

# The BEAUTIFUL Study

## – Backgrounder –

### About the BEAUTIFUL study

The BEAUTIFUL (MorBidity-mortality EvAIUaTion of the I<sub>f</sub> inhibitor Procoralan in patients with coronary disease and left ventricULar dysfunction) study evaluated the benefits of Procoralan (ivabradine) in reducing cardiovascular events in patients with coronary artery disease (CAD) receiving current preventative therapy. It is the first trial to assess the cardiovascular benefits of pure heart rate reduction in coronary patients, over and above conventional treatment. BEAUTIFUL is a large international study being carried out at 781 centres worldwide. It was initiated in December 2004 and the first patient was enrolled in early 2005. 10,917 patients from 33 different countries, across four continents were enrolled in the BEAUTIFUL study. The first results were presented at the ESC Congress in 2008.

### Main findings

Important findings from BEAUTIFUL that were presented in 2008 have shown that:<sup>1</sup>

- Coronary patients with associated left ventricular dysfunction (LVD) who have a heart rate more than 70 bpm are at significantly higher risk of cardiovascular death, MI and heart failure. This raised risk is independent of all other risk factors or concomitant treatments
- In CAD patients with a heart rate  $\geq 70$  bpm, Procoralan significantly reduces important coronary events like MI (by 36%,  $P = 0.001$ ) and coronary revascularisation (by 30%,  $P = 0.016$ )

### New results – important benefits in angina patients

Results from a new subgroup analysis of patients in the BEAUTIFUL study with limiting angina showed that overall, Procoralan reduced the risk of the combination primary endpoint – cardiovascular death, hospitalisation for acute MI or new or worsening heart failure – by 24% ( $P = 0.048$ ) in all angina patients, and by 31% ( $P = 0.06$ ) in those with a heart rate  $\geq 70$  bpm.

Procoralan dramatically reduces hospitalisation for heart attack and coronary revascularisation, with particular benefits for patients with a heart rate  $\geq 70$  beats per minute (bpm). The risk of hospitalisation for acute or non-fatal myocardial infarction (MI) was reduced by 42% ( $P = 0.022$ ) in angina patients treated with Procoralan.

This benefit was even more striking in those with a high heart rate, where hospitalisation for heart attack was reduced by 73% (P = 0.02). The need for coronary revascularisation was also reduced in patients receiving Procoralan treatment, decreasing by 30% (P = 0.397) in all angina patients and by 59% (P = 0.04) in those with a heart rate  $\geq 70$  bpm.

A total of 1507 patients with angina were included in this BEAUTIFUL subgroup analysis. Of these, 734 patients were treated with Procoralan, while 773 received placebo. Nearly all patients were additionally receiving conventional treatment aimed at protecting against cardiovascular events, with approximately nine out of every 10 patients on beta blockers.

### BEAUTIFUL design

BEAUTIFUL is an international, multicentre, randomised, double-blind, placebo-controlled, two-arm trial. The study was set up to show the superiority of Procoralan over placebo in reducing:

- Cardiovascular mortality
- Hospital admission for acute MI
- Hospitalisation for new-onset or worsening heart failure.

Together these outcomes make up the study's primary endpoint. BEAUTIFUL is also examining the effects of elevated heart rate ( $\geq 70$  beats per minute) on cardiovascular events in CAD patients.

### *Objectives*

BEAUTIFUL has two key objectives:

- I. To explore the benefits of Procoralan in reducing cardiovascular events in CAD patients receiving current preventative therapy, such as beta blockers
- II. To explore the role which heart rate plays in determining the risk of cardiovascular events.

### Participating patients

BEAUTIFUL focused on patients who are likely to benefit from the heart rate-lowering effect of Procoralan and who are at high risk of experiencing a cardiovascular event. This includes CAD patients with sinus rhythm and left ventricular systolic dysfunction (LVD). Coronary patients with LVD were chosen because LVD has a dramatic and negative effect on survival.<sup>2,3</sup>

Specific inclusion criteria for the BEAUTIFUL study were:

- Male or female

- Non-diabetic  $\geq 55$  years, or diabetic  $\geq 18$  years
- Documented CAD
- Sinus rhythm and resting heart rate higher than 60 beats per minute
- Documented left ventricular systolic dysfunction ( $<40\%$ )
- Clinically stable for three months in terms of angina or heart failure symptoms, or both
- Therapeutically stable for one month, with appropriate or stable doses of conventional medication.

According to the BEAUTIFUL study protocol, patients underwent baseline evaluation before being randomised to one of the two treatment arms – i.e. double-blind Procoralan or placebo. After a two-week run-in period, Procoralan or placebo were started at a dose of 5 mg twice daily in all patients. If heart rate was  $\geq 60$  bpm after 2 weeks of treatment, this dose was increased to the target of 7.5 mg twice daily. Similarly, if a patient's heart rate dropped below 50 bpm or there were signs of bradycardia, the patient was discontinued from the trial. Similar heart rate assessments were performed at each study visit with the aim of maintaining heart rate between 50 and 60 bpm for 18 to 36 weeks for each patient.

#### *Clinical characteristics*

Of the 10,917 CAD patients participating in BEAUTIFUL, 83% are male and the average age is 65 years. Patients' average resting heart rate was 71.6 bpm at baseline, mean BP was 128/77.5 and the average body mass index was 28.5. Overall, half of patients had a resting heart rate slightly above 70 bpm. Heart rate was lower in patients taking beta blockers, 71.1 bpm versus 74.1 bpm on average.

In terms of baseline comorbidities, 70% of patients had a history of hypertension, 88% had suffered a heart attack (6.1 years ago on average) and 52% had undergone previous coronary revascularisation. All patients enrolled in BEAUTIFUL were also receiving optimal guidelines-based treatment for their CAD. This background therapy included high prescription rates of ACE inhibitors (80%), angiotensin receptor blockers (11%), anti-thrombotic agents (94%), lipid-lowering drugs (76%), beta blockers (87%) and diuretics. These preventative treatments are all aimed at reducing the risk of cardiovascular events in CAD patients.

## Rationale for BEAUTIFUL?

BEAUTIFUL was conceived on the basis of strong evidence supporting the role of resting heart rate in predicting mortality in CAD and heart attack patients:

- CASS registry data from nearly 25,000 patients followed-up for 14.1 years prove that heart rate is an important prognostic factor in CAD<sup>4</sup>
- All-cause and cardiovascular mortality, as well as rehospitalisations, were increased in patients with high heart rate
- This association between heart rate and total mortality was seen in all analysed subgroups.

There is also a wealth of data showing that cardiovascular benefits can be gained from preventative therapy to reduce resting heart rate:

- Beta blockers decrease heart rate, improve cardiac function and reduce cardiovascular events in postmyocardial infarction patients and in heart failure patients<sup>5</sup>
- Experimental and clinical data have demonstrated that heart rate reduction is the main mechanism by which beta blockers reduce ischemia, improve left ventricular function and reduce post-MI mortality<sup>6,7</sup>
- A meta analysis of randomised clinical trials suggests that the beneficial effects of beta blockers and some calcium channel antagonists in post-MI patients are proportionally related to resting heart rate reduction. Each 10 bpm decrease in heart rate was associated with a 30% drop in cardiovascular mortality<sup>6</sup>

Despite this overwhelming evidence for the role of heart rate in predicting cardiovascular events, current heart rate lowering intervention in CAD patients is suboptimal. Resting heart rate may not be sufficiently controlled on beta blocker therapy and prescribed doses are often too low.<sup>8</sup> The ability to reach target heart rate is also compromised by beta blockers' side effects such as low blood pressure and impotence which result in poor long-term compliance.<sup>9</sup>

BEAUTIFUL was devised to assess if further heart rate lowering with Procoralan on top of conventional background therapy could be beneficial in patients with CAD, particularly those with LVD.

## Why Procoralan?

Procoralan is the first selective and specific inhibitor of the sinus node I<sub>f</sub> current. It was selected for BEAUTIFUL as it is an efficient and exclusive pure heart rate lowering agent with good tolerability. Procoralan acts specifically on the sinoatrial node and lowers heart rate by selectively inhibiting the I<sub>f</sub> pacemaker current, without affecting other cardiac ionic currents. It is the first agent to provide effective pure heart rate reduction while maintaining myocardial contractility, atrioventricular contraction and ventricular repolarisation.

The anti-anginal and anti-ischemic efficacy of Procoralan has been proven in the clinical development program.<sup>10,11,12,13</sup>

Procoralan has also demonstrated excellent tolerance and a good safety profile.

## References

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