NEW FRONTIERS IN THE MANAGEMENT OF HEART FAILURE:

integrated approaches for optimizing patient outcomes

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Nowadays, there are many drug options available for heart failure patients with reduced ejection fraction (HFrEF). At a recent conference organized by the Hong Kong College of Cardiology, Professor Martin Cowie of Imperial College London has shared his insights into integrated approaches for optimizing outcomes in patients with HFrEF. He reviewed add-on benefits of ivabradine on top of ß-blocker, and the Optimize Heart Failure Care (OHFC) program for improving outcomes in patients with HFrEF worldwide. This article summarizes the key points delivered in the presentation.

Key discussion focus

- Many effective and well-proven drug options are available for patients who have HFrEF nowadays
- Heart rate (HR) is an independent and substantial biomarker associated with the prognosis of HFrEF
- Ivabradine in combination with ß-blockers results in lower HR, fewer rehospitalization events owing to worsening heart failure (HF) and better survival outcomes than ß-blockers alone, regardless of ethnicity
- Hospitalization is the prime time for drug optimization. Early initiation of ivabradine prior to discharge brings add-on cardiovascular (CV) benefits for patients with HFrEF, compared with usual care. This approach is hence advocated before discharge or at early follow-up after discharge
- The OHFC program improves outcomes for patients hospitalized with HFrEF worldwide by using simple clinician- and patient-based tools. Structural, multi-disciplinary and standardized management is the key to further improve outcomes for HFrEF patients

Heart rate – the key prognostic biomarker for patients with HFrEF

ß-blocker is one of the five pillars ("five alive") of HFrEF therapy.[1] Many large-scale clinical studies have shown that ß-blockers significantly reduce mortality in patients with HFrEF.[2-5] Despite the proven efficacy of the conventional and novel therapies for HFrEF, Professor Cowie mentioned that they may not be deployed effectively in real-world clinical practice. Multiple surveys have discovered that 15–28% of patients with HFrEF received ß-blockers at the target dose and different factors may contribute to underdosing.[6-8] Hence, it is necessary to optimize HF treatment to improve survival outcomes further.[6-8]

In addition to routine practice, a meta-analysis has revealed that the survival benefit of ß-blockers in HFrEF is significantly associated with the reduction of HR.[9] In the study, 23 ß-blocker trials were included for determining the factors contributing to the survival benefits of ß-blockade in HFrEF.[9] The authors found that the risk of mortality was decreased by 18% for each 5 bpm decrease in HR (p = 0.006), regardless of the ß-blocker dosage.[9]

Other studies also support that high HR is the key mediator of HFrEF associated with an increased risk of mortality.[10-12] A post-hoc analysis of PARADIGM-HF and ATMOSPHERE trials has examined the association between baseline HR and outcomes by stratifying patients into groups according to baseline HR. The report demonstrated that, in terms of sinus rhythm (SR) at baseline, the risk of HF outcomes was significantly higher in patients with high HR (≥ 64 bpm) than low HR (≤ 63 bpm), even after adjustment for other prognostic variables (Figure 1).[11] One study has further suggested that achieving a lower HR in SR of around 60 bpm is optimal for patients with HFrEF.[10] From this point of view, add-on ivabradine is a reasonable and sensible approach if HR is higher than 70 bpm.[1] "Don't forget the simple thing: the measure of HR interprets a lot about the prognosis of patients", Professor Cowie commented.

Elevated heart rate in ß-blockers treated patients with HFrEF

In reality, not all patients on ß-blockers have "favorable and optimal" HR.[13,14] A few years ago, Professor Cowie and his colleague published an audit assessing the HR control in 100 outpatients in SR and with ejection fraction ≤ 40% in his clinic.[13] The result showed that one in five patients with HFrEF were intolerant of ß-blockers. For patients who completed ß-blockers up-titration and were at maximally tolerated dose or intolerant of ß-blockers, 53% of them still experienced a HR > 70 bpm.[13] Furthermore, a large-scale US study demonstrated that the majority (73%) of patients were taking ß-blockers at discharge but 71% of them still had a discharge HR ≥ 70 bpm.[14] Therefore, he suggested that additional therapy, such as ivabradine, is suitable for patients with HFrEF and elevated HR.[13]

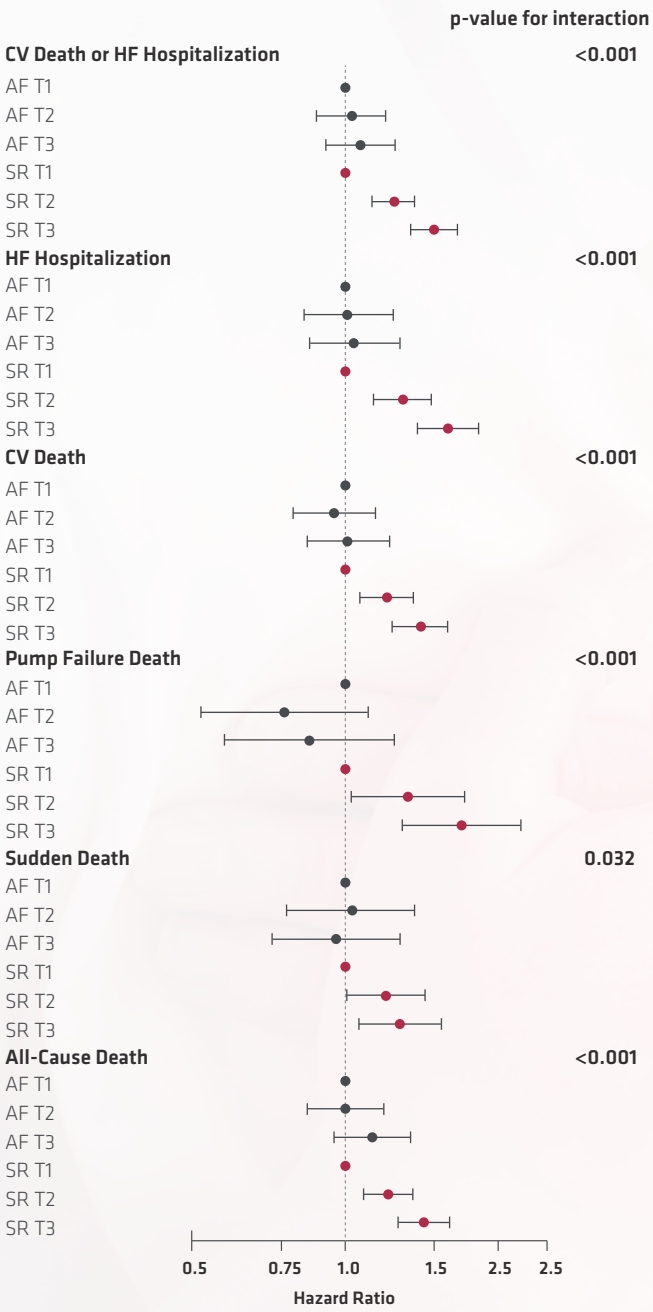


Figure 1 – Forest plot of relationship between baseline heart rate and outcomes. Hazard ratios of outcomes according to heart rhythm [AF or SR] using each group T1 as reference. AF T1: ≤ 72 bpm; AF T2: 73–85 bpm; AF T3: ≥ 86 bpm. SR T1: ≤ 63 bpm; SR T2: 64–75 bpm; SR T3: ≥ 76 bpm. Hazard ratios with 95% CI were calculated using Cox models adjusted for the same variables.[11]
AF=atrial fibrillation; CI=confidence interval; CV=cardiovascular; HF=heart failure; SR=sinus rhythm.

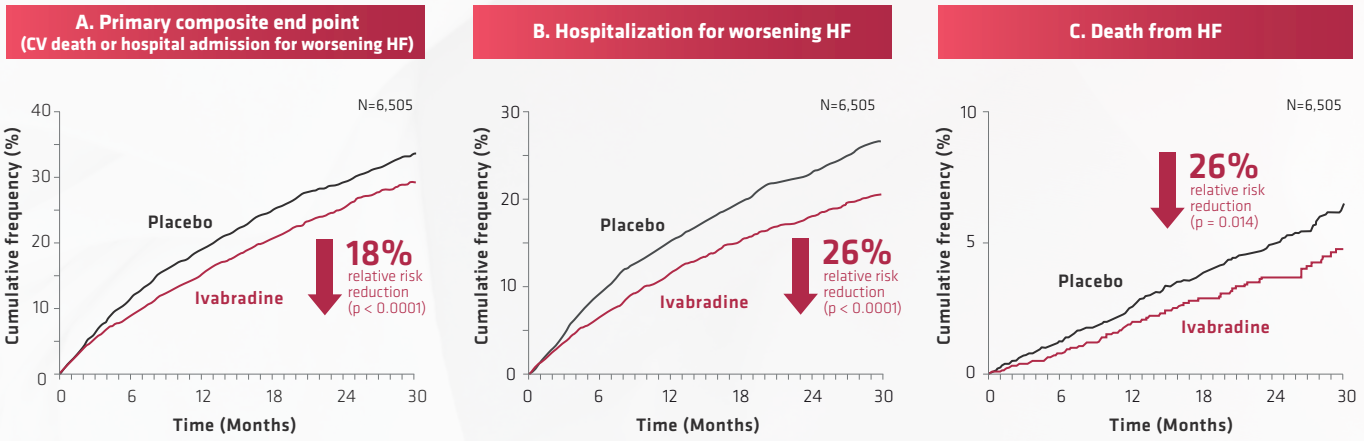


Figure 2 – SHIFT: outcomes of add-on ivabradine and placebo in patients with symptomatic HFrEF on stable background therapy, including high usage rates of ß-blockers and angiotensin-converting enzyme inhibitors.[16]
CI=confidence interval; CV=cardiovascular; HF=heart failure; HFrEF=heart failure with reduced ejection fraction.

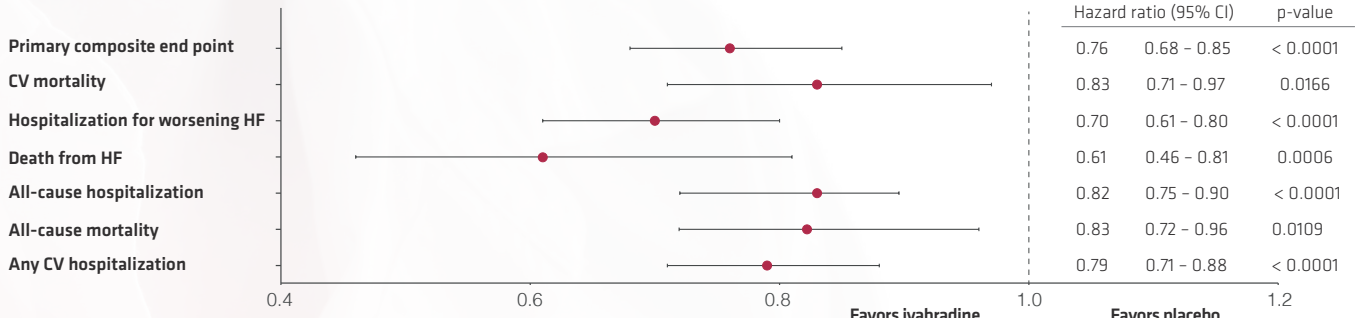


Figure 3 – SHIFT: effect of ivabradine on major outcomes in high-risk patients with baseline HR ≥ 75 bpm.[12]
CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=heart rate.

Lowered heart rate and better outcomes with add-on ivabradine

Ivabradine is a selective I_f ('funny') channel inhibitor that reduces HR by regulating mixed sodium and potassium ion current flow.[15] To evaluate the effects of the combination of ivabradine and other guideline-directed HF drug therapies on HF outcomes, a randomized, multinational, double-blind, parallel-group, placebo-controlled clinical trial named SHIFT recruited 6,558 patients with chronic HF and systolic dysfunction on stable background therapy, including high rates of use of ß-blockers and angiotensin-converting enzyme inhibitors (ACEi).[16] It showed that HR in patients on ivabradine was 10.9 bpm lower than those receiving placebo at Day 28. With a median follow-up of 22.9 months, the risk of CV mortality or hospitalization for worsening HF in ivabradine was significantly decreased by 18%, compared with placebo (Figure 2A).[16] The relative risk of both hospitalization for worsening HF and death from HF in the ivabradine group were significantly reduced by 26%, compared with the placebo group (Figure 2B & C).[16] Also, ivabradine demonstrated consistent efficacy across Chinese and Japanese patients in the SHIFT sub-study or SHIFT-like study.[17,18] Therefore, the results have indicated that ivabradine effectively reduces both HR and the risk of HF outcomes in patients with HFrEF, including East Asian populations.[16-18]

Of note, ivabradine provides even greater benefits for patients with a higher baseline of HR (≥ 75 bpm).[12] A subsequent analysis of the SHIFT trial has demonstrated that the risk of CV death or hospitalization in ivabradine (primary composite end point) was significantly decreased by 24%, compared with placebo (Figure 3).[12] Moreover, the ivabradine group was significantly associated with prominent gains, in terms of both CV mortality (a 17% relative risk reduction, RRR) and all-cause mortality (a 17% RRR) (Figure 3).[12]

HFrEF has a major impact on health-related quality of life (QoL). In a subordinate SHIFT study, health-related QoL was measured with disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ) at study visits.[19] After 12 months of treatment, patients on ivabradine had significant improvement in KCCQ, in both clinical and overall summary score, compared with placebo ($p = 0.018$ and $p < 0.001$, respectively). Interestingly, the reduction in HR was associated with increased health-related QoL.[19] Overall, the results of the comprehensive study have shown that ivabradine not only substantially reduces HR, mortality and hospitalization, but also improves health-related QoL when added to evidence-based treatment for patients with HFrEF.[12,16,19,20]

Lowered heart rate and rehospitalization risk with early treatment of ivabradine

The hospital setting is crucial to initiate proper treatment for patients with HFrEF for long-term benefits.[21] PRIME-HF was a randomized, investigator-initiated, open-label study to evaluate the implementation of an evidence-based therapy following stabilization in 104 patients hospitalized for HF, with HR ≥ 70 bpm and on maximally tolerated ß-blocker.[21] Over 180 days after discharge, 40.4% and 11.5% of patients were treated with ivabradine in the pre-discharge initiation group and the usual care group respectively (Figure 4A). Among patients with HR ≥ 70 bpm, almost all (26/27) in pre-discharge initiation received ivabradine but less than one-fifth (4/23) of those in usual care (Figure 4A).[21] Professor Cowie pointed out that most patients would not receive appropriate medication post-discharge if it is not started in the hospital.

The PRIME-HF trial has shown that initiation of ivabradine prior to discharge not lowers HR without reducing ß-blocker therapy, or increasing adverse events.[21] Compared with the baseline level, pre-discharge initiation of ivabradine led to a 10 bpm reduction in HR but a 7 bpm increase was found in usual care (Figure 4B) through 180 days.[21] A total of 39% of patients in pre-discharge initiation achieved HR < 70 bpm while only 21% of patients in usual care at Day 180 (Figure 4C).[21] In terms of adverse events, the rate of bradycardia in the pre-discharge initiation group was less common than the usual care group (1.9% vs 3.8%).[21]

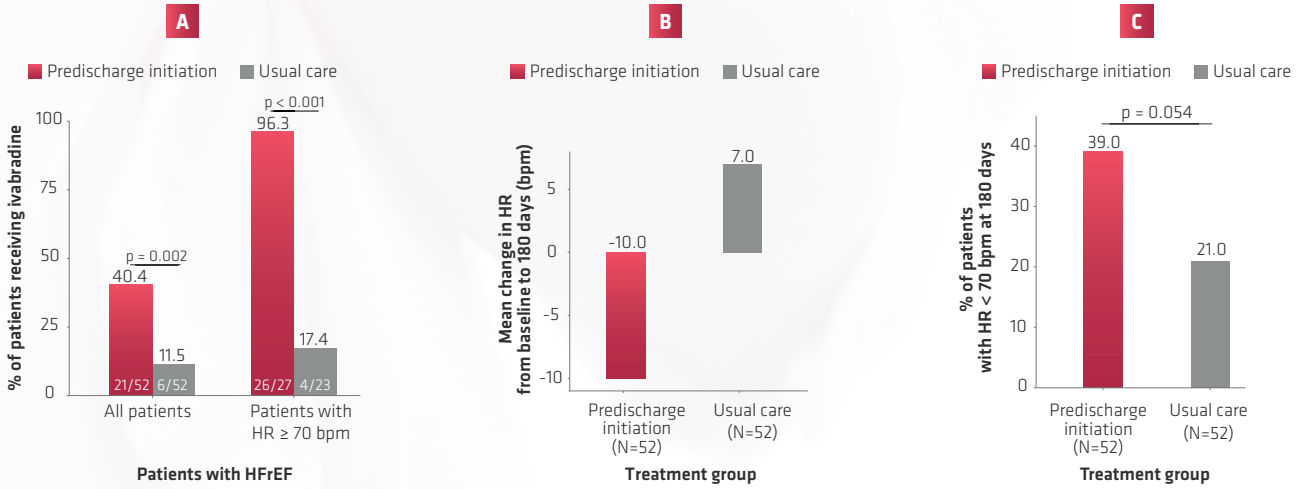


Figure 4 – PRIME-HF trial: (A) The use of ivabradine at 180 days among all patients with HFrEF and those with HR ≥ 70 bpm. (B) The mean change of HR to 180 days from baseline. (C) Proportional of patients achieved HR < 70 bpm at 180 days.[21]
CI=confidence interval; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; HR=heart rate.

More importantly, ivabradine reduces the risk of early readmission in patients with HFrEF.[20] In a post-hoc SHIFT analysis, the cumulative incidence of all-cause hospitalization was significantly lower in patients receiving ivabradine than placebo over the 3 months after a first hospitalization for worsening HF.[20] Taken together, early initiation of ivabradine during pre-discharge or early follow-up after discharge effectively reduces HR and the risk of recurrent hospitalization, particularly in the vulnerable period following a first HF hospitalization.[20,21]

The OHFC program: a further step for heart failure care

To improve outcomes for patients hospitalized with HFrEF, the OHFC program has been implemented worldwide.[22] The program is aimed at improving prescription of appropriate and guideline-directed HF drug therapies, post-discharge planning, and patient education and engagement. It consists of three elements: (1) practical protocols to participate hospitals for optimizing HF management, (2) pre- and post-discharge checklist for follow-up, and (3) HF education booklet for patient education and self-management.[22] Professor Cowie encouraged cardiologists and hospitals to join the program for improving patients' education and HF outcomes with regular meetings and simple-to-use tools.[22]

The program serves to raise awareness of HF and collect real-world data on current practice and evidence-based care with the use of simple clinician- and patient-focused tools.[22] For example, a recent publication showed that the combination use of ivabradine and ß-blockers before hospital discharge was associated with a 55% reduction in the risk of all-cause mortality or HF hospitalization, compared with ß-blockers alone (Figure 5).[23] This result has further demonstrated the benefits of early administration of ivabradine among HFrEF patients with elevated HR.

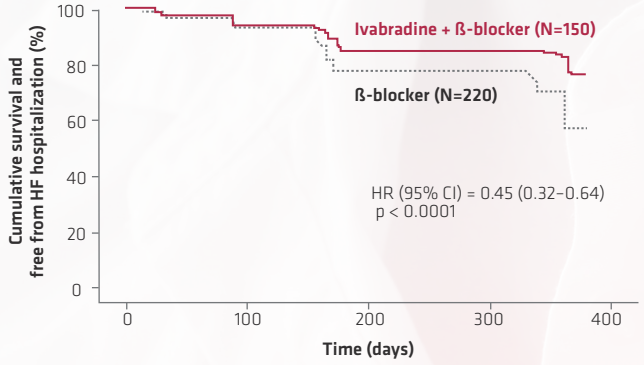
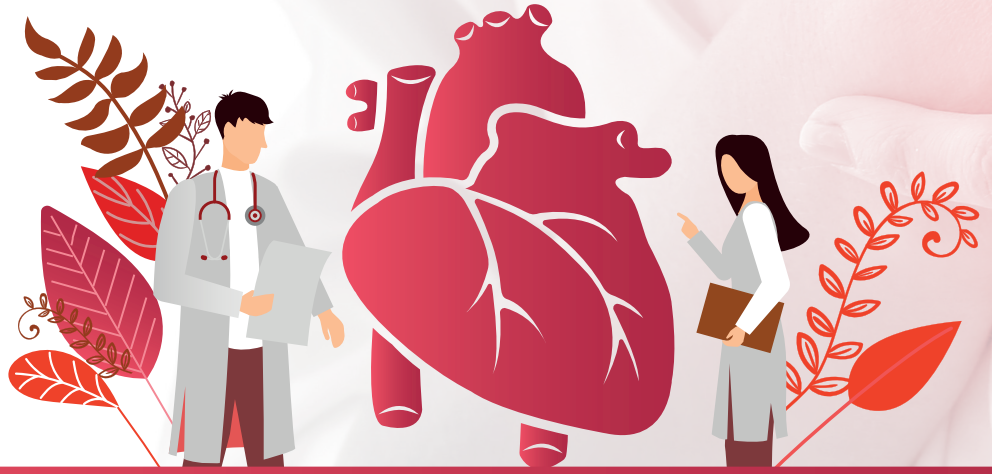


Figure 5 – OPTIMIZE HF: The Kaplan-Meier curves for the probability of all-cause mortality or HF hospitalization in HFrEF patients on the combination of ivabradine and ß-blockers or ß-blockers monotherapy.[23]
CI=confidence interval; HF=heart failure; HFrEF=heart failure with reduced ejection fraction;HR=hazard ratio.

Conclusions

An integrated approach to the management of HFrEF helps optimize therapy and care for patients with HFrEF. Heart rate is one of the key primary determinants and has been established as a prognostic factor in HFrEF patients.[10-12] Clinical trials have comprehensively demonstrated that the addition of ivabradine leads to a reduction in HR, mortality and hospitalization in patients with HFrEF receiving guideline-based treatment.[16,21,23] Remarkably, early initiation of ivabradine reduces the risk of recurrent hospitalization in the first 3 months following HF hospitalization.[20] In conclusion, ivabradine is the optimal therapy for HFrEF patients in SR with elevated HR regardless of background HF treatment.



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