Indian Heart Journal 70 (2018) 201–203

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Editorial

Adding ivabradine to beta-blockers in chronic heart failure: Do not rest without lowering the resting heart rate sufficiently

Elevated resting heart rate (HR) is an established marker of adverse cardiovascular (CV) outcomes in a wide variety of patient populations.[1–6] Several epidemiological, observational and interventional studies have demonstrated that not only elevated resting HR is associated with increased risk of mortality [1–6] but also that reducing it through different approaches results in improved clinical outcomes.[7–11]

Among various cardiac conditions, chronic heart failure (HF) [for the purpose of this discussion, term HF is used to imply HF with reduced left ventricular (LV) ejection fraction] best exemplifies the association between elevated resting HR and increased mortality. HF is a complex clinical syndrome characterized by a diverse array of cardiac structural and functional abnormalities. Neuro-endocrine system, comprising the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system, plays a crucial role in the pathophysiology of HF. Activation of SNS clinically manifests as increased resting HR, which, at least during the initial period, serves as an important compensatory mechanism to maintain cardiac output in the presence of compromised cardiac pump function. However, when sustained, the persistent activation of SNS with persistently elevated HR results in several deleterious effects on cardiac homeostasis which eventually culminate into increased risk for HF hospitalization and mortality. Elevated HR is not merely a manifestation of SNS activation, it also contributes to myocardial injury, thus initiating a vicious cycle. The mechanisms underlying this deleterious impact include- increased myocardial oxygen demand, reduced diastolic duration with impaired coronary perfusion, downregulation of β-adrenergic receptors with suppressed signal transductions, impaired intracellular calcium handling and excitation–contraction coupling mechanisms, accumulation of oxygen free radicals, etc.

Given the role of SNS activation in the pathogenesis of HF, its suppression with beta-blockers has been one of the most important therapeutic strategies in the management of HF. Several large-scale trials have demonstrated that in patients with HF, addition of a beta-blocker to background therapy significantly reduces all-cause and CV mortality.[9,12–14] Unfortunately, despite the strong evidence supporting their efficacy, beta-blockers are often underused in HF as has been reported not only in observational studies in routine clinical practice but also in large clinical trials. A substantial proportion of patients are unable to tolerate target dosages of beta-blockers due to their undesirable hemodynamic effects. Moreover, optimal up-titration of beta-blockers is a time-spanning exercise that involves frequent visits to the physician. All these factors end up in many patients receiving suboptimal dosages. Indeed, it has been observed that only about 25% of all patients with HF treated with a beta-blocker actually receive the recommended target dose.[11] This is in addition to the 10–15% of the patients who never receive a beta-blocker due to comorbidities such as obstructive airway disease. Given these challenges, development of novel and complementary non-beta-blockade therapeutic targets that can synergistically reduce HR is crucial to achieve better cardiac outcomes in HF.

The discovery of I_f current, that modulates the slope of spontaneous diastolic depolarisation of the sinoatrial node, has led to a novel non-beta-blockade approach to HR reduction. Ivabradine, a selective I_f channel inhibitor, has been investigated in the Systolic Heart Failure Treatment with the I_f inhibitor Ivabradine Trial (SHIFT), a landmark trial in patients with HF.[11] A total 6558 patients with resting HR $\geq$70 beats/min (bpm) in sinus rhythm and receiving stable background therapy including beta-blockers were randomised to receive either ivabradine (up to 7.5 mg twice daily) or placebo. Ivabradine treatment resulted in 18% reduction in the primary composite endpoint of CV death or hospitalisation for worsening HF at the median follow up of 22.9 months. There was a 26% reduction in hospitalisation for worsening HF and 26% reduction in pump failure death. Given that the majority of the patients in SHIFT were receiving beta-blockers, it was postulated that the combination of ivabradine and beta-blocker as against the dose of beta-blocker was relevant to these findings.[11]

The availability of ivabradine as an alternative to beta-blockers for HR reduction in HF has raised several pertinent questions. How relevant is HR reduction as a therapeutic target in HF patients? How relevant is the choice of therapy for achieving HR reduction? And, what role does ivabradine have vis-à-vis beta-blockers in HF? Several exploratory analyses of large-scale trials have attempted to answer these questions. The Beta-Blockers in Heart Failure Collaborative Group performed a meta-analysis of 11 double-blind randomized controlled trials that compared beta-blockers with placebo in HF.[15] It was found that among patients in sinus rhythm, a higher HR at baseline was associated with greater all-cause mortality with an 11% increase in mortality for every 10 bpm increase in the baseline HR. Beta-blockers reduced the HR by 12 bpm on an average and resulted in lower mortality regardless of the baseline HR. However, the most importantly, a lower achieved resting HR, irrespective of the treatment, was associated with better prognosis (16% increase in all-cause mortality for every 10

https://doi.org/10.1016/j.ihj.2018.03.009

bpm increase in the achieved HR). Similar findings were noted by another meta-analysis which directly addressed the question whether the magnitude of HR reduction was more important, or the dose of beta-blockers achieved.[8] A total of 23 beta-blocker trials were included in this analysis. For every 5 bpm reduction in HR with beta-blocker treatment, there was an 18% reduction in the mortality rate. No significant relationship between all-cause mortality and beta-blocker dosing was observed in high-dose vs. low-dose trials. Collectively, these findings suggest that regardless of the mechanisms underlying the beneficial effects of beta-blockers, the magnitude of HR reduction is a critical determinant of outcomes, with a lower achieved HR being associated with lower subsequent mortality. Since a higher dose of beta-blocker is usually associated with greater HR reduction, the achieved HR serves as a good surrogate measure of the adequacy of beta-blockade achieved. Additionally, the archived HR also provides a sum total of the treatment-related and other hemodynamic factors that influence HR and clinical outcomes in these patients.

The second important question is that if the achieved HR is a key determinant of clinical outcomes in HF, does further reduction of HR with a non-beta-blocker therapy such as ivabradine lead to incremental reduction in mortality? As discussed above, the SHIFT trial did indeed suggest so.[11] Subsequent subgroup analyses of SHIFT have shown that irrespective of the individual beta-blocker prescribed, ivabradine combination consistently improved primary endpoints of CV death and hospitalisation.[16,17] Not only that, the observed benefit of ivabradine in the overall population was comparable to that seen in patients who did not receive a beta-blocker. The risk reduction with the combination therapy depended mainly on the HR achieved. The best protection was observed for those with HR $<$60 bpm or $>$10 bpm reduction in HR at 28 days after initiation of the treatment.[18] Even among patients with baseline HR $<$75 bpm, in whom no overall benefit was seen with ivabradine, there were trends for reductions in HF mortality and HF hospitalizations for HR $<$60 bpm and reductions $>$10 bpm. Thus, it appears that among HF patients, when sufficient HR reduction cannot be achieved with a beta-blocker alone, further HR reduction with ivabradine leads to substantial improvements in clinical outcomes.

Consistent with these evidences from large regulatory clinical trials, a study by Raja DC et al. published in this issue of Indian Heart Journal, provides further evidence supporting the role of ivabradine as add-on to optimal standard management of patients with HF.[19] A total of 125 patients with non-ischemic dilated cardiomyopathy were randomized to receive ivabradine or a placebo on top of standard background medical therapy. In both the groups, all patients were on beta-blockers and angiotensin converting enzyme inhibitors. The beta-blocker dose was up-titrated in both the groups. It was found that at 6 months, compared to controls, those receiving ivabradine had significantly better New York Heart Association functional class, longer 6-min walk duration, lower Minnesota Living With Heart Failure scores and lower brain-natriuretic peptide levels. The patients on ivabradine also had lower LV volumes, LV mass, LV wall stress and calculated LV work; higher LV ejection fraction; and more favourable LV global strain. These effects were more pronounced in patients who were able to reach a HR of $<$70 bpm as compared to those who failed to reach this target. While several previous studies have evaluated the impact of ivabradine treatment on LV ejection fraction,[20–22] this is the first trial to comprehensively assess the effect of ivabradine on various echocardiographic measures of LV systolic and diastolic functions. It thus provides objective evidence of improved cardiac function with ivabradine and provides a mechanistical explanation for the improved clinical outcomes seen with ivabradine. Although the improvement observed in ejection fraction in this study was more pronounced than other studies,[20–22] the concomitant improvement in LV strain supports robustness of these findings. It is noteworthy that LV global longitudinal strain has been demonstrated to be a highly reproducible measure of LV systolic function and has better reproducibility than LV ejection fraction.[23]

The trial by Raja et al. also provides several important messages which are relevant for regular clinical practice. In this study, the patients receiving ivabradine had their HR reduced from 95 bpm at the beginning of the study to 64 bpm at 6 months as compared to a reduction from 95 bpm to 76 bpm in the controls. The greater reduction in HR in the ivabradine group was achieved without any significant difference in the systolic blood pressure. Further, only approximately 9% of the overall patient population was able to achieve the maximum tolerated dose of beta-blocker, as compared to 71.1% for ivabradine. The percentage of patients able to achieve at least 50% of target dose of carvedilol (25 mg of 50 mg) was 80% while only 50% were able to achieve the 50% target dose (100 mg of 200 mg) of metoprolol. These findings reinforce the practical challenges encountered in routine clinical practice in achieving sufficient HR reduction with beta-blockers alone in HF patients.

The complementary modes of action may provide rational for improved efficacy when ivabradine is given in combination with beta-blocker. Ivabradine and beta-blockers both prolong diastolic duration by reducing HR. However, with beta-blockers, the combined effect of inhibition of isovolumetric ventricular relaxation and coronary vasoconstriction mediated via alpha-adrenergic pathway, may partially offset the benefits achieved with prolonged diastole. On the contrary, ivabradine protects ventricular relaxation and does not exhibit vasoconstrictor effect, and hence, the resultant increase in diastolic time, perfusion duration and volume are greater than with beta-blocker for the same level of HR reduction.[24] Ivabradine reduces LV end-diastolic pressure that results in increased stroke volume and maintenance of cardiac output in patients with severe HF. Since beta-blockers reduce stroke volume during initial months of treatment, by compensating for the reduced stroke volume, co-administration of ivabradine may facilitate initiation and up-titration of beta-blockers, which might be of a great clinical relevance. The increased stroke volume improves exercise tolerance and may ultimately lead to a better quality of life in patients with HF. Ivabradine treatment exhibits significant reverse cardiac remodelling as demonstrated by several previous studies as well as the one by Raja et al. Interestingly, this effect on cardiac remodelling has been shown to be beta-blocker independent.[22]

Current European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association guidelines on HF recommend the use of ivabradine in symptomatic patients with LV ejection fraction $\leq$35% who are in sinus rhythm and have a resting HR $\geq$70 bpm.[25,26] Ivabradine is indicated in patients who remain symptomatic despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that or those who are unable to tolerate or have contraindications to a beta-blocker), angiotensin converting enzyme inhibitor, angiotensin receptor blocker and mineralocorticoid receptor antagonist. As mentioned previously, only about a quarter of the patients achieve the recommended ESC target dose of beta-blocker. In such patients in whom sufficient HR reduction is not achieved with beta-blockers alone, reducing HR within the target range with ivabradine might be a more practical therapeutic strategy than waiting to further up-titrate and optimize beta-blocker dose.[27] Indeed, a recent study in acute HF has shown that early co-administration of ivabradine and beta-blockers is feasible and safe, produces a significant decrease in HR and leads to better clinical outcomes at short-term.[28]

In summary, the available evidence suggests that adequate reduction in resting HR should be one of the primary goals of therapy in HF patients. The lowest CV risk is observed in those with

resting HR reduced to 60 bpm or lower.[15,18] Therefore, it might be reasonable, at present, to recommend this target in daily practice, unless there are some tolerability issues. Beta-blockers remain the drugs of choice to achieve this goal. However, since achieving this target with beta-blockers alone is often difficult in majority of the patients with HF, combining ivabradine is a safe and effective alternative approach. Moreover, early initiation of combination therapy may expedite attainment of target HR at relatively lower beta-blocker doses and help reduce probability of dose-dependent adverse events. It should be remembered that in HF patients, inadequate reduction of HR is a job only half done. Given the profound adverse implications of insufficient HR reduction in HF, as treating clinicians onus is on us to ensure that we do not rest without sufficiently lowering the resting HR in these patients.

Conflict of interests

The authors declare that they have no conflict of interest.

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