

Angina

Coronary heart disease (CHD) incorporates a range of conditions including chronic stable angina, acute coronary syndromes and myocardial infarction. Chronic stable angina pectoris is a common problem in the UK, with a prevalence of just under two million and an annual incidence of 28,000.¹

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There has undoubtedly been a shift in the epidemiology of coronary heart disease (CHD) in the UK. Incidence has fallen and prognosis has improved, especially in people aged 55–64 years, as more patients survive their myocardial infarctions (MI) and other cardiac events.¹ Because the burden of disease has shifted towards the older age groups, we must adopt a holistic approach to assessment. Many of the increasingly elderly CHD population have comorbid conditions—for example, hypertension, chronic obstructive pulmonary disease (COPD) or chronic heart failure (CHF)—that will influence our choice of medical treatment.²

Each year about 1% of the population consult their GPs about angina, but the greatest proportion of the £700 million annual direct cost of angina relates to hospital bed occupancy and revascularisation procedures.³ Angina has an important impact on patients in terms of poor prognosis. The annual mortality of 1 to 3% is double that of age-matched controls⁴ and reduced

quality of life. Angina affects physical functioning, emotional wellbeing, perception of pain and general health.⁵ Reducing the number of angina attacks improves all these parameters,⁵ and consequently appropriate treatment is very important. Moreover, recent NICE guidance for management of stable angina state that age alone should not exclude treatment.⁶

CHD is not equally distributed within the UK. Certain population groups have been identified as more vulnerable to developing the disease. The likelihood of developing the disease varies according to:

- Sex: it is more common in men than women, although women develop the disease at the same rate as men after menopause
- Social class: the prevalence is higher in unskilled men
- Region: the incidence is higher in the north of the UK
- Ethnicity: it is higher in people born in the Indian sub-continent
- Other existing factors: these include diabetes, high

cholesterol, high blood pressure, smoking and obesity.⁷

Pathophysiology of angina

The pathophysiology of angina is driven by loss of luminal diameter due to accumulation of lipid deposits within the vessel wall. Critical to the stability of plaque is the integrity of the fibrous cap that acts as a barrier between vessel lumen and the lipid core. In stable angina, coronary artery lesions tend to have a thick fibrous cap and be relatively placid. There is, therefore, a constant haemodynamic obstruction with predictable symptoms.⁸ The diagnosis of angina implies myocardial ischaemia, which will occur at a threshold point, dictated by the balance between coronary artery flow and metabolic demands of the myocardium.⁸

The coronary arteries deliver oxygenated blood to the heart's muscle. Angina occurs when atheroma (fatty plaques) develop

along the coronary arteries, this process is called atherosclerosis. In time, the artery may become so narrow that it cannot deliver enough oxygenated blood when the demand is high, such as when exercising. The pain or discomfort experienced is known as angina. Angina may also be precipitated by emotional upset, cold and windy weather, extreme heat or after a heavy meal. MI occurs if there is plaque rupture and a thrombus develops, blocking the artery.⁷

Epidemiology

Incidence

Estimates of the incidence of angina can be provided from representative samples of GP registries. The General Practice Research Database (GPRD) contains anonymised records from such a sample in England, Wales, Scotland and Northern Ireland. GPRD data suggest that in 2009 the incidence rate of angina was the highest in Scotland and lowest in England for both men and women. Overall in the UK, incidence rates were 75% higher in men compared to women. Incidence rates generally increase with age, and are highest in the 65 to 74 age group in both men and women at 215.4 and 136.6 per 100,000 population respectively. Rates in those 75 years and over are 136.7 and 99.9 per 100,000 respectively in men and women with overall incidence at all ages of 48.7 for men and 28 for women per 100,000. Using these incidence rates, the British Heart Foundation estimate there are nearly 28,000

new cases of angina in the UK every year.¹

Prevalence

In general, different studies on the prevalence of angina in the UK give similar prevalence rates, although the rate appears to be higher in Scotland than in England.¹ Figures from the 2006 Health Survey for England suggest that about 8% of men and 3% of women aged 55 to 64 and about 14% of men and 8% of women aged 65 to 74 have or have had angina. Prevalence is highest in those 75 years and over at 16% in men and 11.9% in women.¹

Diagnosis

Signs and symptoms of angina

Stable angina is characterised by a pain or discomfort in the chest, jaw, arms, shoulder, back or epigastric area (particularly after a heavy meal). It is usually brought on by physical exertion. In some people with angina there is no pain but they experience shortness of breath. Unstable angina results in pain or discomfort at rest. In a small number of people silent ischaemia prevails and they may have only experienced pain or discomfort once, with no further episodes.

Diagnosis of angina

Diagnosis and assessment of angina involves clinical assessment, selected laboratory tests and cardiac investigations. On presentation to the GP by a person experiencing symptoms

a careful history will, in most cases give a confident diagnosis, although a physical examination and blood tests will need to be undertaken. Bloods will be taken for total cholesterol, liver function, renal function, thyroid function and blood glucose. An ECG will also be undertaken. Current practice in the UK advises that patient will then be referred to a rapid access clinic and ideally seen within two weeks. The patient, if possible will undergo an exercise tolerance test (ETT) using the Bruce protocol and any ECG changes monitored. For this procedure the patient walks on a treadmill or rides an exercise bicycle for nine minutes with a gradual increase in incline and speed. Angina only shows on an ECG during an attack so this procedure is enforcing an angina attack under safe conditions.⁷

Women and the elderly represent particular groups of patients in whom the non-invasive diagnosis of CAD may be challenging. Exercise ECG is often used as the initial diagnostic test; however, studies have demonstrated that it has a high false positive rate in women^{9,10} and poses problems in the elderly.¹¹ This is thought to be partly caused by the lower prevalence of CAD in women, and partly because the classic ECG criteria for a positive test are based on data obtained in men, with no data from patients over 75 years. Furthermore, the ST response to exercise appears to be gender related with less sensitivity of exercise-induced ST depression in women.¹² Non-Bayesian factors including the greater prevalence

Prescribing information (SPF – 08) PRADAXA® (dabigatran etexilate)

Capsules containing 110 mg or 150 mg dabigatran etexilate (as trihydrate). **Action:** Direct thrombin inhibitor. **Indications:** Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors: Previous stroke, transient ischaemic attack, or systemic embolism (SEE), Left ventricular ejection fraction < 43 %, Symptomatic heart failure, > 70th Year Heart Association (YHA) Class 2, Age ≥ 75 years, Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension. **Dose and Administration:** Recommended daily dose 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term. In case of intolerance to dabigatran, patients should be switched to immediately consult their doctor. **Elderly:** Age ≥ 80 years consider 220 mg taken as one 110 mg capsule twice daily. 75 – 80 years consider 220 mg taken as one 110 mg capsule twice daily. As renal impairment may be frequent in the elderly (> 75 years), assess renal function by calculating CrCl, prior to initiation to exclude patients with severe renal impairment (CrCl < 30 ml/min). Renal function should also be assessed at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate. Patients with an increased risk of bleeding, closely monitor clinically looking for signs of bleeding or anaemia. Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test may help identify increased risk patients. Patients with gastritis, esophagitis, or gastroesophageal reflux consider 220 mg taken as one 110 mg capsule twice daily due to the elevated risk of major gastro-intestinal bleeding. Renal impairment, contraindicated in severe renal impairment (CrCl < 30 ml/min); patients with renal impairment and a high risk of bleeding consider 220 mg taken as one 110 mg capsule twice daily. Close clinical surveillance is recommended in patients with renal impairment. An above average renal function prior to initiation to exclude patients with severe renal impairment and assess renal function at least once a year or more frequently as needed. Concomitant venaprost 220 mg taken as one 110 mg capsule twice daily; Pradaxa and venaprost should be taken at the same time. No dose adjustment required but close clinical surveillance in patients < 50 kg. Not recommended if liver enzymes > 2 Upper Limit of Normal (ULN). If switching from Pradaxa to parenteral anticoagulant wait 12 hours after the last dose of Pradaxa; if switching from parenteral anticoagulant to Pradaxa then Pradaxa should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment. If switching from Pradaxa to VKA adjust the starting time of the VKA based on CrCl. If switching from VKA to Pradaxa stop VKA and give Pradaxa once (0H) < 2D. Cardioversion patients can stay on Pradaxa whilst being cardioverted. Not recommended aged < 18 years. Pradaxa should be swallowed whole with water, with or without food. Patients should be instructed not to open the capsule as this may increase the risk of bleeding. **Contraindications:** Hypersensitivity to any component, severe renal impairment (CrCl < 30 ml/min), active clinically significant bleeding, organic lesions at risk of bleeding, impairment of haemostasis, hepatic impairment or liver disease expected to have any impact on survival, concomitant systemic anticoagulant, cytopenia, haematuria, leucopenia. **Warnings and Precautions:** Not recommended if liver enzymes > 2 ULN, haemorrhagic risk. Close clinical surveillance (signs of bleeding or anaemia) is recommended throughout the treatment period, especially when haemorrhagic risk is increased or risk factors combined. Factors which may increase haemorrhagic risk: age ≥ 75 years; moderate renal impairment (CrCl 30 – 50 ml/min); P-glycoprotein inhibitor co-medication; body weight < 50 kg; acetylsalicylic acid (aspirin), NSAIDs; clopidogrel; diathermy procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional platelet defects, active alcoholic GI disease, recent GI bleeding, recent biopsy or major trauma, recent CHI or brain, spinal or ophthalmic surgery, bacterial endocarditis. The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Patients who develop acute renal failure must discontinue Pradaxa. If severe bleeding occurs, discontinue treatment and investigate the source of the bleeding. Avoid or use with caution agents which may increase the risk of haemorrhage. Avoid concomitant administration with P-gp inducers. Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate; prescribers should consult the Summary of Product Characteristics for further information. Procedures such as spinal anaesthesia may require complete haemostatic function. The risk of spinal or epidural haematomas may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate; these patients require frequent observation for neurological signs and symptoms of spinal or epidural haematomas. Treat with caution patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events. Myocardial infarction. Contains Sunset Yellow (E110) which may cause allergic reactions. **Interactions:** Anticoagulants and antiplatelet aggregation agents; Strong P-gp inhibitors e.g. amiodarone, quinidine, verapamil, diltiazem; co-administration (close clinical surveillance); venaprost co-administration – add up Pradaxa dose to 220 mg (see above); not recommended for concomitant treatment with clopidogrel, dipyridole, protease inhibitors including ritonavir and its combinations with other protease inhibitors; avoid with P-gp inducers e.g. rifampicin, St John's wort, carbamazepine, phenytoin. Dabigatran etexilate and dabigatran are not metabolised by cytochrome CYP450 system, therefore related medicinal product interactions not expected. Pantoprazole and other proton pump inhibitors (PPI) were co-administered with Pradaxa in clinical trials and concomitant PPI treatment did not appear to reduce the efficacy of Pradaxa. Routine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran. **Fertility, pregnancy and lactation:** Avoid pregnancy during treatment. Do not use in pregnancy unless clearly necessary. Discontinue breast-feeding during treatment. **Undesirable effects:** Most commonly reported adverse reactions are bleedings occurring in total in approximately 16.5% in patients with atrial fibrillation treated for the prevention of stroke and SEE. Common (≥ 1/100, <1/10): anaemia; epistaxis; gastrointestinal haemorrhage; abnormal pain; diarrhoea; dyspepsia; nausea; genitourinary haemorrhage (150 mg). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 110mg 60 capsules (£75.60) 150 mg 60 capsules (£75.60) **Legal category POM. MA numbers:** 119mg BU13/08/442/007 (60 capsules) 150 mg BU13/08/442/011 (60 capsules). **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55278 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. Prepared in December 2011.

of CAD, cardiac syndrome X, differences in microvascular function (leading to coronary spasm), and possibly hormonal differences add to the diagnostic difficulties of establishing an accurate diagnosis in women.¹² It is also recommended that patients unable to exercise sufficiently to achieve maximum predicted heart rate for their age and sex should be risk stratified using MPI coupled with pharmacological stress.¹³

Because of the diagnostic challenges largely in the elderly and women outlined above diagnostic pathways in the UK are set to undergo major changes and recent NICE guidelines have been issued.

Diagnosis

NICE guidance¹⁴ recommends that the diagnosis of angina can be based either on clinical assessment alone or with additional diagnostic testing. Clinical assessment includes patient age, sex, cardiovascular disease history, chest pain characteristics and presence of cardiovascular risk factors in addition to physical examination. Risk factors for CAD should be used to estimate the likelihood of CAD. Risk assessment should include a 12 lead ECG.

In a patient with features of typical angina and an estimated likelihood of CAD >90%, further diagnostic tests are unnecessary and the patient should be managed as stable angina. If the estimated likelihood of CAD is <10% the guidelines recommend looking for alternative causes other than angina for chest pain.

Further investigations are divided into anatomical techniques (x-ray angiography), used to demonstrate coronary artery stenosis, and functional techniques (eg. stress perfusion magnetic resonance, myocardial nuclear perfusion imaging or stress echo), designed to demonstrate reversible myocardial ischaemia as a consequence of coronary artery stenosis.

In individuals without confirmed CAD, in whom angina cannot be ruled in or out on clinical assessment alone and where estimated likelihood is 10-90%, further investigations are recommended:

- Estimated likelihood of CAD 10–29%: offer CT calcium scoring
- Estimated likelihood of CAD 30–60%: offer functional testing as above
- Estimated likelihood of CAD 31-90%: offer invasive coronary angiography

In those with calcium scores of 1–400 offer CT coronary angiography. For those with known CAD in whom angina cannot be excluded or diagnosed by clinical assessment, non-invasive functional testing or exercise ECG is recommended.

These guidelines do not recommend exercise ECG as a means of confirming or refuting a diagnosis of stable angina in patients without known CAD. This is due to the low predictive value of the exercise ECG.

Management

The medical management of patients at high risk of or

Adverse events should be reported. Reporting forms and information can be found at www.medicines.gov.uk. Adverse events should also be reported to Boehringer.ingelheim@brg.safety (Drug Safety on 0800 328 1627 (toll-free)).

References: 1. [Boehringer Ingelheim](http://www.boehringer-ingelheim.com), Pradaxa® 150mg hard capsules Summary of Product Characteristics; 2. [Boehringer Ingelheim](http://www.boehringer-ingelheim.com), Pradaxa® 110mg hard capsules Summary of Product Characteristics; 3. [BMJ Risk Calculator](http://www.bmj.com), http://clinicalcalculator.bmj.com/conditions/vascular/calculation_risk.jsp. Accessed December 2011; 4. Connolly S, Ezekowitz MD, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2009; 361:1130-1139; 5. Connolly S, Ezekowitz MD, et al. Newly identified events in the RE-LY trial. *N Engl J Med* 2010; 363:1875-1876.

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with established CHD has undoubtedly improved in the UK since the publication of the National Service Framework for Coronary Heart Disease¹⁵ in 2000, with a substantial rise in the prescription of lipid-lowering and antihypertensive agents, and some increase in use of calcium channel blockers (used in both angina and hypertension) and nitrates. In contrast, there has been very little change in prescribing rates of β -blockers.¹⁶

At present, despite being on two or more anti-anginal agents, only about half of patients benefit from medical treatment in terms of reduced angina frequency and improved quality of life.¹⁷ Furthermore, while guidelines recommend that revascularisation should be considered in patients with symptoms despite optimal medical therapy for chronic stable angina, there are no good data demonstrating that revascularisation improves prognosis, and many patients still have symptoms and remain on anti-anginal medication 12 months after undergoing the procedure.¹⁸

In patients with stable angina three treatment strategies are necessary. Initially education, lifestyle modification (including dietary advice, weight reduction, smoking cessation and exercise), and management of risk factors (especially hypertension and diabetes) are important. The second is disease modification with anti-platelet agents, statins and ACE inhibitors. The third is symptom management with β -blockers and sublingual Glyceryl nitrate and a variety of other anti-

anginal agents including calcium channel blockers, oral nitrates, nicorandil, ivabradine and ranolazine.

Patients should be referred to community cardiac rehabilitation teams who in many areas have adapted the Angina plan¹⁹ for newly diagnosed patients. All patients with CAD should be encouraged to increase their aerobic exercise levels within limits set by their disease state²⁰ and there is a new emphasis on a Mediterranean diet and fatty fish intake, although this evidence is based only on survivors of MI.²¹

Disease modification

The benefits of aspirin and lipid lowering with statins are now undisputed, and all patients with CAD should be on these agents lifelong. Clopidogrel may be considered in patients truly allergic or intolerant to aspirin.²²⁻²⁴

Statin therapy should be considered in all patients with CAD²⁰ or at high CVD risk.²⁵ Whilst studies such as the Heart Protection Study²⁶ and PROVE-IT²⁷ support the concept of lowering cholesterol aggressively a recent meta-analysis suggested a stronger association of stroke reduction with statin treatment than with the extent of cholesterol reduction.²⁸ Furthermore, a recent study of intensive versus delayed conservative simvastatin strategy in patients with acute coronary syndromes showed that the higher dose regimen failed to show a significant benefit on the primary endpoints

of cardiovascular death, MI and readmissions for ACS or stroke at four months, although there were some later benefits from aggressive therapy.²⁹

ACE inhibitors have considerable experimental evidence supporting a beneficial role in CAD^{30,31} Guidelines do not yet fully reflect this evidence but most clinicians would support the concept of disease modification with a triad of aspirin, statin and ACE inhibitor. The EUROPA study³¹ demonstrated a 20% reduction in the primary endpoint of cardiovascular death, MI and cardiac arrest in 12,000 patients at a generally lower risk than those enrolled in the HOPE study.³⁰

NICE guidance

Key points on management of stable angina³¹ include:

- Diagnose stable angina according to NICE guidance on chest pain of recent onset¹⁴
- Offer advice and provide information and support—eg. lifestyle advice, factors that may provoke angina, risks and benefits of their treatment, when to seek professional help
- Offer a short-acting nitrate for preventing and treating episodes of angina and advise on the correct administration, including possible side effects
- Offer one or two anti-anginal drugs as necessary—either a β -blocker or calcium channel blocker first-line. Choice should

be based on comorbidities, contraindications and patient preference. If symptoms are not satisfactorily controlled on one anti-anginal drug, consider either switching to the other option, or use both in combination. If using in combination, a dihydropyridine calcium channel blocker (eg. slow release nifedipine, amlodipine or felodipine) should be combined with a β -blocker. Do not routinely offer other anti-anginal drugs first-line

- Review response to treatment, including side-effects, two to four weeks after starting or changing drug treatment. Titrate the dosage against the person's symptoms, up to the maximum tolerated dose
- Other anti-anginals—long-acting nitrate, or ivabradine, or nicorandil, or ranolazine may be considered in certain circumstances (eg. if β -blockers and/or calcium channel blockers are contraindicated or not tolerated). Choice should be based on comorbidities, contraindications, patient preference and drug costs.
- A third anti-anginal drug should be considered only when two anti-anginal drugs do not satisfactorily control symptoms, and the person is awaiting revascularisation or revascularisation is not appropriate or acceptable
- Consider aspirin 75mg, taking into account the risk of bleeding and comorbidities
- Consider ACE inhibitors in

people with stable angina and type 2 diabetes

- If symptoms are not satisfactorily controlled with optimal drug treatment (two anti-anginal drugs plus secondary prevention drugs), consider revascularisation—either CABG or PCI. CABG is also an option for people whose symptoms are satisfactorily controlled on optimal drug treatment to improve prognosis in a sub group of people with left main stem or proximal three-vessel disease.

Newer treatments

Newer treatments, such as ranolazine and ivabradine, do not have some of the effects of traditional antianginal treatments and can be used as alternatives if patients fail on or are intolerant of first-line therapies.

Ivabradine acts on the *If* channels of the sinus node within the heart. It inhibits the *If* channel and selectively slows the heart rate to improve myocardial oxygen supply and demand without reducing myocardial contractility. Short-term randomised controlled trials (RCTs) have shown that ivabradine is more effective than placebo at improving exercise tolerance, reducing the frequency of episodes of angina, and reducing use of short-acting nitrates.³² Evidence from two further RCTs, both over three months, suggests that ivabradine is similarly effective to atenolol and amlodipine.^{33,34}

In one large, long-term

morbidity study in people with CAD, ivabradine had no significant effect on a composite outcome of cardiovascular death, admission to hospital for acute MI, and admission to hospital for new-onset or worsening heart failure.³⁵

Visual disturbances were commonly reported in these studies in people taking ivabradine, but were tolerated by many patients.

Ranolazine is an antianginal drug that affects the sodium dependent calcium channels and prevents calcium overload with cardiac ischaemia. It may reduce exertional angina when added to other medication, but can cause long QT syndrome with risk of arrhythmias. Various studies have confirmed its efficacy in angina and it is now considered as add on therapy to standard medications in most guidelines.³⁶

Conclusion

Angina has a significant impact on the lives of many elderly patients. Age alone should not be a barrier to accurate diagnosis and effective treatment of this common chronic condition. Changing guidelines on diagnosis and treatment options will impose significant pressures on the NHS but will need to be implemented for the benefit of patients.

Conflict of interest: none declared

References are available with online version at www.gerimed.co.uk