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Advancing heart failure management: A comparative analysis of Ivabradine and Sacubitril / valsartan

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Abstract
This review provides a comprehensive analysis of two prominent heart failure treatments, Ivabradine and Sacubitril/Valsartan, highlighting their distinct mechanisms and clinical efficacy. Ivabradine primarily reduces heart rate by inhibiting the funny current in the sinoatrial node, offering benefits particularly in chronic heart failure patients with elevated heart rates. On the other hand, Sacubitril/Valsartan, an ARNI, has shown significant benefits in reducing mortality and hospitalization rates in heart failure with reduced ejection fraction (HFrEF), but its effects in HFpEF and HFmrEF are less conclusive. While Sacubitril/Valsartan offers a ground-breaking approach in heart failure treatment, it also presents an increased risk of hypotension. This review suggests that the choice of therapy should be tailored to individual patient profiles to optimize outcomes in heart failure management.

Keywords: Heart failure treatments, ivabradine, sacubitril/valsartan, clinical efficacy, patient profiles

Introduction
The gold standard for visualising the peri coronary and epicardial adipose tissues is modern coronary computed tomography angiography (CTA) (PCAT). The visceral pericardium encloses the metabolically active fat depot known as the EAT, which encircles the coronary arteries. Adipocytokines are secreted by EAT in disease states where there is an increase in the volume of EAT and dysfunctional adipocytes. This imbalance between pro- and anti-inflammatory mediators may have atherogenic effects on the coronary vessel wall through a paracrine mechanism known as "outside-to-inside" signalling. It has been shown that these atherogenic effects of EAT raise the risk of coronary artery disease, myocardial ischemia, high-risk plaque characteristics, and significant adverse cardiac events in the future. Coronary inflammation is a major factor in the onset and course of coronary artery disease, yet noninvasively detecting it is still difficult. In the future, the PCAT's CTA-derived analysis may alter this clinical conundrum. Promising imaging biomarker and "sensor" to noninvasively detect coronary inflammation is PCAT computed tomography attenuation, especially around the right coronary artery derived from routine CTA. This is based on the idea of an "inside-to-outside" signalling between the inflamed coronary vessel wall and the surrounding PCAT [1]. Cardiology Patients' Modern Therapy-Though cardiovascular problems still provide a major concern; haemodialysis procedures have been improved by advances in nephrology. The intricate interaction of several risk factors and the immediate consequences of haemodialysis must be taken into account in therapeutic approaches. For CKD patients, effective cardiovascular health care regimens that cover traditional risk factors as well as those unique to uraemia and haemodialysis require ongoing research and clinical trials [2].

Ivabradine: Ivabradine is in a class of medications called hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers. It works by slowing the heart rate so the heart can pump more blood through the body each time it beats.

Mechanism of Action: Ivabradine selectively inhibits the pacemaker if current in a dose-dependent manner. Blocking this channel reduces cardiac pacemaker activity, selectively slowing the heart rate and allowing more time for blood to flow to the myocardium.

Ivabradine in Heart Failure Management

Table 1: Table provides a concise view of various clinical outcomes related to Ivabradine therapy across different patient groups with heart failure, underlining the efficacy and adjustments in dosage during treatment trials

Patient Group	Dose of Ivabradine	Study type	Key Findings
Patients with HF (LVEF < 40%, HR > 70 bpm)	2.5–7.5 mg, b.i.d. for >12 months	Retrospective cohort study	Decreased risk and number of hospitalizations, unchanged length of hospitalization and death rate [3]
Moderate-to-severe HF patients with HR > 70 bpm (SHIFT study)	Started at 5 mg b.i.d., titrated to 7.5 mg b.i.d. or 2.5 mg b.i.d.	Randomized, double-blind, placebo-controlled trial	Lower event rates in patients with 0 or 3+ comorbidities, reduced HF hospitalization [3]
Hemodynamically stable acute HF patients	Started at 5 mg daily, followed by 10 mg daily for >90 days	Retrospective cohort	Reduced length of hospitalization, rehospitalization, high dose of β-blockers, improved NYHA class [4]
Moderate-to-severe HF patients with HR > 77 bpm (SHIFT study)	Started at 5 mg b.i.d., titrated to 7.5 mg b.i.d. or 2.5 mg b.i.d. for 31–35 months	Randomized, double-blind, placebo-controlled trial	Improved NYHA class, global self-assessment, health-related quality of life, reduced all-cause cardiovascular death, hospitalization, and mortality [5]
Patients with chronic HF (RELIf-CHF study)	5 mg b.i.d., titrated to 7.5 mg or 2.5 mg b.i.d. for 12 months	Observational follow-up study	Improved NYHA class, general health, quality of life, reduced decompensation and HF hospitalizations [6]
Moderate-to-severe HF patients with HR < 75 and >75 bpm (SHIFT study)	5 mg b.i.d., titrated to 7.5 mg b.i.d. for a median follow-up of 22.5 months	Randomized, double-blind, placebo-controlled trial	In HR > 75 bpm group: reduced cardiovascular death, death from HF, hospitalization; In HR < 75 bpm group: no difference in outcomes [7]
Hospitalized HF patients in the SHIFT study	Started at 5 mg b.i.d., titrated to 7.5 mg b.i.d. or 2.5 mg b.i.d. for 3 months	Randomized, double-blind, placebo-controlled trial	Reduced all-cause hospitalization at 1, 2, and 3 months, unchanged hospitalization due to cardiovascular causes, unchanged death rate [8]

Pharmacology of Ivabradine

Pharmacodynamics & Pharmacokinetic

Ivabradine inhibits the transmembrane hyperpolarization-activated cyclic nucleotide (HCN) gated channel, which regulates the "funny" current (If) and consequently impacts the automaticity of sinus nodes. The action potential's slow diastolic depolarization phase, which is characteristic of myocytes in the sinoatrial (SA) node, is what causes the SA node to produce recurrent action potentials and spontaneous activity. It was first explained in 1979 as an inward current that is carried by both Na+ and K+ ions and passes through the HCN channels. These channels are activated at the end of the action potential when the potential is hyperpolarized to between -40 and 50 mV (Fig. 1) [9]. The diastolic depolarization phase's slope and, consequently, the heart rate are influenced by the current's amplitude. Cyclic adenosine monophosphate (cAMP) facilitates if, which is responsible for mediating control of automaticity at the SA node. cAMP is increased with stimulation of beta-adrenergic receptors and decreased upon release of acetylcholine (ACh). The heart rate decreases when cAMP levels mediated by ACh fall, which also results in a decrease in the slope of depolarization via If; the opposite is also true when cAMP levels rise in response to beta adrenergic stimulation. By altering the voltage dependency of activation, the cyclic nucleotide-binding domain in the carboxyl terminus of the channel enhances channel activation once cAMP binds to it. The intracellular binding site of the HCN channel is particularly bound by ivabradine, which inhibits cation transport and lowers the slope of the action potential's depolarization phase, hence lowering the heart rate [10, 11, 12]. A number of channels, including T and L type calcium channels that influence inotropy and IK1/K2 that impact the action potential's length, are unaffected by ivabradine's inhibition of the If current. Ivabradine reduces conductance by selectively binding the open HCN channel. This leads to a higher drop-in heart rate at faster heart rates and a use-dependent block, with the kinetics depending on the availability of open channels [13]. There are four distinct isoforms of HCN channel, with HCN4 being the main target, and ivabradine's method of action varies depending on which isoform is present [14]. The inhibitory activity of ivabradine differs from that of other rate-reducing drugs in that it is based on current rather than voltage and is influenced by the direction of ion passage across the channel [15]. Ivabradine, in contrast to beta-blockers, lengthens the diastolic phase and lowers the cardiac oxygen demand without affecting the short-term left ventricular ejection fraction (LVEF) or stroke volume [16, 17, 18].

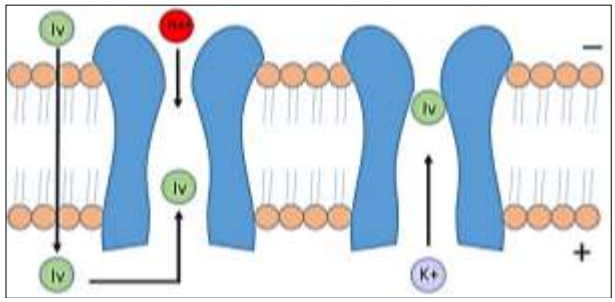

Fig 1: Ivabradine is a use-dependent antagonist of the hyperpolarization-activated cyclic nucleotide (HCN) gated channel which carries the “funny” current (If), located primarily in the SA node of the heart. Ivabradine enters the pore of the HCN channel from the intracellular side when the channel is in the open state. Outward current drives ivabradine into the pore where it binds to its binding site

The effect on lowering heart rate is dose-dependent, meaning that lowering heart rate is correlated with higher doses. With a plateau effect occurring at around 20 mg twice daily, heart rate is lowered by about 10 bpm at typical doses of 2.5 mg to 10 mg twice daily. It takes about one to two hours to achieve peak concentrations. It has an effective half-life of six to twelve hours and is 70% protein bound. It has an oral bioavailability of about forty percent and is metabolised in the liver and intestines by cytochrome P450 3A4 (CYP3A4) enzymes.

As a weak competitive inhibitor of CYP3A4, ivabradine has no effect on the pharmacokinetics of other CYP3A4 substrates. However, strong inhibitors of CYP3A4, like ketoconazole or macrolide antibiotics, can change the pharmacokinetics of ivabradine and should not be used in combination with it. Studies have demonstrated that concurrent administration of ivabradine and those drugs worsens cardiovascular outcomes [19, 20].

Moderate CYP3A4 inhibitors, such as diltiazem and verapamil, can also exacerbate the negative effects of ivabradine. Also, individuals with severe liver impairment that increases the risk of accumulation and bradycardia should not use ivabradine. For mild to severe hepatic impairment, however, there is currently no dose modification used [21].

Based on inherited genetic variations in either CYP3A4 or HCN4, certain patient groups may respond well to treatment while others may not; however, conclusive evidence is still missing [22]. For patients with GFR greater than 15 mL/min and chronic renal disease, no dose change is necessary; however, little information is available for those with GFR less than 15 mL/min [23].

In contrast to beta-blockers, which also lower sympathetic activity and have additional effects, ivabradine just lowers heart rate. The use of free fatty acids can be decreased by beta-blockers. permitting increased glucose utilisation, which could be a possible explanation for the reduced oxygen consumption and enhanced energy efficiency of the heart that are observed when beta blocking is used to treat heart failure and ischemic heart disease [24]. Heart rate is governed by a multitude of intricate processes, all of which are mediated by the autonomic nervous system. These mechanisms include baroreceptors found in the atria and ventricles, reflexes mediated via the carotid and aortic sinuses, and neurohormonal and metabolic regulation [25]. Ivabradine does not impact the level of other elements that can influence heart rate availability of open channels, but it does affect the myocardium's ability to generate an electrical impulse. Since there are four distinct isoforms of the HCN channel, with HCN4 being the primary target, ivabradine's method of action varies depending on which isoform is present [26]. In addition to being different from other rate-reducing substances, ivabradine's inhibitory activity is based on current rather than voltage and is influenced by the direction of ion passage across the channel. Ivabradine, in contrast to beta-blockers, short-term increases diastolic duration and decreases myocardial oxygen demand without affecting short-term left ventricular ejection fraction (LVEF) or stroke volume.

The effect on lowering heart rate is dose-dependent, meaning that lowering heart rate is correlated with higher doses. With a plateau effect occurring at around 20 mg twice daily, heart rate is lowered by about 10 bpm at standard doses of 2.5 mg to 10 mg twice daily. It takes about one to two hours to achieve peak concentrations. It is metabolised in the liver and intestines by cytochrome P450 3A4 (CYP3A4) enzymes, with an effective half-life varying from 6 to 12 hours. It is 70% protein bound and has an approximate 40% oral bioavailability. Although strong CYP3A4 inhibitors like ketoconazole or macrolide antibiotics, which are contraindicated when taken with ivabradine, can change the pharmacokinetics of ivabradine, the drug is not a weak competitive inhibitor of CYP3A4 and does not affect the pharmacokinetics of other CYP3A4 substrates. Studies have demonstrated that concurrent administration of ivabradine with those medicines worsens cardiovascular outcomes. Moderate CYP3A4 inhibitors, such as diltiazem and verapamil, can further exacerbate the deleterious effects of ivabradine.

Ivabradine should also not be used in people with severe liver impairment since this increases the risk of build-up and bradycardia. For mild to severe hepatic impairment, however, no dosage adjustment is currently used.

Based on inherited genetic variations in either CYP3A4 or HCN4, some patient groups may respond well while others do not; however, conclusive evidence is still missing. For patients with chronic kidney disease and a GFR of 15 mL/min or higher, there is no need to change the dosage; however, for those with a GFR of less than 15 mL/min, there is insufficient information.

In contrast to beta-blockers, which also lower sympathetic activity and have additional effects, ivabradine just lowers heart rate. The reduced myocardial oxygen consumption and increased energy efficiency observed with beta blockade in the treatment of ischemic heart disease and heart failure may be explained by beta-blockers' ability to reduce the utilisation of free fatty acids, which permits greater utilisation of glucose. A multitude of intricate systems govern heart rate regulation, including baroreceptors found in the atria and ventricles, reflexes mediated by the carotid and aortic sinuses, and neurohormonal and metabolic regulators. Ivabradine does not change other factors that can affect heart rate, but it does affect the myocardium's ability to generate an electrical impulse.

Sacubitril/Valsartan: A Paradigm Shift

The PARADIGM-HF Trial showed that, when compared to enalapril, sacubitril/valsartan significantly decreased the risk of cardiovascular death and heart failure hospitalisation in patients with heart failure with reduced ejection fraction (HFrEF). In patients hospitalised for acute decompensated heart failure, the PIONEER-HF Trial demonstrated that sacubitril/valsartan reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) more than enalapril. The TRANSITION Trial revealed that beginning sacubitril/valsartan before or after discharge was equally safe, indicating that an early start to the therapy may be possible.

Guidelines: Given its demonstrated effectiveness, the 2022 AHA/ACC/HFSA guidelines advise patients with HFrEF to use an ARNI (angiotensin receptor-neprilysin inhibitor) to lower morbidity and mortality. Meta-Studies: Compared to ACE inhibitors and ARBs, sacubitril/valsartan consistently lowers cardiovascular death and all-cause mortality; nevertheless, an increased risk of hypotension is mentioned as a side effect.

Trials of HFmrEF and HFpEF: Trials such as PARAMOUNT, PARAGON-HF, PARALLAX, and PARAGLIDE-HF investigated, with varying degrees of success, the benefits of sacubitril/valsartan in heart failure with preserved ejection fraction (HFpEF) and mid-range (HFmrEF). Biomarkers such as NT-proBNP showed improvements, however clinical outcomes like hospitalisation rates and mortality did not always show the same trend. Particular Results for HFpEF and HFmrEF: Trials with PARAMOUNT and PARAGON-HF: shown NT-ProBNP improvement, but long-term clinical results did

not significantly improve. The PARALLAX and PARAGLIDE-HF trials showed promise in terms of biomarkers and quality of life indicators, however there was inconsistent evidence of a benefit in terms of hospitalisation and death. This substantial body of data demonstrates the complex efficacy profile of sacubitril/valsartan, showing more nuanced outcomes in HFmrEF and HFpEF populations and evident advantages in HFrEF patients.

Conclusion

Ivabradine and Sacubitril/Valsartan, two cardiac drugs, are thoroughly examined in this study, highlighting their importance in the treatment of heart failure. Ivabradine efficiently reduces heart rate and has demonstrated positive effects in a number of patient groups with heart failure, especially in patients with elevated heart rates. Its mechanism of action, which involves selectively inhibiting the sinoatrial node's funny current, enables tailored therapy with a reduced risk of side effects. However, sacubitril/valsartan, an ARNI, has proven revolutionary in the treatment of heart failure. It has been shown to increase survival and decrease hospitalisations in patients with heart failure with reduced ejection fraction (HFrEF), thereby establishing new guidelines for the field.

The effects of Sacubitril/Valsartan, however, are more complex and differ in terms of biomarker improvements and clinical outcomes in heart failure with preserved ejection fraction (HFpEF) and mid-range ejection fraction (HFmrEF). The review emphasises that although sacubitril/valsartan is significantly more beneficial than conventional therapies such as ACE inhibitors or ARBs in some patient populations, more clinical trials and studies are necessary to fully understand its efficacy and safety profile before applying it to HFpEF and HFmrEF. This thorough comparison study emphasises how critical it is to customise heart failure therapies to the unique needs of each patient, keeping in mind the advantages and disadvantages of each option. To optimise patient outcomes and enhance the quality of life for individuals afflicted with this crippling illness, the care of heart failure remains largely dependent on clinical innovation and strong evidence.

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