardium. The coronary microcirculation can also play an important role. An imbalance between myocardial oxygen supply and metabolic oxygen demand causes the symptoms of angina pectoris and represents a major therapeutic target. Rational treatment requires a multi-faceted approach combining lifestyle changes, aggressive management of modifiable coronary artery disease risk factors, pharmacological therapy and myocardial revascularisation when appropriate. Despite modern therapies, many patients continue to suffer from angina. Several new anti-anginal drugs have been introduced that might allow more effective symptom control. These novel agents have specific mechanisms of action and fewer side effects compared to conventional drugs. The combined use of traditional and novel treatments is likely to increase the proportion of patients who are managed successfully with medical therapy alone. This article briefly reviews recent advances in the pharmacological management of chronic stable angina pectoris, highlighting how an understanding of the prevailing pathogenic mechanisms in the individual patient can aid appropriate selection of therapeutic strategies and improve clinical outcome.

Introduction

Current treatment strategies for chronic stable angina aim to control symptoms, reduce the ischaemic burden and improve prognosis by preventing the progression of atherosclerotic coronary artery disease (CAD) and its consequences. Ideally, the treatment of angina should be tailored to the individual patient's needs, taking into consideration the characteristics and severity of symptoms, the location, severity and functional significance of coronary artery stenoses, the presence of co-morbidities and patient preference. For each individual patient, the efficacy of the agent and their side effects, together with patient compliance, are important determinants for the success or the failure of a given treatment.

Jason M Tarkin, cardiology trainee, London Deanery and honorary research fellow; **Juan Carlos Kaski,** professor of cardiovascular science and head of Cardiovascular Sciences Research Centre

Cardiovascular Sciences Research Centre, University of London, UK

Overview of chronic stable angina

The term angina pectoris refers to William Heberden's classic description of the clinical symptoms of angina, as reported to the Royal College of Physicians in 1768.[1] There is currently no systematically agreed definition for angina pectoris and the term is used to define both the typical chest pain associated with myocardial ischaemia and the syndrome characterised by chest pain, myocardial ischaemia and obstructive atherosclerotic coronary artery disease. In this article, we use the term 'angina' in relation to the occurrence of typical central chest pain associated with myocardial ischaemia, irrespective of the presence or absence of flow-limiting organic coronary artery stenosis.

Angina is considered to be 'chronic' and 'stable' when symptoms are present for at least two months, without changes in severity, character or triggering circumstances.[2]

Stable angina is the most common clinical manifestation of ischaemic heart disease, affecting 58% of patients with CAD.[3] Its prevalence increases with age, rising from roughly 8% in men and 3% in women aged 55–64 years, to 14% in men and 8% in women aged 65–74 years, in England.[4] The annual mortality rate resulting from coronary heart disease in patients with stable angina is 0.9–1.4% per year.[5]

Stable angina results from an imbalance between coronary blood supply and myocardial oxygen demand, which is often, but not always, associated with the presence of obstructive CAD. Transient myocardial ischaemia typically causes 'constrictive' chest discomfort, resulting from the activation of mechano- and chemo-sensitive myocardial receptors. Patients with stable angina might or might not present with typical symptoms, and 'silent' myocardial ischaemia can be present in patients with diabetes mellitus and in the elderly. The typical clinical characteristics of chronic stable angina are summarised in Box 1.

Pathophysiological and pathogenic mechanisms: determinants of clinical presentation

The pathogenesis of angina is often multi-factorial. The basic underlying mechanism that leads to angina is an imbalance of myocardial oxygen supply and demand. This often occurs as a direct result of flow-limiting CAD, but it can also be due to coronary artery spasm limiting blood supply, coronary microvascular dysfunction and/or several other contributing mechanisms. To a great extent, the underlying pathogenic mechanism determines the pattern of clinical presentation, leading to effort-induced angina, mixed angina or angina at rest.

© Royal College of Physicians, 2013. All rights reserved.

Box 1. Typical clinical characteristics of stable angina. Adapted from current clinical practice guidelines.[5,15]

- Constricting, tight, heavy or pressure-like chest discomfort (often felt near the sternum) that may radiate along the ulnar border of the left arm and hand, to the neck and jaw, the epigastrium or back
- Precipitated by a predictable and reproducible level of physical exertion (symptoms may also be triggered by emotional stress, cold weather or a heavy meal)
- Relieved by rest or GTN, usually within 1–5 minutes.

*All three of the features above are defined as typical angina. Two of the three features above are defined as atypical angina. One or none of the features above is likely to represent non-anginal chest pain.

NB Shortness of breath, faintness or fatigue may represent 'angina equivalents' in the elderly and 'silent' ischaemia may also occur, particularly in those with diabetes mellitius.

Effort-induced angina

Long-standing obstructive epicardial CAD causes angina by providing a fixed limitation of coronary blood flow, which prevents physiological matching of coronary blood supply to exercise-induced increases in myocardial metabolic demand. A stenosis of 50% or more in the left main coronary artery, or 70% or more in another major epicardial artery, is defined as 'obstructive'.[6] Symptoms of effort-induced stable angina resulting from flow-limiting coronary stenoses often occur at a predictable and reproducible threshold, triggered by physical activity and/or emotional stress. The Canadian Cardiovascular Society (CCS) grading of angina is a functional classification of exercise tolerance that can be related to metabolic equivalent units (METs) and it is used in the assessment of exercise stress testing.[7,8]

'Mixed' angina

The imbalance of myocardial oxygen supply and demand in angina can also result from combined mechanisms. Excessive coronary artery vasoconstriction at the site of organic stenoses manifests clinically as 'mixed angina pectoris', in which patients present with variable-threshold effort angina and occasionally angina at rest.[5,9]

Microvascular angina

Coronary microvascular resistance is the main determinant of coronary flow reserve (the ratio of maximal induced myocardial flow to resting coronary blood flow). Abnormal vasodilatory responses of the coronary microcirculation can cause effort-related angina (microvascular angina). It is important to note that as few as 38% of patients without previously known heart disease who undergo elective diagnostic coronary angiography are found to have obstructive CAD.[6] In many of these patients with typical angina symptoms, exercise-induced myocardial ischaemia is caused by coronary microvascular dysfunction. Patients with cardiac syndrome X — defined as typical exertional angina, positive stress test responses and normal coronary angiograms — experience transient myocardial ischaemia resulting from impaired endothelial function, which leads to abnormal coronary microvascular vasodilatation, increased coronary vasoconstriction, or both.[10–12]

In the ACOVA (Abnormal Coronary VAsomotion in patients with stable angina and unobstructed coronary arteries) study, approximately two-thirds of patients without significant epicardial CAD had positive intra-coronary acetylcholine tests for distal epicardial or microvascular spasm.[13] Clinicians should be encouraged to think about the possibility of microvascular dysfunction or coronary microvascular spasm in patients who present with typical angina despite having angiographically normal coronary arteries.

Other contributing mechanisms

Following transient myocardial ischaemia, impaired diastolic relaxation and increased wall tension caused by calcium overload, which results from intracellular acidosis, and activation of late inward sodium currents worsens the oxygen imbalance and prolongs the angina episode.[2] Further metabolic derangement, including abnormalities of substrate supply and utilisation, enzymatic activities and mitochondrial function, can also contribute to the pathogenesis.[8] Aortic stenosis, hypertrophic cardiomyopathy, severe anaemia and thyrotoxicosis (when present) are other potential contributory factors that can worsen myocardial ischaemia.[2]

Diagnosis and management

Importance of the clinical history for diagnosis and management of stable angina pectoris

The accurate diagnosis of chronic stable angina (and the recognition of possible underlying pathogenic mechanisms) relies largely on obtaining a detailed clinical history. The severity of chest pain does not necessarily correlate to the extent of underlying CAD, but the burden of symptoms experienced by an individual patient will guide the nature and extent of the anti-anginal treatments used.

The CCS classification of angina can provide clinically useful diagnostic and prognostic clues that are important for patient management. In CCS grade I patients, angina is only precipitated by strenuous or severe and prolonged exertion; whereas at the other end of the spectrum, CCS grade IV patients, develop angina with minor exertion or even at rest.[7] It is important to remember that CCS grade does not necessarily reflect CAD severity.[14] By contrast, the occurrence of chest pain with progressively increased frequency and/or severity ('crescendo' angina), compared to the usual chronic stable symptoms, can be an expression of acute coronary syndrome (unstable angina and myocardial infarction) and must be monitored carefully and investigated promptly.

© Royal College of Physicians, 2013. All rights reserved.

Diagnostic investigation

Further investigation is guided by a risk stratification that is based on pre-test probability, derived from age, sex, character of symptoms and cardiovascular risk factors, as outlined by the NICE (National Institute for Health and Clinical Excellence) guideline on chest pain.[15] For low-risk CAD patients (10–29%) with stable symptoms, NICE recommends CT coronary calcium scoring as the first-line investigation.[15] While the reasons behind this recommendation are sound, the practical implementation of this strategy is not always feasible or straightforward, and cardiologists often resort to alternative diagnostic testing with stress echocardiography or even exercise stress testing. Functional imaging with stress echocardiography, nuclear myocardial perfusion scanning or first-pass cardiac magnetic resonance scanning is advised for patients with moderate cardiovascular risk (30–60%).[15] For high-risk patients (61–90%), NICE recommends proceeding directly to invasive coronary angiography.[15] The use of ECG exercise tolerance testing to diagnose CAD is not recommended,[15] albeit this relatively inexpensive test can often give useful functional information and, in practice, is still a useful diagnostic tool.

Pharmacological management of angina pectoris

Although the general principles of treatment (ie lifestyle modification and risk-factor management) are applicable to all patients with angina, treatment should be individualised where possible. It should aim to reverse or reduce the underlying pathophysiological mechanisms in order to relieve symptoms and improve cardiovascular risk profile. Key interventions include lifestyle changes (eg smoking cessation, dietary modification and increased physical exercise), management of hypertension, diabetes and obesity, and other secondary cardiovascular disease prevention measures, such as the use of anti-platelet and lipid-lowering agents, pharmacological anti-anginal therapies and percutaneous and/or surgical revascularisation when appropriate.[4,5]

Fig 1 provides a proposed practical therapeutic algorithm that is based on recently updated NICE guidelines, and Table 1 summarises important clinical information for each of the currently used anti-anginal agents included in this treatment algorithm.[4]

Treatment of chest pain episodes

Episodes of angina are best treated with sublingual glyceryltrinitrate (GTN). GTN acts as a nitric oxide donor, causing systemic and coronary vasodilatation. GTN is rapidly absorbed in the sublingual mucosae and its effects usually occur within 2–10 minutes. Common side effects of sublingual nitrate administration are headaches, dizziness, hot flushing and nausea. Contraindications for the use of GTN include aortic stenosis, hypertrophic cardiomyopathy, systemic hypotension and co-administration with phosphodiesterase-5 inhibitors (eg sildenafil). GTN is recommended for all patients with stable angina, unless contraindicated. When prescribing GTN, patients should be given advice regarding how and when to use GTN and potential side effects that they may experience. They should be advised to inform their doctor if the symptoms are not controlled. GTN can also be useful in preventing episodes of exertional angina when used prior to undertaking physical exertion.

First-line anti-anginal drugs

β-adrenergic receptor blockers (beta-blockers) and calcium-channel blockers are considered to be first-line anti-anginal drugs and have been shown in many studies to prevent angina and myocardial ischaemia. The TIBET (Total Ischaemic Burden European Trial) study showed that atenolol produced similar anti-anginal benefits when compared to slow-release nifedipine; no significant additional benefits were seen when the two agents were combined.[16] In the APSIS (Angina Prognosis Study in Stockholm) study, patients with stable angina treated with either metoprolol or verapamil had similar rates of cardiovascular events and mortality.[17] The choice between these two drug classes is generally guided by contraindications, the presence of co-morbidities and patient preference. If one of these agents is not well tolerated, the other can be tried instead. If combination therapy is required, the use of a non-heart-rate limiting dihydropiridine calcium channel blocker (eg amlodipine or slow-release nifedipine) is recommended. The anti-anginal actions of

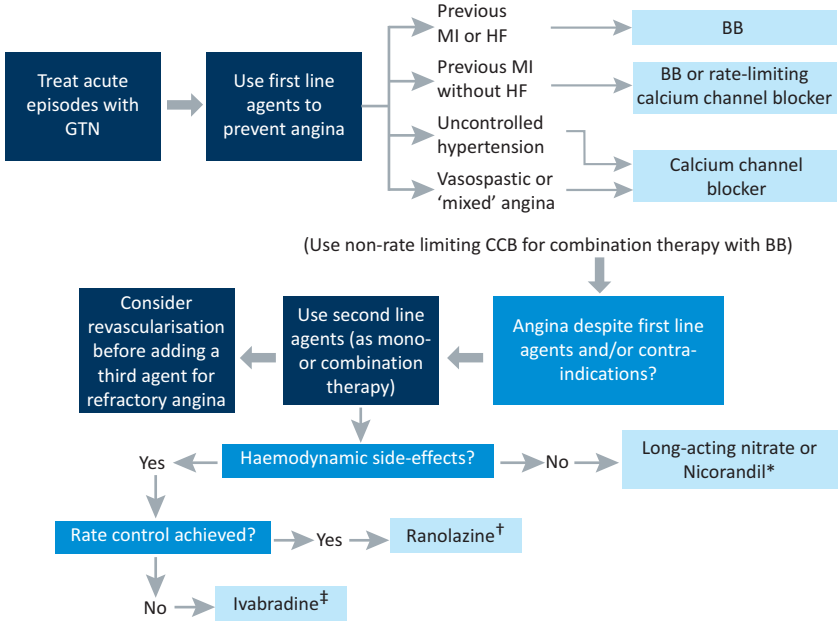

Fig 1. Proposed practical algorithm for pharmacological treatment of chronic stable angina based on NICE guidance.[4] BB = beta-blocker; CCB = calcium channel blocker; DM = diabetes mellitus; GTN = glyceryltrinitrate; HF = heart failure; MI = myocardial infarction. *added cardio-protective properties; †improves HbA1c in DM; ‡prognostic benefit in HF.

© Royal College of Physicians, 2013. All rights reserved.

beta-blockers result from a reduction in heart rate, contractility and blood pressure, which result in a reduced myocardial oxygen requirements. Also, by lowering the heart rate, the diastolic component of the cardiac cycle is prolonged, which improves myocardial flow. For maximal efficacy, long-acting, cardioselective beta-blockers that have no intrinsic sympathomimetic activity are preferred. The dose should be titrated to achieve a target resting heart rate of 50–60 beats per minute. The prognostic benefit of beta-blockers in angina has been extrapolated from studies of post myocardial infarction but has not yet been documented in stable angina.[16]

The potential benefits of beta-blocker therapy are often limited by side effects and contraindications. Among the most common side effects of beta-blockers are fatigue, dizziness, syncope, bronchospam, hyperglycaemia, depression and erectile dysfunction. These agents are contraindicated in patients with reactive airway diseases, severe bradycardia, 2nd or 3rd degree heart block, sick sinus syndrome, hypotension, acute heart failure and peripheral vascular disease. Beta-blockers are not generally used in patients with vasospastic angina because of the possibility that unopposed α-adrenergic receptors might have unwanted effects. Abrupt withdrawal of beta-blockers can cause rebound myocardial ischaemia.

Calcium channel blockers act on L-type Ca^{2+} receptors and lead to systemic and coronary vasodilatation, reducing afterload and improving myocardial blood flow. Like beta-blockers,

Table 1. Summary of anti-anginal drugs supported by NICE guidance.[4]

Anti-anginal agent	Therapeutic target	Mechanism of action	Prognostic benefit	Haemodynamic side effects	Notes
Beta-blockers	• Block β_1-adrenergic channels	• Reduce HR, BP and contractility • Prolong diastolic filling time	• Proven prognostic benefit for patients with previous MI or HF	Yes	• Contraindicated in patients with reactive airways diseases, severe bradycrdia, 2nd or 3rd degree heart block, sick sinus syndrome, hypotension and acute HF
Calcium channel blockers	• Block L-type Ca^{2+} channels	• Act as systemic and coronary vasodilators • Rate-limiting agents also reduce HR, BP and contractility, and prolong diastole	• Proven prognostic benefit for patients with previous MI seen with rate-limiting calcium channel blockers	Yes	• Rate-limiting calcium channel blockers are contraindicated in patient with severe bradycardia, 2nd or 3rd degree heart block, sick sinus syndrome, hypotension, acute heart failure and impaired left ventricular function
Nitrate	• NO donor	• Act as systemic and coronary vasodilators	• No proven prognostic benefit	Yes	• Not to be used with PDE inhibitors (eg sildenafil) due to risk of profound hypotension • Contraindicated in patient with significant hypotension
Nicorandil	• NO donor • K_{ATP} channel opener	• Acts as systemic and coronary vasodilators	• Proven prognostic benefit seen in patients with stable angina	Yes	• Not to be used with PDE inhibitors as per nitrates • Metformin may reduce efficacy • Contraindicated in patients with significant hypotension
Ivabradine	• Blocks I_f channels	• Cause pure reduction in heart rate	• Proven prognostic benefit in patients with heart failure	No	• Effective for patients with sinus rhythm and resting HR ≥70 bpm • Side effects may include 'flashing lights' (typically mild and transient) • Contraindicated in patient with severe bradycardia, acute MI or HF, and renal or hepatic failure • Caution with drugs that interfere with CYP3A4 hepatic enzymes
Ranolazine	• Blocks late inward Na^+ current	• Reduces diastolic wall tension and improves myocardial metabolic performance	• No currently proven prognostic benefit	No	• Improves HbA1c • May prolong QT-interval • Contraindicated in patients with prolonged QT-interval, previous VT and hepatic or renal failure • Caution with drugs that interfere with CYP3A4 hepatic enzymes

BP = blood pressure; HF = heart failure; HR = heart rate; MI = myocardial infarction; NO = nitric oxide; PDE = phosphodiesterase.

© Royal College of Physicians, 2013. All rights reserved.

non-dihydropyridines (eg verapamil and diltiazem) have additional anti-anginal affects through reductions in heart rate and contractility. Long-acting preparations are preferred. Common side effects of blockers include dizziness, headache, fatigue, flushing, abdominal pain, nausea and peripheral oedema. Like beta-blockers, non-diydropyridine calcium channel blockers are contraindicated by severe bradycardia, 2nd or 3rd degree heart block, sick sinus syndrome, hypotension and acute heart failure.

Second-line anti-angina therapies

For patients whose symptoms are not well controlled by beta-blockers and calcium-channel blockers, or if contraindications exist for these agents, several options supported by NICE guidelines[4] are available. These include: vasodilators such as long-acting nitrates and nicorandil, a drug that selectively slows the heart rate; ivabradine, and ranolazine, an agent that acts on the fast sodium current to improve cardiac metabolism. When and in which order these second-line agents are used in clinical practice is based on several variables, including pathogenic mechanisms, patient characteristics and co-morbidities, drug interactions and patient preference.

Long-acting nitrates

Although there is no evidence that nitrates improve patient prognosis, long-acting nitrates (eg isosorbide mononitrate or isosorbide dinitrate) have been shown to reduce the frequency and severity of angina attacks in patients with stable angina when given alone or in combination with first-line anti-anginal agents. The mechanisms of action, side effects and contraindications for these drugs are similar to those described under sublingual nitrates above. The development of nitrate tolerance and the adverse effects of long-acting nitrates reported recently require consideration before these drugs are prescribed for a given patient.[18,19]

Nicorandil

Nicorandil acts as both a nitric oxide donor and a sarcolemmal K^+-adenosine triphosphate (K-ATP)-dependant channel opener, causing K^+ efflux and subsequent hyperpolarisation and inhibition of L-type Ca^{2+} channels, leading to systemic and coronary vasodilatation. The beneficial effects of nicorandil monotherapy are similar to those of metoprolol, amlodipine, diltiazem and nitrates.[20–23] In the IONA (Impact Of Nicorandil in Angina) study, a reduced rate of fatal and non-fatal myocardial infarction and reduced admission for cardiac chest pain were seen in patients taking nicorandil in addition to other standard anti-anginal therapies.[24] The cardioprotective properties of nicorandil might be due to ischaemic preconditioning mediated by activation of mitochondrial K-ATP channels.[24] Common side effects of nicorandil are headaches, dizziness, nausea, vomiting and flushing. Metformin might antagonise the effects of nicorandil by closing K-ATP channels.[25] The use of phosphodiesterase-5 inhibitors and nitrates should be avoided by those taking nicorandil because of the risk of profound systemic hypotension.

Ivabradine

Ivabradine is a novel selective heart-rate-lowering anti-anginal drug. Ivabradine inhibits I_f channels, thereby affecting the intrinsic pacemaker cells of the sino-atrial node. When activated by hyperpolarisation in diastolic range voltages and by adrenergically driven increases in cyclic adenosine monophosphate, the I_f channel, causes an inward Na^+/K^+ ionic current across the sarcolemma, leading to spontaneous depolarisation of myocytes in the sino-atrial node.[26] Inhibition of the I_f current lwers the heart rate. Ivabradine is more effective in patients who have increased I_f channel activity.[26] It does not affect blood pressure, atrio-ventricular node conduction or contractility. On average, ivabradine reduces resting heart rate by 10 beats per minute.[25] Complete I_f blockade results in a maximum 30–40% reduction in heart rate due to compensation from other populations of pacemaker cells.[27]

The anti-anginal efficacy of ivabradine has been shown not to be inferior to atenolol and amlodipine in major trials.[28,29] In the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction) trial, lower rates of hospital admission for fatal and non-fatal myocardial infarction and coronary revascularisation were seen with ivabradine compared to placebo in patients with stable angina and heart rate $\geqslant$70 beats per minute.[30]

Ivabradine is indicated for patients with stable angina who are in sinus rhythm and cannot tolerate or have contraindications for conventional heart-rate-lowering agents (ie beta-blockers and non-dyhidropyridine calcium channel blockers), and for patients established on conventional monotherapy whose resting heart rate is sub-optimal. Common side effects include visual 'flashing lights' that are often mild and transient, headache, dizziness, blurred vision, 1st degree heart block and ventricular extra-systoles. Contraindications are bradycardia, sick-sinus syndrome, heart block, atrial fibrillation, acute myocardial infarction, acute heart failure, hypotension, and renal and hepatic failure. Ivabradine is metabolised by the CYP3A4 liver enzymes, and significant interactions might occur with drugs that interfere with these enzymes (eg azole anti-fungals, diltiazem, verapamil, macrolide antibiotics and grapefruit juice). Ivabradine can be used safely in patients with asthma and chronic obstructive pulmonary disease.[31]

Ranolazine

Ranolazine is a piperazine derivative that is thought to exert its anti-anginal effect by inhibiting ischaemic-induced late inward Na^+ currents, preventing Ca^{2+} overload and reducing diastolic wall tension and extrinsic coronary artery compression.[32] It

© Royal College of Physicians, 2013. All rights reserved.

might also improve endothelial-mediated coronary vasodilatation.[33] It was originally thought to act as an anti-metabolic drug, but the concentration required to inhibit myocardial fatty-acid oxidation is much higher than the therapeutic levels used to treat angina.[32] An advantage of ranolazine is that it does not cause significant haemodynamic changes, with on average less than 2 beats per minute reduction in heart rate and less than 3 mmHg decrease in systolic blood pressure.[25] It is, however, associated with a dose-dependant increase in QT-interval.[25]

The clinical efficacy of ranolazine in chronic stable angina as monotherapy and in combination with other anti-anginal drugs has been shown in MARISA (Monotherapy Assessment of Ranolazine in Stable Angina),[34] CARISA (Combination Assessment of Ranolazine In Stable Angina)[34] and ERICA (Efficacy of Ranolazine in Chronic Angina) trials.[36] No reduction in cardiovascular death, acute myocardial infarction or recurrent ischaemia was seen in the MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes) trial when ranolazine was taken instead of placebo.[37]

Common side effects of ranolazine are dizziness, nausea, constipation, abdominal pain and headaches. Contraindications to ranolazine are prolonged QT-interval and co-administration with other QT-prolonging drugs, previous history of ventricular tachycardia, and moderate to severe renal impairment or severe hepatic failure. Ranolazine is metabolised by liver CYP3A4 and to a lesser extent by CYP2D6 enzymes, consequently there is a potential for drug interactions. Ranolazine is also a weak inhibitor of cytochrome p450 enzymes and therefore doses of P-glycoprotein substrates (eg simvasatin and digoxin) might need to be reduced for those taking ranolazine.[25]

Other anti-anginal drugs

A number of other anti-anginal drugs exist. These are not currently included in NICE guidance, but could in future become available for use in the UK. Trimetazedine, a thiolase that efficiently inhibits beta-oxidation of fatty acids in the myocardium, shifting cardiac metabolism towards more efficient pathways, is used in many European countries as a metabolic modulator.[38] Angiotensin-converting-enzyme inhibitors are not strictly speaking anti-anginal agents but they have been shown to improve prognosis in patients with diabetes or heart failure and following a myocardial infarction. They are therefore indicated in those circumstances and studies are required to determine their true role in stable angina pectoris.

F 15845 (3-(R)-[3-(2-methoxyphenylthio-2-(S)-methylpropyl]amino-3,4-dihydro-2H-1,5-benzoxathiepine bromhydrate) is a newly described selective inhibitor of the persistent Na^+ current, which has shown anti-ischaemic properties and an ability to prevent ischaemia-induced arrhythmias in animal models; it currently is being assessed in phase II clinical trials.[39–41]

Individual approach to anti-anginal drug selection

In many patients, multiple drugs with different mechanisms of action might be necessary for successful symptom control. Many patients, however, are unable to tolerate conventional angina therapies, mainly those eliciting haemodynamic side effects. The NICE guideline recommends adding a third drug only when two anti-anginal drugs do not satisfactorily control symptoms and the patient is awaiting revascularisation, or in patients for whom revascularisation is not appropriate.[4]

For patients with previous myocardial infarction or heart failure, beta-blockers are the preferred first-line agent because of their proven prognostic benefit.[5] Rate-limiting calcium channel blockers can also improve prognosis in post-myocardial-infarction patients who do not have heart failure.[5] Calcium channel blockers are preferred in patients with angina who require good hypertensive control.[27] Long-acting nitrates are a logical choice for patients whose symptoms persist despite their taking beta-blockers or calcium channel blockers but who tolerate short-acting nitrates. As nitrates do not improve prognosis, however nicorandil might provide similar anti-anginal effects but with added cardio-protective benefit.

For patients who develop hypotension or other haemodynamic side effects with conventional anti-anginal therapies, ivabradine and ranolazine are suitable options as they do not exert vasoactive actions. Ivabradine controls heart rate efficiently without significantly causing haemodynamic effects and can be used safely by patients with obstructive airways disease. Ivabradine can also be used in combination with beta-blockers. In the ASSOCIATE (Antianginal efficacy and Safety of the aSsociation Of the I_f Current Inhibitor ivAbradine with a beTa-blockEr) trial, the combination of ivabradine and atenolol was effective and well tolerated in patients with stable angina, and it was not associated with untoward effects.[42] Ivabradine has also been shown to reduce cardiovascular death and hospital admission in patients with systolic heart failure.[43] In patients with diabetes, ranolazine has an added metabolic benefit in that it has been associated with a significant reduction in HbA1c concentrations.[44,45]

It is important to remember that angina results from the interplay of a number of complex vascular and metabolic mechanisms and does not result solely from the presence of obstructive epicardial CAD. Anti-anginal regimes should be, as much as possible, aimed at addressing the prevailing underlying pathophysiological mechanisms in the individual patient. This is particularly important for patients who have chest pain, objective documentation of myocardial ischaemia and angiographically 'normal' coronary arteries, in whom coronary microvascular dysfunction and distal epicardial vasoconstriction often play an import role. Calcium channel blockers and other vasodilator agents are useful to these individuals. In patients with true vasospastic angina, ie Prinzmetal's variant angina, calcium channel blockers (usually at high doses) are the best treatment option and are preferred over nitrates for long-term control of symptoms, albeit nitrates (particularly sublingual GTN) can also play an important role in management.[5]

© Royal College of Physicians, 2013. All rights reserved.

Conclusions and future directions

Medical management of stable angina includes lifestyle modification and optimal medical therapy, which encompasses both aggressive pharmacological control of the cardiovascular and metabolic risk profiles, and individualised anti-anginal drug regimes, targeted at specific underlying pathogenic mechanisms. Medical treatment should be regarded as the most important initial intervention and as such should be implemented for all patients as it might reduce the need for invasive coronary intervention, particularly for patients with mild to moderate CAD in whom the prognostic benefit of revascularisation remains unproven.

Recent advances in the pharmacological management of chronic stable angina offer more precise and individualised solutions. Drug selection can be tailored to the individual on the basis of their underlying pathophysiological mechanisms, which often can be identified from the clinical history. The main aims of therapy remain to control symptoms, thereby improving quality of life, and ultimately to prevent progression of the underlying atherosclerotic coronary heart disease and its long-term complications. For the future, angiogenic gene therapy, using genes that encode vascular endothelial growth factors and fibroblast growth factors, and intramyocardial hematopoietic stem cell therapy are currently being developed. At present and in theory, these offer reasonable promise.[27,46]

References

1 Silverman ME. William Heberden and some account of a disorder of the breast. *Clin Cardiol* 1987;10:211–3.
2 Kaski JC, Arrebola-Moreno A, Dungu J. Treatment strategies for chronic stable angina. *Expert Opin Pharmacother* 2011;12:2833–44.
3 Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D *et al.* on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction. The American Heart Association's strategic impact goal through 2020 and beyond. *Circulation* 2010;121:586–613.
4 National Institute for Health and Clinical Excellence. *Management of stable angina.* Clinical guideline CG126. London: NICE, 2011. http://guidance.nice.org.uk/CG126 [Accessed 3 January 2013].
5 Fox K, Garcia MA, Ardissino D *et al.* Guidelines on the management of stable angina pectoris: executive summary: the task force on the management of stable angina pectoris of the European Society of Cardiology. *Eur Heart J* 2006;27:1341–81.
6 Patel MR, Peterson ED, Dai D *et al.* Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886–95.
7 Campeau L. Grading of angina pectoris. *Circulation* 1976;54:522–3.
8 Kones R. Recent advances in the management of chronic stable angina I: approach to the patient, diagnosis, pathophysiology, risk stratification and gender disparities. *Vasc Health Risk Manag* 2010;6:635–56.
9 Maseri A, Chierchia S, Kaski JC. Mixed angina pectoris. *Am J Cardiol* 1985;56:30E–33E.
10 Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X). *Circulation* 2004;109:568–72.
11 Kaski JC . Cardiac syndrome X in women: the role of oestrogen deficiency. *Heart* 2006;92(Suppl III):iii5–9.
12 Ong P, Athanasiadis A, Mahrholdt H *et al.* Increased coronary vasoconstrictor response to acetylcholine in women with chest pain and normal coronary arteriograms (cardiac syndrome X). *Clin Res Cardiol* 2012;101:673–81.
13 Ong P, Athanasiadis A, Borgulya G *et al.* High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol* 2012;59:655–6.
14 Chockalingam A, Gnanavelu G, Subramaniam T *et al.* Canadian Cardiovascular Society classification of effort angina: an angiographic correlation. *Coron Artery Dis* 2004;15:111–4.
15 National Institute for Health and Clinical Excellence. *Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Clinical guideline CG95.* London: NICE, 2010. http://guidance.nice.org.uk/CG95 [Accessed 3 January 2013].
16 Fox KM, Mulcahy D, Findlay I *et al.* for the TIBET study group. The total ischaemic burden European trial (TIBET): effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. *Eur Heart J* 1996;17:96–103.
17 Rehnqvist N, Hjemdahl P, Billing E *et al.* Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J* 1996;17:76–81.
18 Kim D, Rybalkin SD, Pi X *et al.* Upregulation of phosphodiesterase 1A1 expression is associated with the development of nitrate tolerance. *Circ* 2001 104:2338–43.
19 Tarkin J. Chapter 2a: chronic stable angina. In: Kaski JC, Baker S, Hayward C, Khong TK, Mahida S, Tamargo J (eds). *Drugs in cardiology: a comprehensive guide to cardiovascular pharmacotherapy.* Oxford: OUP 2010; 31–43.
20 Doring G. Anti-anginal and anti-ischemic efficacy of nicorandil in comparison with isosorbide-5 mononitrate and isosorbidedinitrate: results from two multicenter, double-blind, randomized studies with stable coronary heart disease patients. *J Cardiovasc Pharmacol* 1992;20(Suppl 3):S74–81.
21 Di Somma S, Liguori V, Petitto M *et al.* A double-blind comparison of nicorandil and metoprolol in stable effort angina pectoris. *Cardiovasc Drugs Ther* 1993;7:119–23.
22 The SWAN study group. Comparison of the anti-ischemic and anti-anginal effects of nicorandil and amlodipine in patients with stable angina pectoris: the SWAN study. *J Clin Basic Cardiol* 1999;2:213–7.
23 Guermonprez JL, Blin P, Peterlongo F. A double-blind comparison of the long term efficacy of a potassium channel opener and a calcium antagonist in stable angina pectoris. *Eur Heart J* 1993;14(Suppl B):30–4.
24 IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002;359:1269–75.
25 Kaski JC, Baker S, Hayward C *et al.* (Eds). *Drugs in cardiology: a comprehensive guide to cardiovascular pharmacotherapy.* Oxford: Oxford University Press, 2010.
26 Sulfi S, Timmis AD. Ivabradine: the first selective sinus node I_f channel inhibitor in the treatment of stable angina. *Eur Heart J* 2005;26:2529–36.
27 Chaitman BR, Laddu AA. Stable angina pectoris: antianginal therapies and future directions. *Nat Rev Cardiol* 2012; 9:40–52.
28 Tardif J-C, Ford I, Tendera M *et al.* for the INITIATIVE investigators. Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005;26:2529–36.
29 Ruzyllo W, Tendera M, Ford I, Fox KM. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs* 2007;67:393–405.
30 Fox K, Ford I, Steg PG *et al.* on behalf of the BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:807–16.

© Royal College of Physicians, 2013. All rights reserved.

31 Majewski S, Slomka S, Zielinska-Wyderkiewicz E *et al.* Heart rate-lowering efficacy and respiratory safety of ivabradine in patients with obstructive airway disease: a randomized, double-blind, placebo-controlled, crossover study. *Am J Cardiovasc Drugs* 2012;12:179–88.
32 Reddy BM, Weintraub HS, Schwartzbard AZ. Ranolazine: a new approach to treating an old problem. *Tex Heart Inst J* 2010;37:641–7.
33 Deshmukh SH, Patel SR, Pinassi E *et al.* Ranolazine improves endothelial function in patients with stable coronary artery disease. *Coron Artery Dis* 2009;20:343–7.
34 Chaitman BR, Skettino SL, Parker JO *et al.* Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol* 2004;43:1375–82.
35 Chaitman BR, Pepine CJ, Parker JO *et al.* Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA* 2004;291:309–16.
36 Stone PH, Gratsiansky NA, Blokhin A *et al.* for the ERICA Investigators. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol* 2006;48:566–75.
37 Morrow DA, Scirica BM, Karwatowska-Prokopczuk E *et al.* Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* 2007;297:1775–83.
38 Marzilli M, Klein WW. Efficacy and tolerability of trimetazidine in stable angina: a meta-analysis of randomized, double-blind, controlled trials. *Coron Artery Dis* 2003;14:171–9.
39 Vacher B, Pignier C, Létienne R *et al.* F 15845 inhibits persistent sodium current in the heart and prevents angina in animal models. *Br J Pharmacol* 2009;156:214–25.
40 Bocquet A, Sablayrolles S, Vacher B, Grand B Le. F 15845, a new blocker of the persistent sodium current prevents consequences of hypoxia in rat femoral artery. *Br J Pharmacol* 2010;161:405–15.
41 Pignier C, Rougier J-S, Vié B *et al.* Selective inhibition of persistent sodium current by F 15845 prevents ischaemia-induced arrhythmias. *Br J Pharmacol* 2010;161:79–91.
42 Tardif J-C, Ponikowski P, Kahan T for the ASSOCIATE study Investigators. Efficacy of the If current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009;30:540–8.
43 Michael B, Swedberg K, Komajda M *et al.* on behalf of the SHIFT Investigators. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010;376:886–94.
44 Morrow DA, Scirica BM, Chaitman BR *et al.* MERLIN-TIMI 36 Investigators. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. *Circulation* 2009;119:2032–9.
45 Timmis AD, Chaitman BR, Carger R. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes. *Eur Heart J* 2005;27:43–8.
46 Fernandez SF, Tandar A, Boden WE. Emerging medical treatment for angina pectoris. *Expert Opin Emerging Drugs* 2010;15:283–98.

Address for correspondence: Prof JC Kaski, Cardiovascular Sciences Research Centre, St. George's University of London, Cranmer Terrace, London SW17 0RE. Email: jkaski@sgul.ac.uk

© Royal College of Physicians, 2013. All rights reserved.