

Elevated heart rate proven to increase coronary events

Ivabradine shows benefit in coronary artery disease patients with left ventricular dysfunction and an elevated heart rate



Kim Fox

Ivabradine, the only pure heart rate-reducing agent registered for anti-anginal and anti-ischaemic properties, has provided a unique opportunity to test and quantify the hypothesis that elevated heart rate increases cardiac risk. It has also highlighted its own value in the setting of increased heart rate.

In the overall population of coronary artery disease (CAD) patients with left ventricular systolic dysfunction (LVD) and normal sinus rhythm included in the BEAUTIFUL study, treatment with ivabradine did not result in a significant reduction of the primary composite endpoint of cardiovascular death, namely admission to hospital for acute myocardial infarction (MI) and for heart failure.¹

However, in those patients whose heart rate remained high [above 70 beats per minute (bpm)] despite being well managed and also on beta-blocker therapy (87%), the addition of ivabradine therapy resulted in a reduced risk of hospitalisation for fatal and non-fatal MI and a reduced risk of undergoing revascularisation procedures.

‘These patients with elevated heart rates are at increased risk of virtually every cardiovascular event you can think of. In this setting, ivabradine shows huge promise and it will be further tested in this patient group in additional prospective trials such as SIGNIFY and SHIfT’, Prof Fox noted.

The increase in overall cardiovascular risk in patients with heart rates of 70 or more beats per minute, from the placebo arm of the study, was shown to be 34% for cardiovascular death, 46% for myocardial infarction, 56% for heart failure and 38% for coronary revascularisation.² Ivabradine can offset this increased risk of elevated heart rate, as the BEAUTIFUL results suggest, with a 36% reduction in risk of hospitalisation for fatal and non-fatal MI and a 30% reduction in the risk of cardiac revascularisation.

‘This is a very important benefit and is commensurate with ivabradine’s anti-anginal and anti-ischaemic action’, Prof Fox pointed out. ‘At this juncture therefore, with the knowledge we as clinicians currently have at our disposal, we should consider ivabradine for use in conjunction with beta-blockade in this population group’, he recommended.

Chairman of the investigator team, Prof Kim Fox from the Royal Brompton Hospital, London, and co-investigators released the detailed results of this study were on 31 August 2008 in the hot-line session at the European Society of Cardiology congress held in Munich.

The BEAUTIFUL study (morbidity–mortality Evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) was initiated in December 2004, under the guidance of an independent executive committee, with the first patient being enrolled in early 2005. CAD patients (10 917) with LVD were recruited in 781 centres in 33 countries across four continents.

The study was prompted by the introduction of ivabradine (approved by the European Medicines Evaluation Authorities in 2005), which specifically inhibits the I_f current in the sinoatrial node, thus offering an opportunity to assess the effect of lowering heart rate without otherwise directly affecting cardiac function. ‘It causes pure heart rate reduction without any effect on the catecholamines, so for the first time this has allowed us to explore pure heart rate reduction’, Prof Fox explained.

While there may be some disappointment that the study’s primary endpoint of significant reduction in cardiovascu-



Phillippe Gabriel Steg

lar death and hospitalisation for acute myocardial infarction or new-onset or worsening heart failure was not reached, the protocol had pre-specified the analysis of two heart rate groups. One group contained patients with heart rates below 70 bpm, and the other with heart rates above this level, following the results of the INVEST trial.³ The mean heart rate of the patients in the BEAUTIFUL study was 71 bpm and half of the patients had a heart rate of more than 70 bpm.

Prof Kim Fox also pointed out that patients in the study were receiving the best background management therapy ever seen in a CAD clinical trial. Ninety-four per cent of the patients were on anti-thrombotic treatment, mainly aspirin, 74% were on a statin and 90% were on either an ACE inhibitor or an angiotensin receptor blocker (ARB) and, as mentioned, beta-blocker usage was high (87%).

Overall, according to the investigators, the patients were sicker than initially envisaged, with very few patients in NYHA class I (14%), most being in class II, and with a high rate of patients with diabetes (20%) and hypertension (70%). The mean left ventricular ejection fraction rate was 32%. This led to a higher event rate than initially planned and a minor change in the protocol from event driven to time driven, in order to ensure that the last patients recruited were evaluated for a minimum of 12 months. ‘This

may help to explain the lack of benefit in the primary endpoint, as hospitalisation for heart failure largely dominated this endpoint', Prof Fox said.

A high event rate in CAD is still reflected in ordinary clinical practice, in, for example the REACH registry, and highlights the need to improve outcomes for patients with stable coronary artery disease. This was noted by Prof Philippe Steg, director of the Coronary Care Unit, Claude Bichat-Bernard Hospital, Paris. 'In the REACH registry⁴ of clinical practice in Europe, we are still seeing annual cardiovascular mortality, myocardial infarction, stroke and annual hospitalisation for atherothrombotic events of 15% in CAD patients treated as outpatients', he said.

'In clinical practice it is very difficult to achieve a full dose of beta-blocker and the positive lesson from this study is that ivabradine can be safely used in addition to beta-blockers. Ivabradine was well tolerated and adverse effects were the same as with placebo, rarely leading to discontinuation of therapy', Prof Steg noted.

Heart rate increases cardiac risk – evaluation of the placebo arm of BEAUTIFUL

As part of the BEAUTIFUL study, the placebo arm of the study was used to quantify the effect of heart rate increases on cardiovascular events in this population.² After adjustment for baseline char-

acteristics, patients with heart rates of 70 bpm or more had increased risk for cardiovascular death (34%, $p = 0.0041$), hospital admission for heart failure (53%, $p < 0.0001$), for myocardial infarction (46%, $p = 0.0066$) and for coronary revascularisation (38%, $p = 0.037$).

For every increase of 5 bpm in heart rate, there were increases in cardiovascular death (8%, $p = 0.0005$), hospital admission for heart failure (16%, $p < 0.0001$), for myocardial infarction (7%, $p = 0.052$) and for coronary revascularisation (8%, $p = 0.034$). Further analysis of finer groupings of heart rate suggested that the increase in mortality and heart failure outcomes rose continuously above 70 bpm, whereas the relation was less pronounced for coronary outcomes.

Comment from South African experts attending the European Society of Cardiology congress

Dr Naomi Rapeport, specialist physician, private practice, Milpark Hospital, Johannesburg

I think, firstly, it is important to reflect on where we have come from with regard to treatment of left ventricular dysfunction and heart failure. In the 1990s, at the time of the introduction of ACE inhibitors, the SOLVD trial using enalapril treatment over a maximum period of 48 months resulted in an increased life expectancy of less than five months over those patients on placebo.

Today, our patients with heart failure are better treated and are living longer, making it more difficult for studies such as BEAUTIFUL to show benefits over a relatively short period of time. Consequently, even within the context of a neutral study, these findings are relevant to improving our understanding and therapy of heart failure.

The results of this trial with ivabradine are consistent with the drug's current registration for angina in CAD patients. Ivabradine's reduction of events of an ischaemic nature in this trial is supportive of this registration.

Dr Colin Schamroth, cardiologist, private practice, Milpark, Johannesburg

This was an extremely well treated group

of patients, probably the best treated of any trial to date. Also, the study was conducted over a relatively brief period of time, but it is reassuring that our current strategies, which are reflected in the so-called placebo group, are working.

The question as to whether the patients were treated adequately to the recommended target dose of the beta-blocker selected was answered by the investigators in broad terms only; no further data were supplied on dosages in the published article. The investigators said that patients were not under-treated with beta-blockers but that they were frequently not able to up-titrate the beta-blocker to recommended levels due to side effects such as hypotension, impotence and fatigue.

In my experience, there are clear limitations on how far you can up-titrate beta-blockers. I would therefore consider the additional use of ivabradine, when available in South Africa, in well-treated coronary artery disease patients with ischaemic symptoms and relative tachycardia. The safety of ivabradine is good, with very few patients experiencing symptomatic bradycardia (146 of 5 744 patients), while discontinuation of therapy due to protocol-predetermined bradycardia of 50 bpm (patients who were asymptomatic) occurred in 13%.

While one would prefer to see trials over longer periods of time and therefore with long-term benefits, in the results of this particular study I am sure the reductions in myocardial infarction and the need for revascularisation will translate into long-term benefit. It would be preferable though to see an ongoing, open-label surveillance and report of the outcomes for patients in this study, as has been done with other studies.

Implications of the study on heart rate and risk for coronary events

Dr Colin Schamroth

I think that we have got to actively start monitoring heart rate in our coronary artery disease patients. In those without left ventricular dysfunction, heart rate should be considered as a marker of risk, and in those with left ventricular dysfunction, as a risk factor. Good standards for measuring heart rate have been published by the European Hypertension Society. This is important, as the BEAUTIFUL study is the first prospective study looking at heart rate, and the results are compelling. None of the previous beta-blocker studies have targeted heart rate prospectively or as a specific target of therapy. The definition of tachycardia

may also require redefinition to a lower rate (eg, 90 bpm at rest) rather than our much earlier definition of 100 bpm.

Dr Naomi Rapeport

We will have to examine this parameter of risk more closely. Perhaps we already have a useful opportunity with the 24-hour Holter blood pressure measurements, which also record heart rate, and this could be correlated with periods of rest. Seeing the results of this study raises the question as to whether the results would have been more definitive if a

higher cut-off heart rate had been chosen, such as 80 bpm. The SIGNIFY study will be of great interest in this regard.

1. Fox K, Ford I, Steg PG, on behalf of the BEAUTIfUL investigators. *Lancet*, published online 31 August 2008. DOI:10.1016/S0140-6736(08)61170-8.
2. Fox K, Ford I, Steg PG, on behalf of the BEAUTIfUL investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left ventricular dysfunction: a subgroup analysis of a randomised controlled trial. *Lancet*, published online. DOI:10.1016/s0140-6736(08)61171-X.
3. Kolloch R, Legler UF, Champion A, *et al.* Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease; findings from the International Verapamil-SR/Trandolapril study. *Eur Heart J* 2008; **29**: 1327–1334.
4. Steg PG, Bhatt DL, Wilson PW, *et al.* One-year cardiovascular event rate in outpatients with atherothrombosis. *J Am Med Assoc* 2007; **297**(1): 1197–1206.
5. SOLVD investigators. *Am J Cardiol* 1990; **66**: 315–322.

Report compiled by JAalbers, C Schamroth and N Rapeport.
