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Multi-management of ischaemic heart disease: do we have the COURAGE of our convictions?

A report from a satellite symposium at the British Cardiovascular Society Annual Scientific Conference

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Editors
Kim Fox
Terry McCormack
Henry Purcell

Associate Editor
Katharine White

Supplement Editor
Rachel Arthur

Editorial Office and Publishers
MediNews (Cardiology) Limited
9 Langton Street,
London, SW10 0JL
(production@bjcardio.co.uk)
Tel: +44 (0)20 7823 3315

Design and Layout
Consultants in Design

Authors instructions
Can be obtained from the editorial office or from the website.
See contact details above.

Advertising and sales enquiries:
Nik Screen
Business Development Manager
c/o Versatility Consultants Ltd
35 Castle Road, Isleworth,
Middlesex TW7 6QR
(nscreen@bjcardio.co.uk)
Tel: +44 (0)77 1044 2911

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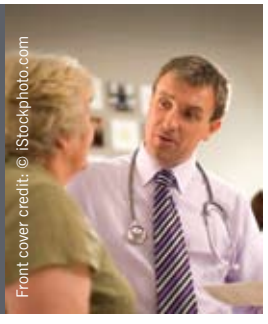
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Introduction

Highlights from the A Menarini Pharma UK SRL and CV Therapeutics Europe-sponsored symposium at the British Cardiovascular Society Annual Scientific Conference 2009

Community studies confirm that angina pectoris is a common, debilitating and unrelenting condition, which takes its toll on individuals' working lives and leisure activities and imposes a significant financial burden on the nation's health services. The prevalence of angina increases with age and the UK, in common with most of Europe, has an ageing population. A general practitioner will see, on average, four new cases each year. This is the background to what has become a challenging public health problem with continuing resource requirements.

This symposium, chaired by Professor Robert Wilcox (Division of Cardiovascular Medicine, University of Nottingham), addressed these issues and reviewed modern approaches to the medical and interventional management of angina. Findings from the Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial have awakened interest in optimising medical treatment; in selected patients, medical treatment appears to be as effective as percutaneous coronary intervention (PCI).

The symposium also offered an opportunity to review the recently introduced antianginal compound, ranolazine – an inhibitor of the late sodium current.

Dr Rachel Arthur
Supplements Editor

Treating chronic stable angina: who's winning, who's losing and why

Professor Harry Hemingway

The extent of the problem

Most people with stable angina, irrespective of treatment, will get symptoms again over a prolonged follow-up period. The ACRE (Appropriateness of Coronary Revascularisation) study, for example, showed that in a consecutive unselected patient series of 1,020 patients, more than 50% treated with percutaneous coronary intervention (PCI) or medical treatment had symptoms at six years.[1]

Healthcare professionals may perhaps be motivated more by coronary death rates and acute coronary syndrome events. Primary care registry data from Finland in some 27,000 patients are shown in **figure 1**[2]. The coronary standardised mortality rates (SMRs) from coronary heart disease in patients with test-positive angina are strongly elevated in the younger age groups; although the SMR declines by the time patients reach their ninth decade, it is still double the rate in the general population.

Interestingly, data from Hemingway[3] suggest that there is no evidence of male excess with respect to the prevalence of typical symptoms of angina. This systematic review and meta-analysis looked at 74 population studies in 31 countries across the world: the countries varied dramatically in terms of underlying myocardial infarction (MI) mortality rates, smoking rates and access to healthcare for women. Nevertheless, for the 24,000 patients included, stable angina prevalence showed a small female excess, with a pooled sex ratio of 1.20.

Other data from Hemingway[2] also suggest no marked evidence of male excess in physician-diagnosed angina cases. The findings imply that the risk factors for chronic stable coronary disease may be slightly different from the risk factors for acute coronary syndromes, where one would expect to see a marked male excess. They also raise issues about what is appropriate investigation and management in women.

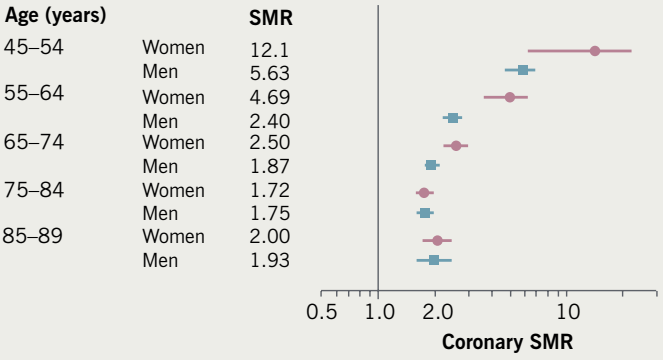
In a study of patients enrolled consecutively without exclusion criteria, the highest probability of death or acute MI was found to occur among people who are appropriate for coronary artery bypass graft (CABG) but who receive only medical management[4]. There is a large difference in event rates between these patients and rates in those who are appropriate for CABG and who actually receive it. The discrepancy is consistent with the difference that might be expected from randomised trials.

Decision support

The advantage of being able to define each individual patient according to the likely effectiveness of their treatment is that it then becomes possible to measure systematically in all patients whether that treatment is given. This is also a valid approach to the use of investigations, such as angiography. Clinicians may be invited to assess whether angiography should be done on a nine-point scale of appropriateness, for example. An estimate of overall appropriateness can be obtained from epidemiological evidence and clinical judgement, and can then be tested empirically to see whether it is valid.

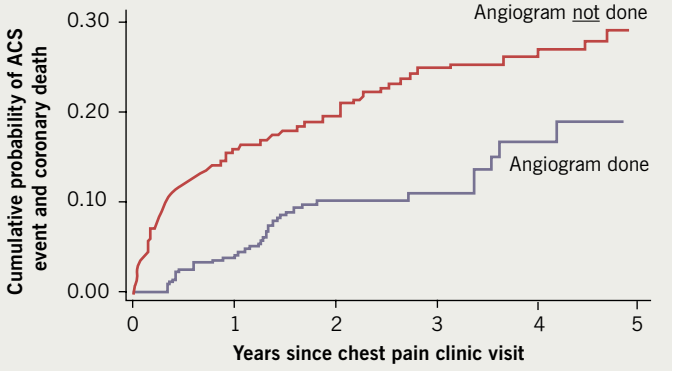
There is some observational evidence that people who are appropriate for angiography but in whom it is not done have a higher

Figure 1. Standardised Mortality Rates (SMR) among test-positive angina patients



Adapted from: Hemingway *et al JAMA* 2006[2]
Key: SMR = standardised mortality rates

Figure 2. Coronary event rates in patients deemed appropriate for angiography



Adapted from: Hemingway *et al Ann Intern Med* 2008[5], Sekhri *et al BMJ* 2008[6]
Key: ACS = acute coronary syndromes

coronary event rate than patients appropriate for angiography in whom it is done (**figure 2**)[5,6]. We are interested in discovering whether clinicians can be supported to make the right decisions, and to make them systematically. Results from a randomised trial, the Appropriateness of Referral and Investigation in Angina (ARIA) trial[7], imply that clinicians (n=300) given patient vignettes make better decisions compared with those using broad clinical guidelines. In this trial, patient-specific ratings, unlike conventional guidelines from the American Heart Association (AHA) and European Society of Cardiology (ESC), had the potential to reduce practice variations and to increase the appropriate use of exercise ECG and angiography.

This observation is now going to be tested in a real patient cluster randomised trial looking at optimising management of angina (OMA). In this trial, 50 chest pain clinics will be randomised to either usual care or to an intervention which includes decision support for angiography as well as risk-based decision support for secondary prevention drugs and behaviour change for smoking cessation and exercise.

At initial presentation many patients do not fulfil the same criteria as patients selected into randomised trials for initiation of many of the classes of agents used for secondary prevention. They are in diagnostic purgatory for some time yet treatment decisions still need to be made.

Looking ahead

There is a role for much better prognosis research, observational studies that understand the progression of people with a pre-existing disease. Myocardial infarction mortality is decreasing rapidly in the general population, but the prevalence of doctor-diagnosed angina in the general population assessed over five waves of Health Survey for England data between 1991 and 2003 in approximately 70,000 patients is not showing any evidence of decline. So, with an ageing population, the absolute number of people living with a diagnosis of angina is increasing.

Conflict of interest statement

None declared.

Professor Harry Hemingway
Department of Epidemiology and Public Health,
UCL School of Life and Medical Sciences,
1-19 Torrington Place,
London WC1E 7HB.
(h.hemingway@ucl.ac.uk)

References

1. Griffin SC, Barber JA, Manca A *et al*. Cost-effectiveness of clinically appropriate decisions on alternative treatments for angina pectoris: prospective observational study. *BMJ* 2007;**334**:624-31.

2. Hemingway H, McCallum A, Shipley M *et al*. Incidence and prognostic implications of stable angina pectoris among women and men. *JAMA* 2006;**295**:1404-11.

3. Hemingway H, Langenberg C, Damant J *et al*. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. *Circulation* 2008;**117**:1526-36.

4. Hemingway H, Crook AM, Feder G *et al*. Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med* 2001;**344**:645-64.

5. Hemingway H, Chen R, Junghans C *et al*. Appropriateness criteria for coronary angiography in angina: reliability and validity. *Ann Intern Med* 2008;**149**:221-31.

6. Sekhri N, Timmis A, Chen R *et al*. Inequity of access to investigation and effect on clinical outcomes: prognostic study of coronary angiography for suspected stable angina pectoris. *BMJ* 2008;**336**:1058-61.

7. Junghans C, Feder G, Timmis AD *et al*. Effect of patient-specific ratings vs conventional guidelines on investigation decisions in angina. *Arch Intern Med* 2007; **167**:195-202.

Perspectives to ponder: pills, pipework or both?

Professor William E Boden

Introduction

Evidence from randomised trials supports percutaneous coronary intervention (PCI) in patients with acute coronary syndromes (ACS): PCI has been shown to improve clinical outcomes and to reduce events. Its role in the broader group of patients with chronic angina and stable coronary artery disease has been less certain, however. We have known for two decades that PCI improves angina and short-term exercise capacity but we have been unable to answer five key questions. Compared to optimal medical therapy in patients with chronic angina and stable coronary artery disease (CAD), does PCI:

- prolong survival?
- decrease the risk of subsequent myocardial infarction (MI)?
- reduce hospitalisation for unstable angina?
- decrease the need for subsequent surgery?
- improve the quality of life?

Perhaps the most important trial that was never accorded much significance was the Randomised Intervention Treatment of Angina (RITA-2) trial[1]. It randomised 1,018 patients with stable CAD to either balloon angioplasty or medical therapy (which at this time consisted principally of aspirin, nitrates and beta blockers since it was the pre-statin, pre-ACE-inhibitor, pre-clopidogrel era). Nevertheless, there was a two-fold difference in death and definite MI between the two groups in favour of medical therapy over 2.7 years of follow-up, with very convincing Kaplan-Meier curves (3.3% versus 6.3%).

At the time of Katritsis' 2005 meta-analysis, the totality of randomised controlled trial data in patients with stable angina comprised fewer than 3,000 patients[2]. Meta-analysis of these data showed no significant treatment difference between PCI and conservative therapy with regard to mortality, cardiac death or MI, non-fatal MI or need for subsequent revascularisation.

The COURAGE trial

This then was the background to the COURAGE (Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation) trial[3]. A total of 1,149 patients were randomised to PCI combined with optimal medical therapy and 1,138 to optimal medical therapy alone. The primary outcome was death from any cause and non-fatal MI during a follow-up period of 2.5 to 7.0 years (median 4.6 years).

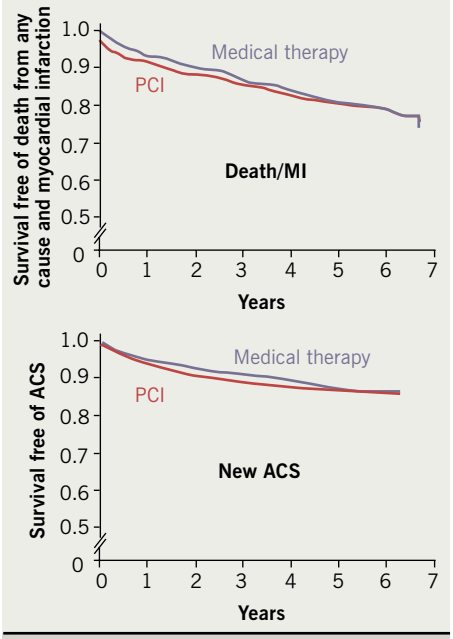
The optimal medical therapy used in the study was really robust by contemporary standards: every drug within drug classes that had been shown individually in placebo-controlled studies to be of clinical benefit was employed. Thus, patients received antiplatelet agents, statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, beta blockers, calcium channel blockers and nitrates, as required. Lifestyle interventions included smoking cessation, exercise programmes, nutrition counselling and weight control. These were applied equally to both arms by protocol and case-managed by nurses. Good control of blood pressure and blood lipids was achieved and maintained throughout the seven years of follow-up.

Although the trial has been criticised for enrolling low-risk patients, in the trial population 34% of patients had diabetes, 71% had dyslipidaemia, 67% had hypertension, 29% were smokers, 39% had prior MI, 26% had prior revascularisation, 70% had multivessel CAD and 68% had left anterior descending (LAD) disease. At baseline, patients had experienced angina for a duration of 26 months, and angina frequency was six or more episodes per week. Eighty-five percent had inducible ischaemia, 67% had multiple reversible perfusion defects on stress myocardial perfusion imaging, and the death/event rate was 4.3% per annum. So this was at least an intermediate-risk group.

The primary end point in the COURAGE trial, the composite outcome of survival free of death from any cause or MI in the two treatment groups, showed no significant differences at the end of a 4.6-year median follow-up, with a hazard ratio of 1.05 (p=0.62), and if anything with a trend in favour of better clinical outcomes for patients in the optimal medical therapy group in roughly the first two years. The Kaplan-Meier curves are very similar (**figure 1**): in particular, the mortality rate curves are virtually superimposable over the whole follow-up period. No incremental benefit could be identified for PCI on top of a background of optimal medical therapy for any of these prognostically important end points.

There was an overall crossover rate of 33% from optimal medical therapy to PCI during the

Figure 1. Value of Optimal Medical Therapy in the COURAGE trial



Key: ACS = acute coronary syndromes; PCI = percutaneous coronary intervention; MI = myocardial infarction

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Table 1. Freedom from CCS angina during follow-up in the COURAGE trial

CCS class 0	PCI+OMT	OMT	p
Baseline	12%	13%	ns
1 year	66%	58%	<0.001
3 years	72%	67%	0.02
5 years	74%	72%	ns

Key: CCS=Canadian Cardiovascular Society; PCI=percutaneous coronary intervention; OMT=optimal medical therapy

seven-year follow-up period. The median time to revascularisation was approximately 11 months and thus, only 16.5% of medically-treated patients crossed over to PCI during this interval. After this time, the crossover rate was only 2.8% per year. Importantly, 67% of patients did not ever require even a first revascularisation procedure after their initial assignment.

As expected, PCI was superior to optimal medical therapy for the relief of angina using the Canadian Cardiovascular Society (CCS) classification (**table 1**). At one year and even at three years there was a statistically significant benefit for PCI compared with medical therapy. But the medical therapy group also improved greatly over one year and, with more prolonged follow-up, the differences attenuated and narrowed between the groups.

A recent paper has looked at quality of life[4]. This employed the Seattle Angina Questionnaire (SAQ), a well validated metric scale, which ranges from 0 to 100, with 0 being very symptomatic and 100 asymptomatic. Patients in both treatment groups were very symptomatic at baseline (score 51 in each group). Within a month, the SAQ score rose from 51 to 62 in the optimal medical therapy group and to 68 in the optimal medical therapy plus PCI group. At one year, the differences between the two groups were statistically significant but numerically small. At two years, the difference between the groups was not statistically significant.

PCI is of benefit in patients with ACS and acute MI but apparently not so in patients with stable CAD because the two conditions have a different pathobiology. Most patients with stable CAD have severe fibrotic and calcified plaques, which are easily detected angiographically, are mostly found on histology to have a very thick fibrous cap, a very small lipid core, and a thick circumferentially calcified artery. These changes cause exertional angina and a positive exercise test. By contrast, in acute coronary syndrome patients with the so-called 'vulnerable' plaque, which has a much larger lipid core and a much thinner fibrous cap, plaque rupture is more likely to occur at the shoulder margin, resulting in acute MI, unstable angina and sudden death.

Paradoxically, two thirds to three quarters of MIs occur in the presence of non-flow-limiting stenoses[5]. Therefore it is progression in non-flow-limiting lesions that causes plaque rupture to occur.

A study evaluating long-term outcome after PCI[6] has shown that major cardiac events occur in non-target areas (or non-instrumented vessels) following a successful procedure. In this study, some 1,228 patients implanted with a bare metal stent were followed up for five years. After the first year, the average annual hazard rate was 1.7% for target-lesion events whereas it was 6.3% for non-target-lesion events. About 37% of events emanated from disease progression in native non-flow-limiting stenoses. Thus, a substantial number of cardiac events could be prevented if we knew how to identify them.

What are key opinion leaders saying about PCI versus optimal medical therapy? Holmes and others[7] concluded that "in trials of patients with stable coronary artery disease, no reductions in death or MI have been observed, and these limitations of PCI in this clinical setting need to be emphasised."

The case for optimal medical management

There is much evidence to support optimal medical therapy as the initial approach to stable CAD management. For patients undergoing elective angiography for chronic angina:

- 12 randomised controlled trials (RCTs) in more than 5,200 patients showed no difference in death, MI, stroke or other hard end points between PCI and optimal medical therapy
- an initial course of optimal medical therapy preserves the option for PCI if medical therapy fails (although only 16.5% of COURAGE optimal medical therapy patients crossed over to PCI within one year)
- over a full seven-year follow-up period, two thirds of all optimal medical therapy patients never required even a first PCI procedure

The COURAGE study has given us clarity in management of patients with chronic angina and stable CAD. Whereas PCI offers better angina relief over one to three years and better quality of life over one to two years, optimal medical therapy is a safe and viable option in selected patients who may not be good candidates for PCI (for example, those who are frail, suffer from chronic kidney disease or have multiple co-morbidities). If optimal medical therapy is used as an initial approach, this preserves PCI as a subsequent option for symptomatic/quality of life relief, if needed

Conflict of interest statement

WEB has received research grants, speakers' bureau honoraria or has acted as a consultant to Abbott, Bristol Myers Squibb, Gilead Scientific, Merck, Pfizer, and Sanofi-Aventis.

Professor William E Boden
Medical Director, Cardiovascular Services, Kaleida Health; Chief of Cardiology, Buffalo General and Millard Fillmore Hospitals, 100 High Street, Buffalo, NY 14203, US.
(WBoden@KaleidaHealth.Org)

References

1. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet* 1997;**350**:461–8.

2. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation* 2005;**111**:2906–12.

3. Boden WE, O'Rourke RA, Teo KK *et al* for the COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;**356**:1503–16.

4. Weintraub WS, Spertus JA, Kolm P *et al*. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 2008;**359**:677–87.

5. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;**92**: 657–71.

6. Cutlip DE, Chhabra AG, Baim DS *et al*. Beyond restenosis. Five-year clinical outcomes from second-generation coronary stent trials. *Circulation* 2004;**110**:226–30.

7. Holmes DR, Gersh BJ, Whitlow P *et al*. Percutaneous coronary intervention for chronic stable angina : a reassessment. *JACC Cardiovasc Interv* 2008;**1**:34–43.

Chronic stable angina and the late sodium current

Professor John Camm

The pathological paradigm

The use of a slow sodium inhibitor may improve angina pectoris. This is based on the following pathological paradigm. The transient, or peak, sodium current occurs at the beginning of the action potential: the rapid influx of sodium causes the upstroke of the action potential. This current does not immediately die away: it has a tail, known as the late, delayed or slow sodium current. In an abnormal situation, the late sodium current can be enhanced. Normally this current transports about half the sodium from outside the cell to the inside but under certain situations, when it becomes enhanced, it transports far more sodium into the cell and sodium accumulates within the cell. An enhanced current prolongs the action potential and, with it, the QT interval. There is a mechanical consequence to this enhancement: instead of the simple phasic twitch when myocardium is activated, the pattern of mechanical contraction is phasic followed by a tonic component. This tonic component extends into diastole, meaning that muscle is still tense during the early part of diastole.

Figure 1 shows a diagram of the sodium channel. Inadequate inactivation of this channel leads to higher intracellular sodium levels. High levels of sodium then exchange with calcium, leading to intracellular calcium overload. Inactivation failure of the sodium channel occurs in several clinical situations in the heart, particularly in ischaemia and heart failure, and also in a congenital condition known as long QT3 syndrome, where the late sodium channel continues to prolong the QT interval.

Ischaemia leads to late sodium current activation, which leads to calcium overload, which, in turn, leads to increased myocardial tension and further ischaemia.

We know that angina occurs when oxygen demand outstrips the oxygen supply. Reduced oxygen supply can occur through vasospasm, thrombus and atherosclerosis, for example. This ischaemia gives rise to a sodium-induced calcium overload leading to impaired myocardial diastolic relaxation, which feeds back onto both the demand (increased left ventricular end-diastolic pressure) and supply (decreased diastolic flow) of myocardial oxygen. We can treat angina pectoris in a variety of ways, by reducing afterload (calcium channel blockers [CCBs]), reducing heart rate (beta blockers, I_f blocker), reducing contractility (beta blockers), reducing preload (nitrates [GTN]), or by preventing vasospasm (GTN, CCBs), thrombus (aspirin) and atherosclerosis (statins). But an alternative possibility now exists: use of a late sodium channel current inhibitor.

The late sodium current inhibitor, ranolazine, has hardly any effect on the peak sodium current but it can dramatically reduce the late sodium current[1] in situations where there is an increase in the late sodium current, such as in failing myocytes.

Moss[2] demonstrated convincingly that ranolazine affects the slow sodium current in five patients with long-QT type-3 syndrome (LQT3), where a molecular abnormality causes an increase in slow sodium current. When ranolazine was infused into these patients, the QT interval was reduced as the ranolazine concentration increased. When the ranolazine infusion was switched off, the QT interval increased again as the ranolazine concentration fell.

Results in angina

The beta blocker, atenolol, was compared with ranolazine in a study of 154 patients with chronic stable angina pectoris[3]. Immediate-release ranolazine 400mg tds was used in this trial. * Atenolol prolonged exercise duration, reducing the rate-pressure product. Ranolazine was equally effective, if not more effective, at increasing exercise duration but it did not affect heart rate, blood pressure or the rate-pressure product. Ranolazine was indistinguishable from atenolol for time to onset of angina and ST-segment depression.

Ranolazine also has anti-ischaemic properties. For example, in one study using SPECT MPI polar scans, the reversible perfusion defect size on exercise reduced from 25% to 10%, and in a group of 21 patients the ischaemia perfusion defect size roughly halved after treatment with ranolazine[4].

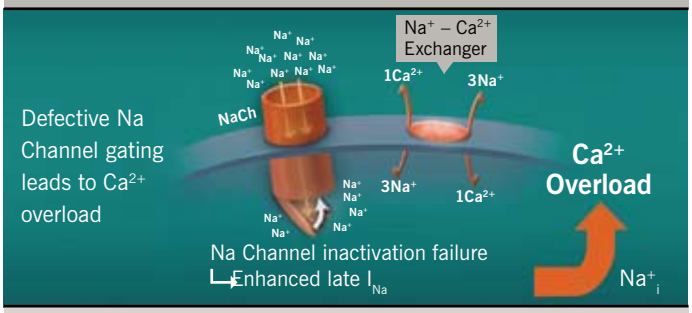
The MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) study was the first dose-response study conducted with prolonged-release ranolazine[5]. It compared the effects of various different doses of ranolazine versus placebo on exercise duration, time to angina and time to 1mm ST-segment depression at trough and at peak levels. There was a statistically significant, dose-related increase in exercise duration.*

A second trial, CARISA (Combination Assessment of Ranolazine In Stable Angina)[6], included patients with severe chronic angina who were taking standard doses of beta blocker or calcium channel blocker. They were treated for three months with 750 or 1,000 mg ranolazine twice daily compared to placebo.* Exercise testing was the main end point: statistically significant increases in exercise duration occurred in the ranolazine group but there was no dose response. Trough exercise duration increased by 115.6 seconds from baseline in both ranolazine groups versus 91.7 seconds in the placebo group (p=0.01). This study helped to derive the European maximum dosage of ranolazine of 750 mg twice daily.

This study also provided an interesting finding with regard to a marker of diabetes control in patients treated with ranolazine[7]. In a post-hoc analysis of the patients with diabetes included in CARISA, a reduction in glycosylated haemoglobin (HbA1c) of 0.48% was observed in patients treated with ranolazine 750 mg twice daily when adjusted against placebo (p=0.008) from baseline to week 12: the clinical relevance of this has yet to be defined.

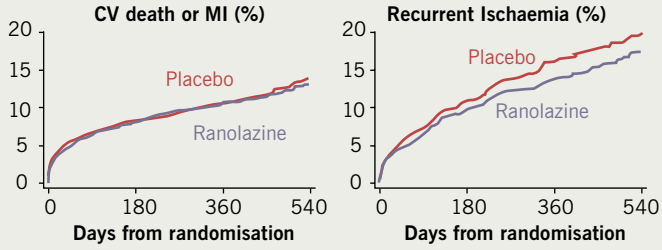
* In Europe, the licensed doses of Ranexa® (ranolazine) are 375mg bd, 500mg bd and 750mg bd prolonged-release tablets.

Figure 1. A diagram of a sodium channel



Key: Na = sodium; Ca = calcium; I_{Na}; sodium current

Figure 2. Results from the Merlin TIMI 36 trial



Adapted from Morrow DA *et al JAMA* 2007[9]

Key: CV = cardiovascular; MI = myocardial infarction

The last of the clinical pre-registration studies for ranolazine, ERICA (Efficacy of Ranolazine in Chronic Angina)[8], randomised stable patients with coronary disease and three or more angina attacks per week to ranolazine against placebo in an ascending ranolazine dose of 500 to 1,000 mg twice daily for six weeks.* Patients (n=565) were already pre-treated with amlodipine 10 mg daily. Results showed a significant reduction in the number of angina attacks per week from 3.2 with placebo to 2.8 with ranolazine (p=0.028) and reduction in average nitroglycerin doses per week from 2.6 with placebo to 2.0 with ranolazine (p=0.014).

The MERLIN-TIMI 36 trial

MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes) was the landmark outcome study carried out with ranolazine[9] in 6,500 patients with unstable angina or non-ST elevation myocardial infarction (NSTEMI). They were randomised to receive ranolazine or placebo, initially intravenously and then orally (extended-release, 1000mg bd*), for up to one year. The primary efficacy end point for the study was cardiovascular death, myocardial infarction (MI) or recurrent ischaemia.

The primary end point was not met: it occurred in 21.8% of the ranolazine group and 23.5% of the placebo group (hazard ratio 0.92, p=0.11). Results for the two components of the primary end point are shown in **figure 2**. For death or MI, the two curves for ranolazine or placebo treatment were superimposed (hazard ratio 0.99, log-rank p=0.87). For recurrent ischaemia, there was a statistically significant reduction associated with ranolazine (16.1% for placebo versus 13.9% for ranolazine; hazard ratio 0.87; p=0.030). There was no difference between ranolazine and placebo in the risk of all-cause mortality, sudden cardiac death or frequency of symptomatic documented arrhythmias.

In a pre-specified subgroup of patients who presented with a history of chronic stable angina before their acute coronary syndrome/NSTEMI presentation, there was a highly significant reduction of recurrent ischaemia events and this also drove the reduction in the primary end point.[10]

These studies led to ranolazine being licensed as add-on therapy for the symptomatic treatment of patients with stable angina who are inadequately controlled or intolerant to first-line antianginal therapies

Conflict of interest statement

JC has received speaker's and adviser's honoraria from Menarini, CV Therapeutics and Servier.

Professor John Camm
Department of Cardiological Sciences,
St George's Hospital Medical School,
Cranmer Terrace,
London SW17 0RE.
(jcamm@sgul.ac.uk)

* In Europe, the licensed doses of Ranexa® (ranolazine) are 375mg bd, 500mg bd and 750mg bd prolonged-release tablets.

References

1. Maltsev VA, Undrovinas A. Late sodium current in failing heart: friend or foe? *Prog Biophy Mol Biol* 2008;**96**:421–51.

2. Moss AJ, Zareba W, Schwarz KQ *et al*. Ranolazine shortens repolarisation in patients with sustained inward sodium current due to type-3 long-QT syndrome. *J Cardiovas Electrophysiol* 2008;**19**:1289–93.

3. Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. *Am J Cardiol* 2005;**95**:311–16.

4. Venkataraman R, Belardinelli L, Blackburn B *et al*. Ranolazine improves myocardial perfusion in patients with coronary artery disease. ICNC9 2009 (Nuclear Cardiology and Cardiac CT), abstract 64.

5. Chaitman BR, Skettino SL, Parker JO *et al* for the MARISA Investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol* 2004;**43**:1375–82.

6. Chaitman BR, Pepine CJ, Parker JO *et al* for the combination assessment of ranolazine in stable angina (CARISA) Investigators. 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.

7. Timmis AD, Chaitman BR, Crager M. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes. *Eur Heart J* 2006;**27**:42–8.

8. 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.

9. 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.

10. Wilson SR, Scirica BM, Braunwald E *et al*. Efficacy of ranolazine in patients with chronic angina. Observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (metabolic efficiency with ranolazine for less ischemia in non-ST-segment elevation acute coronary syndromes) 36 trial. *J Am Coll Cardiol* 2009;**53**:1510–16.