THERAPEUTICS

# Novel drugs for treating angina

Daniel A Jones,[1 2] Adam Timmis,[1 2] Andrew Wragg[1 2]

[1]NIHR Cardiovascular Biomedical Research Unit, London E2 9JX, UK
[2]London Chest Hospital, Barts Health NHS Trust, London, UK
Correspondence to: A Timmis
adamtimmis@mac.com

Cite this as: *BMJ* 2013;347:f4726
doi: 10.1136/bmj.f4726

This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic, please email us at practice@bmj.com.

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- Maintenance drugs to treat opioid dependence (*BMJ* 2012;344:e2823)
- Cholinesterase inhibitors and memantine for symptomatic treatment of dementia (*BMJ* 2012;344:e2986)

Angina is the pain caused by myocardial ischaemia, usually as a result of obstructive coronary artery disease. Although angina typically presents as chest pain on exertion, patients can also present with atypical symptoms such as shortness of breath without pain. Guidelines[1 2] recommend initial treatment with one or two antianginal drugs, plus aspirin, and a statin for secondary prevention of cardiovascular disease. If symptoms are not adequately controlled, coronary revascularisation by percutaneous coronary intervention or coronary artery bypass surgery is often effective.[1 2]

The antianginal drugs recommended for initial treatment are β blockers and calcium channel blockers, which reduce myocardial ischaemia by heart rate reduction and vasodilatory mechanisms, respectively. Either or both of these drug classes should be prescribed, together with a short acting nitrate for prompt alleviation of angina attacks (figure) However, if these drugs are not tolerated, are contraindicated, or fail to correct symptoms, alternative antianginals are available, such as oral nitrates and newer antianginal drugs, which are the subject of this review. Although oral nitrates have been used for many years to treat stable angina, the National Institute for Health and Care Excellence concluded that evidence related to their efficacy was insufficient and hence advised that oral nitrates should be used as second line therapy after β blockers and calcium channel blockers. NICE also concluded that evidence was insufficient to make a firm recommendation about the choice of second line antianginals, which we present here in alphabetical order.

## Novel antianginal drugs

Alternative antianginal drugs include older less familiar ones such as nicorandil, which has been available for the past 20 years, and newer antianginal drugs such as ivabradine and ranolazine. Also available in many countries (not the United Kingdom) is trimetazidine.

If patients with stable angina cannot tolerate or have a contraindication to β blockers and calcium channel blockers, then monotherapy with ivabradine, nicorandil, ranolazine, or a long acting nitrate should be considered. These agents are also indicated for people who remain symptomatic while receiving monotherapy with a β blocker or calcium channel blocker in whom the other option is contraindicated or not tolerated; however, there is no evidence of further benefit when three or more drugs are used. Generally speaking, therefore, triple therapy should only be considered when patients have persisting symptoms and are awaiting revascularisation, or when revascularisation is considered inappropriate.[1]

## How do they work?

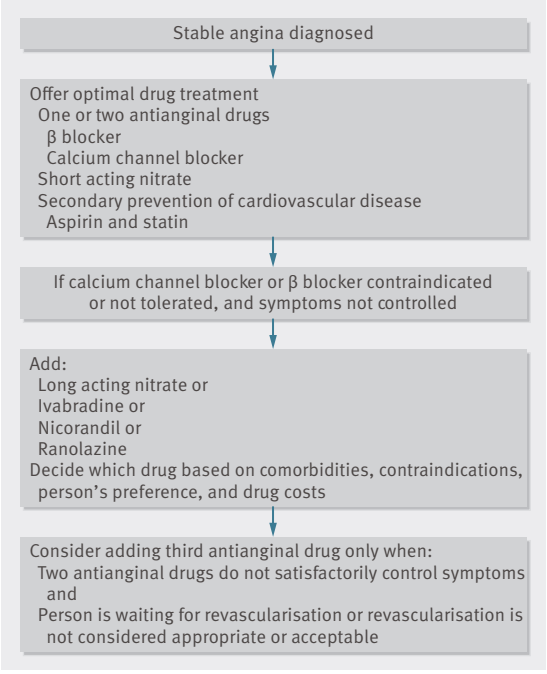
Antianginal drugs reduce myocardial ischaemia by augmentation of oxygen delivery, reduction of oxygen demand, or a combination of both. Nicorandil augments oxygen delivery through coronary vasodilatation (table 1). Ivabradine reduces myocardial oxygen demand by reducing heart rate, whereas both ranolazine and trimetazidine are thought to do so through metabolic modulation, increasing the efficiency of myocardial energy production.

## How well do they work?

For all these novel antianginal drugs there is evidence for short term improvements in exercise capacity and decreases in the frequency of angina. Few studies have looked at long term symptomatic effects or effects on cardiovascular mortality.

### Ivabradine

Short term randomised controlled trials of ivabradine monotherapy have shown similar increases in total exercise duration and similar reductions in the frequency of angina compared with atenolol or amlodipine.[6 7] One trial found that the addition of ivabradine to atenolol resulted in small increases in total exercise duration and time to angina on the treadmill, but did not reduce the frequency of angina. Ivabradine is ineffective in atrial fibrillation but finds its main indication in patients in sinus rhythm who cannot tolerate or have contraindications to conventional heart rate lowering agents (β blockers, non-dihydropyridine calcium channel blockers), when it can be used safely in obstructive pulmonary disease.[8] Ivabradine is associated with an absolute reduction in all cause mortality of 2% in patients with heart failure[9]; it may thus have a role in angina complicated by heart failure, when heart rate is not reduced sufficiently by β blockade (>75 bpm) or when β blockers are not tolerated.




Treatment algorithm for novel antianginal drugs. Modified from National Institute for Health and Care Excellence[1]

**Table 1 | Comparison of novel with older antianginal drugs**

| Drug | Mechanism | Haemodynamic effect | Key indication | Contraindications |
|---|---|---|---|---|
| β blockers | Block β adrenergic receptors | Lower heart rate and blood pressure, and contractility | 1st line antianginal | Reactive airways disease, bradycardia, sick sinus syndrome, 2nd or 3rd degree atrioventricular block, hypotension, acute heart failure |
| Calcium channel blockers (dihydropyridine, for example, amlodipine; non-dihydropyridine, for example, diltiazem) | Inhibit L-type calcium channels | Dihydropyridine: lowers blood pressure. Non-dihydropyridine: lowers heart rate and blood pressure | 1st line antianginal | Dihydropyridine: hypotension. Non-dihydropyridine: bradycardia, left ventricular dysfunction |
| Long acting nitrates | Act as nitric oxide donor that dilates coronary arteries and systemic venous capacitance vessels | Lower blood pressure | If β blockers or calcium channel blockers are contraindicated, not tolerated, or fail to control symptoms | Concurrent use with phosphodiesterase 5 inhibitors (for example, sildenafil) is contraindicated owing to risk of profound hypotension |
| Nicorandil | Dual mechanism of action. Firstly, acts as nitric oxide donor that dilates coronary arteries and systemic venous capacitance vessels. Secondly, opens adenosine triphosphate sensitive potassium channels in vascular smooth muscle cells, resulting in systemic and coronary vasodilatation | Lowers blood pressure | If β blockers or calcium channel blockers are contraindicated, not tolerated, or fail to control symptoms | As with nitrates concurrent use with phosphodiesterase 5 inhibitors (for example, sildenafil) is contraindicated. Significant hypotension, cardiogenic shock, left ventricular failure |
| Ivabradine | Blocks I(f) channel in the pacemaker cells of the sinoatrial node. This slows the heart rate without affecting myocardial contractile function or peripheral vascular resistance[3] | No effect on blood pressure but lowers heart rate at rest and exercise | If β blockers or calcium channel blockers are contraindicated, not tolerated, or fail to control symptoms | Bradycardia (heart rate <60), sick sinus syndrome, heart block, atrial fibrillation, acute myocardial infarction, hypotension (<90/50 mm Hg). Strong inhibitors of CYP3A4 system, and significant interactions may occur with drugs such as HIV protease inhibitors, macrolide antibiotics, and phenytoin that inhibit or induce these enzymes. Severe hepatic or renal impairment |
| Ranolazine | Inhibits late inward sodium current in cardiac myocytes.[4] This prevents calcium overload and improves myocardial metabolic activity | Minimal effect on heart rate or blood pressure | If β blockers or calcium channel blockers are contraindicated, not tolerated, or fail to control symptoms | Pre-existing QT prolongation (>500 msec) or receiving any QT prolonging drugs, including class Ia (for example, quinidine) or certain class III (for example, sotalol) antiarrhythmic drugs.25 Strong inhibitors of CYP3A4 enzymes. Severe hepatic or renal impairment |
| Trimetazidine | A piperazine derivative that is thought to act by reducing myocardial fatty acid oxidation, with a shift to more oxygen efficient glucose oxidation[5] | Minimal effect on heart rate or blood pressure | If β blockers or calcium channel blockers are contraindicated, not tolerated, or fail to control symptoms | Parkinsons disease, parkinsonian symptoms, other movement disorders, restless legs syndrome. Severe renal impairment (creatinine clearance<30 mL/min). In moderate renal impairment (creatine clearance 30-60 mL/min) and in elderly patients, starting does should be reduced and monitor for side effects |

### Nicorandil

Randomised controlled trials of nicorandil monotherapy have found similar reductions in the short term frequency of angina and similar increases in exercise capacity compared with other antianginal drugs (diltiazem, amlodipine, or propranolol) without differences in adverse effects.[10-12] No studies have been done of nicorandil monotherapy on fatal and non-fatal cardiovascular events. The Impact Of Nicorandil in Angina (IONA) trial compared adding nicorandil versus placebo to standard antianginal treatment; nicorandil reduced the risk of a composite outcome (coronary heart disease death, myocardial infarction, and unplanned admission to hospital for chest pain) (event rate 13.1% v 15.5%, P=0.014), but did not significantly affect individual components of the composite outcome or the severity/frequency of angina.[13] Withdrawal from treatment was increased in the nicorandil arm because of adverse effects.

### Ranolazine

Randomised clinical controlled trials show that ranolazine improves exercise performance and decreases the frequency of angina and nitrate consumption, both as monotherapy[14] and in combination with other antianginal drugs.[15 16] These symptomatic benefits are not associated with prognostic benefits, the MERLIN-TIMI 36 trial reporting no difference in fatal and non-fatal cardiovascular endpoints after non-ST elevation myocardial infarction compared with the control group.[17] Evidence is emerging that, in patients with angina and suboptimally controlled type 2 diabetes, ranolazine may have both antianginal and glucose lowering effects; further study is, however, required.[18 19] At present, as with the other novel antianginal drugs, the main guideline indication for ranolazine is in patients who cannot tolerate, or have contraindications to, β blockers or calcium channel blockers.

### Trimetazidine

A Cochrane Collaboration meta-analysis of trimetazidine use in stable angina found that it significantly reduced angina attacks, nitrate use, and time to onset of important ST segment depression in patients with stable angina.[5] These benefits were apparent independently of whether trimetazidine was given as monotherapy or combined with another antianginal agent. A more recent meta-analysis comparing trimetazidine with other non-heart rate lowering antianginal agents (nicorandil, ranolazine, long acting nitrates) confirmed comparable efficacy.[20] Emerging

Table 2 | Drug costs, dosage, and monitoring

| Drug | Cost (£) | Initial dose | Up-titrated dose | Key adverse effects |
|---|---|---|---|---|
| Long acting nitrates (isosorbide mononitrate) | £19/year | Long acting 30 mg once daily | Long acting: up-titrated in units of 30 mg to 120 mg once daily | Low blood pressure, headache |
| Nicorandil | 10 mg £99/year. 20 mg £190/year | Initial dose 10 mg twice daily | Up-titrate in units of 10 mg to 30 mg twice daily | Monitor for new gastrointestinal upset or either gastrointestinal or genital ulceration: drug should be stopped |
| Ivabradine | £507 per year | Initial dose 5 mg twice daily. In elderly patients start at 2.5 mg twice daily | Up-titrate to 7.5 mg twice daily if heart rate is >60 after 2-4 weeks | Monitor for bradycardia (stop if heart rate is <50 bpm) |
| Ranolazine | £595/year | 375mg twice daily | Up-titrate to 500 mg twice daily and then to maximum 750 mg twice daily | Monitor QTc interval (stop if >500 msec) |
| Trimetazidine | Not licensed in United Kingdom | Short-acting: 20 mg three times daily. Long acting: 35 mg twice daily. 35 mg one daily in elderly patients or those with moderate renal impairment | None | Monitor for features of Parkinson's symptoms, for example, tremor; drug should be stopped |

evidence also suggests that, in patients with heart failure, the haemodynamic and symptomatic benefits of trimetazidine may be associated with lower all cause mortality.[21]

## How safe are they?

### Ivabradine

The rate of discontinuation of ivabradine owing to unwanted adverse effects (21% per patient year) when prescribed for angina is comparable to that of amlodipine (22%) and higher than that of atenolol (16%).[22] Adverse effects include visual "flashing lights" known as phosphenes in up to 16% of patients, which are usually only mild to moderate in intensity and transient.[23] They result from blockage of the Ih current in the retina, which is similar to the cardiac If current. Other unwanted effects include blurred vision, dizziness, headache, and arrhythmias (first degree atrioventricular block, ventricular extrasystoles).

### Nicorandil

Common adverse effects include headache (>10% of cases) (especially on initiation of treatment), flushing, dizziness, decreased blood pressure and/or increase in heart rate, and gastrointestinal side effects (all >1%).[24] Mucosal ulceration is increasingly recognised, and although rare (<0.01%), ranges from multiple intractable oral aphthous ulcers to anal fissure and rectovaginal fistula, and includes complications such as perforation, fistula, and abscess formation; if any of these are detected, nicorandil should be stopped.[24]

### Ranolazine

Undesirable effects with ranolazine tend to be mild to moderate in severity and often develop within the first two weeks of treatment.[25] The most common are constipation, nausea, and weakness. In trials, the incidence of adverse events leading to study discontinuation was 6.3% in patients treated with ranolazine and 3.0% in patients treated with placebo.[26] Ranolazine has been associated with small dose related increases in the heart rate corrected QT interval (2/6 msec/1000 ng/mL), but this has not been associated with an increase in the incidence of arrhythmias.[27]

### Trimetazidine

The commonest adverse effects reported in clinical trials have been gastrointestinal disturbance, dizziness, and headache.[5] However, a recent review by the European Medicines Agency highlighted that trimetazidine can result in movement disorders such as parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, and restless legs.[26] The incidence of these is low (0.36/100 000 patient years) and are usually reversible (within a few weeks to a few months) after withdrawal of treatment.[28] If reversal is incomplete, referral to a neurologist is recommended.

**CASE**

A 69 year old man presented with typical exertional angina, which was stable. After discussion the patient requested to be managed medically and declined the offer of diagnostic angiography. As he had longstanding sinus bradycardia, β blockers were contraindicated and he was initially treated with amlodipine 5 mg daily, together with aspirin, ramipril, and a statin. Four weeks later he reported little change to his angina. He remained reluctant to have angiography and requested other medical therapies.

**CASE OUTCOME**

As the patient took sildenafil occasionally and was keen to continue this, nitrates and nicorandil were contraindicated. Ivabradine was contraindicated owing to sinus bradycardia. Ranolazine was chosen, and his angina improved. However, symptoms became more problematic nine months later and he agreed to diagnostic angiography, which revealed severe three vessel disease requiring coronary artery bypass grafting. While awaiting surgery he agreed to stop taking sildenafil and to start isosorbide mononitrate for interim symptomatic relief.

## What are the precautions?

Table 1 details the contraindications.

## How cost effective are they?

The availability of economic data for these new antianginal drugs is limited (table 2). The costs of ranolazine and ivabradine are comparable, higher than nicorandil, and substantially higher than β blockers, calcium channel blockers, and long acting nitrates.[1] Nicorandil is less expensive than ranolazine or ivabradine. Trimetazidine is currently not licensed in the United Kingdom where cost data are unavailable, although a Russian analysis found it was cost effective as an adjunct to treatment for heart failure.[29]

## How are they taken and monitored?

These novel antianginal drugs are taken orally twice daily. Table 2 shows the starting doses. For ivabradine and trimetazidine consider a lower starting dose in

**TIPS FOR PATIENTS**

- Nicorandil, ivabradine, and ranolazine are novel drugs for treating angina. Trimetazidine is also available in many countries (not the United Kingdom)
- Antianginal drugs are generally used when other drugs such as a β blocker have not worked because of either side effects or not controlling angina chest pain. They may be used if treatments such as stents or bypass surgery are not possible
- Before starting treatment you must tell your doctor about other medicines you are taking
- It is important to see your doctor a few weeks after starting treatment so the effect of treatment can be assessed and the dose adjusted as necessary
- Important side effects to be aware of are:
- Nicorandil: headache, abdominal pain, nausea and vomiting , mouth ulcers
- Ivabradine: blurred vision, flashing lights, low heart rate
- Ranolazine: abdominal pain, altered bowel habit (for example, constipation), nausea and vomiting
- Trimetazidine: abdominal pain, nausea and vomiting, altered bowel habit (for example, diarrhoea), tremor, unsteadiness when walking

adults aged 75 or more.[3] NICE guidelines[1] recommend review 2-4 weeks after starting or changing any antianginal drug, to assess treatment response and monitor for adverse effects. If angina is not controlled, the dose should be titrated up. Patients taking ivabradine should be monitored for symptomatic bradycardia (for example, dizziness, fatigue, hypotension), and if symptoms persist, treatment must be stopped. For patients taking ranolazine, an electrocardiogram should be obtained at baseline and follow-up to evaluate effects on QT interval. People taking trimetazidine, especially elderly patients, need to be monitored for the development or worsening of parkinsonian symptoms. If these occur the drug should be stopped.

Contributors: AT outlined the initial structure of the article. DAJ and AW then wrote the first draft of the manuscript. All authors were involved in editing and reviewing changes and approving the final version. All three authors are guarantors.

Competing interests: Servier (Ivabradine) and Menorini (Ranolazine) have sponsored educational events at Barts Health NHS trust. The pharmaceutical sponsorship of the educational events at Barts was unconditional. AW has received sponsorship from Servier (Ivabradine) for conference attendance. AT has sat on a Servier advisory board (Ivabradine) and chaired the NICE angina guideline (2012).

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Accepted: 12 July 2013