BJC
www.bjcardio.co.uk

The British Journal of Cardiology

Supplement 1

Volume 15 Supplement 1 | September/October 2008

Clinical implications of the inhibition of the late sodium current: a new paradigm in the treatment of ischaemic heart disease

ISSN 0969-6113 (Print) ISSN 1753-4313 (Online)

This supplement is supported by

CVT | CV Therapeutics Europe Limited

BJC
www.bjcardio.co.uk

The British Journal of Cardiology

The peer-reviewed journal linking primary and secondary care

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:
Michael Young
42 Avondale Avenue,
Hinchley Wood, Esher,
Surrey, KT10 0DA.
(michael-young@btconnect.com)
Tel: +44 (0)20 8339 0300
Fax: +44 (0)20 8398 3361

Annual subscriptions
UK & Europe:
Individual GBP 92.00
Institution GBP 139.00
Elsewhere:
Individual GBP 149.00
Institution GBP 200.00

Published bi-monthly and distributed on a controlled circulation to general practitioners with an interest in cardiology, hospital cardiologists, diabetologists, vascular and cardiothoracic surgeons. The Journal may be provided, free, on request to other registered medical practitioners and GP trainees.

ISSN 0969-6113 (Print)
ISSN 1753-4313 (Online)

www.bjcardio.co.uk

Clinical implications of the inhibition of the late sodium current: a new paradigm in the treatment of ischaemic heart disease

Introduction

Angina is a common, debilitating and unrelenting condition which takes its toll on individuals both in their leisure and occupational life and which can impose a significant financial burden on the health services of a nation.

Opening the meeting, Co-Chair, Professor John Camm (St George's Hospital, London) described the new antianginal compound, ranolazine. Whilst the mechanism of action of ranolazine is largely unknown, it may have some antianginal effects by inhibition of the late sodium current in cardiac cells. This reduces intracellular sodium accumulation and consequently decreases intracellular calcium overload. Ranolazine, via its action to decrease the late sodium current, is considered to reduce these intracellular ionic imbalances during ischaemia. This reduction in cellular calcium overload is expected to improve myocardial relaxation and thereby decrease left ventricular diastolic stiffness. Symptoms of angina are improved.

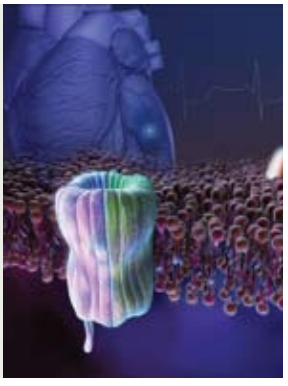
Ranolazine is available in the US and has recently received approval from the European Medicines Agency (EMEA). Ranolazine can be used in the EU as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies such as beta blockers and calcium antagonists.

A symposium, sponsored by CV Therapeutics Europe Ltd, was held during the British Cardiovascular Society (BCS) meeting in Manchester on 2 June 2008. This report is a summary of the symposium.

Sponsorship statement

This supplement is supported by CV Therapeutics Europe Ltd. It may contain information on uses outside the approved Summary of Product Characteristics (SmPC) for ranolazine. CV Therapeutics does not recommend the use of ranolazine in any other manner than as described in the Summary of Product Characteristics.

CVTE/CORP/00115



Cover: Artistic rendition of a sodium channel within the ischaemic cardiomyocyte. (Credit: CV Therapeutics, Inc.)

Angina: benign or a target for aggressive treatment?

Reviewing whether chronic stable angina is a benign condition or whether it requires aggressive management, Professor Robert Wilcox (University Hospital, Nottingham) outlined how the subject of angina is fraught with problems of terms and definitions. What, for example, is 'stable angina'? Does this relate to the frequency, predictability, duration, severity or the tolerability of the symptoms in an individual? Similarly, when does chronic stable angina become 'refractory'? A patient who has previously had a myocardial infarction (MI) or an intervention such as a percutaneous coronary intervention (PCI) and now has chronic stable angina, must presumably be different from someone with angina who has not had an intervention, who presents to his general practitioner with exertional chest pain. It is reasonable to suppose that these two individuals will have different prognoses, he said.

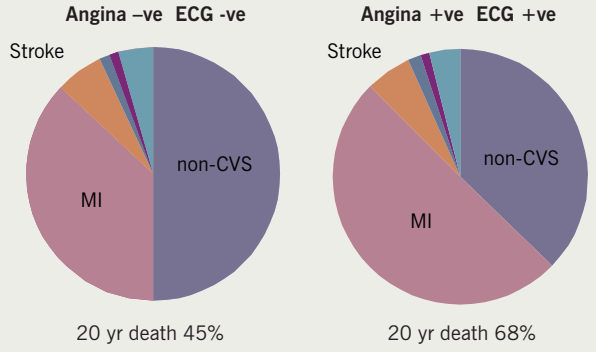
Professor Wilcox proposed his own definition: *"chronic stable angina is angina occurring at a frequency and severity, acceptable and tolerable to the patient whilst on optimal medical therapy and having made appropriate lifestyle changes, irrespective of prior interventional therapy".* This depends on how much treatment an individual is prepared to take and how many lifestyle changes they are prepared to make.

A recent systematic review and meta-analysis of 74 reports across 31 countries, including more than 400,000 men and women, using the Rose Angina Questionnaire, identified more than 13,000 cases of angina among women and more than 11,000 cases in men (Hemingway H *et al*. *Circulation* 2008;117:1526–36). There was considerable heterogeneity in the prevalence of angina but the population-weighted mean for women was just over 6% and for men just under 6%, respectively, so "there's an awful lot of angina about", said Professor Wilcox.

The Renfrew-Paisley Study, in the early 1970s, enrolled 15,000 individuals, and found that 2% of the population were Rose Angina Questionnaire-positive (RAQ+ve) and had a resting ECG abnormality (ECG+ve), while another 7% were RAQ+ve but with normal ECGs (ECG-ve). More worrying, however, were the 7% of the population who were RAQ-ve and ECG +ve, representing a "big invisible part of the ischaemia iceberg". We do not yet have a clear strategy for dealing with these patients, but the 20-year follow-up showed that survival among this group was much worse than among patients with the clinical features of angina but without ischaemic changes, or of course those with neither ischaemia or angina (about 83% of the population), who fare best. Similar gradations are seen for hospital admissions and cardiovascular death.

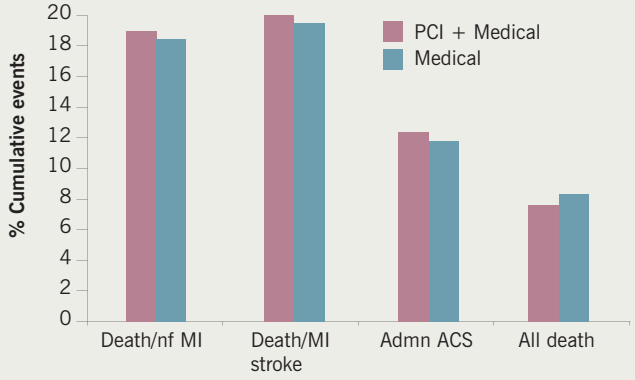
Men without angina or ischaemia had a 45% death rate over 20 years compared to men who had both ischaemia and angina, who had a 68% death rate. The results for women were similar but at slightly lower rates. Over half the deaths were cardiovascular, of which between one and two thirds were due to myocardial infarction (**figure 1**). There is therefore a gradation of risk within the community according to symptoms and ECG changes. A similar gradation was seen in the British Regional Heart Survey (Lampe RC *et al*; *Eur Heart J* 2000;21:1052–63). From the European Heart Survey, Daly and colleagues produced a risk score for prognosis in angina and constructed a risk curve which shows

Figure 1: Cause of death in men by baseline status in the Renfrew-Paisley Rose angina study



Adapted from Murphy *et al. Heart* 2006;**92:**1739–
Key: MI = Myocardial Infarction; CVS = Cardiovascular System

Figure 2: Cumulative events over 4.6 yrs in the COURAGE trial



Adapted from Boden WE *et al. NEJM* 2007;**356:**1503–
Key: ACS = Acute Coronary Syndrome; Admn = Admission; MI = Myocardial Infarction; nf = non-fatal; PCI = Percutaneous Coronary Intervention

the greatly amplified risk according to the presence of co-morbidities, left ventricular dysfunction and so forth across the spectrum of patients with stable angina (Daly C *et al*. *BMJ* 2006;332:262)

The risk of having ischaemia does not abate with time. In the Whitehall Civil Servants study, for example, "the risk of this disease carries on throughout life and has a major impact on life expectancy," said Professor Wilcox (Clarke R *et al*. *Eur J Cardiovasc Prev Rehabil* 2007;14:280–6).

The mass of available evidence suggests that the prevalence of angina is probably about 5% in those aged >40 years; the death rate from that group is about 1 to 3% per annum, depending on co-morbidity and other factors, and the risk of MI is about 2%, but it is highly variable.

What then has been done to improve the outcome in angina? Professor Wilcox looked at some of the older data on coronary artery bypass surgery (CABG) versus medical treatment, including a meta-analysis of seven trials but enrolling only 2,649 patients (Yusuf S *et al*. *Lancet* 1994;344:563). The data showed an advantage for surgery with a "deferring of death" of about two years, but the survival curves converge at around 12 years, as "no treatment will impart immortality". He reminded the audience that both the surgery and the drugs deployed were rather "old fashioned" and rudimentary compared to what is currently available; however, these are the only data we have comparing the two treatments of angina.

The situation for PCI is probably less good than for surgery. Whereas PCI is extremely good at reducing angina symptoms, "it does not reduce the incidence of death or non-fatal MI" and the likelihood of a repeat procedure is much greater compared to CABG. Some of the best information on PCI comes from the Second Randomised Intervention Treatment of Angina Trial (RITA-2), which evaluated the long-term effects of PCI versus medical management as initial treatment strategies in angina patients with angiographically proven coronary artery disease (CAD). Current symptoms were not mandatory and patients with multivessel disease and ventricular impairment were included. (Patients with significant left main stem disease or previous revascularisation were excluded.) Seven-year follow up data from the trial showed "no difference whatsoever" in overall death between medical treatment and PCI (Henderson R *et al*. *J Am Coll Cardiol* 2003;42:1161).

In contrast, medical treatment was associated with lower rates of death/MI, due mainly to the early risk of intervention, and 60% or more of medically treated patients "were saved an intervention by continuing medical therapy". The RITA-2 authors therefore concluded that, as an initial strategy, intervention will not significantly influence outcomes but it will improve angina symptoms and exercise tolerance. Also, patients considered equally suitable for intervention or medical therapy can be safely managed with continued medical therapy, but PCI is appropriate if symptoms are not controlled.

The trial was criticised by US workers, who are regarded as more prone to intervention bias, but this criticism has in turn been challenged by findings from the COURAGE trial (Boden *WE et al. N Engl J Med* 2007;356:1503–16). This landmark study investigated whether PCI plus optimal medical therapy result in superior outcomes when compared with optimal medical therapy alone. Conducted in 2,287 stable angina patients, the trial was arguably over-represented by white males (86%), but they were high-risk patients: one third had diabetes, two thirds hypertension and nearly 40% had a previous MI. The medical therapy was "really quite intensive", comprising antiplatelet agents, long-acting metoprolol, amlodipine, isosorbide mononitrate, lisinopril or losartan, simvastatin +/- ezetimibe (target low-density lipoprotein cholesterol [LDL-C] < 2 mmol/L), exercise, niacin and fibrate (target high-density lipoprotein cholesterol [HDL-C] >1.03 mmol/L and triglycerides [TG] <1.69 mmol/L).

After a mean of 4.6 years, "no difference whatsoever" was found between the two treatment arms in the rates of death or non-fatal MI, stroke, admission for acute coronary syndrome or all-cause mortality **(figure 2)**. COURAGE was criticised for being unrepresentative, for not including high enough risk patients and because one third or more of the medical group went on to have an intervention. This was good news"as that means two thirds didn't need it!", said Professor Wilcox. About 20% of patients who had PCI needed a repeat procedure. Such findings are important and they "should influence our attitude to dealing with patients with chronic stable angina," in his view.

There are many non-interventional strategies for stable angina **(Table 1)**: not all of which have been shown to improve survival and supportive data for many of these agents are limited in the stable angina setting. "There is a lot now medically that can be offered to patients which was not available in the past, and certainly was not available when the early trials of medicine versus surgery were conducted," said Professor Wilcox.

Table 1. Non-interventional therapies for chronic stable angina

- Aspirin/clopidogrel
- Angiotensin-converting enzyme inhibitors
- Beta blockers
- Calcium channel blockers
- Cardiac rehabilitation
- Exercise training
- Lipid-lowering agents
- Nitrates
- Omega-3 fatty acids
- Potassium channel activators
- Sinus node I_f channel inhibitor
- Late sodium current inhibitor

In summary, chronic stable angina is not a benign condition in Professor Wilcox's view. He said that "chronic stable angina has variable risk depending on co-morbidity, gender and prior cardiovascular events….Modern aggressive medical therapy performs well against PCI, but has not been compared with CABG. And, as newer anti-anginal drugs become available, their place in risk reduction rather than just symptom control will need to be assessed. Because we are adding on treatments, we are looking for small incremental benefits of these new drugs."

The best approach to screening for and dealing with silent ischaemia is not established. Once ischaemia is proven as the likely cause of chest pain, should an angiogram be performed to look for "interventionally-preferred treatment?" This is one of the dilemmas in managing patients who present with new-onset angina. Alternatively, we might say to the patient that we can safely treat him medically, Professor Wilcox concluded.

RW acknowledges research income from CV Therapeutics Europe Ltd to the University of Nottingham.

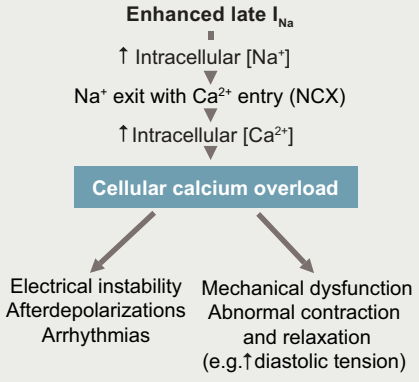
The late sodium current and ranolazine

Professor John Camm addressed the role of the late sodium current as a new target in ischaemic heart disease (IHD). The sodium channel itself spans the cardiac myocyte membrane and allows sodium transport from outside the cell to the inside of the cell.

The sodium current peaks at the onset of the action potential and continues throughout systole, with a so-called late component, or late I_{Na} **(see figure 1)**, which decays gradually. It is responsible in part for maintaining the plateau of the action potential, and it is therefore one of the determinants of the QTc interval.

"This particular channel may be responsible for a number of pathologies and may be a target in a variety of diseases" in addition to angina, said Professor Camm. He explained a pathological paradigm of the inability of the sodium channel to inactivate, which occurs in both acquired and congenital conditions. Inability of sodium channel inactivation, ie 'enhanced late I_{Na}' **(figure 2)**, leads to greater influx of sodium into the cell and an increased level of intracellular sodium. This in turn engages the sodium/calcium exchange mechanism: sodium leaves the cell and calcium enters, giving rise to calcium overload. This defective sodium channel gating therefore leads to calcium overload and a wide array of 'channelopathy' disorders, including ischaemia and heart failure and the congenital Long QTc 3 syndrome (LQT3) which is associated with a specific genetic abnormality. Similar abnormalities may occur in other muscles and nerves, giving rise to seizures and myotonia and neuropathic pain **(figure 3)**.

Figure 2: The enhanced late I_{Na}



What is ranolazine?

Professor Camm went on to describe how the novel antianginal anti-ischaemic agent, ranolazine is thought to selectively inhibit the late I_{Na} and to attenuate the abnormalities of ventricular repolarisation and electrical instability associated with ischaemia and heart failure. This inhibition is concentration-dependent. Ranolazine has been shown to cause modest QTc interval prolongation, but without causing torsade de pointes. It does not slow heart rate or decrease blood pressure to a clinically relevant degree. Additionally, it does not decrease left ventricular (LV) systolic pressure or LV dp/dt (a measure of ventricular function) or increase coronary blood flow.

Studies in which increasing doses of ranolazine were administered to volunteers confirm that the drug does not have chronotropic effects. This is confirmed in studies where ranolazine (compared to placebo) produced no increases in rate-pressure product (RPP) during exercise; in contrast, beta blockade decreases RPP.

Professor Camm then reviewed clinical studies with ranolazine. This agent has been evaluated

Figure 1: The cardiac sodium channel current

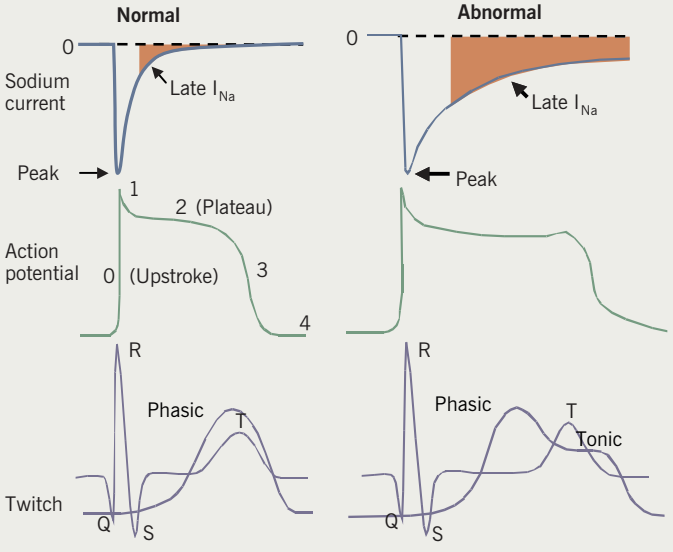


Figure 3: Potential pathological roles of late I_{Na} in cardiac and other diseases

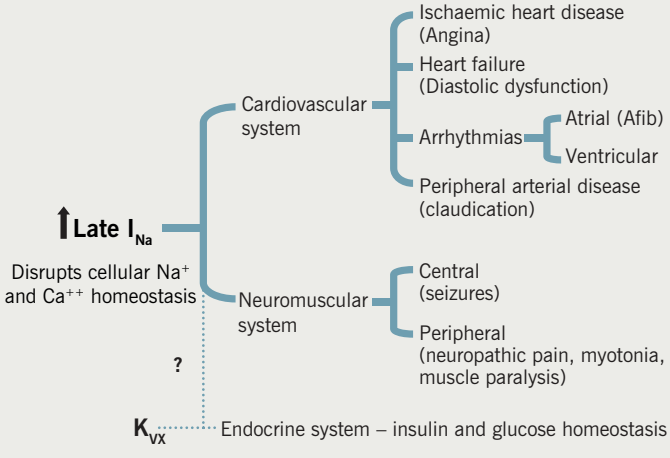


Table 1. Ranolazine efficacy trials

MARISA: Monotherapy Assessment of Ranolazine In Stable Angina (a)

CARISA: Combination Assessment of Ranolazine In Stable Angina (b)

ERICA: Efficacy of Ranolazine In Chronic Angina (c)

a) Chaitman BR *et al*. *J Am Coll Cardiol* 2004;**43**:1375–82.
b) Chaitman BR et al. *JAMA* 2004;**291**:309–16.
c) Stone PH et al. *J Am Coll Cardiol* 2006;**48**:566–75.

in three principal efficacy trials **(table 1).**

MARISA compared three doses of ranolazine--500 mg, 1,000 mg and 1,500 mg twice daily--with placebo in 191 randomised patients. A clear dose-response relationship was seen in standard exercise testing parameters i.e. exercise duration, time to 1 mm ST-segment depression, and time to angina onset, assessed at trough and at peak. Improvements with ranolazine were significant versus placebo at both peak and trough (the latter being the important criterion for regulatory purposes). There was only a minor change in RPP whereas "the ST-segment change was significant and highly dose-related at each point during the exercise test," said Professor Camm.

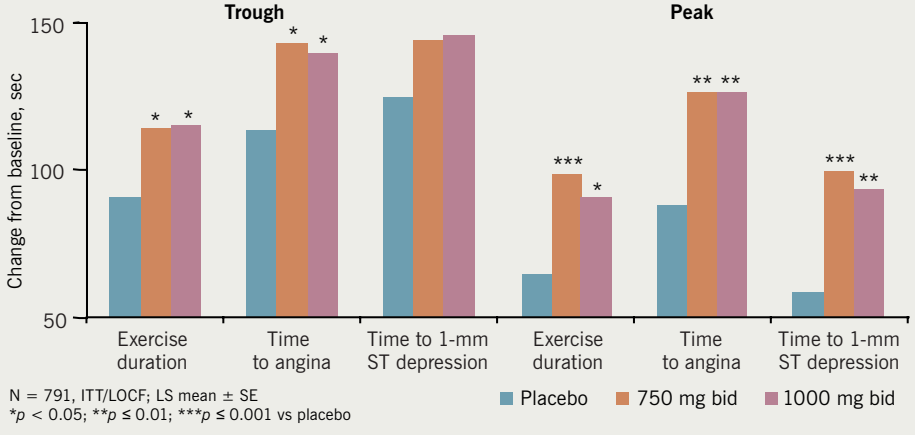
CARISA randomised patients to ranolazine 750 mg and 1,000 mg twice daily and placebo, on a background of atenolol 50 mg OD (43%), amlodipine 5 mg OD (31%) and diltiazem 180 mg OD (26%), respectively. This study also showed significant increases in exercise times (as well as decreased angina attacks and nitroglycerin [GTN] consumption) but "there was no dose-related change in these exercise parameters," said Professor Camm **(figure 4)**.

ERICA randomised patients to receive placebo or ranolazine 500 mg twice daily for one week initially before the dose was titrated up to ranolazine 1,000 mg twice daily and continued for another six weeks. All patients received amlodipine 10 mg OD with (45% of patents at baseline) or without long-acting nitrates. Frequency of angina attacks, the primary end point, and mean weekly GTN consumption were reduced significantly with ranolazine versus placebo **(figure 5)**.

Professor Camm went on to discuss two reports from the large mortality, outcome trial, MERLIN-TIMI 36 **(table 2)**. This was a double-blind, randomised, placebo-controlled trial conducted in 17 countries, which enrolled 6,560 patients with non-ST-elevation acute coronary syndromes within 48 hours of ischaemic symptoms.

Patients were treated with ranolazine (initially intravenously and followed by oral ranolazine 1,000 mg twice daily or matching placebo, and followed up for a median of 348 days. Follow-up assessments were conducted every four months **(figure 6)**. The primary end point was a composite of cardiovascular death, MI or recurrent ischaemia at 12 months.

Figure 4: Results from the CARISA study



N = 791, ITT/LOCF; LS mean ± SE
*$p < 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ vs placebo

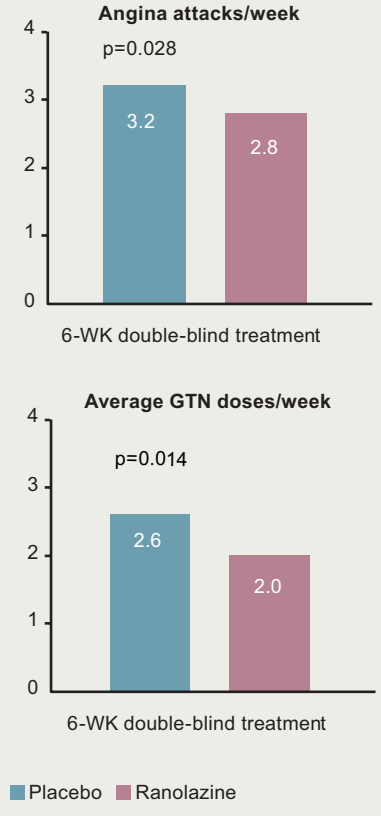
Key: CARISA = Combination Assessment of Ranolazine in Stable Angina

Table 2. The MERLIN-TIMI 36 trial

MERLIN-TIMI 36 Metabolic efficiency With Ranolazine for Less Ischaemia in Non ST_Elevation Acute Coronary Syndrome Thromboloysis in Myocardial Infarction 36.

a) Morrow DA, Scirica BM, Karwatowoska DA *et al*. Effects of Ranolazine on Recurrent Cardiovascular Events in Patients With Non-ST-Elevation Acute Coronary Syndromes. *JAMA* 2007;**297**:1775–83.
b) Scirica BM, Morrow DA, Hod H *et al*. Effect of Ranolazine, an Antianginal Agent With Non ST-Segment Elevation Acute Coronary Syndrome:Results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) Randomized Controlled Trial. *Circulation* 2007;**116**:1647-52).

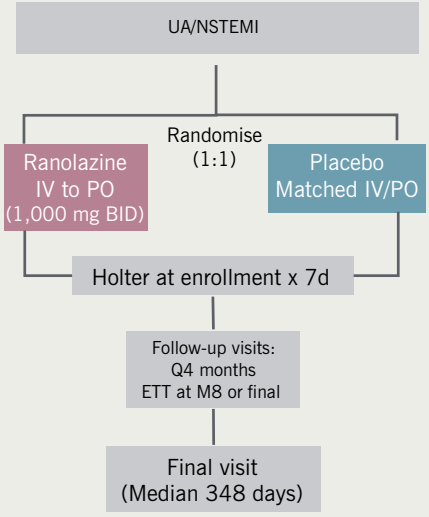
Figure 5: Efficacy results in the ERICA trial



*Excludes patients in the top 2% of each treatment group to reduce the influence of outlying data points.

Key: ERICA = Efficacy of Ranolazine in Chronic Angina; GTN = Glyceryl Trinitrate

Figure 6: Design of the MERLIN-TIMI 36 trial



Adapted from Morrow DA *et al. JAMA* 2007;**297:**1775–1783
Key: ETT = Exercise Tolerance Test; NSTEMI = Non-ST segment Elevation Myocardial Infarction; U/A = Unstable Angina

Figure 7: Kaplan-Meier curves for the MERLIN-TIMI 36 trial

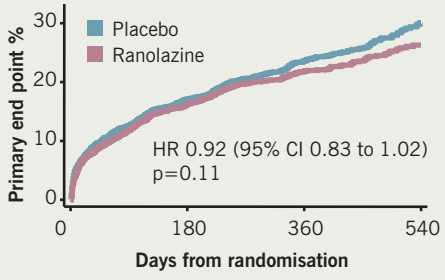
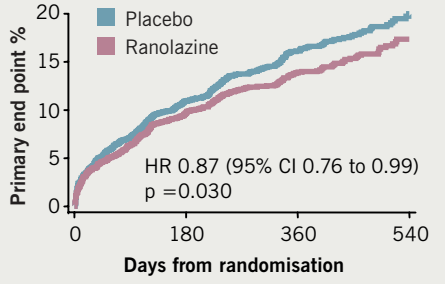


Figure 8: Occurence of recurrent ischaemia in the MERLIN-TIMI 36 trial



Adapted from Morrow DA *et al. JAMA* 2007;**297:**1775–1783

Continuous ECG Holter recording was performed for the first seven days after randomisation, and a pre-specified set of arrhythmias was evaluated. The major safety end points were death from any cause and symptomatic documented arrhythmia.

The Kaplan-Meier estimated rates of the primary end point (cardiovascular death, MI or recurrent ischaemia at 12 months) are shown in **figure 7** and no significant difference was observed between ranolazine and placebo "but recurrent ischaemia was significantly reduced in the patients who were taking ranolazine," said Professor Camm **(figure 8)**.

Similarly, the number of patients with worsening angina was significantly lower with ranolazine compared to placebo and there was less requirement for increased anti-anginal treatment with ranolazine **(figure 9)**. In terms of major safety end points, "none of them is greater in association with ranolazine than with placebo," said Professor Camm, who noted that clinically significant arrhythmias on Holter were observed in 74% of patients treated with ranolazine and in 83% of patients in the placebo group (p<0.001**) (table 3)**. This difference was particularly noteworthy with ventricular tachycardia lasting eight beats or more; there was a "substantial reduction associated with ranolazine" (5.3% vs 8.3%;p<0.001) over seven days of Holter monitoring **(figure 10)**.

Summarising, Professor Camm said that ranolazine is thought to be a late sodium current inhibitor, which thereby reduces myocardial oxygen consumption (MVO_2). It does not reduce the rate pressure product significantly but does reduce myocardial ischaemia. It has been assessed in a number of clinical trials where it shows an improvement in exercise performance, a decrease in angina attacks, GTN consumption, and a 23% risk reduction for worsening angina or ischaemia. "Ranolazine seems to be an effective and safe antianginal agent," he concluded.

JC is an advisor to CV Therapeutics and Servier.

Figure 9: Anti-anginal effects of ranolazine in the MERLIN-TIMI 36 trial

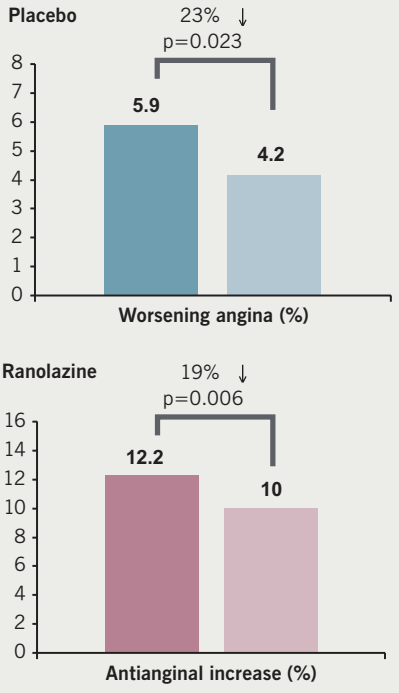
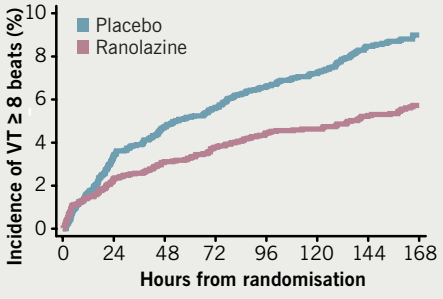


Figure 10: First occurrence of ventricular tachycardia lasting ≥ 8 beats in the MERLIN-TIMI 36 trial



Adapted from Scirica *et al. Circulation.* 2007;**116:** 1449–1457

Table 3: Major safety endpoints in the MERLIN-TIMI 36 trial

	Ranolazine (N=3,268)	Placebo (N=3,273)	HR	P-value
Death – any cause (N)	172	175	0.99	p=0.91
Sudden cardiac death	56	65	0.87	p=0.43
Death or CV hospitalization	1037	1065	0.98	p=0.67
Symptomatic documented arrhythmia	99	102	0.97	p=0.84
Clinically significant arrhythmia on Holter (%)	73.7	83.1	0.89	p<0.001

MEETING REPORT

Ischaemic heart disease: diabetic patients are different

"Diabetic patients, despite current therapies, have significant residual risk of cardiovascular events such that we need to think about new agents," said Professor Mark Kearney (University of Leeds) in a review of the increased pernicious nature of ischaemic heart disease (IHD) in the setting of type 2 diabetes.

He said that it was heartening to see that there has been a significant improvement in cancer survival rates over the past three decades in the UK. Using the cancer analogy, he said that "stable angina in patients with diabetes might be described as a "pre-malignant condition"; once angina becomes unstable, "it becomes malignant".

Diabetes starts very early in life, with insulin resistance. As this progresses, there is an initial compensatory increase in plasma insulin, re-setting glucose at normal levels, but "ultimately the pancreas fails" with a resulting increase in blood glucose. All the time during this process, the blood vessel is exposed "to a portfolio of risk factors" that changes the artery. By the time the diabetic patient presents with an MI, the atherosclerotic phenotype and the prognosis are very different in comparison to those of a non-diabetic patient presenting with an MI.

Coronary artery disease is characterised by a series of changes within the arterial wall that culminates in plaque rupture. An early step in this process is endothelial dysfunction, which is characterised by a reduction in nitric oxide (NO), a change which occurs before there are any physical changes within the artery, Professor Kearney explained. This can be measured in a number of ways, including blood flow in the forearm after occlusion and release of a blood pressure cuff, ie. flow-mediated dilatation (FMD), detected by ultrasound. This can be equated to the amount of NO that an individual produces. These techniques have been used to study vascular function and to form a model of insulin resistance in young Asian men, confirming the presence of early atherosclerosis-- "biochemical atherosclerosis, which we think is linked to insulin resistance".

Asian males in the UK are three times more likely to die from an acute MI than European males and their post-MI mortality is worse, although we really do not understand why. Conventional risk factors, while important, do not account for all of this risk and there is a residual risk that is poorly understood. Progressive insulin resistance and glucose intolerance may play an important pathophysiological role in this process. Professor Kearney described a study he and co-workers have undertaken, (Murphy C *et al*. *Arterioscler Thromb Vasc Biol* 2007;27:936–42) that examined differences in risk factors, vascular function and circulating endothelial progenitor cells among 24 young South Asian men and 25 age-matched, healthy, non-smoking Caucasian men. They looked at the balance between damage to the artery, caused by atherosclerosis and insulin resistance, and other cardiovascular risk factors, and endothelial repair, in the form of endothelial circulating progenitor cells (EPCs) which home in to sites of damage and can repair such damaged arteries **(figure 1)**.

Risk factors between the two groups of men were very similar. The Asian men had normal fasting glucose levels but their fasting insulin and HOMA (a measure of insulin resistance) were significantly greater than in the Caucasian men, "showing that they have compensated insulin resistance". Looking at endothelial function with FMD and forearm blood flow, these young Asian men also "had good evidence of a reduction in nitric oxide production, even at the age of 25. I put it to you that this is early atherosclerosis," said Professor Kearney. Both the numbers and colonies of EPCs and their function were also reduced, indicating "impaired repair systems".

Further along this paradigm, Professor Kearney's group have also investigated determinants of endothelial function in 100 asymptomatic subjects with and without the metabolic syndrome, "the central core of which is insulin resistance and glucose intolerance" (Melikian N *et al*. *Atherosclerosis* 2008;197:375–82). Those with the metabolic syndrome still had normoglycaemia but they had an increase in fasting glucose, increased fasting insulin and a doubling of the HOMA index: that is, "they had worsening glucose control". Similarly, endothelial function in this group was worse that that seen in the study of young Asian men, and they are starting to exhibit systemic inflammation and other

Figure 1: The balance between endothelial damage and repair

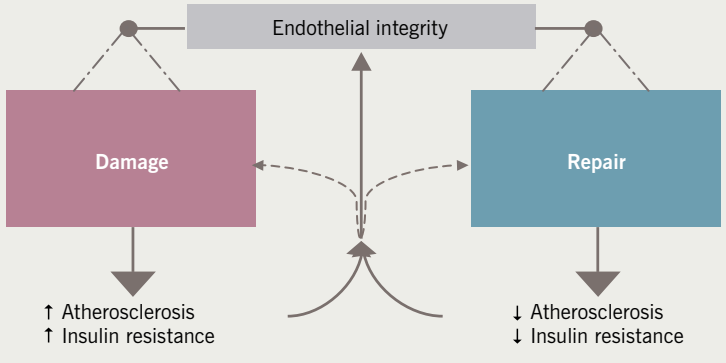


Table 1: Mortality in EMMACE

	Male			Female		
BS (mmol/L)	< 7.8	7.8–11.1	11.1	<7.8	7.8–11.1	>11.1
Age (years)	65 (13)	67 (13)	70 (12)	73 (13)	77 (9)	77(10)
Mortality (%)	20	28	45	24	40	50

Key: BS = Blood Sugar; EMMACE = Evaluation of Methods and Management of Acute Coronary Events

Table 2: Patient characteristics and treatment in EMMACE

	Diabetes		No Diabetes	
	1995	2003	1995	2003
Age (yrs)	71 (0.7)	71 (0.7)	70 (0.3)	70 (0.4)
Male (%)	53	60	65	65
Hypertension (%)	37	57	28	40
Heart failure (%)	12	9	8	5
IHD (%)	55	62	46	41
Aspirin	66	86	74	85
Statin	7.2	79	7	80
ACEI	40	73	31	65
BB	28	62	37	66

Key: CV Hosp = Cardiovascular hospitalisation, ACEI = Angiotensin-converting enzyme inhibitor; BB = beta blocker; IHD = ischaemic heart disease

markers of vascular/metabolic dysfunction, and a worsening of atherosclerosis.

Professor Kearney described the effect of diabetes on outcomes after coronary events, looking at patients with impaired glucose tolerance (IGT) compared to patients with overt diabetes after MI. He presented data looking at new-onset hyperglycaemia following MI, as part of the EMMACE (Evaluation of Methods and Management of Acute Coronary Events) Study Group (Cubbon RM *et al*. *Eur J Cardiovasc Preven Rehab* 2007;14:666–71). Post-MI patients in 12 Yorkshire hospitals were followed up in EMMACE 1 (three months in 1995; n=1,770) and EMMACE 2 (six months during 2003; n=1,542) for 18 months overall to determine treatment effects. In women admitted to hospitals in 2003, the mortality associated with blood sugar > 11.1 mmol/L was 50% **(table 1)**. When compared with stage III carcinoma of the breast, a woman with diabetes post-MI has a survival rate which is three years shorter. "I do not intend to trivialise carcinoma of the breast but this puts into perspective the need for new therapies in patients with diabetes and coronary artery disease," said Professor Kearney.

How have new therapies, introduced over the past 10 years, impacted on outcomes following MI? The two EMMACE 1 and EMMACE 2 databases have been examined to try and answer this (Cubbon RM *et al*. *Eur Heart J* 2007;128:540–45). The characteristics and treatments of the patients with and without diabetes in 1995 and 2003 are shown in **table 2**. "These secondary prevention therapies after myocardial infarction are very good," with 86% of diabetic patients receiving aspirin in 2003 versus 66% in 1995, for example. How did this translate into outcomes? Two-year mortality among non-diabetic patients in 1995 was about 30%; in 2003, this was reduced by about an absolute percentage of 6% and a relative reduction of about 20%. Despite contemporary therapies and increased use of statins, aspirin, ACE inhibitors and beta blockers, mortality in diabetic patients remains "totally unchanged over the last ten years".

To explore this further, Professor Kearney and colleagues have looked at responses to therapies (Cubbon RM *et al*. *Diabetes Care* 2008;31:363–5).They quantified the effects of different agents in diabetic and non-diabetic patients. Conventional agents such as beta blockers, ACE inhibitors and statins have very similar effects in diabetics and non-diabetics: "they all have a beneficial effect on mortality in the two groups, but aspirin seems not to have as good an effect".

Outcomes remain poor in diabetes

Summarising the presentation, Professor Kearney said that "the pathology of diabetic coronary artery disease is different, despite the use of contemporary therapies. There is no doubt that even now, in 2008, outcomes for patients with diabetes after myocardial infarction are very poor. Contemporary therapies help these patients but they do not address all of the risk that these patients have. And we really need to assess new agents to address this residual risk that is not addressed by current therapies".

Asked whether the glitazones may have a role in acute coronary syndromes (ACS), Professor Kearney said that there are controversies about these agents. There is no evidence for the two marketed agents in ACS, but in stable coronary disease there is evidence that pioglitazone has a favourable effect on mortality. In the context of stable coronary disease, diabetes and poor glycaemic control, pioglitazone does have a place, but whether it actually affects the pathophysiology of the arterial wall is a debate which is still ongoing, in his view. He commented also on the controversial findings from the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction-2 trial (DIGAMI-2), which suggests that long-term glucose-insulin infusion improves survival in diabetic patients compared to 'usual care'. He said that in-hospital mortality improves with tight glycaemic control but that "something happens to these patients when they leave hospital as the mortality suddenly shoots up." It may be because patients become tired of taking so many medications, but he supports the DIGAMI criteria for treatment.

MK has received an honorarium from CV Therapeutics.

Copyright Medinews (Cardiology) Limited Reproduction Prohibited

MEETING REPORT

Inequity in angina management: it's not fair, but does it matter?

Professor Adam Timmis (Barts and the London NHS Trust) discussed the thorny issue of inequity in the management of angina, and he started by distinguishing between inequality and inequity. Inequality, such as differences in health between populations, is "an interesting observation". For instance, in East London, standardised admission ratios with myocardial infarction rates are twice as high for South Asians as for whites. Also, mortality in women is twice as high following MI (for various reasons). Inequities, in contrast, are represented in different opportunities for healthcare between populations, for example, and "are potential embarrassments for us as cardiologists." Thus, in 2003, prolonged door-to-needle times were observed in South Asians versus whites (42.5 vs. 26.0 minutes, respectively); and rates of discharge on beta blockers post-MI were lower in women (31.6%) than in men (44.9%).

Key questions on inequity are shown in **table 1**, many of which are infrequently addressed.

Table 1: Questions on inequity of treatment in angina

- Is there evidence of inequity in the management of angina?
- Does inequity matter – does it affect patient outcomes?
- What factors are responsible for inequitable management?
- What can be done about it?

Professor Timmis presented evidence that inequity exists from a study involving six UK rapid access chest pain clinics. They had shared databases including almost 9,000 patients with stable chest pain, about 27% of whom were diagnosed with angina and some 73% with non-cardiac chest pain. Patients were rated appropriate or not appropriate for angiography, using the established RAND-UCLA method, by experts. They found that among patients appropriate for angiography only 31% actually received it. This is clear evidence of under-investigation and under-treatment in patients with angina. Analysis showed that patients over 65 years, women and South Asians along with those in the most deprived socio-economic groups were less likely to receive angiography. The study also showed inequity of access to these clinics, most notable in elderly patients and those in the most deprived socio-economic group, reminding us that "deprivation is one of the biggest drivers of coronary mortality in the country," said Professor Timmis.

Does inequity in the investigation of angina matter? "Here the data are quite consistent and show that in the patients attending chest pain clinics who are deemed appropriate for angiography, failure to obtain angiography in appropriate cases "is associated with worse outcomes," so inequity "certainly does matter". This pattern is seen across the board in medicine and these groups, especially the elderly, "don't do so well in the hands of doctors," said Professor Timmis.

Physician bias was investigated in a study of 4,121 patients (2,974 of whom were white and 502 south Asian [SA]), referred to a tertiary centre for coronary angiography in the appropriateness for coronary revascularisation (ACRE) study (Feder G *et al*. *BMJ* 324:511–16). The intended management by ethnicity for revascularisation was recorded, and was identical between the two patient groups (39% for SA and 40% for whites). However, actual receipt of revascularisation was "significantly lower" in south Asians, so inequity in this particular cohort was not explained by physician bias, "for reasons we have no answers to," said Professor Timmis. Factors such as coronary anatomy and the patients' wishes may have been an influence.

Patient-specific factors are other potential drivers of inequity. Many cardiologists are programmed to think that "there is something funny in the way that women present with angina," similarly with ethnic minorities, yet there is no evidence to support these notions.

Test-specific factors may play a role in inequity. False positive and false negative exercise tests do occur more commonly in women but the prevalence of disease is somewhat lower in women, so the tests will perform less well. Professor Timmis presented data from a large cohort of almost 8,000 patients examining whether women or south Asians present with chest pain symptoms in a "funny way". Findings show that the prognostic validity of chest pain typically is independent of gender or ethnicity. In women and ethnic minorities "we found absolutely no difference in the prognostic validity of the history they give with angina, nor indeed in the results of stress testing".

Evidence supports the view that south Asians and female patients do not present in "funny ways". Women present in exactly the same way as men, and men with positive exercise tests have exactly the same event rate over 2.5 years as women. But men with a negative test "if anything have a rather higher event rate than women with a negative test." So "if a woman's got a positive test, she needs investigating in exactly the same way as a man," in Professor Timmis's view.

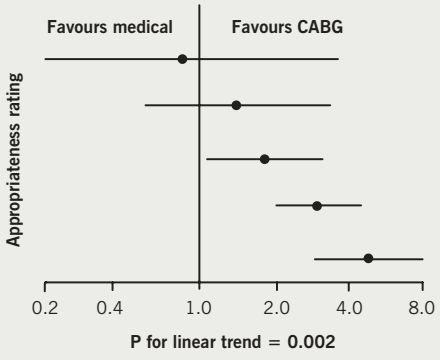
How to tackle inequity

What can be done about inequity in angina? Professor Timmis cited a challenging lead article by Nicole Lurie (Health disparities, less talk, more action. *N Engl J Med* 2005;353:727–9). This describes the 'data deluge' in terms of inequity, which has led many observers to suggest that "it is time to stop documenting disparities and turn our efforts to doing something about them." To these ends, Professor Timmis described recent work in the development of objective tools for guiding management in the application

of appropriateness ratings. Further data from the ACRE study look at five levels of appropriateness. The scale runs from 1–2 (inappropriate) up to 9 (completely appropriate). The grades are determined by an expert panel, which shows a graded dose-related effect of appropriateness which is related to hard outcomes such as MI or death, when comparing medical treatment versus CABG **(figure 1)**. These data appeared to be showing important messages on how patients should be managed.

The technique was applied in a recent randomised controlled study of aids to decision making, in the Appropriateness of Referral and Investigation in Angina (ARIA) Trial (Junghans C *et al*. *Arch Intern Med* 2007;167:195–202). This compared the effect of conventional guidelines with appropriateness of investigational decisions in angina, namely exercise testing and angiography. It involved 145 physicians who received patient-specific appropriateness ratings and 147 physicians who received guideline support. All physicians made their recommendations on 12 web-based patient vignettes before and on 12 vignettes after these interventions. Results showed that where decisions were guided by appropriateness ratings, there was a significant increase in the appropriate decisions they made, whereas, the conventional guidelines had no effect.

Figure 1: Adjusted hazard (95% CI) of non-fatal MI or death after 2.5 years for medical management vs CABG stratified by appropriateness ratings for CABG



Adapted from Hemingway *et al NEJM* 2001
Key: MI = Myocardial infarction; CABG = coronary artery bypass graft

What, then, is the solution to inequity in the management of suspected angina? Conventional guidelines, although widely used, are not patient-specific and there is little evidence that they change management behaviour. Often "the patient you have in front of you in a clinic just never quite fits the guideline," said Professor Timmis. The ARIA Trial has shown that, unlike conventional guidelines, patient-specific ratings changed physician testing behaviour and have the potential to reduce practice-based variations and to increase the appropriate use of investigation.

Similarly, risk scores are widely used and objective in their assessment of risk but they provide no information to the physician on appropriate management responses to the risk score.

The message is therefore, that, "appropriate ratings we like". They are informative, and deployment of patient-specific ratings may be part of the solution to inequity in the management of suspected angina. They are not widely used but "there is increasing recognition of this methodology…and I think this is something for the future which hopefully will have some impact on the inequity in management that patients with angina are receiving," Professor Timmis concluded.

AT has been a CAB member for CV Therapeutics.