

# SHIFTING the burden of heart failure

## Ivabradine, the pure heart rate-lowering drug, shown to reduce morbidity and mortality in heart failure

‘The results of the SHI<sub>T</sub> study, announced this week at the European Society of Cardiology (ESC) 2010 congress in Stockholm, are likely to change the clinical treatment of chronic heart failure as they provide the first positive results for many years in this difficult field of treatment. The great interest in the outcome of this study was evident from the large number of delegates attending this hot-line session on the first day of the congress.

SHI<sub>T</sub> has now shown for the first time that treatment with ivabradine, added to close-to-optimal guideline-directed therapies, was able to further reduce the risk of cardiovascular death and hospitalisation from worsening heart failure in patients with moderate to severe heart failure (LVEF ≤ 35%) and a raised heart rate (above 70 beats per minute).<sup>1</sup> Ivabradine is a specific inhibitor of the I<sub>f</sub> current in the sino-atrial node.

The significant relative risk reduction (RRR) of 18% in this primary composite outcome in patients receiving ivabradine therapy was primarily the consequence of the 26% reduction in hospital admissions; 16% of patients taking ivabradine were admitted to hospital with worsening heart failure compared to 21% in the placebo group. The absolute risk reduction achieved was 4.2%. This means that 26 patients would need to be treated for one year to prevent one cardiovascular death or one hospital admission for heart failure.

Importantly, the benefit of ivabradine therapy was seen early on in the first three months of therapy (Figs 1, 2). The other component of the composite endpoint,

cardiovascular death, was reduced by 9%, which was not statistically significant.

The 10% reduction in all-cause mortality achieved in the ivabradine arm (16%) compared to 17% in the placebo arm did not reach statistical significance. There were no differences in the incidence of sudden death between the two treatment arms. Heart failure-related deaths were however significantly reduced from 5% in the placebo arm to 3% in the ivabradine arm (RRR: 26%).

This SHI<sub>T</sub> study of systolic heart failure treatment with the I<sub>f</sub> current inhibitor ivabradine was undertaken to investigate whether lowering heart rate with ivabradine could reduce cardiovascular deaths and hospital admissions from worsening heart failure among patients with chronic heart failure, systolic dysfunction, normal sinus rhythm and an elevated heart rate.

The study included 6 505 patients and was conducted over a median follow-up period of 22.9 months. Patients were mainly men, with an average age of 60 years, and in NYHA classes II and III. Duration of heart failure was three years and patients had to have experienced a hospitalisation event in the 12 months prior to entering the study. Heart failure was mainly of ischaemic origin with 32% of patients (2 086) in both the ivabradine and placebo arms being categorised as having heart failure of non-ischaemic origin.

Presenting the results, Prof Michel Komajda, professor of Cardiology, Université Pierre et Marie Curie, Paris, stressed that the investigators from 37 countries, which excluded the United States of America, where ivabradine is not

registered, and Africa, had been encouraged to prescribe the best current standard of care as recommended by the ESC guidelines. These guidelines also form the basis of the South African heart failure treatment guidelines.

The excellent background standard of care was evident at randomisation, with 90% of patients receiving beta-blocker therapy, 93% on ACE inhibitors/angiotensin receptor blocker (ARB) therapy, 84% on diuretics and 60% receiving anti-aldosterone agents. Device usage was low as per protocol (3%).

Patients entering the study were given a starting dose of 5 mg ivabradine twice daily, which was up-titrated or lowered, depending on the heart rate response. Heart rate was measured by ECG at regular four-monthly intervals throughout the study.

‘The results of SHI<sub>T</sub> are vital as there is still a clear unmet clinical need in the treatment of heart failure, which, despite advances in therapy with five drug classes which form the basis of recommended therapy, 50% of patients still die during the first four years. In addition, quality of life can be very poor; commonly 25% of patients are re-hospitalised within three months after their first admission for heart failure-related complications’, Prof Komajda concluded.

1. Swedberg K, Komajda M, Bohmm, Borer JS, *et al.* Ivabradine and outcomes in chronic heart failure (SHI<sub>T</sub>): a randomised placebo-controlled study. *Lancet* 2010; e-pub 29/8/2010-DOI:10.1016/S0140-6736(10)61198-1.

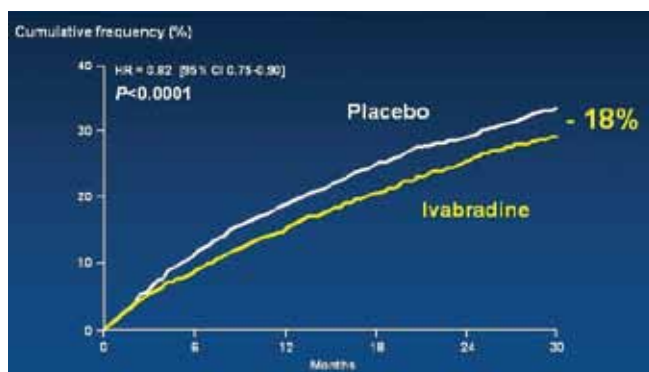


Fig. 1. Cardiovascular mortality/heart failure hospitalisation.

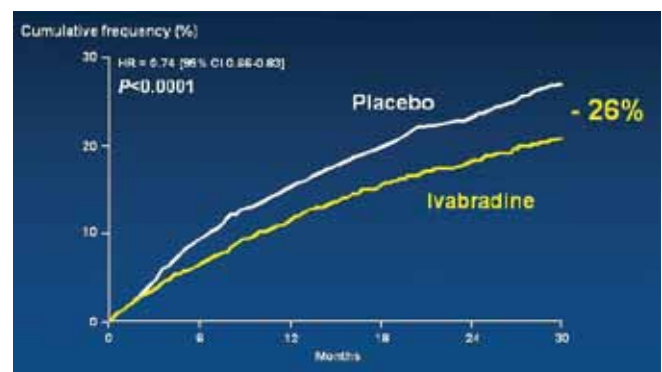


Fig. 2. Hospitalisation for heart failure.

**Prof Jeffrey Borer, head of the Department of Medicine, State University of New York, Downstate Medical Centre**

Prof Jeffrey Borer helped to design the SHIT study and was a member of the executive committee despite there being no USA investigating sites. His expertise relates mainly to device trials in heart failure. He talked to *CVAfrica* about his experience with this trial.

‘SHIT was a well-performed trial and the results are very impressive. During the trial, I became more and more impressed with Servier’s oversight of the trial. They worked hard to encourage the executive to ensure that investigators used best-practice treatment protocols so that the addition of ivabradine was truly a study of the drug above standard best practice. Therefore the additive effect of ivabradine is really solid in this trial; there can be little doubt about the benefits.’

‘The number of events that occurred during the trial, about 1 650 events in total, gave us a solid data set and confidence intervals were so narrow that there is very little chance of the benefits being due to chance. The reduced costs to heart failure patients and funders, of the 26% reduction in hospitalisation, is extremely important as more than 50% of the costs of heart failure relate to hospital admissions.’

## South African experts’ views on SHIT

**Dr Tony Dalby, Milpark Hospital, Johannesburg**

‘It is interesting, but one would have liked to have seen a significant drop in cardiovascular mortality. However, these patients are in and out of hospital and the benefit in reducing hospitalisation is very important. We do not have experience of using ivabradine in this group of patients in South Africa so we will have to feel our way.’

**Prof DP Naidoo, head of Cardiology, University of KwaZulu-Natal**

‘This is a landmark study in heart failure because we have all been saying that raised heart rate is an important determinant of heart failure outcomes. Evidence from beta-blocker trials has shown over many years that lowering heart rate benefits morbidity and mortality. A substantial percentage of patients cannot tolerate beta-blockers in full doses; this occurs frequently in advanced heart failure.’

‘Adding beta-blockers in this situation can cause an immediate worsening of their heart failure. Ivabradine’s pure heart rate-lowering action without nega-

tive inotropic action or affecting conduction across the AV node is very useful for these patients. SHIT has shown that a further lowering of the heart rate is accompanied by a reduction in heart failure-related hospitalisation and deaths. Ivabradine is safe; the ocular disturbances are restored to normal after withdrawal of the drug in the 3% of patients affected.’

**Prof Karen Sliwa, chairperson of the Heart Failure Society of South Africa**

‘There is a particular use for ivabradine in South Africa in non-ischaemic cardiomyopathy, including peripartum cardiomyopathy, where you would like to lower heart rate without lowering an already low blood pressure.’

‘The SHIT study is also relevant to both South Africa and Africa because it included 30% of patients with non-ischaemic heart failure, who benefited from ivabradine. In Africa, acute heart failure is a problem and ivabradine can be useful in this setting, as the THESUS study also showed that in this condition, a raised heart rate above 75 bpm is a common problem.’