

## Ivabradine reduces cardiovascular events in angina patients

Slowing heart rate selectively with ivabradine (Coralan) therapy has been shown in a subgroup of angina patients in the BEAUTIFUL study to significantly reduce the primary endpoint of the risk of cardiovascular death, hospitalisation for myocardial infarction and new-onset or worsening heart failure by 24%. Hospitalisation for fatal or non-fatal myocardial infarction was reduced by a very significant 42% in all angina patients receiving ivabradine, regardless of whether their heart rate was raised or not (Fig. 1).

In addition, in those angina patients whose heart rate remained elevated above 70 beats per minute (bpm) despite being on beta-blocker therapy in most cases (90%), the benefits achieved with ivabradine were even greater. A 31% reduction was achieved in the primary endpoint of cardiovascular death, hospitalisation for myocardial infarction and heart failure in these patients. Also the patients with a higher heart rate showed a 73% reduction in hospitalisation for myocardial infarction and a 59% reduction in coronary revascularisation.<sup>1</sup>

Announcing these findings at the 2009 European Society of Cardiology hot-line session, Prof Roberto Ferrari, director of cardiology, Ferrara, Italy and currently president of the ESC pointed out that

these substudy results in angina patients are concordant with the main findings of the BEAUTIFUL study as announced last year in Munich. ‘The sample size of angina patients in the substudy is relevant and the results are plausible’, he pointed out.

The BEAUTIFUL trial (morbidity–mortality Evaluation of the I<sub>f</sub> inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) recruited 10 917 patients from 33 different countries. It had two key objectives – to explore the value of ivabradine in patients receiving contemporary current treatment, and to explore the role which heart rate plays in determining the risk of cardiovascular events.

The BEAUTIFUL trial showed that coronary patients with associated left ventricular dysfunction who had a heart rate of more than 70 bpm were at greater risk of cardiovascular mortality, myocardial infarction and heart failure. In these patients, ivabradine therapy, although not achieving the primary endpoint, did show that ivabradine reduced the relative risk of hospitalisation for myocardial infarction by 36% and the need for coronary revascularisation by 30%.

The angina substudy of BEAUTIFUL included 1 507 patients (13.8% of the total cohort) with limiting angina at

the outset of the study. Of these, 734 were treated with ivabradine, while 773 received placebo. A total of 712 patients had a resting heart rate ≥ 70 bpm; 349 of these patients were randomised to ivabradine treatment and 363 to placebo.

There were no major differences between the angina patients and the overall BEAUTIFUL patients. Prof Ferrari pointed out that only 50% of angina patients received the full beta-blocker dose, again reflecting the reality of everyday practice where beta-blockers are frequently not prescribed to target doses.

These findings with ivabradine have set this therapy apart from traditional anti-anginal drugs, as ivabradine is now the only agent that has been able to show reduction of cardiovascular events in angina patients (Fig. 2). This occurred over a relatively short period of time (18 months).

The evidence for a benefit of anti-anginal drugs is scarce. With calcium channel blockers, the ACTION trial did not demonstrate a significant benefit in the reduction of cardiovascular events. In the CAMELOT trial, amlodipine tended to reduce the incidence of hard events but the results were also not statistically significant.

1. Fox KM, *et al.* *Eur Heart J* 2009; doi: 10.1093/eurheartj/eph358.

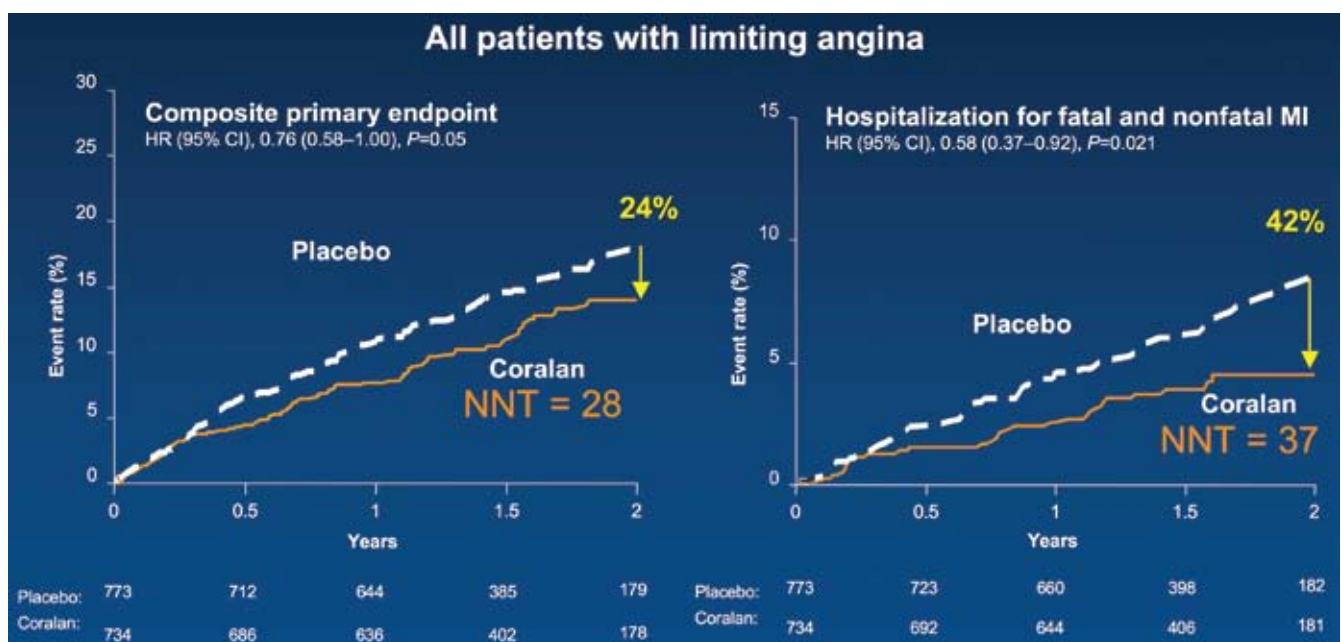


Fig. 1. Coralan reduces risk for primary composite endpoint and myocardial infarction in all patients with symptomatic ischaemia (angina).

	Improved total exercise duration	Improved time to onset of ST segment depression	Decrease in anginal episodes	Reduced revascularisation	Prevention of MI
$\beta$ -Blockers	+	+	+	-	-
Calcium antag.	+	+	+	+	-
Nitrates	+	+	+	-	-
<b>Coralan</b>	<b>+</b>	<b>+</b>	<b>+</b>	<b>+</b>	<b>+</b>

Adapted from: Guidelines on the management of stable angina pectoris. *Eur Heart J.* 2006;27:1341-1381. Fox K et al. *Lancet* Online August 31, 2008.

Fig. 2. Ivabradine, the first anti-anginal agent proven to reduce myocardial infarction in patients with stable symptomatic ischaemia (angina).

## Comment from attending South African specialists

**Dr JM Bennett, Wilgers Hospital, Pretoria**

It appears to me that South African cardiologists are aggressive when it comes to interventions in patients with coronary artery disease and presenting angina. This study places a more conservative medical management of these patients in the limelight.

Until now, medical management could only offer symptomatic relief of angina symptoms. Now we have an agent, ivabradine that offers better outcomes, with hard data on reduction of events such as hospitalisation for myocardial infarction and revascularisation. At minimum, postponing the time to the next event is a worthwhile benefit to the patient and the funder.

Interestingly only 30% of patients in the angina subset had undergone PCI/CABG prior to the commencement of the study. Keeping them free of interventions is a worthwhile achievement.

We do need an evaluation of the cost-effectiveness of ivabradine versus other interventions in the South African situa-

tion to bolster this approach. I do regular pulse-rate measurements on my patients when they come for check-ups and if an ECG is done, heart rate is also measured.

This study showed that the outcome benefit of ivabradine was in all angina patients, irrespective of their heart rate. The NNT (numbers needed to treat) of 28 patients in 18 months to avoid one serious event seems to be reasonable.

**Prof Lionel Opie, Hatter Institute for Heart Research, Cape Town**

'Limiting angina' was defined in this study as 'slight or marked limitation of physical activity due to angina', which surely includes all angina patients, since all angina is limiting. In this *post hoc* analysis of the BEAUTifUL trial, only 1 507 patients had limiting angina and 9 410 were without such angina.

All patients had proven coronary artery disease (CAD) for which they were mostly receiving optimal therapy. Ninety per cent of those with angina were using beta-blockers, but the target doses were not reached in almost half because

of bradycardia, fatigue, hypotension, cardiac failure, dizziness and/or vertigo and sexual dysfunction. These are all side effects uncommon or unknown with ivabradine, except for bradycardia, which is a mechanism of action common to both beta-blockers and ivabradine.

With the advent of ivabradine, a specific inhibitor of the pacemaker current  $I_f$  (inward 'funny' current), selective inhibition of the heart rate can be achieved without any of the disadvantages of beta-blockade, such as fatigue, bronchoconstriction and male sexual dysfunction. Which patients with angina are likely to benefit most from ivabradine? Logically, those with a higher heart rate.

What does this analysis show? Let's look at the first paragraph of the Discussion, which traditionally summarises the most important findings of any study: 'Treatment with ivabradine in the BEAUTifUL subpopulation with limiting angina was associated with a 24% reduction in risk for the primary endpoint and a 31% reduction of the primary endpoint in patients with limiting angina and heart

rate  $\geq 70$  bpm.’

However the *p*-values are not given in this text. These were *p* = 0.05 for the 24% reduction and *p* = 0.06 for the 31% reduction, the latter value for those with the higher heart rates. *P* = 0.06 is usually considered not significant and *p* = 0.05 as borderline.

Examination of Tables 3 and 4 shows that the consistent effects of ivabradine lay in coronary endpoints, namely hospitalisation for myocardial infarction (*p* = 0.02) for all anginal patients, with a 42% reduction, versus a 73% reduction (*p* = 0.002) for those with both angina and initial heart rates  $\geq 70$  bpm, but note a 28% reduction (*p* = 0.025) in those without angina. These changes in this single endpoint explained the borderline reductions in the composite endpoints. There may be two mechanisms, one being anti-anginal and the other seems to be protective even in the absence of angina.

There are several messages. The first is that, as the authors state, these interesting findings are only provisional. This is a *post hoc* analysis and therefore hypothesis generating, which needs prospective testing, as is being undertaken in the SIGNIFY study. Second, ivabradine gave benefit to CAD patients whether there was angina or not, and the benefit seemed greater in those with angina, although we are not given the *p*-values for this direct comparison. Third, symptomatic bradycardia (heart rate < 50 bpm) was rare, whereas in the majority of bradycardia,

the reason was protocol-driven despite being asymptomatic.

Overall, we are slowly edging towards the obvious, which however still needs formal proof. Ivabradine is an effective anti-anginal agent that alters outcomes even when added to beta-blockade, and works better in those anginal patients with higher heart rates. At present the practical issue is that before considering any intervention (PCI) for stable angina in any given patient, there should be a therapeutic trial of full medical therapy, such as ivabradine added to beta-blockade.

**Prof DP Naidoo, University of KwaZulu-Natal, Durban**

The recognition and use of heart rate as a risk factor for coronary artery disease has come along way since the original Framingham report (Levy 1945) on an association between heart rate and cardiovascular events in hypertensive subjects. More recently, the CASS registry some five years ago also noted the importance of heart rate as a marker in subjects with coronary artery disease. The availability of ivabradine has rekindled an interest in this risk factor for cardiovascular disease.

Clinicians have long used heart rate reduction as a marker to guide the efficacy of adequate beta-blockade. Yet in the EUROHEART survey of 5 000 subjects with coronary artery disease, more than half the subjects on beta-blockers had heart rates above 70 bpm. Similarly, the original BEAUTIfUL study, although neutral

with regard to the primary endpoints, did alert clinicians to the fact that among their coronary artery disease patients, half still had raised heart rates.

This new subgroup analysis of 1 507 subjects in the BEAUTIfUL study, in whom angina was the predominant symptom, showed that by using ivabradine, an agent with known anti-ischaemic properties, coronary events could be effectively prevented. Ivabradine reduced both the primary endpoint and myocardial infarction in all the patients, irrespective of their heart rates. In fact, none of the known anti-anginal agents used to manage symptoms have data on cardiovascular event reduction in angina patients.

This is the basis for the SIGNIFY study, which will focus on patients with CAD without heart failure or left ventricular dysfunction, and with a heart rate over 70 bpm at study entry. Recruiting is starting now and South Africa will contribute significant numbers of patients to the study.

Also, as national coordinator of the new CLARIFY registry for CAD announced at ESC, I am keen to see what this snapshot of the current care of patients with CAD in South Africa will show. The EUROHEART survey of angina, for example, was very valuable to alert clinicians to areas of neglect or potential for improvement in the management of the patient with coronary artery disease.

**The CLARIFY registry**

CLARIFY, the largest international registry to ever be carried out in stable coronary artery disease outpatients, was launched at the ESC congress in around 40 countries worldwide, including South Africa. The CLARIFY registry (prospective observational Longitudinal Registry of patients with stable coronary artery disease) is designed to increase knowledge and understanding of CAD.

Most of the data available on CAD stem from randomised clinical trials, which have limited generalisability due to the stringent selection process of participants, or include patients hospitalised for

acute events or procedures, or focus on patients with anginal symptoms. There are limited data regarding stable outpatients with CAD, and their contemporary management and outcomes.

The new registry is designed to provide important epidemiological and clinical data, including an assessment of the role of heart rate in the prognosis of CAD patients, and will hopefully help improve disease management by identifying gaps between evidence and actual practice.

CAD remains the leading cause of death worldwide. Improved understanding of the management and outcomes of

these patients is paramount to reducing the disease burden. Reducing elevated heart rate is a new approach that could potentially help decrease morbidity and mortality in these patients.

‘Despite the growing importance of heart rate in the treatment of CAD, there is little existing data on resting heart rate in patients seen in day-to-day clinical practice, so a registry of CAD patients involving heart rate is long overdue, particularly as heart rate needs to be carefully measured’, comments study lead Prof Philippe Gabriel Steg, Bichat-Claude Bernard Hospital, Paris, France. ‘Results

from CLARIFY will provide important new clinical evidence to help improve the treatment of CAD and eventually save patients' lives', adds Prof Tendera, Medical University of Silesia, Katowice, Poland.

Commenting on behalf of Servier, who provided an educational grant for the registry, Jason Walden of Servier South Africa is hoping we will recruit some 1 000 patients, which will provide relevant data in the African setting.

CLARIFY will involve a minimum of 30 000 outpatients with stable CAD from around 40 countries worldwide, who will be followed for five years. These subjects

will be representative of CAD patients seen by cardiologists and primary-care physicians in daily clinical practice. The first patients will be enrolled in October 2009.

The registry will gather important information about the characteristics, management, outcomes and prognosis of CAD patients, with data collected prospectively at annual visits (12, 24, 36, 48 and 60 months). Patients will be evaluated not only on heart rate but also on their medical history, risk factors, and current chronic medical treatments, to name a few criteria. The overall aim of CLARIFY is to identify:

- the current profile of the CAD patient population, including demographics and clinical features
- the current daily treatment practices in CAD, and variations according to treatment setting and geography
- the clinical outcomes and changing patterns in stable CAD management during the five-year follow-up period.

CLARIFY will also determine long-term prognosis in this contemporary-treated stable patient population, with a view to developing a powerful and comprehensive risk-prediction model, including all potential prognostic factors, such as resting heart rate.

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