REVIEW ARTICLE

Ivabradine: pre-clinical and clinical evidence in the setting of ventricular arrhythmias

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Abstract

Background: Ivabradine, an agent lowering the heart rate, acting as a funny current (I_f) specific inhibitor, is responsible for the sinoatrial node's spontaneous depolarization. According to current guidelines, it is indicated in specific heart failure populations and as a second-line treatment option to improve angina in chronic coronary syndromes.

Review of literature: The role of ivabradine in the setting of ventricular arrhythmias has been studied in both experimental and clinical studies. Specifically, experimental studies have examined the role of ivabradine in acute myocardial ischemia, reperfusion, digitalis-induced ventricular arrhythmias, and catecholaminergic polymorphic ventricular tachycardia showing promising results. In addition, clinical studies have shown a beneficial role of ivabradine in reducing ventricular arrhythmias. Ivabradine reduced premature ventricular contractions in combination with beta-blockers in dilated cardiomyopathy patients. Similarly, in catecholaminergic polymorphic ventricular tachycardia, ivabradine reduced dobutamine-induced premature ventricular complexes and improved ventricular arrhythmias burden. On the other hand, current data show no beneficial role of ivabradine in reducing ventricular arrhythmias in myocardial ischemia.

Conclusions: Randomized clinical trials are needed to elucidate the role of ivabradine in reducing the burden of ventricular arrhythmias in various clinical settings. HIPPOKRATIA 2022, 26 (2):49-54.

Keywords: Ivabradine, ventricular tachycardia, ventricular arrhythmias

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Introduction

Ivabradine is an agent lowering the heart rate (HR), acting as a specific inhibitor of the cardiac pacemaker or "funny" current (I_f). At present, ivabradine is indicated in patients with symptomatic heart failure (HF) and an ejection fraction (EF) lower than 35 % and a heart rate >70 beats per minute in sinus rhythm, despite treatment with an evidence-based dose of beta-blocker, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor neprilysin inhibitor (ARNI), and a mineralocorticoid receptor antagonist (MRA), to reduce the risk of HF hospitalization and cardiovascular death[1,2]. Ivabradine should be considered in these patients even if they have contraindications or cannot tolerate beta-blocker therapy[2,3]. Furthermore, ivabradine should be considered a second-line treatment in chronic coronary syndrome to reduce the frequency of angina and improve exercise tolerance[4]. Pre-clinical studies have demonstrated the potential use of ivabradine in reducing the incidence and inducibility of atrial fibrillation (AF) in animal models[5-8]. However, multiple large placebo-controlled randomized clinical trials have provided evidence of an increased incidence of AF in coronary artery disease and HF patients treated with ivabradine[1,9,10]. This has been further corroborated by three meta-analyses which suggest that ivabradine therapy increases the relative risk of AF by 15-24 %[11-13]. Despite these findings, some clinical studies noted a reduced incidence of AF when ivabradine was administered in combination with bisoprolol or metoprolol in patients undergoing cardiac surgery[14,15]. Additional evidence suggests that ivabradine use may reduce the risk of AF in patients with severe HF with left ventricular ejec-

tion fraction (LVEF) ≤35-40 %[12,16]. As such, the current literature regarding the association of ivabradine with AF remains inconclusive. Clinical studies suggest that ivabradine may increase the relative risk and incidence of AF in patients, despite limited pre-clinical and clinical studies proposing an opposite effect. The mechanism of ivabradine's potential effect in inducing AF remains uncertain, although several hypotheses have been proposed. One such theory is the possibility of ivabradine-induced bradycardia shifting the autonomic balance toward sympathetic activation, stimulating sympathetic-vagal dysregulation and the development of AF[12]. This review aims to present pre-clinical and clinical studies that provide data regarding the role of ivabradine in ventricular arrhythmias (VA).

Mechanism of action

The sinoatrial node generates repetitive spontaneous action potentials, which facilitate the pacemaker ability of the heart. This depolarization is initiated by the opening of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels within sinoatrial nodal cells which conduct a slow, inward-depolarizing sodium-potassium current, the I_f current[4]. Ivabradine exerts its therapeutic effect through selective inhibition of the intracellular aspect of HCN channels, disrupting sodium and potassium ion movement through the channel and thus controlling the flux through the HCN channels. This leads to a prolonged diastolic depolarization phase and thereby slows HR[17]. As the activity of ivabradine is dependent on its inhibition of HCN channels in their open state, it is, therefore, more potent at faster HRs[18]. Furthermore, ivabradine inhibits HCN channels in a dose-dependent manner, preventing adverse reductions in HR as its activity saturates at higher concentrations[19].

Experimental studies

Baseline characteristics and key outcomes of the included experimental studies and clinical trials are presented in Table 1. Experimental models have studied the role of ivabradine in the following clinical settings: acute myocardial ischemia, reperfusion, digitalis-induced VAs and catecholaminergic polymorphic ventricular tachycardia (CPVT).

The impact of metoprolol and ivabradine has been studied in acute non-reperfused myocardial infarction in rat models. Both ivabradine and metoprolol reduced arrhythmic mortality and VAs in post-myocardial infarction rats and also reduced QTc prolongation[20]. In another model, ivabradine reduced the combined ventricular tachycardia/ventricular fibrillation (VT/VF) incidence and arrhythmic mortality in the setting of acute myocardial infarction (AMI)[21]. Vaillant et al showed that ivabradine induced a 2.9-fold increase in VF threshold and prevented ischemia-induced monophasic action potential duration compared to controls. At the same time, a significant reduction was noted in the hypoxic area[22]. Mechanisms proposed for the ivabradine-related cardioprotection from ischemia-induced VF include the associated reduction in HR, increased regional myocardial blood flow, and preservation of cardiomyocyte and mitochondrial ultrastructure[22,23]. In another experimental study, ivabradine, but not propranolol, delayed the onset of ischemia-induced VF by preserving myocardial energy status[24]. An additional experimental study showed that ivabradine might be useful to prevent reperfusion arrhythmias if given early during acute myocardial ischemia before percutaneous interventions[25]. Specifically, the authors showed that ivabradine administered throughout ischemia and reperfusion reduced reperfusion VF incidence through HR reduction[25].

Frommeyer et al provided data about the role of ivabradine in digitalis-induced VAs. In this setting, ivabradine demonstrated potent anti-arrhythmic properties by increasing the effective refractory period and post-repolarization refractoriness. Using a standardized pacing protocol, a significant suppression of VF following the infusion of ivabradine was noted[26]. In the setting of CPVT, ivabradine did not reduce *in vivo* ventricular tachyarrhythmias in transgenic CPVT mice[27]. As a result, ivabradine showed to have no role in this setting.

Clinical data

Ivabradine has been found to reduce premature ventricular contractions (PVCs) in various clinical settings. Rayan et al[28] regarding ivabradine's safety and efficacy in idiopathic dilated cardiomyopathy patients using ivabradine as an add-on therapy to the maximally tolerated beta-blocker. PR, QTc, or QRS durations were not prolonged at three months' follow-up, while ventricular ectopic activity was significantly reduced[28]. Mughal et al[29] described the impact of ivabradine in ventricular ectopic beats in a patient with non-ischemic dilated cardiomyopathy. Specifically, carvedilol was changed to ivabradine, and the 24-hour Holter monitor revealed a significant reduction in the burden of ventricular ectopic beats from over 20 % to 4 %[29]. Recently, a case report demonstrated the efficacy of ivabradine in the reduction of PVCs burden originating from the left ventricular summit[30]. Although oral beta-blocker, verapamil, flecainide, and amiodarone were not efficacious, administering ivabradine reduced the PVC burden[30].

Ivabradine has also been used in the setting of CPVT[31]. Specifically, in a young female with CPVT, ivabradine completely suppressed VAs[31]. In addition, in a young boy with CPVT, adding ivabradine to flecainide reduced premature ventricular beats during the exercise test[31]. Kohli et al[32], described an 18-year-old male with CPVT refractory to flecainide, nadolol, and sympathectomy. In this case, VAs were successfully suppressed after the initiation of ivabradine[32].

Ivabradine has been reported to have a beneficial role in dobutamine-induced VAs. Specifically, ivabradine was studied in decompensated HF patients requiring inotropic support, with LVEF <35 %, and sinus rhythm. Compared to the control group, ivabradine at 5 μg/kg/min of do-

Table 1: Characteristics and key outcomes of pre-clinical and clinical studies included in the review.

1st Author (year)	Study Design	Sample Size	Age (years)	Male (%)	Clinical Setting	Dose of Ivabradine	Other Concurrent Medication	Outcomes
Case reports								
Çinier (2022)[18]	CR	1	18	0%	Efficacy of ivabradine therapy for idiopathic VA originating from LV summit and resistant to multiple anti-arrhythmic drugs and catheter ablation.	5 mg BID, up-titrated to 7.5 mg BID at discharge	None reported	Ivabradine 5 mg BID improved the patient's symptoms significantly, and reduced mean HR to 84 bpm, with no side effects observed. After the dose was increased to 7.5 mg BID and the patient was discharged from the hospital, the patient reported no palpitations with ECG showing normal sinus rhythm and mean HR of 79 bpm at 1-week follow-up. 72-hour Holter recording showed 12,000 PVC burden, which was significantly lower compared to before ivabradine treatment. To exclude the effect of catheter ablation and emphasize the effect of ivabradine, ivabradine treatment was discontinued for one week. 72-hour Holter recording revealed an overall burden of 45,000 PVC's, indicating that the suppression of PVC's was due to ivabradine and not a delayed effect of catheter ablation.
Kohli (2020)[20]	CR	1	18	100%	Efficacy of ivabradine therapy in patient with severe CPVT phenotype refractory to flecainide, nadolol, and sympathectomy.	5 mg BID	Flecainide (150 mg BID); nadolol (60 mg BID)	Ivabradine therapy showed suppression of ventricular ectopy and arrhythmias and a reduction in HR. Five days after discontinuing ivabradine, patient experienced syncopal episode due to polymorphic VT which terminated after ICD shock. After restarting ivabradine, patient continued to do well with no side effects.
Mughal (2019)[17]	CR	1	79	0%	Effect of ivabradine therapy on ventricular ectopic beats in patient with non-ischemic dilated cardiomyopathy undergoing cardiac resynchronization device implantation.	2.5 mg BID, up-titrated to 5 mg BID	None reported	Ivabradine therapy resulted in a significant reduction in ventricular ectopic beats load from over 20% prior to commencement of ivabradine, to 4%. Additionally, cardiac resynchronization device ventricular pacing improved to 70%.
Vaksmann (2018)[19]	CS	2	18	50%	Efficacy of ivabradine therapy in patients with CPVT in whom side effects of treatment prompted discontinuation of flecainide or nadolol.	Case 1: 0.08mg/kg or 5 mg QD. Case 2: 0.09 mg/kg or 5 mg BID.	Case 1: Nadolol (1.35 mg/kg BID). Case 2: Flecainide (2.8 mg/kg or 150 mg QD).	Case 1: Ivabradine in combination with nadolol resulted in complete suppression of VA upon repeat exercise tests at 8, 36, and 62 weeks after starting therapy. Treatment was well tolerated. Case 2: Ivabradine in combination with flecainide showed significant reduction of PVCs upon repeat exercise testing 2 weeks after starting therapy. Treatment was well tolerated.
Experimental studies								
Bueno-Levy (2019)[15]	PC	38 stem cell cultures, 15 sinoatrial nodal tissue samples, 36 mice	N/A	N/A	Anti-arrhythmic properties of ivabradine in CPVT in *in vitro* human induced-pluripotent stem cell culture, *ex vivo* mouse sinoatrial node tissue, and *in vivo* transgenic CPVT mice, compared to SK4 channel inhibitor TRAM-34.	6 mg/kg ivabradine or 20 mg/kg TRAM-34	None reported	Ivabradine did not prevent arrhythmic pacing of hiPSC-CMs from CPVT patients. Ivabradine did not reduce the arrhythmic phenotype of calcium transients in sinoatrial nodal tissue of transgenic CPVT mice. Compared to TRAM-34, ivabradine was unable to reduce *in vivo* the ventricular premature complexes and ventricular tachyarrhythmias in transgenic CPVT mice.
Frommeyer (2017)[14]	PC	13	N/A	N/A	Effect of ivabradine on digitalis-induced VAs in *ex-vivo* Langendorff-perfused rabbit hearts.	7.5 mg BID	Ouabain (0.2 μM)	Ivabradine exerted no significant effect on length of QT interval (–4 ms, p=ns) or action potential duration (–15 ms, p=ns), but did result in an increase in effective refractory period (+17 ms, $p<0.05$). Ivabradine treatment significantly increased post-repolarization refractoriness (+32 ms, $p<0.01$) compared to sole ouabain treatment. Ivabradine treatment led to significant suppression of VF, with VF being inducible in only 2 of 13 hearts (15%).
Mackiewicz (2014)[9]	PC	114	N/A	N/A	Effect of ivabradine on VAs in non-reperfused AMI-induced male wistar rats	10 mg/kg	10% chloral hydrate (3 ml/kg body weight); acetaminophen (67 mg/ml drinking water)	Ivabradine reduced average HR by 17%. Combined incidence of VT/VF and arrhythmic mortality post-induced AMI was reduced in rats given ivabradine compared to control. Ivabradine partially prevented proarrhyhmic effects of AMI including increased Ca^{2+} sensitivity of ryanodine receptors, increase in HCN4 expression in the LV and I_f current in LV cardiomyocytes 24 hours post-AMI, and dispersion of monophasic action potential duration 45 minutes and and 24 hours post-AMI.
Marciszek (2020)[8]	PC	180	N/A	N/A	Effect of ivabradine vs. metoprolol on VA in non-reperfused AMI-induced male wistar rats	5 mg/kg ivabradine compared to 20 mg/kg metoprolol	10% chloral hydrate (3 ml/kg body weight); acetaminophen (67 mg/ml drinking water)	Both ivabradine and metoprolol reduced HR by 17% and arrhythmic mortality (14% and 19%, respectively, versus 33% in control, $p < 0.05$) and VAs in post-AMI rats. Both drugs reduced QTc prolongation and decreased sensitivity of ryanodine receptors in isolated cardiomyocytes, but otherwise had no effect on Ca^{2+} handling, velocity of conduction or repolarization. No effects of potential IKr inhibition by ivabradine were found in this setting.
Ng (2013)[13]	PC	35	N/A	N/A	Effect of ivabradine on reperfusion VAs in AMI-induced *ex-vivo* male Sprague-Dawley rat hearts	1 μM	None reported	Ivabradine induced HR reduction both during ischemia (195±14 bpm vs. control 272±14 bpm, $p<0.05$) and at reperfusion (168±13 bpm vs. 276±14 bpm, $p<0.05$), and was associated with reduced reperfusion VF incidence (20% vs. 90%, $p<0.05$). Optical mapping showed a delay to ischemia-induced conduction slowing (time to 50% conduction slowing: 10.2±1.3 min vs. 5.1±0.7 min, $p<0.05$) and to loss of electrical excitability in ivabradine-perfused hearts (27.7±4.3 min vs. 14.5±0.6 min, $p<0.05$).

Vaillant (2008)[10]	PC	54	N/A	N/A	Effect of ivabradine on VF in AMI-induced domestic pigs	0.5mg/kg	Midazolam (0.1 mg/kg); chloralose (100 mg/kg)	Compared to controls, ivabradine reduced HR by 31% and was associated with a significant decrease in VF occurrence and 2.9-fold increase in VF threshold (p<0.001). Ivabradine prevented ischemia-induced monophasic action potential duration shortening without affecting peak LV pressure time derivative. Ivabradine significantly reduced the hypoxic area compared to controls (26% vs 38%, p<0.0001).
Vaillant (2011)[11]	PC	12	N/A	N/A	Effect of ivabradine on VF, myocyte ultrastructure, and regional myocardial blood flow in AMI-induced domestic pigs	0.25 mg/kg	Ketamine (20 mg/kg); propofol (3 mg/kg), alpha-chloralose (100 mg/kg)	Compared to controls, ivabradine reduced HR by 32% (p<0.01), increased VF threshold by 2.9 times (p<0.001) and reduced the hypoxic area without change to LV pressure time derivative. Ivabradine preserved cardiomyocyte morphology, particularly mitochondrial ultrastructure. Regional myocardial blood flow to hypoxic areas was increased following ivabradine administration compared to baseline (+218% vs +97%, p<0.05)
Vaillant (2013)[12]	PC	80	N/A	N/A	Effect of ivabradine on time to onset of VF in AMI-induced domestic pigs, compared to control (saline) and comparator (propranolol).	0.25 mg/kg	Ketamine (20 mg/kg); propofol (3 mg/kg), alpha-chloralose (100 mg/kg)	Ivabradine and propranolol induced similar reduction in HR (22–26% vs. 20–21%, p<0.01 vs. control). Ivabradine was associated with a significant increase in time to onset of VF (2325 s) compared to propranolol (682 s) and control (401 s). Only ivabradine partially prevented the decrease in phosphocreatine-to-ATP ratio and ADP accumulation at onset of VF.
RCTs and observational studies								
Rayan (2011)[16]	C	35	18	100%	Safety and efficacy of ivabradine in reducing HR in patients with idiopathic dilated cardiomyopathy.	2.5 mg BID for 2 weeks, up-titrated to 5 mg BID for 2 weeks, up-titrated to 7.5 mg BID until end of 3 months.	Spironolactone (25 mg/day); digoxin; ACE-inhibitor and carvedilol up-titrated to maximally tolerated dose.	Ivabradine significantly reduced resting HR by a mean of 25.9±9.4%, without significant change in blood pressure. There was no prolongation of PR, QTc, or QRS interval durations. Ventricular ectopic activity was significantly reduced (p<0.001). There was a significant correlation between resting HR, NYHA class, and LVEF (p<0.001).
Fox (2014)[22]	RCT	19102	65	72%	Morbidity-mortality benefits of ivabradine compared to placebo in patients with CAD without clinical HF.	7.5 mg BID	Background therapy of aspirin, statins, ACE-inhibitors, and beta-blockers.	At 3 months, mean HR was 60.7±9.0 bpm in ivabradine group and 70.6±10.1 bpm in placebo group. After median follow-up of 27.8 months, there was no significant difference between the ivabradine group and placebo group in incidence of mortality from cardiovascular causes or nonfatal AMI (6.8% vs. 6.4%; hazard ratio, 1.08; 95% CI, 0.96 to 1.20; p=0.20). Ivabradine was associated with an increase in the incidence of mortality from cardiovascular causes or nonfatal AMI among patients with activity-limiting angina but not among those without activity-limiting angina (p=0.02). The incidence of bradycardia was higher for ivabradine than placebo group (p<0.001).
Mert (2017)[21]	RCT	73	65	69%	Effects of ivabradine on dobutamine-induced VAs compared to beta-blocker therapy	7.5 mg BID	Dobutamine (incremental doses of 5, 10, and 15 μg/kg/min at 6 hour steps)	The positive chronotropic effect of incremental dobutamine doses was blunted by beta-blockers and was completely removed by ivabradine. The median number of PVCs, ventricular couplets, and total VAs significantly increased with incremental doses of dobutamine in the control group (p=0.018) and, to a lesser extent in the ivabradine group (p=0.015). In the beta-blocker group the absolute number of PVCs was smaller than in control or ivabradine group. Ivabradine reduced PVCs by 43% at 5 μg/kg/min dobutamine and by 38% at 10 μg/kg/min dobutamine compared to control (PVCs median 256 vs. 147 and 251 vs. 158), with no significant difference at 15 μg/kg/min dobutamine between control and ivabradine groups (p>0.05). Thus, ivabradine administered without background beta-blockage attenuated the arrhythmogenic effect of increasing doses of dobutamine in the low and moderate dobutamine dose but not in the high dobutamine dose groups.
Steg (2013)[23]	RCT	124	59	78%	Effect and tolerability of IV ivabradine on HR and hemodynamic parameters after PCI for STEMI.	IV bolus (5 mg ivabradine or placebo) over 30 seconds, immediately followed by IV infusion (5 mg ivabradine or placebo) over 8 hours	All drugs usually administered to patients with AMI and PCI (statins, aspirin, ACE inhibitors, anti-platelets, beta-blockers).	In both ivabradine and placebo groups, HR was reduced over 8 h, with a faster and more substantial decrease on ivabradine than placebo (22.3±1.3 vs. 8.9±1.8 bpm, p<0.0001). After treatment discontinuation, HR was similar in both groups. Throughout the study, there was no difference in blood pressure or cardiac biomarkers between groups. On echocardiography at baseline and post-treatment, final LV volumes were lower in ivabradine group both for LV end-diastolic volume (87.1±28.2 vs. 117.8±21.4 ml, p=0.01) and LV end-systolic volume (42.5±19.0 vs. 59.1±11.3 mL, p=0.03) without differences in volume change or LVEF.

Age (years) is reported as mean. ACE: Angiotensin-converting-enzyme, AMI: Acute myocardial infarction, BID: Bis in die (twice per day), CAD: Coronary artery disease, CPVT: Catecholaminergic polymorphic ventricular tachycardia, HF: Heart failure, hiPSC-CM: human induced pluripotent stem cells derived cardiomyocyte, HR: Heart rate, ICD: Implantable cardioverter-defibrillator, IV: Intravenous, LV: Left ventricle, LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, PCI: Percutaneous coronary intervention, PVC: Premature ventricular contraction, CR: Case report, CS: Case Series, PC: Pre-clinical, C: Cohort, RCT: Randomized controlled trial, STEMI: ST-elevated myocardial infarction, VA: Ventricular arrhythmia, VF: Ventricular fibrillation, VT: Ventricular tachycardia.

butamine dose reduced PVCs by 43 % and at 10 μg/kg/min by 38 %. However, ivabradine did not attenuate the arrhythmogenic effect of dobutamine at high dobutamine doses (15 μg/kg/min)[33].

Clinical trials in myocardial ischemia have not shown a positive effect of ivabradine in reducing VAs. In the SIGNIFY trial, administering ivabradine in stable coronary artery disease (CAD) patients without HF did not improve outcomes[9]. Regarding the safety outcomes of this study, the occurrence of severe VAs did not differ significantly between the ivabradine and control groups[9]. Steg et al[34], studied the impact of intravenous ivabradine on

HR in patients with ST-elevation myocardial infarction (STEMI)[34]. The authors concluded that ivabradine might be used safely in this setting. Furthermore, no significant differences in the occurrence of VAs were found between ivabradine and control groups[34].

Conclusions

Experimental studies have demonstrated the beneficial role of ivabradine in acute myocardial ischemia, reperfusion, and digitalis-induced VAs. Furthermore, clinical data have provided evidence that ivabradine may reduce dobutamine-induced VAs and arrhythmias in the setting of CPVT and dilated cardiomyopathy. However, randomized clinical trials are needed to elucidate the role of ivabradine in reducing the burden of VAs in various clinical settings.

Conflicts of interest

The authors declare no conflicts of interest.

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