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Forthcoming cardiology meetings:

Heart Failure 2008

14th to 17th June 2008  Milan, Italy

European Society of Cardiology (ESC) Congress 2008

30th August to 3rd September 2008  Munich, Germany
Web site: www.escardio.org

5th Global Cardiovascular Clinical Trialists Forum (CVCT)

25th to 27th September 2008  Cannes, France
Web site: www.globalcvctforum.com

American Heart Association (AHA)

8th to 12th November 2008  New Orleans, USA
Web site: scientificsessions.americanheart.org
Heart rate is among the most fundamentally important of all physiological characteristics. It is one of the two primary determinants of cardiac output. Bodily function is directly dependent on the adequacy of the cardiac output; indeed, adequate cardiac output is a requisite for maintenance of life. Heart rate (or, more properly, peripheral pulse rate) variations have been associated with disease states for millennia, but the impact of heart rate variations on the pathophysiology of cardiac disorders has only been understood, to a greater or lesser extent, for a little over a century. Epidemiologically, the relation of heart rate to survival has been well demonstrated. Indeed, the highly significant direct association of heart rate with mortality, evidenced from epidemiological studies and actuarial data gathered by insurers, from long-term follow-up of patients with coronary artery disease, and from the effects of drugs in survivors of acute myocardial infarction and those with heart failure, strongly suggests the recognition of heart rate as a cardiovascular risk factor.

The potential benefits of modulating heart rate and, specifically, of heart rate slowing, have been demonstrated experimentally in animal models for decades, supported by epidemiological data in patients, and inferred from pharmacological interventions. However, until recently, heart rate–lowering interventions also have invariably affected other cardiac and systemic characteristics. Therefore, evaluation of the benefits of pure heart rate slowing could not previously be undertaken, because no available therapeutic modality was capable of producing such an isolated effect.

Nevertheless, the basis for pure pharmacological heart rate slowing had been well understood for more than a quarter century, since the discovery of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, or f-channels. These ion channels modulate the rate of rise of the spontaneous diastolic depolarization current of the specialized sinoatrial nodal cardiomyocytes, are responsive to hyperpolarization, and require the availability of cyclic adenosine monophosphate for their activation. The If current generated by the f-channels is of very low amplitude, but the effect of its modulation is striking. However, clinically useful pure heart rate slowing via f-channel blockade requires a drug that is specific for the channel, has no other cardiovascular effects, and has no untoward noncardiac actions that would limit its use in any important way. Attempts to develop such an agent began with the discovery of the channel, but the path to a practical therapy was arduous. The first drug with the relevant pharmacological and clinical characteristics was approved by regulatory bodies for marketing in 2005, 26 years after its target had been identified. This drug, ivabradine (Procoralan®), has now entered clinical practice in Europe and elsewhere.

The most obvious benefit of heart rate slowing is in preventing manifestations of coronary artery disease. The most common symptom of coronary artery disease, angina pectoris, affects almost 4% of the population of Europe, and has a similar prevalence in the United States. Angina is triggered by transient imbalances in myocardial oxygen supply and myocardial oxygen demand. Drugs that can cause heart rate slowing, such as β-adrenergic receptor blocking drugs and certain calcium channel blockers, have been highly efficient in preventing angina. However, these agents have additional cardiovascular effects, including vasodilation, reduction in inotropy and, in certain instances, reduction in lusitropy and dromotropy, that can mitigate clinical benefits. Also, like all drugs, they have other noncardiovascular effects that can reduce tolerability. Depending upon the specific type of drug, these can include constipation, abnormal fatigability, depression, sexual dysfunction, etc.

Heart rate slowing is particularly well suited for improving the balance between myocardial oxygen supply and demand. As a primary determinant of cardiac work, heart rate defines the heart’s metabolic requirements and is the single most important determinant of myocardial oxygen demand. However, it is less well appreciated that heart rate also modulates myocardial oxygen supply. Coronary blood flow is greatest during diastole; heart rate variations predominantly affect duration of diastole and, thus, impact on flow. Diastole increases disproportionately as heart rate slows, enabling progressively greater increments in coronary flow with constant decrements in heart rate. In addition, among patients with atherosclerotic narrowing of the coronary arteries, heart rate increase causes coronary constriction with parallel reduction in coronary flow, an effect potentially preventable with therapeutic heart rate slowing. Moreover, because its lack of negative inotropic effect precludes lengthening of systolic ejection time, ivabradine is more efficient than β-blockade in enhancing diastolic coro...
nary flow. Finally, recent experimental data suggest that heart rate reduction may stimulate angiogenesis, improving microvascular coronary flow, a further potential mechanism for mitigating inadequate myocardial oxygen supply.26

The effectiveness of ivabradine in preventing angina has been demonstrated in the largest clinical development program ever carried out for an antianginal anti-ischemic drug, involving almost 5000 patients in clinical trials. In these studies, ivabradine has been superior to placebo17 and equivalent to commonly used doses of atenolol14 and amlodipine.19 Indeed, in the formal comparison with atenolol 100 mg daily, ivabradine 7.5 mg twice daily was more efficient than atenolol, manifesting greater increment in treadmill exercise tolerance per decrement in heart rate than the more established drug, while demonstrating a parallel increase in time to electrocardiographic ST-segment depression, the measure of myocardial ischemia regularly employed in clinical studies.

Because of the profound effect of angina on capacity for work and recreation, angina prevention may be the most important therapeutic benefit of a drug that can mitigate ischemia. When tested formally, patients with angina report marked diminution in quality of life (QoL) compared with that of asymptomatic individuals. QoL scores correlate with the number of angina attacks experienced per week,20,21 and are impaired even by mild angina. Angina affects not only physical functioning, but also emotional well-being, quality of sleep and sexual function.22 Treatment-related reduction of angina is associated with improved QoL.21

Manifestations of coronary artery disease other than angina also may be mitigated by heart rate slowing, though additional data, from ongoing and future studies, must demonstrate that the theoretical and experimental data are confirmed in clinical practice. Thus, plaque rupture, which can trigger potentially lethal acute coronary events, is directly related to heart rate.23 The utility of pure heart rate slowing with ivabradine to prevent death and nonfatal infarction is now being assessed in the BEAUTIFUL trial (Systolic Heart failure treatment with the I inhibitor I Fradine Trial), which is assessing the effects of heart rate slowing on heart failure hospitalizations, mortality, symptomatic debility, and left ventricular function. At the time of writing, almost 1000 of the projected 5500 study patients with heart failure and systolic left ventricular dysfunction have been randomized, including patients with and without underlying coronary artery disease.

Early clinical studies suggest that these theoretical benefits may have practical clinical correlates. Thus, in patients with systolic dysfunction, a single intravenous dose of ivabradine preserved left ventricular performance despite heart rate reduction.27 In more recent unpublished studies, oral ivabradine administered for 3 months to a small group of patients with heart failure and systolic dysfunction tended to increase left ventricular ejection fraction, while reducing left ventricular end-systolic and end-diastolic volumes. These findings were most marked among patients with the lowest ejection fractions prior to therapy. The implications of these suggestive findings are now being explored more rigorously in the SHY/T trial (Systolic Heart failure treatment with the I inhibitor I Fradine Trial), which is assessing the effects of heart rate slowing on heart failure hospitalizations, mortality, symptomatic debility, and left ventricular function. At the time of writing, almost 1000 of the project- ed 5500 study patients with heart failure and systolic left ventricular dysfunction have been randomized, including patients with and without underlying coronary artery disease.

Taken together, rapidly emerging data support the concept that heart rate is a legitimate and important cardiovascular risk factor. In addition, they suggest that pure heart rate slowing can relieve symptoms and, perhaps, improve the natural history of patients with coronary artery disease and, possibly, with heart failure of any etiology. I inhibition is the only available therapeutic modality that can modulate the isolated risk factor to prevent angina and to determine if the other theoretical benefits can be translated into clinical practice.
References

What new insights is BEAUTIFUL expected to bring to clinical practice?

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What is the rationale for the BEAUTIFUL trial?

The BEAUTIFUL trial was developed in 2003 based on our knowledge of cardiovascular disease and its treatment. Since then, more recent data have further substantiated our reasoning.

Heart rate (HR) reduction provides important clinical benefits in patients with different subsets of coronary artery disease (CAD). Heart rate is a major determinant of oxygen consumption, and precipitates most episodes of ischemia, both symptomatic and silent. Resting heart rate has also been shown to be a strong predictor of overall and cardiovascular mortality in a wide range of patients, including patients with CAD and post-myocardial infarction (MI) patients (Figure 1A). In addition, recent data have shown that heart rate reduction in post-MI patients is essential for improvement of prognosis; with each 10 beats per minute (bpm) decrease in heart rate, the odds of cardiac death is estimated to be reduced by approximately 30% (Figure 1B).

Among current treatment options, beta-blockers have been shown to lower heart rate, improve cardiac function, and significantly reduce mortality and sudden cardiac death particularly in post-MI patients and in patients with heart failure. Experimental and clinical data have demonstrated that heart rate reduction is an important mediator of effects of beta-blockers on ischemia, left ventricular (LV) function, and in reduction in post-MI mortality. However, despite the availability of beta-blockers, resting heart rate may not be sufficiently controlled. In one study of data compiled in the Duke Databank for Cardiovascular Disease, patients with CAD had a mean heart rate of 70 bpm despite use of beta-blockers by 61% of patients. Furthermore, not all patients can take beta-blockers due to their side effects and contraindications (asthma, hypotension, and atrioventricular conduction disorders), and also because their blood pressure may be too low.

Based on this understanding of the importance of heart rate, we reasoned that patients with CAD and particularly those with left ventricular dysfunction (LVD) could derive benefits from further heart rate lowering. For this strategy we chose ivabradine, an I<sub>if</sub> inhibitor which provides pure heart rate reduction by a direct effect on the sinoatrial node without any effect

Figure 1. Effects of heart rate on cardiovascular mortality. A. Survival curve in patients with suspected or proven coronary artery disease. Over time, the odds of cardiovascular mortality survival decrease with increasing resting heart rate. Data were adjusted for age, gender, body mass index, hypertension, diabetes mellitus, cigarette smoking, clinically significant coronary vessel disease, ejection fraction, recreational activity, treatment with antiplatelets, diuretics, beta-blockers, and lipid-lowering drugs. B. Cardiac death curve in post-myocardial infarction patients: odds of cardiac death decrease with reductions in heart rate (P<0.001).
on other cardiac ionic currents.\textsuperscript{14-16} In clinical trials, ivabradine has been shown to produce dose-dependent improvements in ischemia and to be well tolerated, including in patients with LVD.\textsuperscript{17-19}

Thus, the BEAUTIFUL trial was designed to assess the morbidity mortality benefits of pure HR reduction with ivabradine above and beyond conventional treatment in CAD patients with associated LVD.\textsuperscript{20}

\section*{Why was ivabradine chosen for the BEAUTIFUL study?}

Ivabradine was chosen as a treatment because it met our criteria as an efficacious pure HR-lowering agent with good tolerability and combinability.

Ivabradine selectively lowers heart rate leading to a powerful anti-ischemic efficacy.

Ivabradine is the first of a new class of HR-lowering agents that act specifically on the sinoatrial node. Ivabradine lowers heart rate by selective inhibition of the I\textsubscript{f} current of the cardiac pacemaker without affecting other cardiac ionic currents.\textsuperscript{14-16}

Consistent with this mechanistic understanding, ivabradine lowers heart rate, which reduces the myocardial oxygen demand. Moreover, unlike beta blockers, ivabradine fully preserves myocardial contractility and relaxation, thereby increasing the diastolic perfusion time.\textsuperscript{21} During exercise, the alpha receptor-mediated coronary vasoconstriction observed with beta-blockers is not observed with ivabradine, which can result in increased coronary blood flow during exercise.\textsuperscript{22} This results in maximization of myocardial oxygen supply.

The clinical benefits of pure heart rate reduction with ivabradine have been tested in the largest development program for any anti-ischemic agent in chronic stable angina. In patients with stable angina, exercise tolerance and time to limiting angina during exercise were significantly improved with ivabradine compared with placebo. The antianginal and anti-ischemic efficacy of ivabradine has also been compared with that of beta blockers (Figure 2), and calcium channel blockers.

In patients with LVD, a preliminary analysis of a 3-month trial demonstrated an improved myocardial performance with ivabradine treatment: left ventricular volumes were smaller in patients treated with ivabradine than in patients treated with placebo.\textsuperscript{23}

These effects are consistent with those observed in experimental models where long-term treatment with ivabradine modified the extracellular matrix and the function of myocytes, thereby leading to improved left ventricular function, increased stroke volume, and preserved cardiac output.\textsuperscript{24}

\section*{What is the goal of the BEAUTIFUL trial?}

We designed BEAUTIFUL to determine if lowering resting heart rate by adding ivabradine treatment to pre-existing therapy will reduce cardiovascular morbidity and mortality in patients with documented CAD and left ventricular systolic dysfunction.\textsuperscript{25} This study is a landmark trial because it will be the first to assess the effect of pure heart rate reduction on cardiovascular outcome. We are particularly interested in determining if ivabradine treatment on a background of beta-blockers will further reduce morbidity and mortality.

\section*{What is the design of the study?}

BEAUTIFUL is a large, double-blind, randomized, placebo-controlled trial. After a 2-week run-in period, patients were ran-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Effects of treatment on total exercise duration at trough of drug activity. Abbreviations: ate; atenolol; bid, twice daily; CI, confidence interval; Iva, ivabradine; M, month; noninf, noninferiority; od, once daily.\textsuperscript{26}}
\end{figure}
What patient population is included in the study?

We designed the inclusion and exclusion criteria to identify a group of patients who have documented, stable CAD and LVD, normal sinus rhythm, and who are being treated for cardiovascular disease.24

Patients were included if they were ≥55 years of age. Diabetic patients, type 1 or 2, could be enrolled if they were ≥18 years of age. Patients needed to have documented stable CAD, a resting heart rate ≥60 bpm with a normal sinus rhythm, a left ventricular ejection fraction 39%, and a left ventricular dilatation at the end of diastole > 56 mm. Patients had to be following a stable, conventional treatment for cardiovascular disease. This treatment had to be considered optimal by the investigator.

The main exclusion criteria were related to the stability and severity of the CAD. Patients were not included if they had had an MI or coronary revascularization within 6 months of randomization; if they had a history of stroke or cerebral transient ischemic attack within the previous 3 months; if they had severe liver or renal disease, or if they were planning on having a revascularization procedure. Patients were also excluded if they had severe symptoms of heart failure (NYHA IV), severe or uncontrolled hypertension (systolic blood pressure/diastolic blood pressure >180/110 mm Hg), sick sinus syndrome, sinoatrial block, congenital long QT, complete atrioventricular block, valvular disease that might require surgery within the next 3 years, or if they had a pacemaker implanted or an implantable cardioverter defibrillator.

Was the recruitment in line with the study design?

We have recruited 10 917 patients across 781 centers in 33 countries. Based on our preliminary analysis,27 we know that the mean age of the population is 65 years, with 83% male, 88% of patients have a history of MI, and that the mean ejection fraction is 32.3%. Diabetes mellitus is present in 37% of patients and metabolic syndrome in 40%. A large proportion of patients are taking beta-blockers (87%). Other/additional medications include antithrombotics (94%), usually aspirin (84%), angiotensin-converting enzyme inhibitors or angiotensin receptor blocker (89%), lipid-lowering drugs (76%).

Thus, our baseline data suggest that using our inclusion and exclusion criteria we have been able to identify a group of CAD patients as intended in our design and who, for the most part, are receiving substantial cardiovascular therapy. According to the most recent European Society of Cardiology guidelines, these patients, at baseline, can be considered as optimally and adequately treated.28 Thus, any benefit that would be obtained with ivabradine would be beyond the benefits of these ‘established’ preventive therapies.
When do you expect the results of the study?

The study has been completed and we are currently analyzing the results, which will be presented at the ESC Congress in September 2008.

What is the importance of the expected results in clinical practice?

If the results, as expected, show that ivabradine treatment reduces morbidity and mortality in patients with resting heart rates above 60 bpm despite conventional therapy, this trial will constitute a breakthrough in treatment strategies for patients with CAD with LVD.

References

Optimization of pharmacotherapy of angina pectoris: maximizing the chronotropic reserve

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The patient, a 52-year-old male, had suffered from occasional effort-induced chest pain since 2002, but had not consulted a doctor. In February 2005, he was admitted to the local general hospital because of worsening angina symptoms: angina attacks occurred after walking 30 to 50 meters. Coronary angiography was recommended, and the following medications were prescribed: aspirin 125 mg/day, simvastatin 10 mg/day, perindopril 2 mg/day with up titration to 8 mg/day, metoprolol 25 mg bid, and isosorbide dinitrate 40 mg/day. In hospital, the patient was angina-free and felt comfortable.

However, one month after discharge from the hospital, decrease in blood pressure was accompanied by dizziness and weakness (before the start of treatment, blood pressure was normal). Limiting effort angina recurred. Despite withdrawal of angiotensin-converting enzyme (ACE) inhibitor and reduction of the isosorbide dinitrate dose to 20 mg/day, the patient’s blood pressure remained 100-90/70-60 mm Hg. The frequency of angina attacks was rather high (3 to 6 per day depending on the intensity of physical exercise) and it was not possible to up titrate dosage of beta-blocker because of low blood pressure. The patient was reluctant to undergo angiography and was referred to the Cardiology Department of the City Clinical Hospital for correction of therapy.

Life history

The patient is a nonsmoker whose alcohol consumption is moderate. There is no family history of cardiovascular disease.

Physical examination

Height 158 cm, weight 48 kg, body mass index 19.3 kg/m². There were no symptoms of heart failure. Blood pressure in the supine position was 100/70 mm Hg, and heart rate was 63 bpm.

Laboratory tests

Total cholesterol 3.88 mmol/L, LDL cholesterol 2.64 mmol/L, triglycerides 0.66 mmol/L, HDL cholesterol 1.03 mmol/L, glucose 4.5 mmol/L.

Instrumental tests

Echocardiography indicated an end-diastolic volume of 80 mL, end-systolic volume 30 mL, interventricular septum thickness 1.1 cm, left ventricular (LV) posterior wall thickness 1.16 cm. LV ejection fraction was 52%. Resting ECG indicated sinus rhythm, no signs of myocardial infarction, HR 63 bpm.

Exercise testing was positive (Figure 1): at 75 W at 1 min 46 s (HR 121 bpm, blood pressure 120/75 mm Hg), there was onset of angina and dyspnea. ECG showed ST-segment depression in leads II, III, aVF, V4-V6. Down-sloping ST-segment depression and wave T inversion appeared at the 10th minute of the recovery period. Total exercise duration was 4 min 46 s, maximal workload 275 W.

Therapy correction

Isosorbide dinitrate was discontinued as it is known to have a potent blood pressure-lowering effect. Use of short-acting nitroglycerin was recommended before exertion or immediately during an angina attack. Metoprolol dosage could not be increased because of symptomatic arterial hypotension. Taking into account the persistence of effort-induced angina pectoris, which was limiting the patient’s daily activities, we decided to replace metoprolol by ivabradine 5 mg bid.

Results of treatment

Several days after the start of ivabradine therapy, the patient noted significant reduction in the frequency of angina attacks. HR decreased to 54 bpm, blood pressure normalized (120/70 mm Hg), dizziness disappeared.

After 1.5 months of ivabradine treatment, exercise tolerance improved: total exercise duration increased to 5 min 33 s and maximal workload to 337 W. Exercise testing was stopped at 75 W at 2 min 33 s because of the patient’s exhaustion. At peak exercise, ECG showed ST-segment depression of 1.5 mm in lead V5 only (Figure 2). The ST-segment depression at 1 min 40 s and 75 W was 0.6 mm, which was much less than in the first exercise test. Rate-pressure product increased by 27.2%, total exercise duration by 18.9%, and maximal workload by 22.7%.
Figure 1. Baseline exercise test.

Figure 2. Exercise test after prescription of ivabradine.
Discussion

This clinical study highlighted the importance of the increase in chronotropic reserve of the heart provided by ivabradine, which leads to a significant antianginal effect and increased exercise tolerance. This could not be achieved by traditional medications with negative chronotropic effects, because they also decrease blood pressure.

It is necessary to emphasize that heart rate reduction by ivabradine leads to increased coronary blood flow during exercise due to prolongation of diastolic time (Figure 3) and preservation of coronary vasodilation (Figure 4). This is a major advantage of ivabradine compared with beta-blockers, which are known to unmask $\alpha_2$-vasoconstrictor tone. The increase in coronary blood flow with ivabradine during exercise could be one reason why an 18% increase in total exercise duration was observed when this patient was switched from metoprolol to ivabradine.

The pharmacological properties of ivabradine therefore seem to offer a unique opportunity for the treatment of stable effort-induced angina pectoris. The importance of ischemia reduction was confirmed in the Total Ischemic Burden Bisoprolol Study, which showed an inverse correlation between the frequency of ischemic episodes and survival (Figure 5).

Low heart rate is associated with better prognosis, including in patients with coronary artery disease. Conversely, high heart rate promotes atherogenesis and coronary plaque disruption.

The ongoing MorBidity-mortality EvAIuAtion of the $\beta$ inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) study is evaluating the morbidity-mortality benefits of pure heart rate reduction with ivabradine in coronary artery disease patients with associated left ventricular dysfunction.
References

New solution for angina patients needing a new therapeutic approach

Presentation and composition: Procoralan 5 mg: film-coated, scored tablet; Procoralan 7.5 mg: film-coated tablet. Indication: Symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contraindication or intolerance for β-blockers. Dosage and administration: The starting dose is 5 mg orally twice daily, during meals: breakfast and dinner. The dose can be increased to 7.5 mg twice daily after 1 month of treatment, depending on the therapeutic response. If heart rate decreases persistently below 50 beats per minute (bpm) at rest, treatment should be downtitrated to 2.5 mg twice daily. Properties: Procoralan is a pure heart rate–lowering agent, acting by a selective inhibition of the cardiac pacemaker If current that controls spontaneous depolarization in the sinus node and regulates heart rate. Procoralan dose-dependently reduces heart rate and provides significant anti-ischemic and antianginal efficacy.

Contraindications: Hypersensitivity to Procoralan, resting heart rate below 60 bpm prior to treatment, cardiogenic shock, acute myocardial infarction, severe hypotension, sinoatrial block, third-degree AV block, severe heart failure (NYHA class III-IV), severe hepatic insufficiency (in the absence of data), pregnancy and lactation (in the absence of data), coadministration with a strong CYP 3A4 inhibitor.

Interactions: Combination with heart rate–reducing agents, combination with QT-prolonging medicinal products, CYP 3A4 inhibitors and inducers.

Precautions: Use with caution in patients with severe renal insufficiency (creatinine clearance <15 mL/min), use with caution in patients with second-degree AV-block, with cardiac arrhythmias, or stroke. Side effects: Phosphenes, bradycardia, ventricular extrasystoles, headache. Presentation: Pack of 56 tablets of Procoralan 5 mg, Pack of 56 tablets of Procoralan 7.5 mg. Please refer to the complete summary of product characteristics for your country, as country-specific variations may exist.


Procoralan provides all the benefits of pure heart rate reduction:

- Effective heart rate reduction of 10 to 14 bpm
- 66% reduction in anginal attacks and significant improvement in patients' effort capacity
- Free from effects on vasoconstriction and myocardial contractility

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