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Review Article

Optimizing heart failure therapy with enhanced medical management: focus on heart rate management

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ABSTRACT

Heart failure (HF) is a significant global health issue, affecting over 60 million people worldwide, with its prevalence expected to rise due to aging populations and the increasing incidence of comorbidities like hypertension and diabetes. Despite therapeutic advances, including quadruple therapy with renin-angiotensin-system inhibitors, beta blockers (BB), mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors, HF remains a condition with a poor prognosis, particularly for those with reduced ejection fraction (HFrEF), who are predominantly found in low- and middle-income countries like India. Elevated resting heart rate (HR) is a critical prognostic factor in HF, correlating strongly with cardiovascular mortality and morbidity. For every five-beat increase in HR, there is a 16% rise in cardiovascular mortality and HF hospitalization, emphasizing the need for effective HR management. However, challenges persist in optimizing HF treatment, such as the underutilization of BBs, despite their proven efficacy in reducing mortality. In India, the "double burden" of age-related and contemporary diseases complicates HF management further. Addressing unmet needs in HF care requires optimizing therapeutic strategies and improving treatment adherence, particularly in the context of HR control. Studies indicate that tailored approaches, including the use of BBs and ivabradine, could reduce HR and improve clinical outcomes. The ongoing challenges in accessing guideline-directed therapy and ensuring adherence highlight the need for comprehensive strategies to enhance patient outcomes, while personalized treatments and further research remain essential in navigating the complex landscape of HF management.

Keywords: HF, Heart rate management, Guideline-directed medical therapy, BBs, Ivabradine

INTRODUCTION

Heart failure (HF) is a global pandemic, affecting over 60 million individuals worldwide. The prevalence is expected to rise due to aging populations, increasing comorbidities like hypertension and diabetes, and improved acute cardiovascular care. With a grim prognosis, about 50% of HF patients die within 5 years, contributing to a significant economic burden of US$31 billion. HF is classified into HFrEF and HF with preserved ejection fraction (HFpEF), with HFrEF defined by LVEF <35-40%. In low- and middle-income countries like India, approximately 22.7 million patients are affected, predominantly by HFrEF. The evolving epidemiological landscape in India presents a "double burden," combining age-related conditions like rheumatic heart disease (RHD) with the increasing incidence of contemporary diseases like coronary artery disease (CAD), amplifying the risk of HF.[1,2]

Recent years have seen significant advancements in HF treatment, with new therapies showing promise. Quadruple therapy, including renin-angiotensin-system inhibitors, angiotensin converting enzyme inhibitor (ACEI)/ angiotensin receptor blocker (ARB)/angiotensin and neprilysin inhibitor (ARNI), beta-blocker (BB), mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter 2 inhibitor (SGLT2i) MRAs, and SGLT2 inhibitors, is recommended as initial treatment for HFrEF patients. Despite GDMT, patients with HFrEF still face a bleak prognosis, with a high risk of cardiovascular death or HF hospitalization.[3,4]

Elevated resting HR in HF patients strongly predict cardiovascular mortality and morbidity. Therefore, lowering resting HR is a critical treatment target in HF.[5] Focused group meetings were planned with Indian specialists to delve deeper into HR management in HF. This review offers a comprehensive overview of HR management in HF, HF management in India, optimizing HR in HF.

HR MANAGEMENT IN HF

Understanding the impact of HR on cardiovascular risk

Elevated HR has been related to greater lifespan in many animal species, including humans. This link extends to various cardiovascular disorders, including hypertension, atherosclerosis, myocardial infarction, and HF. Heart rate ≥70 beats per minute (bpm) in HF, show a stronger association with increased risk. Studies have shown that every five-beat increase in resting HR is associated with a 16% increase in cardiovascular mortality and HF hospitalization.[6] Additionally, for every five-beat increase in HR, there is an 8% increase in cardiovascular death and an 8% increase in coronary revascularization. [7]As a result, there is hypothesis that lowering HR might reduce these hazards, particularly in HF, where the relationship between HR and risk is very significant. [6]

The HR plays a critical role in the delicate balance between myocardial oxygen demand and coronary blood flow. HR has an important role in CAD, influencing both aspects of myocardial oxygen balance. Elevated HRs introduce a disruptive factor, tipping the delicate equilibrium by reducing oxygen delivery while increasing demand. This delicate interaction eventually leads to myocardial ischemia and angina, emphasising the critical role of HR control in CAD therapy. [8]

Investigating the prognostic implications of HR in HF

In a thorough study conducted by Bui et al 145,221 admissions for heart HF from 295 participating hospitals from the United States of America were methodically analysed to uncover the complicated link between admission HR and in-hospital outcomes. It was found that elevated admission HR emerges as a strong, independent predictor of poor outcomes among patients hospitalised for HF, regardless of their cardiac rhythm status, which includes both sinus rhythm and atrial fibrillation. This study reveals insights into the predictive relevance of admission HR in guiding clinical decision-making and optimising patient care methods for people with HF.[9] In a comprehensive study headed by Laskey et al the relationship between HR at discharge post-hospitalization for HF and subsequent long-term poor outcomes was thoroughly investigated. This study looked at whether this link differed among patient subgroups. The findings highlight a fascinating discovery: in a cohort of elderly patients hospitalised with HF, a higher discharge HR emerged as a critical prognostic indicator, greatly increasing the probability of death and rehospitalization. Notably, this increased risk was most obvious within the first 30 days after discharge. [10]

In the prospective observational chronic HF analysis and registry in the Tohoku district; ASCEND-HF: the acute study of clinical (CHART-2 trial), 2688 consecutive stage C or D HF patients with sinus rhythm were enrolled from the CHART-2 study (n=10,219). Elevated baseline HR was associated with increased all-cause mortality in both HFrEF and HFpEF groups (Hazard ratio [HZR] 1.77 in HFrEF, p=0.008; (HZR 1.82 in HFpEF, p=0.001). However, elevated HR was more strongly associated with cardiovascular death in HFpEF (HZR 2.17, p=0.012) compared to HFrEF (HZR 1.49, p=0.14). [11]

Unmet needs in HF management

Sympathetic nervous system (SNS) activation plays a pivotal role in HF pathogenesis, making BBs a cornerstone therapy. Despite evidence from large-scale trials demonstrating reduced mortality with BB use in HF, their underutilization persists in both clinical practice and trials. Challenges include patients' intolerance to target dosages due to hemodynamic effects and the time-consuming process of up-titration, resulting in suboptimal dosing for many patients. [12] In addition to the above challenges, it has been reported that BB therapies improve long-term survival but are not effective in improving symptoms. [13]

HF IN INDIA: THE DOUBLE BURDEN

Projections based on US prevalence data extrapolated to India suggest a staggering estimated prevalence of 22.7 million cases of HF in India. Considering the burden of HF in India, attention must be paid to prevalent risk factors. India faces a "double burden" with increasing rates of hypertension, diabetes, and CAD alongside persistent conditions like RHD. Unique factors such as aortoarteritis, endomyocardial fibrosis, untreated congenital heart disease, and the high prevalence of chronic obstructive pulmonary disease (COPD) due to biomass fuel use further contribute to the HF burden.[14]

In India, patients present with HF at a younger age compared to Western countries. The mean age at

presentation ranges from 56 to 61 years in India and sub-Saharan Africa, while it is higher at 70-72 years in the USA and Europe. Additionally, the burden of HF falls on a younger population in India, with a male to female ratio of 70:30 and ischemic heart disease (IHD) as a predominant etiology (71%) compared to CAD in Asia (48%).[14]

Furthermore, HF prognosis in India is poorer than in the West, with higher in-hospital mortality rates (8.4% vs. 4% in the USA) and one-year mortality rates (37% in India). Despite this, evidence-based care is underutilized, with only 25% of patients receiving GDMT in the Trivandrum registry, highlighting the need for quality improvement programs. [14]

Chaturvedi et al conducted a study to determine the HF prevalence in rural community as well as tertiary care hospital care setting in North India. In a study of 10,163 rural adults, chronic breathlessness affected 1.3% of the population. HF was found in 9% (n=12), with 67% (n=8) having preserved left ventricular (LV) systolic function and 33% (n=4) having LV systolic dysfunction, resulting in a community prevalence of 1.2/1000 for HF. Among HF patients with preserved ejection fraction, poorly controlled hypertension was universal. In a hospital study involving 500 consecutive patients, 20.4% had HF, predominantly caused by RHD (52%) and ischemic heart disease (17%), with an average presentation age of 39±16 years. In outpatient department patients, HF prevalence was 22.5% among those below 30 years and 14.9% among those above 50 years, indicating a relatively young HF population. Projections for HF burden in India suggest an estimated prevalence of about 1% of the total population, affecting approximately 8-10 million individuals, with an estimated annual mortality of 0.1-0.16 million attributed to HF.[15]

CHALLENGES WITH HF MANAGEMENT IN INDIA

Improving patient outcomes and elevating the standard of care require a comprehensive understanding of treatment patterns, barriers to GDMT access, and shortcomings in drug delivery. However, data from extensive registries such as CHAMP-HF and ASIAN-HF have shed light on concerning trends. In CHAMP-HF, encompassing over 3,500 HFrEF patients, significant disparities in medication usage and dosing were observed despite guideline recommendations. Similarly, ASIAN-HF's findings across 11 Asian nations revealed suboptimal utilization of guideline-directed therapies among HFrEF patients. Despite concerted efforts in guideline dissemination and quality improvement, recent data suggest minimal advancement in outpatient GDMT utilization, indicating a notable discordance between guidelines and clinical practice realities.[2]

Maximizing the adoption of evidence-based treatments offers a pathway to curbing the burden of HF mortality. Within this realm, optimizing HR emerges as a pivotal strategy for managing HFrEF. Notably, insights from the seminal SHIFT trial underscore the critical role of HR control. The study revealed a direct correlation between elevated baseline HR and heightened risks of cardiovascular death and HF hospitalization. Specifically, each incremental beat per minute (bpm) from baseline was associated with a 3% rise in risk, while a 5-bpm increase corresponded to a 16% escalation in risk. Thus, delving into clinicians' perspectives on integrating HR reduction strategies into real-world clinical practice becomes imperative.[2]

CURRENT STATUS AND POTENTIAL THERAPEUTIC STRATEGIES IN HF TREATMENT

Since the inception of clinical studies in the late 1900s, the landscape of HF treatments has undergone remarkable evolution. From traditional diuretics and inotropic agents to the advent of vasodilators, ACEi, BBs, MRAs, and ARBs, the armamentarium against HF has expanded significantly. Moreover, the emergence of combination therapies such as ARNI and, more recently, SGLT2i has further enriched the therapeutic arsenal. These advancements aim not only to alleviate morbidity but also to bolster survival rates among HF patients. Importantly, ongoing research endeavors continue to explore novel therapeutic avenues, promising continued innovation in HF management.[16]

The complexity and diversity of factors contributing to the HF syndrome present a formidable challenge for implementing a universal treatment approach, despite notable pharmacotherapeutic advancements. This underscores the potential benefits of adopting more tailored and individualized treatment strategies, particularly for patients with HFpEF. As we navigate the intricacies of HF management, there arises the possibility of transitioning towards a paradigm shift in therapeutics, where personalized approaches play a pivotal role in addressing the unique needs of each patient. This evolving landscape holds promise for optimizing outcomes and improving the quality of life for individuals grappling with HF.[16]

OPTIMIZING HR IN HF: PATIENT CHARACTERISTICS AND HR DYNAMICS

Tiny Nair et al. conducted a prospective, observational study across 15 sites in India to examine the average resting HR in patients with HFrEF receiving outpatient treatment, both at baseline and at the study's conclusion. Secondary objectives included evaluating blood pressure (BP) in these patients and analyzing the prescription patterns of HR-lowering medications such as BBs, non-dihydropyridine (non-DHP) calcium channel blockers, digoxin, and ivabradine. Additionally, the study aimed to investigate the prevalence of comorbid conditions such as

diabetes mellitus, hypertension, and dyslipidemia, which may impact the prognosis of HFrEF.[17]

In the study, resting heart rate (HR) and BP were measured at baseline and again after three months, along with a documentation of the prescription patterns for β-blockers and ivabradine. The analysis revealed a significant reduction in average resting HR over the three-month period, decreasing from a mean of 79.2 bpm at baseline to 72.6 bpm at three months ($p<0.001$). Most patients (82%) were prescribed BBs as a heart rate-lowering medication, while ivabradine was prescribed to 45% of the patients. At baseline, 65 out of 134 patients were prescribed ivabradine at a dose of 5 mg twice daily, and 41 patients received a once-daily dose of 10 mg. After three months, 53 out of 127 patients were prescribed a once-daily dose of 10 mg, while 47 patients received 5 mg twice daily. The mean NT-proBNP level, initially at 1623.8 pg/mL, significantly reduced to 594.7 pg/mL after three months. Ivabradine was effective in decreasing HR by 10.3 bpm without causing bradycardia.[17]

A distinct pattern in the usage of once-daily (OD) versus twice-daily (BD) ivabradine formulations emerged, with the OD formulation being preferred in patients with a higher baseline HR of 85 bpm, while the BD formulation was favored for those with a baseline HR of less than 80 bpm. Notably, 33.6% of patients initiated on ivabradine at baseline were prescribed the OD formulation. A subgroup analysis demonstrated that healthcare providers tended to change HR-lowering medications primarily when HR exceeded 80 bpm, with the goal of achieving a reduction to around 70 bpm. However, further attention is needed to reach the guideline-recommended HR of less than 65 bpm in these patients.

The study also found that NT-proBNP levels decreased more significantly in patients with lower baseline HRs, particularly around 85 bpm, rather than in those with HRs exceeding 90 bpm. Additionally, older patients generally had lower baseline HRs, resulting in less HR reduction compared to younger patients. Males exhibited higher baseline HRs and experienced greater reductions in HR compared to females. High baseline HRs were observed in patients classified as New York heart association (NYHA) Class 3, with a reduction of more than 13 bpm in this group, underscoring the importance of focused HR management for improving outcomes. Patients with a disease duration of 1 to 5 years initially had high baseline HRs, which showed a significant reduction over time, indicating that HR reduction efforts can effectively bring HR close to 72 bpm regardless of disease duration. The analysis also revealed that etiological factors had little impact on baseline HR and its change over time.

In patients with hypertrophic cardiomyopathy, high baseline HRs were noted, though the small sample size limits the conclusiveness of these findings. An increase in HR was observed in HF patients with RHD as the etiology, but again, the small sample size limits definitive conclusions. Patients with hypertension, diabetes, and obesity generally had baseline HRs greater than 80 bpm, with a reduction of 9.3 bpm observed in patients with CKD, despite their lower baseline HR of 77.1 bpm compared to other comorbidities. Smokers were found to have a higher baseline HR of 88 bpm, but the reduction over three months was modest, only 8 bpm, indicating that smoking may be a limiting factor in achieving lower HRs.

EXPERT SUGGESTIONS

HR management in HF

Increased SNS activity in HF patients leads to elevated HR, higher oxygen demand, reduced ventricular efficiency, increased mortality, and hospital readmissions. Uncontrolled or non-optimized HR is both a risk factor and marker, adversely affecting clinical outcomes and increasing mortality. While quantifying HR reduction benefits in routine practice is challenging, optimizing HR to less than 75 bpm provides significant clinical benefits for HF patients. Common comorbidities in HF patients include hypertension, diabetes, and chronic kidney disease. Lack of awareness, poor adherence to follow-up, and delayed diagnosis are significant challenges in GDMT. Treatment adherence is lower in rural areas due to limited resources, higher addiction rates, and fewer healthcare services compared to urban areas, which face challenges like smoking, stress, sedentary lifestyle, and erratic eating habits. The high cost of HF treatment, unaffordability of newer medications, and unavailability of quality medicines in government hospitals hinder patient compliance. Self-titration of medications and inconsistent treatment by different physicians further complicate adherence. There is a need for more research and data collection to develop new HF guidelines in India, treating HF with the same rigor as oncology, ensuring therapy escalation for better outcomes.

Challenges in GDMT

Common GDMT challenges include underdiagnosis and overdiagnosis, frequent follow-ups and investigations, cost burden, hypotension from medications, non-compliance, self-discontinuation of medications, and poor treatment tolerance. Implementation of GDMT in clinical practice observed as per experts is as follow: SGLT2 inhibitors (100% usage, limited by genito-urinary tract infections). Mineralocorticoid receptor antagonists (60-70% usage, limited by hyperkalemia). ARNI (30-40% on full dose, 60% on a small dose, limited by hypotension and azotemia). BBs (80-90% usage, limited by bradycardia, respiratory diseases, and PR prolongation on ECG).

Only about 60% of patients receive all four pillars of HF therapy in clinical practice. Common factors limiting patient outcomes in HF management in India include

patient drop-out due to cost burden and influence of other medical systems, high salt diet, late specialist referral, physician inertia, and stopping medications due to mild hypotension. High pill burden, multiple comorbidities, and previous cardiovascular surgeries complicate HF management. Lack of awareness among patients and their relatives about HF, treatment importance, drug benefits, and side effects contribute to poor outcomes. Poor fluid intake is a challenge; patients should intake at least 2 liters/day in summer and 1.5 liters/day in winter/spring. HF patients with pulmonary edema require reduced IV fluid administration. A HR above 70 bpm is associated with poor outcomes if not optimized. Cost, reluctance to follow-up, and uncontrolled risk factors are major barriers to better outcomes. Non-compliance is also caused by late diagnosis, misguidance due to bill burden, and lack of awareness about SGLT2 inhibitors among general physicians. Other limiting factors include comorbidities like iron deficiency, smoking, and thyroid disorders. Experts suggest an average reduction in resting HR of approximately 8 to 10 beats per minute over 3 months with GDMT in HF patients, although individual responses may vary based on baseline HR. The severity of HF, indicated by factors like higher NYHA class, multiple comorbidities, frequent hospitalizations, and complications, can elevate HR. Smoking contributes to increased HR in HF patients, emphasizing the importance of advising cessation of smoking and alcohol consumption. Etiologies such as anxiety and thyroid disorders should be excluded to accurately diagnose increased HR. Comorbidities like anaemia, COPD, and tuberculosis and their complications can elevate HR, necessitating proper treatment for HR control. General practitioners should be educated about the importance of maintaining therapy and referring patients to cardiologists, especially when there is a decrease in HR.

Change in heart rate and NT-pro-BNP: correlation

NT-proBNP serves as a crucial prognostic biomarker in HF; however, its interpretation can be influenced by various clinical factors, requiring healthcare providers to consider these factors when making therapeutic decisions. While the reduction in HR positively affects clinical outcomes, experts acknowledge the lack of documented evidence linking it directly to a reduction in NT-proBNP levels. Challenges in using NT-proBNP for HF diagnosis include high cost and limited availability of laboratory services, leading to reliance on symptomatic relief for treatment decisions. Experts agree that reduction in HR has a positive impact on clinical outcome and therefore, there will be reduction in NT-proBNP as a mark of clinical improvement.

Impact of HR lowering medications on clinical outcomes in HF: BB, ivabradine

BBs are the primary HR lowering medications, commonly prescribed in HF, followed by ivabradine and digoxin. Cardio-selective BBs such as bisoprolol are preferred in HF management, with metoprolol and carvedilol also being commonly used. Ivabradine demonstrates the highest average reduction in heart rate, approximately 12 to 14 bpm if the baseline HR is >90 bpm, with minimal risk of bradycardia. BBs typically reduce HR by 6 to 8 bpm if the baseline HR >90 bpm, with dosage adjustments possible after 8 to 12 weeks, while monitoring BP. In cases of atrial fibrillation, BBs are preferred for HR control, while ivabradine is avoided. The typical usage pattern involves initiating BBs, up-titrating if desired HR is not achieved and adding ivabradine if necessary. Ivabradine is often initiated as OD formulation for better adherence and cost-effectiveness. When baseline HR is >90 or 100 bpm, some experts suggest initiating a combination of BB and ivabradine, with dosage adjustments based on HR optimization and tolerability. Digoxin may be added in cases of contradictions to BBs and ivabradine, aiming to increase contractility and decrease HR. Diltiazem is used specifically in preserved HF. Healthcare providers commonly advise single-dose formulations for better compliance, favouring extended-release OD formulations. The threshold for changing HR lowering medication is typically 90 beats/min, with a gradual transition process. Most HCPs agreed that they initiate ivabradine once daily formulation directly without starting with twice daily formulation. This helps to reduce pill burden and cost of therapy.

SUMMARY

HF presents a significant global burden, particularly in low- and middle-income countries like India, affecting approximately 22.7 million individuals, predominantly with HFrEF. Despite therapeutic advancements such as quadruple therapy, patients still face a bleak prognosis, underscoring the imperative for further optimization. Elevated resting HR emerges as a critical prognostic factor in HF, strongly correlated with adverse cardiovascular outcomes. Persistent challenges in HF management include underutilization of GDMT and barriers to treatment adherence. Exploring HR dynamics in HF unveils its prognostic implications, advocating for personalized treatment modalities. Studies on BBs and ivabradine highlight their potential to lower HR and enhance clinical outcomes. Expert recommendations underscore the importance of optimizing HR control in HF management to mitigate mortality and hospitalization risks. Challenges such as limited access to GDMT and suboptimal treatment adherence necessitate comprehensive strategies to enhance patient outcomes. Among the array of therapeutic interventions discussed, ivabradine stands out as a promising medication for HR management in HF patients. Studies highlight its ability to significantly reduce HR without inducing bradycardia, offering a valuable addition to the HF treatment arsenal. Expert suggestions advocate for the integration of ivabradine into personalized treatment regimens to enhance outcomes, particularly in patients with elevated resting HR.

CONCLUSION

In conclusion, the article underscores the urgent need for further optimization of therapeutic strategies in HF management, particularly in regions like India grappling with a substantial disease burden. Despite therapeutic advancements, challenges such as underutilization of guideline-directed therapy and adherence barriers persist. Addressing these challenges requires a multifaceted approach, including tailored treatment strategies. Moreover, optimizing HR control is paramount given its robust association with adverse cardiovascular outcomes. Bridging the gap between evidence-based guidelines and clinical practice is essential for improving outcomes and patient quality of life in HF.

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