Ivabradine: a new strategy for management of stable angina

Ivabradine is not only the first of a new class of selective I_f channel inhibitors, but is also the first new medical treatment for stable angina to be approved in Europe for 10 years. By selectively reducing heart rate without adversely affecting myocardial contractility or blood pressure, ivabradine offers a valuable new option for patients with stable angina in whom beta-blockers are not tolerated or are contraindicated.

Stable angina pectoris is a common and disabling disorder that affects up to 2 million people in the UK (Allender et al, 2006). A clinical syndrome characterized by discomfort in the chest, jaw, shoulders, back or arms, and typically elicited by exertion or emotional stress and relieved by rest or nitroglycerine, stable angina is most commonly caused by atherosclerotic coronary artery disease (CAD) that causes narrowing of the coronary arteries, leading in turn to myocardial ischaemia (Fox et al, 2006).

Despite reduced incidence, the prevalence of angina is rising, since patients with CAD are living longer with the disorder representing a significant health burden (Fox et al, 2006). Angina consumes at least 1.3% of the entire UK NHS expenditure (Stewart et al, 2003) (two-thirds of which is attributable to hospital bed occupancy and procedures) and this does not take into account the indirect costs of workdays lost, reduced productivity, social welfare implications and family carer burden, which may be as much again as direct costs (Gibbons et al, 2003).

Although termed 'stable', such patients have an annual mortality rate of 2–3% (double that of age-matched controls), and are at increased risk of developing acute coronary syndromes such as unstable angina or myocardial infarction (MI), in addition to a marked reduction in multiple measures of health-related quality of life (Brorsson et al, 2002; O'Toole and Grech, 2003; Fox et al, 2006).

Angina and heart rate

Following a diagnosis of stable angina, the aims of treatment are to (Gibbons et al, 2003; Fox et al, 2006):

- Improve prognosis by preventing MI and death, primarily by reducing the incidence of acute thrombotic events and development of ventricular dysfunction
- Minimize or abolish symptoms of angina and the occurrence of ischaemia, since this will improve health-related quality of life (Brorsson et al, 2002)
- Reduce concurrent cardiovascular risk factors.

All patients require pharmacological therapy (and some revascularization depending on patient and/or physician preferences, risk factors and response to treatment) (Fox et al, 2006). As shown in *Table 1*, the latest European guidelines recommend beta-blockers as first-line therapy to prevent symptoms and ischaemia, and to improve prognosis in angina patients with a history of MI or with heart failure (Fox et al, 2006). The anti-ischaemic and anti-anginal effects of beta-blockers derive from their ability to lower heart rate, a major determinant of myocardial oxygen demand and cardiac workload. A high heart rate shortens the duration of diastole, which increases myocardial oxygen consumption and decreases myocardial perfusion, resulting in myocardial ischaemia. Conversely, lowering heart rate reduces cardiac workload and oxygen demand, thereby increasing the threshold for ischaemia and improving cardiac performance.

The adverse physiological consequences of an increased heart rate help explain the association of elevated resting heart rate and adverse outcome. Follow up (median 14.7 years) of 24 913 patients with CAD from the Coronary Artery Surgery Study registry found a resting heart rate of ≥83 beats per minute (bpm) compared with a heart rate <62 bpm was associated with significantly higher total mortality (hazard ratio 1.32 (confidence interval 1.19–1.47); $P<0.0001$) and cardiovascular mortality (hazard ratio 1.31 (confidence interval 1.15–1.48); $P<0.0001$) even after adjustment for multiple clinical variables (*Figure 1*) (Diaz et al, 2005). Heart rate has also been shown to be inversely related to survival following MI (Hjalmarson et al, 1990), in patients with hypertension (Gillman et al, 1993), type 2 diabetes (Stettler et al, 2006), unstable angina with preserved myocardial function (Lanza et al, 2006), or even in epidemiological studies including apparently healthy men and women, whose excess mortality was principally attributable to a higher risk of cardiac death (Habib, 2001).

Heart rate reduction with beta-blockers is thus central to the treatment of stable angina. However, beta-blockers are not recommended in patients with asthma or bronchospasm. Additionally, many patients find it difficult to tolerate beta-blocker side effects, particularly fatigue and sexual dysfunction (a frequently under-recognized problem) (British National Formulary, 2006). Until recently, a non-dihydropyridine calcium-channel blocker (CCB) for example, diltiazem, was the only heart rate-lowering

Dr Ian BA Menown *is Consultant Cardiologist, Craigavon Cardiac Centre, Craigavon Area Hospital, Craigavon, Northern Ireland BT63 5QQ*

Table 1. Pharmacological therapy in chronic stable angina

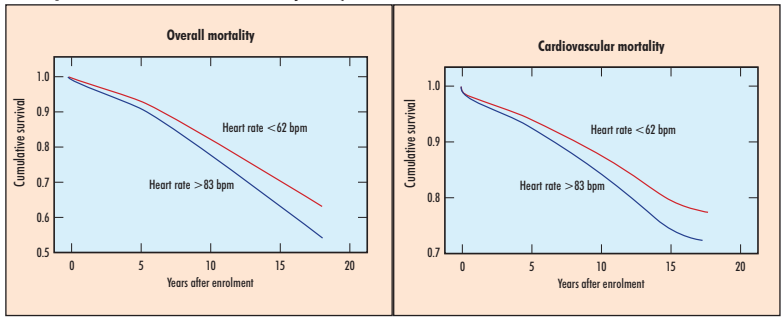
Recommendations	To improve prognosis	To improve symptoms and/or reduce ischaemia
Class I	Aspirin 75 mg daily in all patients without specific contraindication (A) Statin for all patients with coronary disease (A) ACE inhibitor in patients with hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction, or diabetes (A) Oral beta-blocker in patients post-MI or with heart failure (A)	Short-acting nitrate for acute symptom relief and situational prophylaxis (B) Test effect of beta-blocker and titrate to full dose; consider need for 24-hour protection against ischaemia (A) If beta-blocker intolerance or poor efficacy, attempt monotherapy with CCB (A), long-acting nitrate (C) or nicorandil (C) If beta-blocker monotherapy is insufficient, add dihydropyridine CCB (B)
Class IIa	ACE inhibitor in all patients with angina and proven coronary disease (B) Clopidogrel as an alternative antiplatelet agent in patients with stable angina who cannot take aspirin (B) High-dose statin in high-risk (>2% annual CV mortality) patients with proven coronary disease (B)	If beta-blocker intolerance, try sinus node inhibitor If CCB monotherapy or combination therapy (CCB + beta-blocker) is unsuccessful, substitute CCB with a long-acting nitrate or nicorandil, but avoid nitrate tolerance (C)
Class IIb	Fibrate in patients with low HDL and high triglycerides who have diabetes or the metabolic syndrome (B) Fibrate or nicotinic acid as adjunctive therapy to statin in patients with low HDL and high triglycerides and at high risk (>2% annual CV mortality) (C)	Metabolic agents may be used, where available, as add-on therapy or as substitute therapy when conventional drugs are not tolerated

Classes of recommendation: Class I: evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective; Class IIa: conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment or procedure; Class IIb: weight of evidence/opinion in favour of usefulness/efficacy. Levels of evidence are shown in brackets after each recommendation: (A) Data derived from multiple randomized clinical trials or meta-analyses; (B) Data derived from a single randomized clinical trial or large, non-randomized studies; (C) Consensus of opinion of the experts and/or small studies, retrospective studies, or registries. ACE = angiotensin-converting enzyme; CCB = calcium-channel blocker; CV = cardiovascular; HDL = high-density lipoprotein cholesterol; LV = left ventricular; MI = myocardial infarction

alternative and such agents are contraindicated in the setting of impaired left ventricular function (not uncommon in chronic angina patients). Other vasodilating anti-anginals (nitrates, dihydropyridine CCBs or nicorandil) can be used in patients with impaired left ventricular function but do not have the potential prognostic benefit of heart rate lowering and thus are best reserved for second-line use where possible.

Anginal management options have now expanded with the availability of ivabradine (Procoralan, Servier Laboratories, France) – the first new medical treatment for stable angina to become available in Europe for over 10 years, and the first drug in a new class: the selective I_f inhibitors. Ivabradine received European approval in July 2005 and is included in the latest European stable angina guidelines (*Table 1*) (Fox et al, 2006). It is currently licensed for patients with chronic stable angina in whom beta-blockers are contraindicated or not tolerated, and who are in normal sinus rhythm.

Figure 1. Heart rate and cardiovascular outcome in stable coronary heart disease. bpm = beats per minute. From Diaz et al (2005).



Ivabradine: a selective I_f channel inhibitor

In healthy individuals, heart rate is controlled by the sinoatrial node located in the right atrium. Several ion channels or currents control this pacemaker activity, including the I_f or 'funny' channel (so-called because of its unusual properties compared with other current systems). First described in 1980, the I_f channel is an inward mixed sodium and potassium current, directly regulated by intracellular cyclic adenosine monophosphate (excitatory) and muscarinic (inhibitory) receptors (Brown and DiFrancesco, 1980). The I_f current is a key determinant of the slope, hence duration of diastolic depolarization, and thus of overall heart rate (*Figure 2a*).

The I_f channel's central role in controlling heart rate makes its inhibition an attractive target for the development of pure heart rate-lowering drugs. Early I_f channel inhibitors were not found useful in pre-clinical and clinical studies because of their lack of selectivity (Shattock and Camm, 2006). In contrast, ivabradine selectively inhibits the I_f channel (*Figure 2b*), reducing the firing rate of the sinoatrial node without significantly affecting T- and L-type calcium currents, and as a result avoiding the negative inotropic and hypotensive effects of beta-blockers and some CCBs (Ragueneau et al, 1998).

Clinical studies with ivabradine

Efficacy

Ivabradine is licensed at doses of 5 mg bd (twice daily) and 7.5 mg bd which result in predictable, sustained heart rate reductions of ~10 bpm and ~12 bpm respectively (Lopez-Bescos et al, 2004). A 10 mg bd dose of ivabradine has also been trialled but was not found to provide any clinical

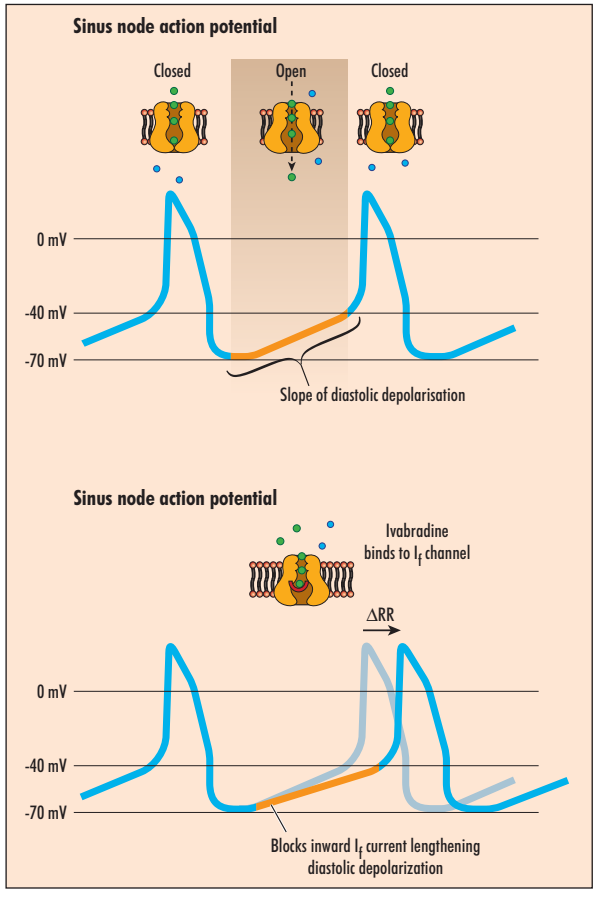


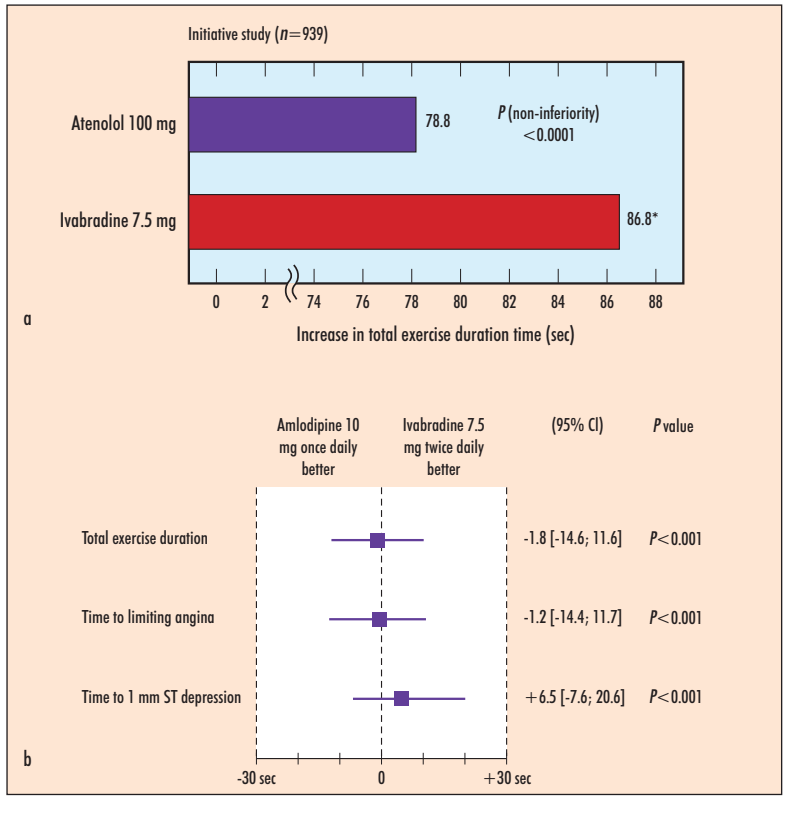
Figure 2. I_f channels determine the slope of the diastolic depolarization which controls the frequency of action potentials. Ivabradine binds to I_f channel blocking the inward I_f current, thus lengthening diastolic depolarization and slowing heart rate. Adapted from DiFrancesco and Camm (2004).

advantage over the 7.5 mg dose. In placebo-controlled trials, ivabradine has demonstrated significant anti-ischaemic and anti-anginal benefits (Borer et al, 2003).

The pivotal INITIATIVE study, a key trial in the submission for regulatory approval, demonstrated that ivabradine was at least as effective as atenolol in patients with stable angina (Tardif et al, 2005a). In INITIATIVE, a randomized double-blind, multicentre trial of 939 patients with stable angina and documented evidence of CAD, ivabradine (5 mg bd for 1 month, then 7.5 mg bd for 3 months) was compared with the currently accepted reference agent, atenolol (50 mg od for 1 month then 100 mg od for 3 months). As shown in *Figure 3a* (Tardif et al, 2005a), at 4 months, the primary end-point, total exercise duration on exercise treadmill testing (at time of trough activity), increased by 86.8 seconds after ivabradine 7.5 mg bd compared with 78.8 seconds after atenolol 100 mg od (P<0.0001 for non-inferiority). Non-inferiority was also shown for ivabradine 5 mg bd *vs* atenolol 50 mg od (at 1 month) and for ivabradine 7.5 mg bd *vs* atenolol 100 mg od (at 4 months) with respect to secondary exercise treadmill end-points including time to limiting angina, time to angina onset, and time to 1 mm ST-segment depression. Reduction in the number of angina attacks per week and consumption of short-acting nitrates was seen with all ivabradine and atenolol doses. No rebound effect following abrupt cessation or treatment, nor development of tolerance with long-term use of ivabradine was noted (Tardif et al, 2005b). Subsequent sub-analyses of INITIATIVE have shown that ivabradine's anti-anginal efficacy is maintained in elderly patients (aged over 65 years) (K Fox et al, oral presentation, 2005) and in patients with diabetes (Doig et al, 2006). These are important data, since three quarters of patients with stable angina are aged over 65 years (Shattock and Camm, 2006) and 20% have diabetes (Bartnik et al, 2004) where impairments in autonomic nervous activity have the potential to compromise the anti-anginal action of some heart rate-lowering agents (Doig et al, 2006).

Another key study comparing ivabradine with the CCB amlodipine randomized 1195 patients with stable angina and documented CAD in double-blind parallel group fashion to 3 months' treatment with either ivabradine 7.5 mg bd or amlodipine 10 mg od (Ruzyllo et al, 2004). At 3 months, on exercise treadmill, all groups showed improvement in the primary end-point (total exercise duration), time to limiting angina, time to angina onset, and time to 1 mm ST-segment depression. Ivabradine 7.5 mg was non-inferior to amlopidine 10 mg (P<0.001) for all exercise parameters (*Figure 3b*) (Ruzyllo et al, 2004), reduced the number of angina

Figure 3. a. Increase in total exercise duration with atenolol and ivabradine, from Tardif et al (2005). b. Comparison of amlodipine with ivabradine with respect to multiple exercise treadmill test measures, from Ruzyllo et al (2004). CI = confidence interval.



attacks by two-thirds and reduced use of short-acting nitrates by half.

Ivabradine has also been shown to be useful in combination therapy. A 12-month, double-blind study of 386 patients receiving nitrates or CCBs for the stable angina demonstrated a significant reduction in the number of angina attacks when adding ivabradine 5 mg bd or 7.5 mg bd to their existing therapy (Lopez-Bescos et al, 2004).

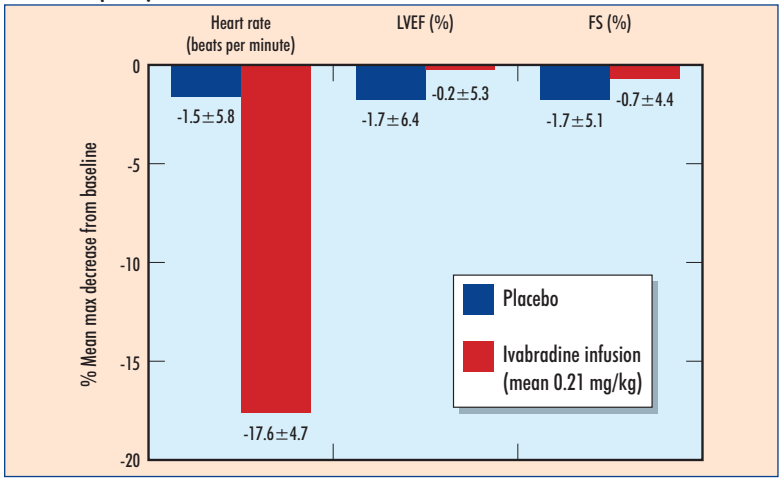
Tolerability

The ivabradine development programme, the largest ever undertaken in stable angina, has found the agent to be well tolerated with <1% withdrawal in clinical trials.

A predictable reduction in heart rate (10–12 bpm) is mediated by selective inhibition of the sinoatrial I_f channel. However, no significant prolongation of PR interval, QRS interval or corrected QT interval has been observed. Unlike beta-blockers, ivabradine is not associated with bronchospasm or erectile dysfunction.

In a few patients, because of an interesting interaction with retinal I_h channel, structurally similar to the I_f channel and which acts to curtail retinal response to light, mild visual symptoms may occur called 'phosphenes' (transient enhanced brightness in a limited visual field area). These may be induced by abrupt changes in light intensity, such as moving from a dark to a brightly lit room, or looking away quickly from a television screen. In clinical trials, phosphenes were reported in only ~1 in 8 patients and in <2% of patients receiving the standard 5 mg bd dose. Most began within 2 months and 97% were well tolerated (only two patients withdrew from INITIATIVE on the higher 7.5 mg bd dose). Most (77%) resolved during treatment and all after withdrawal, with no known long-term retinal effects (Shattock and Camm, 2006). Of practical importance, phosphenes have not been deemed by European regulatory authorities to pose a significant driving risk.

Figure 4. Reduction of heart rate but preservation of haemodynamic parameters following infusion of intravenous ivabradine in patients with left ventricular dysfunction (n=38; per protocol data; LVEF=left ventricular ejection fraction; FS=fractional shortening). From Manz et al (2003).



Ongoing trials

The unique benefit of heart rate reduction without a reduction in myocardial contractility (*Figure 4*) (Manz et al, 2003) raises intriguing therapeutic potential in heart failure patients. The large BEAUTIFUL study has recently completed enrolment of 10 000 patients with stable angina and left ventricular dysfunction (with ejection fraction<40%) who have been randomized, double-blind, to placebo or ivabradine 5–7.5 mg bd in addition to standard medical therapies (including beta-blockers). Follow up for at least 3 years is ongoing with the primary end-point a composite of cardiovascular mortality, hospitalization for acute MI, or new or worsening heart failure (ClinicalTrials.gov, 2005a). Results are anticipated in 2008. The SHIFT trial plans to randomize 7000 patients with symptomatic New York Heart Association class II–IV heart failure and ejection fraction ≤35% to placebo or ivabradine 7.5 mg bd in addition to standard heart failure therapy with primary end-point a composite of cardiovascular mortality or admission with worsening heart failure (J Tardif, unpublished data, 2006).

Ivabradine: real world practice

Ivabradine's current license is for patients with chronic stable angina who are in sinus rhythm and in whom beta-blockers are contraindicated or not tolerated. In the author's clinical practice it has been found to be a useful anti-anginal agent in a wide range of patients, including the elderly and those with diabetes. An additional emerging role is in asymptomatic patients following successful revascularization, in whom a heart rate-lowering agent is still required for prognostic reasons, but beta-blockers are contraindicated or not tolerated.

In the author's experience the 5 mg bd dose is typically adequate (being of similar efficacy to atenolol 50 mg or amlodipine 5 mg) although can be increased to 7.5 mg bd after 3–4 weeks if required. A lower starting dose of 2.5 mg (half a 5 mg tablet) bd can be considered in the elderly (>75 years) but dosage adjustment is not required in patients with renal failure unless creatinine clearance is ≤15 ml/min. Ivabradine is metabolized by CYP3A4, thus as with some statins metabolized by this pathway, patients should avoid concurrent use of other strong CYP3A4 inhibitors such as grapefruit juice, azole antifungals, macrolide antibiotics, human immunodeficiency virus protease inhibitors, or the antidepressant nefazadone.

Being a sinoatrial node inhibitor, ivabradine is not recommended if resting baseline heart rate is below 60 bpm (or falls persistently to <50 bpm during treatment), or if in second or third degree atrioventricular block. A study is underway to investigate the efficacy and safety of the combination of ivabradine and atenolol in patients with stable angina (ClinicalTrials.gov, 2005b). This is an attractive concept although, at present, a lack of trial data means that co-prescription of ivabradine and a beta-blocker is not currently advised, nor is combination with verapamil or diltiazem (Servier Laboratories

Ltd, 2006). Owing to lack of data ivabradine is also not currently indicated in acute coronary syndromes, heart failure or cardiogenic shock (<90/50 mmHg), although further trial results are awaited.

Conclusions

Heart rate reduction is the preferred physiologically based method of managing angina. By selectively inhibiting the I_f channel, ivabradine reduces heart rate without affecting cardiac contractility and lowering blood pressure, so improving symptoms in patients with stable angina without many of the side effects associated with beta-blockers. The clear, inverse relationship between heart rate and risk of mortality makes ivabradine a potentially attractive agent in improving prognosis in patients with CAD, and this hypothesis is being investigated in the ongoing ivabradine clinical development programme. The results of these studies will be awaited with interest, but in the meantime ivabradine offers a valuable option in stable angina when beta-blockers are contraindicated or not tolerated. **BJHM**

Conflict of interest: Dr Menown has received speaker's honoraria from Merck, Menarini and Servier for lectures on the importance of heart rate lowering in angina management.

Allender S, Peto V, Scarborough P, Boxer A, Rayner M (2006) *Coronary heart disease statistics.* British Heart Foundation, London (http://www.heartstats.org/datapage.asp?id=5712; accessed 16 May 2007)

Bartnik M, Ryden L, Ferrari R et al (2004) The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. *Eur Heart J* **25:** 1880–90

Borer JS, Fox K, Jaillon P, Lerebours G; for the Ivabradine Investigators Group (2003) Antianginal and antiischemic effects of ivabradine, an If inhibitor, in stable angina: a randomised, double-blind, multicentered, placebo-controlled trial. *Circulation* **107:** 817–23

British National Formulary (2006) Beta-adrenoceptor blocking drugs. BNF 52. 2.4. British Medical Association and the Royal Pharmaceutical Society of Great Britain, London (www.bnf.org.uk; accessed 9 November 2006)

Brorsson B, Bernstein SJ, Brook RH, Werkö L (2002) Quality of life of patients with chronic stable angina before and four years after coronary revascularisation compared with a normal population. *Heart* **87:** 140–5

Brown H, DiFrancesco D (1980) Voltage-clamp investigations of membrane currents underlying pace-maker activity in rabbit sino-atrial node. *J Physiol* **308:** 331–51

ClinicalTrials.gov (2005a) Efficacy and safety of ivabradine on top of atenolol in stable angina pectoris. NCT00202566. (http://clinicaltrials.gov/ct/show/NCT00202566?order=2; last accessed 15 November 2006)

ClinicalTrials.gov (2005b) The BEAUTIFUL study: effects of ivabradine in patients with stable coronary artery disease and left-ventricular systolic dysfunction. NCT00143507 (http://clinicaltrials.gov/ct/show/NCT00143507?order=1; accessed 15 May 2007)

Diaz A, Bourassa M, Guertin M-C, Tardif JC (2005) Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* **26:** 967–74

DiFrancesco D, Camm JA (2004) Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* **64**(16): 1757–65

Doig C, Fox KM, Borer JS, Ruzyllo W, Barton J (2006) Selective If inhibition with ivabradine is a novel and effective approach to reduce heart rate in diabetic patients with stable angina. Presented at the Annual Meeting of the British Cardiovascular, Glasgow. http://heart.bmj.com/cgi/content/full/92/suppl_2/A4

Fox K, Garcia MA, Ardissino D et al (2006) Guidelines on the management of stable angina pectoris; executive summary. Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* **27:** 1341–81

Gibbons RJ, Abrams J, Chatterjee K et al (2003) ACC/AHA 2002 guideline update for the management of patients with chronic stable angina summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation* **107**(1): 149–58

Gillman MW, Kannel WB, Belanger A, D'Agostino RB (1993) Influence of heart rate on mortality among hypertension: the Framingham Study. *Am Heart J* **125:** 1148–54

Habib G (2001) Is heart rate a risk factor in the general population? *Dialogues Cardiovasc Med* **6:** 25–31

Hjalmarson A, Gilpin EA, Kjekshus J, Schieman G, Nicod P, Henning H, Ross J Jr (1990) Influence of heart rate on mortality after acute myocardial infarction. *Am J Cardiol* **65**(9): 547–53

Lanza GA, Cianflone D, Rebuzzi AG et al (2006) Prognostic value of ventricular arrhythmias and heart rate variability in patients with unstable angina. *Heart* **92:** 1055–63

Lopez-Bescos L, Filipova S, Martos R on behalf of the study investigators (2004) Long-term safety and antianginal efficacy of the If current inhibitor ivabradine in patients with chronic stable angina. A one-year randomized, double-blind, multicentre trial. *Eur Heart J* **25:** 876

Manz M, Reuter M, Lauck G et al (2003) A single intravenous dose of ivabradine, a novel I(f) inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. *Cardiology* **100:** 149–55

O'Toole L, Grech ED (2003) Chronic stable angina: treatment options. *BMJ* **326:** 185–8

Ragueneau I, Laveille C, Jochemsen R, Resplandy G, Funck-Bretano C, Jaillon P (1998) Pharmacokinetic-pharmacodynamic modelling of the effects of ivabradine, a direct sinus node inhibitor, on heart rate in healthy volunteers. *Clin Pharmcol Ther* **64:** 192–203

Ruzyllo W, Ford I, Tendera M et al (2004) Antianginal and anti-ischemic effects of the If current inhibitor ivabradine compared to amlodipine as monotherapy in patients with chronic stable angina: a 3-month randomized, controlled, double-blind, multicenter trial. *Eur Heart J* **25:** 878

Servier Laboratories Ltd (2006) Procoralan SmPC. (http://www.medicines.org.uk/searchresult.aspx?search=procoralan; accessed 30 January 2007)

Shattock M, Camm AJ (2006) Pure heart rate reduction: the If channels from discovery to therapeutic target. *Br J Cardiol* **13:** 27–35

Stettler C, Bearth A, Allemann S et al (2006) QT(c) interval and resting heart rate as long-term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow-up. *Diabetologia* **50:** 186–94

Stewart S, Murphy N, Walker A, McGuire A, McMurray JJV (2003) The current cost of angina pectoris to the National Health Service in the UK. *Heart* **89:** 838–53

Tardif JC, Ford I, Tendera M, Bourassa MG (2005a) Efficacy of Ivabradine, a new selective If inhibitor compared with atenolol in patients with chronic stable angina. *Eur Heart J* **26:** 2529–36

Tardif JC, Fox K, Tendera M, Ford I (2005b) Absence of rebound phenomenon after abrupt discontinuation of ivabradine, a new selective and specific If inhibitor, in patients with coronary artery disease. *Eur Heart J* **26:** 580

KEY POINTS

- Stable angina is a common, disabling disorder that impairs patients' quality of life, increases their risk of death and has major cost implications for the NHS.
- Heart rate reduction is a cornerstone of the medical management of stable angina.
- Beta-blockers are recommended first-line pharmacotherapy for stable angina, but some patients do not respond, do not tolerate, or have contraindications to these drugs.
- Ivabradine is a new option in the management of stable angina: the first in Europe for 10 years.
- Ivabradine is an I_f channel sinoatrial node inhibitor that selectively lowers heart rate, avoiding adverse effects on myocardial contractility and blood pressure.
- Ivabradine is licensed for patients in sinus rhythm in whom beta-blockers are not tolerated or are contraindicated.