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Simplifying heart rate management in patients with chronic heart failure and chronic stable angina-Challenges and role of pharmacotherapy

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Abstract
Heart failure is one of the leading causes of hospitalizations and mortality worldwide, and its risk is increased with presence of angina. Major challenges faced are increased heart rate and other cardiovascular risks, timely diagnosis, presence of comorbidities, monetary burden, and polypharmacotherapy. This consensus was developed from the outcome of 6 online advisory board meetings conducted in September 2020 involving 80 cardiologists across India to simplify management of heart failure and stable angina by providing alternate pharmacotherapy approach using ivabradine. Various studies have accessed the efficacy and safety profile of ivabradine in management of heart failure and angina. The Proficient (Prolonged Release Formulation of Ivabradine once-daily in heart Rate Management) study showed that once daily Ivabradine prolonged release (PR) was equally safe as ivabradine twice daily instant release (IR) in heart failure. The Beautiful, Shift, and Signify trials have shown reduction in heart rate in heart failure and stable angina, with improvement in cardiovascular outcomes. The expert panel recommended to use ivabradine if target blood Pressure is not achieved and is more than 90 mm Hg. Drug interaction of ivabradine and itraconazole, diltiazem, or verapamil needs to be ascertained while prescribing these medications. Further, the experts recommend use of ivabradine when electrocardiogram shows atrial fibrillation and suggest that time of taking ivabradine should be advised considering the circardian rhythm and sympathetic drive and depending on use of single daily dose of ivabradine prolonged release instead of twice daily dose of ivabradine immediate release.

Keywords: heart failure, stable angina, ivabradine prolonged release, polypharmacy, heart rate

Introduction
Heart failure (HF) is a major public health concern affecting more than 37.7 million people in the world with its burden projected to rise swiftly to about 25% by the year 2030. Incidence of HF in India varies widely from 1.3 to 23 million [1] As per 2012 data, global healthcare expenses of HF reached around US $31 billion. Predictions from 2012 to 2030 evaluate the healthcare charges to increase by about 127% [2]. In patients aged >65 years, chronic heart failure (CHF) is the major cause of hospitalisation [3]. Around 50% of patients with HF die within 5 years from diagnosis [4].
On the other hand, between 1990 and 2010, global prevalence of angina decreased significantly [5]. Also, as per the Prospective Observational Longitudinal Registry of patients with stable coronary Artery disease (CLARIFY) registry, angina prevalence in India reduced from 27.8% to 11.2% over a 5-year period (P<0.0001). This prevalence was similar to that in the rest of the world (14.5%) [6].
Furthermore, as per a study by Eisen et al presence of angina increases the risk for heart failure as compared to absence if angina (adjusted odds ratio 1.17; confidence interval [CI]: 1.06–1.28; P = 0.002) [7].

Challenges in managing chronic heart failure and chronic stable angina
A major challenge in HF management remains its timely diagnosis given that it often gets diagnosed at a stage when preserved ejection fraction (pEF) is >50% [8]. Similar diagnostic undertesting was reported in the Stable Angina Observational Registry (STAR), which included a large cohort of Indian patients [9]. Further, HF management is complicated due to non-adherence to guideline-directed medical therapies (GDMT) on account of the various patient profiles that present to the clinic such as patients of varying age groups, patients having comorbidities like diabetes, kidney disease, angina, or other cardiovascular diseases (CVDs). Moreover, early rehospitalizations post discharge, in the general population is a matter of concern [8].
As per a study by Gupta et al, cardiovascular risk factors have even found to increase exponentially in the younger Indian population aged 30-39 years [10]. In a study enrolling six villages under a primary health care center in Northern India, the prevalence of HF in outpatient departments was 22.5% (for patients aged <30 years) and 14.9% (for patients aged >50 years), which reflects a higher prevalence of HF among the younger population

in India compared to that from western countries. This finding is similar to that observed in the Trivandrum Heart Failure Registry (THFR) [11].

Furthermore, an increased heart rate (HR) has been shown to cause increased mortality due to cardiovascular causes. Increased HR correlated with cardiovascular mortality and hospital admission as seen from the outcomes of the Coronary Artery Surgery Study (CASS). A resting HR (RHR) of >83 bpm at the beginning of the study was a risk factor for all-cause and cardiovascular deaths [12]. Evidence suggests that HR is inadequately controlled in more than half of CHF patients being treated with beta-blockers. Larger clinical trials also suggest that a substantial number of patients cannot tolerate target doses and up-titration is not possible [13].

HF and angina management challenges are further escalated due to increasing monetary burden and limited access to diagnostic care and treatment in the secondary and tertiary settings. Moreover, there is a lack of large scale studies encompassing data across India to understand epidemiology of HF and angina that will help improve their management [**Error! Bookmark not defined.**] When considering GDMT, another aspect that leads to its non-compliance is the polypharmacotherapy approach. HF patients often have accompanying comorbidities that require administration of multiple drugs to manage each disease symptom [14]. As per a study from Sudan, non-adherence was significantly higher among those taking five or more medications daily than those taking lesser number of medications. It was apparent that medication adherence could be improved if the total number of pills prescribed per day are reduced [15] Based on the situation-specific theory of HF self-care, when the burden of a symptom interferes with attaining a personal goal, participants respond with medication non-adherence [16].

Polypharmacotherapy has shown to cause drug interactions that may lead to reduced efficacy of treatment or adverse events. As per the Acute Infarction Ramipril Efficacy (AIRE) trial, angiotensin-converting-enzyme (ACE) inhibitor benefit was reduced due to coadministration of aspirin. Production of vasodilating prostaglandins by ACE inhibitors is affected by aspirin. Another study showed that administering aldosterone antagonist along with either ACE inhibitors or angiotensin II receptor blockers (ARBs) may increase the risk of renal failure and hyperkalemia. Further studies have shown that probability of having an adverse drug reaction increases from 13% for individuals taking two drugs, to 82% when more than seven drugs are taken, to 100% when more than 10 drugs are used [17].

Current management of chronic HF and stable angina

Chronic HF and angina are predominantly managed by pharmacological therapy [1]. Both American College of Cardiology/American Heart Association (ACC) guidelines and 2016 European Society of Cardiology (ESC) guidelines recommend the use of ACE inhibitor therapy for patients with current or prior HF symptoms, those with stable coronary artery disease (CAD) even without left ventricular systolic dysfunction. As per ESC guidelines, there is a broader indication for ivabradine for patients who cannot tolerate or are contraindicated for beta-blockers. ACC recommends beta-blockers for patients with HF with reduced ejection fraction (HFrEF), whereas ESC recommends their use for patients with prior myocardial infarction (MI). ARB treatment is considered acceptable as an alternative vasodilator for patients intolerant of ACE inhibitors (ESC) or as a first-line alternative to ACE inhibitor treatment (ACC) [18]. Diuretics are mainly used to manage the signs and symptoms of congestion and may improve clinical outcomes. Per Indian management guidelines, beta-blockers and ivabradine are effective agents for the management of angina in HF patients (Figure 1) [1]. Ivabradine has also been recommended to manage symptoms of angina with nitrates and use of oxygen or continuous positive airway pressure (CPAP) for sleep disordered breathing in older patients [3].

The use of an angiotensin receptor neprilysin inhibitor (ARNI) such as sacubitril or valsartan now receives a Level I recommendation by ACCG for New York Heart Association (NYHA) functional class II/III patients who have been stable on a prior regimen of ACE inhibitor or ARB [17].

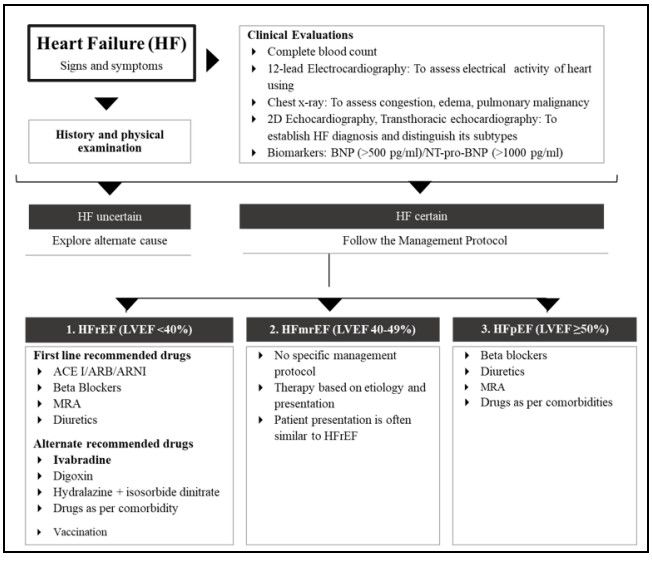

Fig 1: Standard diagnosis and management protocol for heart failure (2017)**Error! Bookmark not defined.**

Aim of The Discussion and Review

An online advisory board meeting was conducted with eminent cardiologists from across India to obtain their perspectives on simplifying heart rate management in patients with HF/stable angina, including the challenges and roles of pharmacotherapy. Based on the meeting, a consensus document was developed to provide a framework for clinicians and healthcare providers on effective management and achieving successful clinical outcomes in people with HF and stable angina in the context of ivabradine use and polypharmacy.

Heart rate management in heart failure: Significance and outcomes

In adults, RHR ranges from 60 to 70 bpm and is proportionally lower with age. This varies depending on physical activity and emotional states as HR is regulated by the autonomic nervous system. Therefore, HR is a prominent biomarker that reflects the activity of the sympathetic and parasympathetic nervous systems [19]. Furthermore, the significance of HR (Figure 2) in the management of HF can be understood by elucidating the mechanism [20] involved in cases of fatalities occurring due to an increased HR.

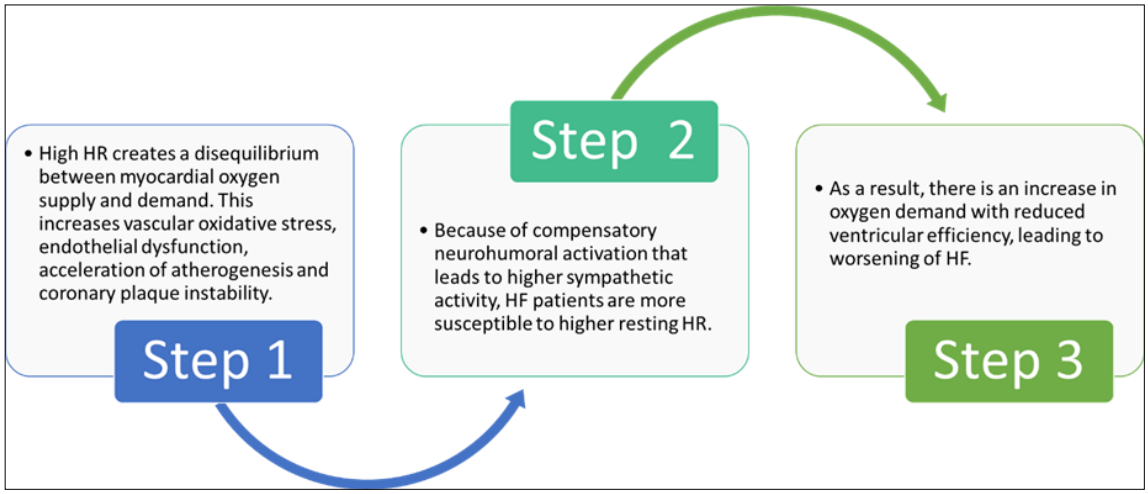

Fig 2: Significance of HR management in HF [20]

With regard to outcomes of HR management, the Framingham study was the first to quantitatively demonstrate that with every 10 bpm rise in HR, all-cause mortality increases by 14% [19]. Similar results were obtained in a meta-analysis conducted by Zhang et al., which revealed that the relative risk for all-cause mortality and cardiovascular mortality increased by 9% and 8% with every 10 bpm rise in HR, respectively [21]. Thus, management of HR seems to play a pivotal role in the pathogenesis of HF.

Ivabradine for heart rate reduction in chronic heart failure

Drug classes such as ACE inhibitors, β-blockers, and ARBs form the first line of therapy in patients with HF. However, drug classes such as β-blocker have a negative ionotropic effect, and this limits their use in HF patients. In such a scenario, a pure heart rate lowering agent without other pharmacological effects such as ivabradine would be a real lifesaver [22]. Furthermore, it is due to this unique property of ivabradine that it has been recommended for use by various latest HF guidelines including those of the ACC, the AHA, and the ESC [18].

Polypharmacotherapy and poor compliance – major challenges in HF affecting outcome in Indian patients

Polypharmacotherapy is defined as the chronic use of five or more medications. The situation gets even worse with age and in those who have HF with or without associated comorbidities, as these form the major proportion of patients who are non-adherent to prescribed treatment. Even more alarming are the consequences accompanying polypharmacy as per the following data:

- Non-adherence to a medical regimen was responsible for 42% of hospital admissions with cardiac decompensation among 179 patients with HF.
- Patients with poor adherence who took <75% of the prescribed beta-blocker regimen had a 2.5 to 3.1-fold increase in the risk of dying within a year.

Therefore, to maximize adherence, it is important to simplify the pharmacological regimen, in terms of both the number of medications and its frequency of intake [17]. This is especially so in the case of Indian patients who are more prone to receive polypharmacotherapy [23].

Ivabradine once daily– The quest for better compliance

Having understood the fatal effects of polypharmacotherapy, there is a need for a regimen that can be safe, effective, and patient compliant. In this regard, the SHI$_f$T trial[24] has shown that ivabradine twice daily (B.D.) was effective in lowering heart rate and in-turn improving cardiovascular outcomes in patients with stable

symptomatic chronic HF. Given the concerns around compliance of cardiovascular medication, an O.D. dose rather than a B.D. dose appears to be a suitable option to tackle this issue.

Landmark phase 3 trial on ivabradine prolonged release

The **Proficient** (**Pro**longed Release **F**ormulation of **I**vabradine On**c**e-Dai**l**y in H**e**art Rate Management) study [25] was a landmark phase 3 trial that established the safety and efficacy of ivabradine prolonged-release (PR) once-daily versus ivabradine immediate-release (IR) twice-daily tablets in patients (n = 180) with stable chronic HF and systolic dysfunction.

The inclusion criteria for the study were adults aged 18-70 years currently receiving a stable dose of ivabradine IR 5 mg /7.5 mg BID for ≥1 month for stable chronic HF with systolic dysfunction and concurrently receiving standard care for stable CHF. Patients had documented stable chronic HF per New York Heart Association (NYHA) Class II to III for ≥6 weeks at the time of screening and had left ventricular ejection fraction (LVEF) ≤40% at screening.

Patients were randomly assigned in a ratio of 1:1 to receive ivabradine PR (10 mg/15 mg) or ivabradine IR (5mg/75 mg). The primary outcome was to compare the efficacy (change in RHR from baseline up to 3 months) of ivabradine PR versus ivabradine IR tablets. The secondary outcomes included safety and tolerability as assessed by incidence of adverse events (AEs), serious adverse events (SAEs), and treatment-emergent adverse events (TEAEs). Exploratory outcomes included incidence of hospitalizations for worsening HF, other CV reasons, CV mortality, or all-cause mortality from baseline to end of 3 months during the trial. For patients in the Holter subgroup, the objective was to compare the changes in HR measured by automated 12-lead ECG to that of HR measured by 24-hour Holter ECG.

The study results are summarized below:

- Baseline HR with ivabradine PR: 62.8 (9.47)
- Baseline HR with Ivabradine IR: 63.6 (8.85)
- Change from baseline at 3 months in Ivabradine PR: 1.1 (8.42)
- Change from baseline at 3 months in Ivabradine IR: 0.0 (7.99)
- For ivabradine PR vs. ivabradine IR, the least-square mean (standard error [SE]) for change in HR from baseline to 3 months was 0.76 (1.188; 95% confidence interval (CI) -1.59:3.11). This was well within the pre-specified limit of 6.5 bpm. This showed that ivabradine PR was non-inferior to ivabradine IR in the management of patients with stable CHF, with a comparable safety and efficacy profile.

The study demonstrated no significant difference in change in HR from baseline to 3 months between the resting HR measured by 12 lead ECG and mean 24-hour HR, mean HR (awake), and mean HR (asleep) baseline measured by 24-hour Holter ECG monitoring.

No new safety concerns were reported during the conduct of the clinical trial. None of the TEAEs in the either of the treatment arms were unexpected. Assessment of laboratory parameters, vitals, physical examination, and visual symptoms showed no clinically significant findings in both the arms. The results supported that ivabradine PR showcased a good safety profile at par with ivabradine IR.

Thus, the study revealed that ivabradine once daily/PR could be used as an alternative to its conventional twice daily/IR formulation.

Ivabradine for stable angina

HR is a determinant of myocardial oxygen demand and therefore its increase can result in the development of myocardial ischemia and angina. Hence, reduction of heart rate is an important treatment strategy for improving both symptoms of myocardial ischemia and quality of life (QOL) in patients with chronic stable angina.

Ivabradine is a selective cyclic nucleotide-gated transmembrane channel inhibitor that generates a pacemaker-like or "funny" current (If) in sinoatrial nodal tissue that results in a dose-dependent reduction in HR without causing any negative ionotropic adverse effect [26] the major trials that hint towards the role of ivabradine in patients with stable angina include Beautiful, Shift, and Signify. Their outcomes are summarized in Table 1.

Table 1: Overview of major trials with ivabradine

Trial name	**Beautiful** [27, 28, 29]		**SHIFT** [24, 30]		**Signify** [31, 32]	
The morBidity-mortality Evaluation of the I(f) inhibitor Ivabradine in patients with coronary disease and left Ventricular dysfunction study						
	Main Trial	**Sub-group Analysis**	**Main Trial**	**Sub-group Analysis** [31]	**Main Trial** [32]	**Sub-group Analysis** [33]
Trial arms	Ivabradine and placebo	Patients with limiting angina and without limiting angina (Placebo-controlled)	Ivabradine and placebo	Angina and non-angina	Ivabradine and placebo	Ivabradine and placebo
Participants	5479 and 5438	1507 and 9410	3241 and 3264	2220 and 4285	9550 and 9552	2618 and 2613

Major outcomes	Ivabradine reduced HR by 6 bpm at 12 months	a. A decrease in primary composite endpoint (cardiovascular death; hospitalization for acute MI; or hospitalization for new or worsening HF) (P=0.05) b. Decrease in hospitalization for acute MI (P=0.021)	Lowering of heart rate and improvement in cardiovascular outcomes in patients with stable symptomatic chronic HF	Ivabradine numerically reduced the primary composite endpoint by 8%, 11%, and 11% in the angina subgroup, non-angina subgroup, and overall population, respectively.	Improvements (P=0.01) in angina of CCS class II or higher at 3 months	Increase in self-reported quality of life in terms of angina frequency (P<0.001) and disease perception (P=0.006)

CCS, Canadian Cardiovascular Society; HF, heart failure; HR, heart rate; MI, myocardial infarction

Experts' comments on the role of ivabradine in patients with stable angina and chronic heart failure

1. Eligibility for ivabradine therapy: All patients are eligible after giving adequate beta blockers and after going up to the maximal tolerated dose, if blood pressure is still more than 90 mmHg and target HR is not achieved then ivabradine will be added.
2. Target HR of 60 BPM is comfortable, but up-titration of beta blockers has several drawbacks and is poorly practiced in physician groups. A small dose of beta blocker with ivabradine is ideal for that case.
3. Drug interaction of itraconazole with ivabradine is significant and should be kept in mind. Diltiazem and verapamil should be avoided. Ivabradine with non-dihydropyridine calcium channel blocker should be avoided.
4. Ivabradine should be added when ECG shows intermittent atrial fibrillation.
5. Recommended time to administer ivabradine is in the morning but is also on the discretion of the physician to either give it in the morning or night considering the circardian rhythm and sympathetic drive. During hospitalization period, IR formulation can be titrated and at the time of discharge, the patient can be put on PR formulation.

Conclusion

Chronic heart failure and angina are leading causes of mortality and economic burden to the society, with management becoming complicated due to comorbidities. The burden further rises due to various factors such as non-adherence to GDMT, which is many a times amplified by use of polypharmacotherapy. The new study on ivabradine PR helps to understand the advantage of the ivabradine PR, in establishing its non-inferiority in achieving clinical outcomes over the conventional IR formulation in patients with stable chronic heart failure and systolic dysfunction on stable dose of ivabradine IR and in reducing the medication frequency burden to patients.

Conflict of interests

None to declare.

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References

1. Mishra S, Mohan JC, Nair T, Chopra VK, Harikrishnan S, Guha S, et al. Management protocols for chronic heart failure in India. Indian Heart J,2018:70:105-127.
2. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev,2017:3:7-11.
3. Azad N, Lemay G. Management of chronic heart failure in the older population. J Geriatr Cardiol,2014:11:329-337.
4. Jones NR, Hobbs FR, Taylor CJ. Prognosis following a diagnosis of heart failure and the role of primary care: a review of the literature. BJGP Open, 2017, 1. bjgpopen17X101013.
5. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, et al. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. Circulation,2014:129:1493-1501.
6. Hiremath S, Vala DR, Roy T, Khera P, Kaul U. Changing patterns in the prevalence and management of cardiovascular risk factors in India and their comparison with the rest of the world along with clinical outcomes at 5-year: An analysis of stable coronary artery disease patients from The Prospective Observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY) registry. Indian Heart J,2018:70:S36-S42.

7. Eisen A, Bhatt DL, Steg PG, Eagle KA, Goto S, Guo J, et al. Angina and future cardiovascular events in stable patients with coronary artery disease: insights from the reduction of atherothrombosis for continued health (REACH) registry. J Am Heart Assoc,2016:28:5:e004080.
8. Komajda M. Current Challenges in the Management of Heart Failure. Circ J,2015:79:948-953.
9. Pahlajani D, Kaul U, Mishra A, Mullasari A, Sawhney J, Dargad R, et al. Medical management and diagnostic testing among stable angina patients in India: The STable Angina obseRvational (STAR) Registry. J Assoc Physicians India,2015:63:20-26.
10. Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India: Current epidemiology and future directions. Circulation,2016:133:1605-1620.
11. Chaturvedi V, Parakh N, Seth S, Bhargava B, Ramakrishnan S, Roy A, et al. Heart failure in India: The INDUS (INDia Ukieri Study) study. J Pract Cardiovasc Sci,2016:2:28-35.
12. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J,2005:26:967-974.
13. Volterrani M, Iellamo F. Complementary and synergic role of combined beta-blockers and ivabradine in patients with chronic heart failure and depressed systolic function: A new therapeutic option? Card Fail Rev,2016:2:130-136.
14. Rushton CA, Kadam UT. Polypharmacy in heart failure: a growing challenge. Br J Card Nurs,2011:6:214-220. https://doi.org/10.12968/bjca.2011.6.5.214.
15. Awad A, Osman N, Altayib S. Medication adherence among cardiac patients in Khartoum state, Sudan: a cross-sectional study. Cardiovasc J Afr,2017:28:350-355.
16. Meraz R. Medication nonadherence or self-care? Understanding the medication decision-making process and experiences of older adults with heart failure. J Cardiovasc Nurs,2020:35:26-34.
17. Mastromarino V, Casenghi M, Testa M, Gabriele E, Coluccia R, Rubattu S, et al. Polypharmacy in heart failure patients. Curr Heart Fail Rep,2014:11:212-219.
18. van der Meer P, Gaggin HK, Dec GW. ACC/AHA versus ESC guidelines on heart failure: JACC guideline comparison. J Am Coll Cardiol,2019:73:2756-2768.
19. Hori M, Okamoto H. Heart rate as a target of treatment of chronic heart failure. J Cardiol 2012;60:86-90.
20. Badu-Boateng C, Jennings R, Hammersley D. The therapeutic role of ivabradine in heart failure. Ther Adv Chronic Dis,2018:9:199-207.
21. Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. CMAJ,2016:188:E53-E63.
22. Nawarskas JJ, Bowman BN, Anderson JR. Ivabradine: A unique and intriguing medication for treating cardiovascular disease. Cardiol Rev,2015:23:201-211.
23. Tandon N, Anjana RM, Mohan V, et al. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990-2016. India state-level disease burden initiative diabetes collaborators. Lancet Glob Health,2018:6:e1352-e1362.
24. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet,2010:376:875-885.
25. Mullasari A. PROFICIENT investigators. Efficacy and safety of ivabradine once-daily prolonged-release versus twice-daily immediate-release formulation in patients with stable chronic heart failure with systolic dysfunction: a randomized, double-blind, phase 3 non-inferiority (PROFICIENT) study. Cardiol Ther,2020:9:505-521.
26. Kim SJ. Ivabradine for the therapy of chronic stable angina pectoris. Korean Circ J,2020:50:787-790.
27. Ferrari R. Ivabradine in the management of coronary artery disease with or without left ventricular dysfunction or heart failure. Eur Heart J,2015:17:G24-G29.
28. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet,2008:372:807-816.
29. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R; BEAUTIFUL Investigators. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur Heart J,2009:30:2337-2345.
30. Borer JS, S Swedberg K, Komajda M, Ford I, Tavazzi L, Böhm M, et al. Efficacy profile of ivabradine in patients with heart failure plus angina pectoris. Cardiology,2017:136:138-144.
31. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Signify Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med,2014:371:1091-1099.
32. Tendera M, Chassany O, Ferrari R, Ford I, Steg PG, Tardif JC, et al. Quality of life with ivabradine in patients with angina pectoris: the study assessing the morbidity-mortality benefits of the If inhibitor ivabradine in patients with coronary artery disease quality of life substudy. Circ Cardiovasc Qual Outcomes,2016:9:31-38.