

Frequently Asked Questions

1. What is Procoralan?

Procoralan is the first selective and specific inhibitor of the sinus node I_f current. This is part of the heart's natural pacemaker and one of the most important currents involved in generating and controlling heart rate. Because of its unique mode of action, Procoralan is able to provide effective pure heart rate reduction while maintaining myocardial contractility, atrioventricular contraction and ventricular repolarisation. Procoralan exclusively reduces heart rate and does not affect other important cardiac currents. The contraction of the heart, as well as blood pressure, are all preserved.

2. What is the BEAUTIFUL trial?

The BEAUTIFUL (MorBidity-mortality EvAlUaTion of the I_f inhibitor Procoralan in patients with coronary disease and left ventricULar dysfunction) trial is a study evaluating 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, above and beyond conventional treatment. BEAUTIFUL was carried out at 781 centres worldwide. 10,917 patients from 33 different countries, across 4 continents were enrolled in the BEAUTIFUL study. The first results were presented at the ESC in Munich in 2008.

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

3. What were the main findings of this study?

Important findings from the BEAUTIFUL trial presented in 2008 showed that:

- 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, myocardial

- infarction (MI) and heart failure. This raised risk is independent of all other risk factors or concomitant treatments
- In CAD patients with a heart rate ≥ 70 bpm, Procoralan significantly reduces important coronary events like MI (by 36%, $P = 0.001$) and coronary revascularisation (by 30%, $P = 0.016$)

4. What is the new analysis presented at this year's European Society Cardiology Congress?

The new data is from a subgroup analysis of 1507 patients in the BEAUTIFUL study with limiting angina.

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 already on beta blockers.

5. Why was the new analysis in angina patients done?

Patients with angina have a higher risk of having a heart attack compared to those without angina. However there is less data available with the current anti-anginals in the reduction of cardiovascular events in angina patients. Procoralan is a powerful anti-anginal and as the BEAUTIFUL study has more than 1,500 patients with limiting angina, this analysis was undertaken to assess the effect on Procoralan in the reduction of cardiovascular events in these patients.

6. What do the new findings show?

The results from a subgroup analysis of patients in the BEAUTIFUL study with limiting angina showed that:

- Procoralan reduced the primary endpoint – a combination of cardiovascular death, myocardial infarction (MI) and heart failure – in all angina patients by 24% ($P = 0.048$)
- This drop in risk was 31% ($P = 0.06$) in patients with a high heart rate
- Hospitalisations for acute or non-fatal MI were also reduced by 42% ($P = 0.022$) with Procoralan

- This benefit was even more striking in angina patients with a heart rate ≥ 70 bpm, where the risk of MI was cut by 73% ($P = 0.02$)
- The need for coronary revascularisations was also reduced with Procoralan treatment, decreasing by 30% ($P = 0.397$) in all angina patients and 59% ($P = 0.04$) in those with a heart rate ≥ 70 bpm.

7. What were the results in patients with elevated heart rate (≥ 70 bpm)?

The benefit of Procoralan was even more striking in angina patients with a heart rate ≥ 70 bpm. In these patients, the risk of MI was cut by 73% ($P = 0.02$). The need for coronary revascularisations was also reduced with Procoralan treatment, decreasing 59% ($P = 0.04$) in those with a heart rate ≥ 70 bpm.

8. Why is heart rate important?

A large body of evidence from epidemiological studies and clinical trials has shown that elevated resting heart rate is associated with a significantly increased risk of heart attack and death in patients with CAD. Heart rate is a major determinant of oxygen consumption and can precipitate most episodes of ischemia, both symptomatic and silent. Because of this emerging role as a risk factor for CAD, resting heart rate is becoming an important consideration for clinicians when choosing optimal therapy for CAD patients. Lowering the resting heart rate in patients with CAD reduces the heart's oxygen requirements and may have beneficial effects in terms of reducing cardiovascular events.

9. Why are results better in angina patients than overall BEAUTIFUL patient population?

Among angina patients, the risk of coronary events like myocardial infarction is much higher than in the overall BEAUTIFUL population. As Procoralan has a powerful effect on the reduction of coronary events, it's not surprising that the benefits are higher for those at a high risk of coronary events. These results reinforce the place of Procoralan in the treatment of angina patients. The clinical implication of these results is that Procoralan should be used for all angina patients as it not only has powerful anti-ischemic efficacy, but also prevents cardiovascular events.

10. Can Procortalan be used in all angina patients, not just those suffering from left-ventricular dysfunction?

Procortalan has demonstrated powerful anti-ischemic and anti-anginal efficacy in coronary patients irrespective of their ejection fraction. Other anti-anginal have not demonstrated the ability to reduce myocardial infarction and cardiovascular death even in angina patients with left ventricular dysfunction. As Procortalan is very effective in reducing coronary events, angina patients with preserved ejection fraction are likely to benefit even more. Therefore, Procortalan can be prescribed first-line to all angina patients.

11. Can Procortalan be used in patients taking other medication?

Yes, Procortalan has also demonstrated excellent tolerance and a good safety profile in all the clinical studies and can be safely co-administrated with most routinely used cardiovascular drugs.