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Achieved targeted heart rate following ivabradine therapy correlates with left ventricular reverse remodeling in non-ischemic dilated cardiomyopathy

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The effect of ivabradine on left ventricular reverse remodeling (LVRR) in heart failure with reduced ejection fraction and its correlation with achieved heart rate (HR) by ivabradine in non-ischemic dilated cardiomyopathy (NIDCM) remain uncertain. A retrospective analysis of 255 sinus rhythm NIDCM patients at a tertiary center (2012–2021) were categorized into four groups based on the ivabradine use (Iva+/−) and achieved HR at 1-year (HR+/−). The HR cut-off of 70 bpm was determined via receiver operating characteristic curve analysis for LVRR, defined as an absolute ≥ 10% improvement in LV ejection fraction (LVEF) from baseline, with a final LVEF ≥ 40%. LVRR incidence at 1-year was, 46.8% in Iva−/HR70+, 46.6% in Iva−/HR70−, 62.9% Iva+/HR70+ and 71.1% in Iva+/HR70−. Ivabradine treated patients with HR < 70 bpm had higher incidence of LVRR than those without ivabradine (Iva+/HR70−vs. Iva−/HR70+, OR 4.85, 95%CI 1.97–11.96 *P* = 0.001; Iva+/HR70−vs. Iva−/HR70−, OR 3.60, 95% CI 1.41–9.18, *P* = 0.007) after adjustment for known predictors in a multivariate model. Consistent adherence to beta-blockers and ivabradine, along with guideline-directed medical therapy (GDMT) for HF, and sex were identified as independent predictors of LVRR. Ivabradine therapy achieving HR < 70 bpm correlated with increased LVRR incidence in NIDCM patients, underscoring the role of ivabradine in HR reduction adjunctive to GDMT.

Keywords Ivabradine, Heart rate, Reverse remodeling, Heart failure with reduced ejection fraction, Non-ischemic dilated cardiomyopathy

Abbreviations

ACEi	Angiotensin-converting-enzyme inhibitor
ARB	Angiotensin-receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitors
NIDCM	Non-ischemic dilated cardiomyopathy
HF	Heart failure
HR	Heart rate
HFrEF	Heart failure with reduced ejection fraction
LVRR	Left ventricular reverse remodeling
MRA	Mineralocorticoid receptor antagonist
RAS	Renin-angiotensin-aldosterone system

Dilated cardiomyopathy (DCM) stands as the most prevalent etiology of heart failure (HF)[1–3]. Despite substantial progress in medical treatments targeting improved clinical outcomes for HF have been made, HF remains a major challenge. Notably, left ventricular reverse remodeling (LVRR) is associated with improved myocardial contractility, fewer HF hospitalizations, and reduced cardiovascular mortality[4]. HF medications such as beta-blockers, renin–angiotensin–aldosterone system (RAS) inhibitors, mineralocorticoid receptor antagonists (MRA), and angiotensin receptor neprilysin inhibitors (ARNI), have exhibited LVRR in HF with

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reduced ejection fraction (HFrEF) patients[5–7]. Adjunct to these established therapies, ivabradine, a selective I_f-channel inhibitor, is recommended for patients with HFrEF who are in sinus rhythm and have a resting heart rate (HR) ≥ 75 bpm despite guideline-directed medical therapy (GDMT)[8,9]. This indication has been given a class IIa recommendation in current HF guidelines[1–3]. In addition, prior studies have demonstrated a favorable effect of ivabradine on LVRR[10–13].

While previous studies demonstrated a correlation between LVRR and heart rate reduction, the precise relationship between LVRR and the achieved heart rate after ivabradine treatment remains incompletely elucidated. As this relationship may vary depending on underlying myocardial characteristics and the degree of diastolic dysfunction, the present study focused exclusively on patients with idiopathic non-ischemic DCM (NIDCM) to minimize heterogeneity and better isolate the effects of GDMT and ivabradine on reverse remodeling. Therefore, our study aims to explore the impact of ivabradine on LVRR and assess its influence on the risk of clinical events based on the achieved heart rate in patients with NIDCM.

Result

Patients' characteristics and medication at baseline and follow-up

The baseline clinical characteristics of the study population (255 patients) are summarized in Table 1. The median age was 56 years (interquartile range [IQR], 43–67), with a male predominance (60.1%) and a median body mass index (BMI) of 24.3 kg/m^2 (IQR, 21.6–26.8). Patients who received ivabradine treatment (Iva+/HR70+ and Iva+/HR70−) had lower systolic blood pressure (BP), lower LVEF, and shorter QRS duration. Moreover, patients in the ivabradine treated group had higher baseline HR and experienced more substantial HR reduction at the first year, with this difference becoming more apparent at the second year of the follow-up. Notably, over 85% of patients in ivabradine-treated groups demonstrated a reduction of HR from baseline, and the change in HR was more pronounced compared to patients without ivabradine (Iva−/HR70+ and Iva−/HR70−). (refer to Supplementary Table 1) The distribution of New York Heart Association (NYHA) functional class, including class III–IV, was comparable across the four groups ($P = 0.731$).

Regarding medication regimens at baseline, patients were treated comparably for guideline-directed medical therapy (GDMT) except for the use of MRA, which was more prescribed (90%~) in groups treated with ivabradine. This finding was consistent throughout the follow up. However, patients with ivabradine treatment showed relatively lower adherence to beta-blockers (74.3%, 81.6% vs. 95.4%, 94.5%, $P < 0.001$) at the one-year

	Group 1 Iva−/HR70+ (N = 109)	Group 2 Iva−/HR70− (N = 73)	Group 3 Iva+/HR70+ (N = 35)	Group 4 Iva+/HR70− (N = 38)	Overall (N = 255)	*P*-value
Age, years	54 [45–66]	62 [49–72]	45 [39–62]	58 [43–66]	56 [43–67]	0.008
Male, n (%)	67 (61.5%)	48 (65.8%)	18 (51.4%)	20 (52.6%)	153 (60.0%)	0.386
BMI, kg/m^2	24.2 [22.1–27.3]	23.2 [21.5–26.1]	25.2 [21.2–27.4]	25.8 [22.1–27.4]	24.3 [21.7–26.8]	0.205
NYHA class, n (%)						0.731
Class III-IV	36 (33.0%)	19 (26.0%)	12 (34.3%)	11 (28.9%)	78 (30.6%)	
Class I-II	73 (67.0%)	54 (74.0%)	23 (65.7%)	27 (71.1%)	177 (69.4%)	
Hypertension	49 (45.0%)	31 (42.5%)	16 (45.7%)	19 (50.0%)	115 (45.1%)	0.901
Diabetes	35 (32.1%)	21 (28.8%)	11 (31.4%)	13 (34.2%)	80 (31.4%)	0.940
Chronic kidney disease	22 (20.2%)	16 (21.9%)	5 (14.3%)	4 (10.5%)	47 (18.4%)	0.425
Laboratory findings						
Hb, mg/dL	13.9 ± 2.2	13.9 ± 1.9	14.2 ± 2.3	13.7 ± 2.0	13.9 ± 2.1	0.842
Anemia, n (%)	12 (11.0%)	9 (12.3%)	3 (8.6%)	1 (2.6%)	25 (9.8%)	0.395
eGFR, ml/min/1.73m^2	89.0 [72.9–103.4]	90.6 [68.8–102.3]	87.3 [79.7–99.3]	86.9 [61.0–94.8]	89.1 [71.1–100.1]	0.433
NT-proBNP, pg/mL	1624.0[521.5–3816.0]	1301.5[530.0–4728.0]	1583.0[597.5–3055.0]	2892.0[912.5–6411.0]	1739.0[567.0–3969.0]	0.248
Clinical parameters						
Systolic BP, mmHg	124 [110–138]	120 [107–132]	116 [104–136]	112 [101–122]	120 [106–135]	0.025
Diastolic BP, mmHg	80 [70–85]	79 [70–88]	75 [68–80]	77 [70–90]	78 [70–86]	0.244
Heart rate, bpm	92 [79–104]	81 [74–89]	97 [89–109]	98 [88–109]	89 [78–101]	< 0.001
QRS duration, ms	102 [94–114]	108 [98–142]	98 [91–114]	99 [92–114]	102 [94–122]	0.007
LBBB, n (%)	16 (14.7%)	18 (24.7%)	6 (17.1%)	5 (13.2%)	45 (17.6%)	0.300
LAVI, ml/m^2	46.5 [35.4–56.3]	48.1 [36.0–62.6]	45.0 [36.9–55.9]	47.4 [40.0–54.8]	46.8 [36.3–58.2]	0.922
LVEDD, mm	65.3 ± 8.4	66.5 ± 6.9	65.7 ± 8.5	65.8 ± 7.2	65.8 ± 7.8	0.797
LVEF, %	26 [21–32]	24 [20–31]	21 [18–26]	19 [17–28]	24 [20–29]	< 0.001

Table 1. Baseline characteristics according to ivabradine treatment and achieved heart rate. * Data are presented as n (%), mean ± standard deviation or median [interquartile range]. BPM, beat per minute; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HR, heart rate; LAVI, left atrial vole index; LBBB, left ventricular bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type brain natriuretic peptide.

follow up and consistently lower adherence at subsequent years ($P = 0.012$). Ivabradine prescription at baseline was approximately 47–48% in the ivabradine-treated groups, as these groups were defined by initiation and sustained ivabradine use at 1-year follow-up (100% usage). (refer to Supplementary Table 2) Loop diuretics use was evaluated using furosemide-equivalent daily doses, and its distribution was comparable across treatment groups, as detailed in Supplementary Tables 2 and 3.

A total of 77 patients (30.2%) received treatment with ivabradine at the baseline. Among these patients, four patients discontinued ivabradine treatment due to dizziness (n = 1), a switch to beta blockers due to high blood pressure (n = 1), bradycardia (n = 2), and were subsequently excluded. At the one-year mark, 73 (94.8%) patients remained on ivabradine treatment. Meanwhile, five patients have been newly diagnosed with atrial fibrillation, but none of them were using ivabradine at the time of the arrhythmia onset.

Clinical characteristics related to LVRR

Table 2 presents the clinical characteristics of the study population stratified by achieved LVRR at follow-up. Patients who achieved LVRR at 1 year showed a higher baseline HR and diastolic BP with a significant reduction HR at the follow-up (−20 bpm vs. −13 bpm, $P = 0.003$). Moreover, the LVRR group showed a smaller baseline LV end-diastolic diameter (LVEDD) and shorter QRS duration with a lower prevalence of LBBB, whereas the baseline LVEF was similar between LVRR and non-LVRR group. Regarding HF medications, the LVRR group showed higher beta-blocker adherence at baseline, though adherence at one-year follow-up was comparable ($P = 0.051$). Adherence to ACEi/ARB (or ARNI) and MRA was similar across groups. However, patients receiving > 50% of the target dose were more frequently observed in the LVRR group (refer to Supplementary Table 3).

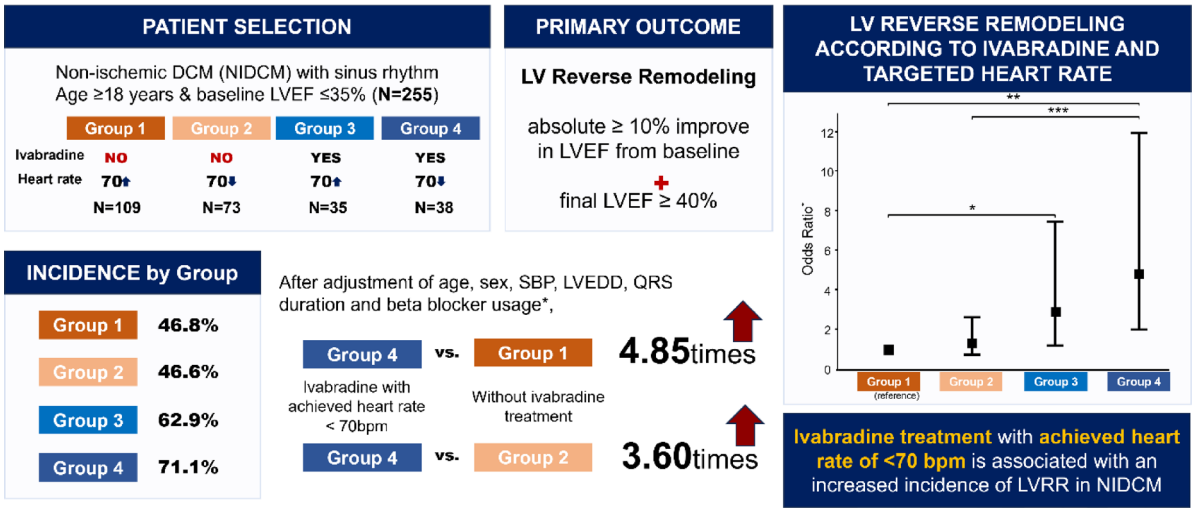
The incidence of LVRR at 1 year in four groups were 46.8% in Iva−/HR70+, 46.6% in Iva−/HR70−, 62.9% Iva+/HR70+ and 71.1% in Iva+/HR70−, respectively, with an overall difference ($P = 0.027$) (Fig. 1). After adjustment for clinically known predictors of LVRR, including sex, systolic BP, QRS duration, and beta-blocker usage, patients achieving HR < 70 bpm with ivabradine (Iva + /HR70 −) had a significantly higher likelihood of LVRR compared to patients without ivabradine treatment (Iva+/HR70− vs. Iva−/HR70+, odds ratio (OR) 4.85 [95% confidence interval (CI) 1.97–11.96], $P = 0.001$; Iva+/HR70− vs. Iva−/HR70−, OR 3.60 [95% CI 1.41–9.18],

	LVRR (N = 134)	Non-LVRR (N = 121)	*P*-value
Age, years	54 [42–67]	57 [45–68]	0.279
Male, n (%)	70 (52.2%)	83 (68.6%)	0.011
BMI, kg/m^2	24.3 [21.7–26.8]	24.3 [21.6–26.8]	0.810
NYHA class, n (%)			0.494
Class III-IV	44 (32.8%)	34 (28.1%)	
Class I-II	90 (67.2%)	87 (71.9%)	
Hypertension	71 (53.0%)	44 (36.4%)	0.011
Diabetes	46 (34.3%)	34 (28.1%)	0.350
Chronic kidney disease	25 (18.7%)	22 (18.2%)	1.000
Laboratory findings			
Hb, mg/dL	13.7 ± 2.2	14.1 ± 2.0	0.141
Anemia, n (%)	9 (6.7%)	16 (13.2%)	0.125
eGFR, ml/min/1.73m^2	89.3 [70.5–100.0]	88.5 [71.9–101.8]	0.918
NT-proBNP, pg/mL	1695.0 [548.0–5349.0]	1907.0 [605.0–3778.0]	0.696
Clinical parameters at baseline			
Systolic BP, mmHg	122 [109–138]	116 [104–130]	0.059
Diastolic BP, mmHg	80 [70–89]	76 [69–84]	0.028
Heart rate, bpm	92 [81–105]	88 [75–98]	0.006
QRS duration, ms	101 [92–112]	108 [96–134]	0.011
LBBB, n (%)	16 (11.9%)	29 (24.0%)	0.019
LAVI, ml/m^2	48.9 [36.5–58.9]	44.2 [35.8–56.3]	0.377
LVEDD, mm	64.2 ± 6.9	67.5 ± 8.4	0.001
LVEF, %	23 [20–29]	25 [20–30]	0.257
Clinical parameters at follow-up			
Systolic BP, mmHg	122 [110–134]	116 [106–126]	0.026
Diastolic BP, mmHg	71 [62–82]	70 [61–77]	0.198
Heart rate, bpm	72 [66–80]	73 [64–82]	0.676
Change in heart rate, bpm	− 20 [− 32 to − 7]	− 13 [− 25 to 0]	0.003
LVEF, %	51 [46–57]	31 [24–36]	< 0.001

Table 2. Patients' clinical characteristics according to left ventricular reverse remodeling at 1-year. * Data are presented as n (%), mean ± standard deviation or median [interquartile range]. Abbreviations as in Table 1. LVRR, left ventricular reverse remodeling.

	Univariate analysis			Multivariate analysis*								
				Model 1			Model 2			Model 3		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Male	0.50	0.30–0.84	0.008	0.55	0.31–0.99	0.045	0.53	0.30–0.95	0.032	0.53	0.30–0.93	0.028
Anemia (Hb < 10 g/dL)	0.47	0.20–1.11	0.086	0.73	0.28–1.90	0.516	0.72	0.28–1.88	0.508	0.73	0.28–1.90	0.524
Systolic BP at baseline, per 10 mmHg	1.16	1.01–1.34	0.035	1.16	0.99–1.36	0.062	1.15	0.99–1.35	0.072	1.18	1.01–1.37	0.040
QRS duration > 120 ms	0.61	0.35–1.06	0.079	0.59	0.32–1.10	0.096	0.64	0.34–1.19	0.160	0.55	0.30–1.02	0.058
Ivabradine continued†	2.33	1.32–4.11	0.004	2.52	1.28–4.98	0.008	2.83	1.44–5.57	0.003	3.09	1.59–6.01	0.001
Beta-blocker continued†	3.26	1.44–7.36	0.004	5.09	1.97–13.16	0.001	4.98	1.95–12.69	0.001	5.01	1.97–12.73	0.001
Reduction in heart rate at follow up, per 10 bpm	1.26	1.10–1.44	0.001	1.20	1.04–1.40	0.016						
Heart rate at baseline, per 10 bpm	1.24	1.07–1.43	0.003				1.13	0.97–1.32	0.129			
Achieved heart rate < 70 bpm	1.19	0.72–1.95	0.500							1.23	0.71–2.12	0.464

Table 3. Univariate and multivariate logistic regression analysis for left ventricular reverse remodeling. † "continued" indicates medication prescribed at baseline and sustained through the 1-year follow-up. * Only variables with $P < 0.10$ in the univariable model were included in the multivariable model. Abbreviations as in Table 1. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; LVRR, left ventricular reverse remodeling; OR, odds ratio; RAASi, renin–angiotensin–aldosterone system inhibitors (ACEi, ARB or ARNI).



Central Illustration. Ivabradine treatment with achieved heart rate < 70 bpm correlated with higher left ventricular reverse remodeling incidence in non-ischemic dilated cardiomyopathy. EDD, end-diastolic diameter; EF, ejection fraction; LV, left ventricle; NIDCMP, non-ischemic dilated cardiomyopathy; SBP, systolic blood pressure.

$P = 0.007$). Although no significant difference was noted within the ivabradine-treated groups based on achieved HR (Iva+/HR70+ vs. Iva+/HR70−, OR 1.65 [95% CI, 0.55–4.94], $P = 0.370$), the significance of the overall trend was confirmed (P for trend = 0.002). Furthermore, among patients not achieving the targeted HR, ivabradine-treated patients (Iva+/HR70+) showed significantly higher rates of LVRR compared to those without ivabradine (Iva−/HR70+) (Fig. 2).

The independent predictors associated with achieving LVRR were analyzed using logistic regression analysis and three multivariate models were constructed as part of sensitivity analysis to assess the association between heart rate parameters and LVRR. (Table 3) A history of hypertension, baseline systolic and diastolic BP were significantly associated with LVRR in univariable analysis, but these associations did not persist after multivariable adjustment. Ultimately, male ($P = 0.008$) and persistent adherence to beta-blockers ($P = 0.004$) and ivabradine ($P = 0.004$) were identified as the independent predictors of LVRR. Furthermore, every 10 bpm decrement of HR during the follow-up was independently associated with LVRR (OR 1.20 [95% CI 1.4–1.40], $P = 0.016$), whereas none of the different HR metrics used to adjust multivariate regression models 2 and 3 achieved statistical significance ($P = 0.129$ for baseline HR and $P = 0.464$ for achieved HR < 70 bpm were significant).

Clinical events according to achieved heart rate with or without ivabradine

The median follow-up duration after the index time was 730 days (interquartile range [IQR] 639–858). The overall incidence of clinical events was low, with fewer than 10% of patients experiencing HF hospitalization or cardiovascular death during follow-up: 24 patients (9.4%) were readmitted for worsening HF, and 1 patient (0.4%) died from a cardiovascular cause. (refer to Supplement Fig. 2).

Discussion

In the present study, we observed the highest prevalence of LVRR among patients achieving HR < 70 bpm after ivabradine treatment (71.1% in Iva+/HR70−, 62.9% in Iva+/HR70+, 46.6% in Iva−/HR70−, and 46.8% in Iva−/HR70+). The relatively high incidence of LVRR observed in our study may be attributed to the inclusion of ARNI as one of the four foundational components of GDMT, which was not available during the SHIFT trial era that included only ACEi/ARB, beta-blocker, and MRA. Although only 49.8% of patients in our cohort received ARNI, the overall use of RAAS inhibitors reached 95.3%, comparable to the 96% reported in the SHIFT sub-analysis[10]. Other than that, the exclusive inclusion of patients with idiopathic NIDCM, which minimized heterogeneity stemming from ischemia, revascularization status, or other myocardial tissue confounders, may have allowed for a more accurate assessment of reverse remodeling potential in response to GDMT and ivabradine. Sustained ivabradine therapy, in conjunction with consistent beta-blocker adherence, remained significantly associated with a higher likelihood of LVRR after multivariable adjustment. While ivabradine adjunctive to optimal GDMT was associated with a higher likelihood of LVRR, the study was not powered to assess its effect on cardiovascular outcomes due to the paucity of events. (Central Illustration)

The importance of HR reduction in HF is widely recognized, as reducing HR can have a protective effect on the heart by decreasing energy expenditure, prolonging diastole to increase blood supply, reducing arterial stiffness[14], and ultimately leading to ventricular unloading[15]. The MERIT–HF, the CIBIS–II, and the COPERNICUS trial have established the role of beta-blockers in lowering the risk of cardiovascular events[16–18]. The positive effect of beta-blockers extend beyond HR reduction where they inhibit the hyperactivated sympathetic tone to prevent the progression of cardiomyocyte apoptosis or interstitial fibrosis, leading to further myocardial injury[19]. Taking a step further, it has been associated with the occurrence of LVRR[20]. However, there is still a topic of debate regarding the maximally titrated dosage, targeted HR, or the degree of HR reduction being more important in beta blocker treatment. Studies investigating its association with clinical outcomes put more emphasis on the dose-dependent improvement[20], while the relationship between achieved HR and the occurrence of LVRR remain elusive or insignificant[21].

Ivabradine, a newly emerged drug, blocks sinoatrial node I_f channels and regulates HR without interfering with cardiac inotropy[22]. The SHIFT trial (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial) that enrolled systolic HF patients with HR above 70 bpm demonstrated an isolated decrement in achieved HR at 28 days with ivabradine augmentation was associated with a direct reduction in cardiovascular events[8,9]. However, limited research has explored the association between the ivabradine and LVRR in HF, aside of HR reduction. *Ceconi* et al. presented a reduction in LV volume was associated with a change in HR from baseline in patients with stable coronary artery disease and LV dysfunction after treatment of ivabradine[11]. Similarly, *Tsutsui* et al. showed that HR reduction was related to the decrease in LV chamber size and an improvement in LVEF[12]. However, the association between the achieved HR by ivabradine and LVRR was not elaborated.

In our cohort of patients with NIDCM, those who achieved a heart rate < 70 bpm through ivabradine therapy exhibited the highest observed rate of LVRR among the four treatment groups. Notably, the increased incidence of LVRR observed in our study population may have been attributed to the HR reduction achieved through optimal medical treatment, aligning with the findings from the SHIFT trial. Optimal medical therapy was implemented in majority of subjects –90.2% patients were under beta-blocker, 93.3% was under ACEi/ARB or ARNI, and 82.4% was under MRA respectively as depicted in Supplementary Table 2. These rates were comparable, if not higher, than those reported in the SHIFT trial. However, the proportion of patients receiving ≥ 50% of target dose of beta blocker was significantly lower in our study (28.3% at baseline and 32.2% at follow up vs. 56%), reflecting the real-world clinical practice of infrequent up-titration to recommended dose of GDMT[23]. This corresponds with the underuse of beta-blocker reported in Asian registry[24,25]. As shown in Table 1, the baseline systolic BP of patients treated with ivabradine was lower than that of the other groups. Physicians may hesitate to prescribe beta-blockers to patients with hypotension or with other concomitant contraindications, despite the need for more aggressive up-titration[2]. However, as presented in Supplementary Tables 1, 2 and 3, no substantial between-group differences were observed in serial blood pressure values or loop diuretic dosing over time. These findings suggest that the lower use of beta-blockers in certain subgroups may not be entirely explained by individual disease severity, raising the possibility of therapeutic inertia in clinical decision-making. Nevertheless, considering that patients treated with ivabradine were less frequently administered beta-blockers than those without ivabradine, the observed association with LVRR may be more specifically attributable to ivabradine therapy. Furthermore, in Iva+/HR70+ adherence to beta-blockers was notably lower compared to the other groups at one-year follow up (74.3% vs. 95.4%, 94.5% or 81.6%, $P = 0.001$). Despite this lower adherence, Iva+/HR70+ exhibited a significantly higher incidence of LVRR, which highlights the inherence significance of ivabradine in HF. Although ivabradine is not indicated for patients with resting HR < 70 bpm, the Iva−/HR70− group was included as a comparator to examine the role of achieved HR independent of ivabradine treatment. Notably, the Iva−/HR70− group demonstrated a lower observed incidence of LVRR compared to the Iva+/HR70+ group. While this may appear paradoxical, the ~47% rate of LVRR in the Iva−/HR70− group was consistent with prior reports. Given the lower baseline HR and older age in this group, the potential for further HR reduction, and its effect on remodeling, may have been limited.

Higher heart rates are likely to make ivabradine more effective by blocking a greater number of the I_f channels at sinoatrial nodes[22]. Likewise, the greatest reduction in HR from baseline at one year follow-up was observed in

Iva+/HR70−, and the significant correlation of the degree of HR reduction with the likelihood of LVRR further supports the highest occurrence of LVRR in Iva+/HR70− in our study. Importantly, our findings also indicate that the extent of HR reduction, independent of an absolute HR target, correlates with LVRR. In a mouse model, ivabradine down regulates the neurohormonal interaction by blunting the renin–angiotensin–aldosterone system[26] and the sympathetic nervous system, improving the HR variability[27]. With attenuated apoptosis and intracellular matrix metalloproteinase expression[28], ivabradine might mitigate the process of adverse remodeling and exert cardio-protection effect[13,29].

Lastly, while the SHIFT trial demonstrated that greater reductions in HR, down to levels below 65 or even 60 bpm, were associated with a lower risk of adverse clinical events[8,21], our study did not observe significant differences in clinical outcomes among the four groups. This inconsistent result might have been due to the small sample size and short follow-up duration of patients. Nevertheless, unlike previous studies, this study restricts the focus to patients with NIDCM, maintaining homogeneity in the etiology of heart disease. Given the extent of revascularization in HF with ischemic origin, whether complete or incomplete, acts as a significant confounding variable, confining the analysis solely to patients with NIDCM allows for a more precise assessment of the effects of GDMT[30]. Furthermore, patients who underwent cardiac resynchronization therapy were also excluded to eliminate the effect of device-guided treatment and to solely isolate the therapeutic effect of medical treatment. In our cohort, prolonged QRS duration (>120 ms), a surrogate for conduction system abnormalities, was associated with a lower likelihood of LVRR (OR 0.55 [0.30–1.02], $P=0.058$), consistent with prior studies linking electromechanical dyssynchrony to impaired remodeling in HFrEF patients not receiving cardiac resynchronization therapy (CRT)[31–33]. These findings suggest that achieved HR should be interpreted in conjunction with the underlying electrophysiological and myocardial substrate.

This study has several limitations. Firstly, despite meticulous review of clinical data, the retrospective, single-center study design inherently leaves some confounding factors related to HR, blood pressure (e.g. caffeine intake, pre-measurement rest, circadian influences), and LVRR were incompletely addressed. Secondly, to ensure only inclusion of patients with NIDCM, patients with other HF etiologies were excluded, potentially introducing patient selection bias. Thirdly, the utilization of four pillar medications is strongly advocated for GDMT, while there has been an insufficient data regarding the usage of SGLT2 inhibitors due to delayed approval and insurance coverage in South Korea. Fourthly, clinical events occurred in fewer than 10% of patients in select subgroups, limiting statistical power for definitive conclusions and rendering these findings exploratory. Fifthly, while ivabradine-treated patients were required to maintain treatment up to 1 year, the lack of a predefined minimum treatment duration prior to follow-up imaging may introduce variability in exposure time and limits causal interpretation. Moreover, the observed association between achieved heart rate and reverse remodeling should therefore be interpreted within the context of observational data. Lastly, although the correlation between the achieved HR through ivabradine and LVRR has been validated, the temporal differences may raise uncertainty on whether LVRR is predominantly facilitated by optimized adjunct GDMT in reducing HR, as retrospective study design inherently hindered the isolation of the exclusive effect of ivabradine. Nevertheless, these limitations in study design are likely to have minimal effect on the validity of our findings. Although the single-center setting and strict inclusion criteria may limit generalizability, the internal consistency afforded by a well-defined, homogeneous NIDCM cohort provides clinically meaningful insight into the role of ivabradine in patients receiving GDMT.

In conclusion, our study has demonstrated that treatment with ivabradine in patients with NIDCM, resulting in an achieved HR of <70 bpm, is associated with an increased incidence of LVRR despite lower use of beta-blockers. This highlights the importance of close monitoring and intensive up-titration to achieve optimal GDMT. Moreover, to obtain a more accurate understanding and assess the clinical impact of the relationship between the prognosis of NIDCM and the target achieved HR after ivabradine treatment, a larger prospective study is warranted, which would merit further validation.

Methods

Patients population and study design

We conducted the retrospective review of patients newly diagnosed with NIDCM at Severance hospital between 2012 and 2021, identified through the use of ICD-10 code I.420, who regularly visited the outpatient clinic and underwent cardiac magnetic resonance imaging (CMR) (Fig. 1). In this study, the time of enrollment was defined as the date of initial diagnosis of NIDCM, exclusively idiopathic DCM, at our institution. The date of diagnosis was used as the index timepoint for all subsequent assessments, including initiation and titration of medical therapy and longitudinal follow-up of echocardiographic outcomes. The inclusion criteria consisted of reduced baseline LVEF and dilated LV, where NIDCM was defined as LVEF ≤ 35% with dilated LV (LVEDD index ≥ 33 mm/m^2 for male, 32 mm/m^2 for female). The cutoff value of 35% for LVEF was determined considering the indication for ivabradine treatment according to the current HF guideline[1–3].

A total of 660 patients were initially enrolled, but cases of HF from alternative etiologies were systematically excluded after a comprehensive review of medical records. Exclusion criteria included: (1) patients with a baseline systolic BP of more than 160 mmHg, suggesting the possibility of HF caused by hypertensive loading conditions; (2) confirmed ischemic etiology of HF through coronary angiography, coronary computed tomography (CT), or myocardial perfusion scan; (3) presence of severe valvular HF necessitating valve operation; and (4) CMR was implemented to support the diagnosis of NIDCM and to aid the exclusion of secondary causes, including, infiltrative, tachycardia-induced, arrhythmogenic, or end-stage (burnout) hypertrophic cardiomyopathy together with information from echocardiography, laboratory data, and clinical course. Lastly, after excluding patients who underwent CRT implantation and those with previously documented paroxysmal atrial fibrillation or who had discontinued HF medications due to poor compliance, a total of 255 patients with sinus rhythm remained in the final analysis. Poor compliance was defined as early discontinuation or irregular intake of

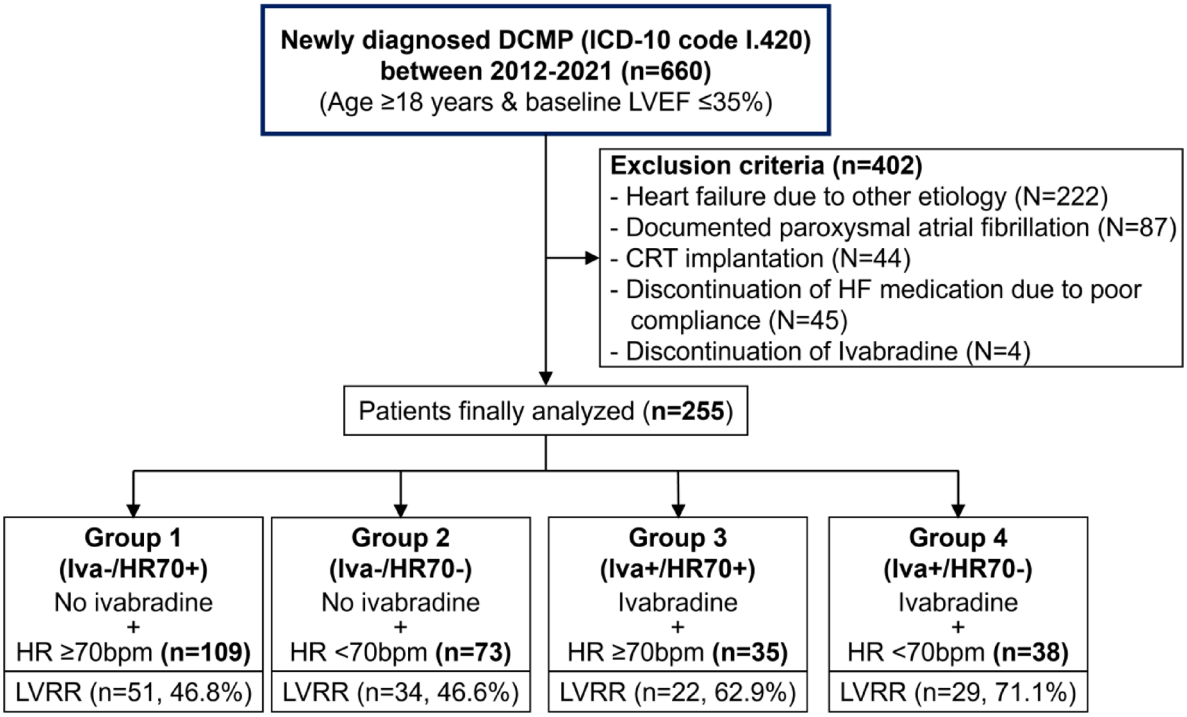


Fig. 1. Study flow. Patients newly diagnosed with non-ischemic dilated cardiomyopathy in sinus rhythm between 2012 and 2021 at a single tertiary center were included in this analysis and were retrospectively categorized into four groups based on the administration of ivabradine and achieved heart rate at 1 year. bpm, beats per minute; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; HR, heart rate; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling.

prescribed heart failure medications prior to the 1-year follow-up, based on patient report or medical records, in the absence of documented intolerance or adverse events.

This study was approved and the need to obtain informed consent was waived by the Institutional Review Board (IRB) of Yonsei University Health System (IRB number: 4-2022-1665). We confirm that all methods were performed in accordance with the relevant guidelines and regulations. The Clinical Data Repository System, Electronic Medical Record system, Picture Archiving and Communication System of Severance Hospital were used to retrieve the clinical and imaging data. All medical records of the subjects were anonymized before analysis.

Definitions and study protocol

Two-dimensional transthoracic echocardiography was performed at baseline and 1 year in every patient, with LVEF and left atrial volume index estimated by biplane method and LV end diastolic diameter (LVEDD) measured by M-mode tracing or 2D-guided linear measurement.

The primary outcome of the study was the incidence of LVRR, defined as fulfilling both of the following criteria: (1) an absolute improvement in LVEF of ≥ 10%, and (2) a follow-up LVEF > 40%[2,4]. The optimal cut-off value of achieved heart rate of 70 bpm at 1-year was determined using the receiver-operating characteristics (ROC) analysis based on occurrence of LVRR at 1-year (with achieved LVRR: positive, without LVRR: negative) in respective cohort along with Youden method. After evaluating the odds ratio (OR) in all patients treated with or without ivabradine according to the achieved heart rate at follow-up for discrimination of the primary endpoint, it was found that the highest OR for LVRR and maximized sensitivity and specificity in the ROC curve were achieved at a heart rate of 70 bpm. Therefore, we utilized 70 bpm as the cut-off value in our study. To examine the relationship between achieved heart rate and LVRR, the study population was categorized into four groups based on their treatment with ivabradine and the achieved HR at 1 year:

Group 1 (Iva−/HR70+) consisted of patients who achieved an HR ≥ 70 bpm without ivabradine, Group 2 (Iva−/HR70−) included patients who achieved an HR < 70 bpm without ivabradine, Group 3 (Iva+/HR70+) consisted of patients who achieved an HR ≥ 70 bpm with ivabradine, and Group 4 (Iva+/HR70−) included patients who achieved an HR < 70 bpm with ivabradine. Ivabradine therapy was initiated after confirmation of persistent symptoms despite GDMT, in accordance with the national indication criteria for NYHA class II–III, sinus rhythm, HR ≥75 bpm, and LVEF <35%. NYHA classification at the time of ivabradine prescription was retrospectively verified to meet the eligibility threshold. The ivabradine group included patients who had initiated ivabradine and continuously maintained ivabradine therapy at the time of the 1-year follow-up.

To evaluate LVRR at 1 year following diagnosis of NIDCM, clinical data at baseline and at 1-year follow-up timepoint were reviewed, including office blood pressure, electrocardiography-derived heart rate, and QRS

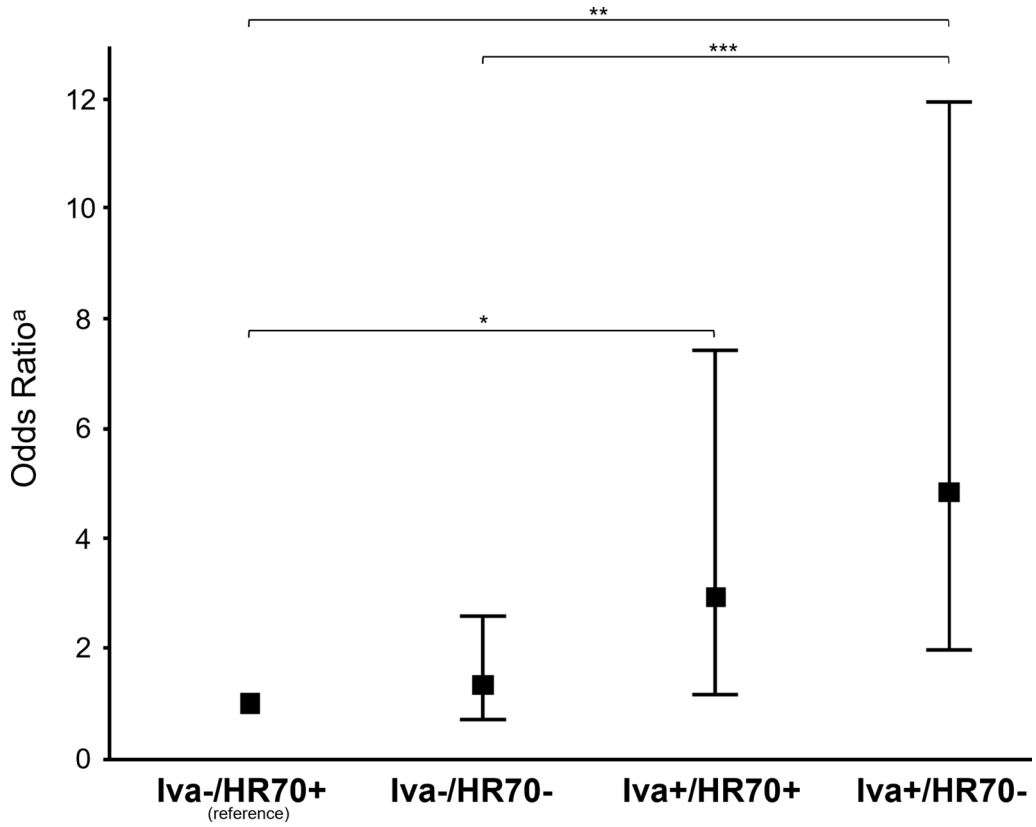


Fig. 2. Left ventricular reverse remodeling at 1-year based on achieved heart rate and ivabradine treatment. [a] Odds ratios were adjusted for known LVRR predictors, including age, sex, baseline systolic blood pressure, QRS duration, and beta-blocker usage. Beta-blocker use was included due to its direct influence on heart rate control with ivabradine therapy. $^{*}P$-value: 0.023, $^{**}P$-value: < 0.001, $^{***}P$-value: 0.007. HR, heart rate; *P* for trend in odds ratio = 0.002. Groups were divided based on the administration of ivabradine and achieved HR at 1-year: Group 1 (Iva−/HR70+), achieved HR ≥ 70 bpm without ivabradine; Group 2 (Iva−/HR70−), achieved HR < 70 bpm without ivabradine; Group 3 (Iva+/HR70+), achieved HR ≥ 70 bpm with ivabradine; Group 4 (Iva+/HR70−), achieved HR < 70 bpm with ivabradine.

duration. Information on HF medications, as in beta-blockers, renin-angiotensin system (RAS) inhibitors, MRA, and ARNI, was reviewed separately according to medication class and prescribed dose, with reference to the target doses recommended by clinical practice guidelines[34]. Patients were further categorized into three groups based on the prescribed dose: no medication, ≥25% of the target dose, and ≥ 50% of the target dose. The ≥25% group included all patients receiving at least 25% of the recommended target dose, including those receiving ≥ 50%, while the ≥50% group was presented as a subset of the ≥25% group. Loop diuretic dosing was categorized according to furosemide-equivalent daily dose as follows: low (< 40 mg/day), medium (40–80 mg/day), and high (>80 mg/day).

The secondary outcomes included the composite events of cardiovascular-related death and hospital readmission due to worsening of heart failure. All patients were followed up until the occurrence of the events, and all clinical events were identified. The decision to start or discontinue ivabradine was solely made at the discretion of the treating cardiologist.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), while categorical variables were expressed as n. For the comparison of continuous variables with a normal distribution among the four groups, one-way analysis of variance with Bonferroni post-hoc test was used. Kruskal–Wallis test with post-hoc Dunn test was utilized for continuous variables with non-normal distribution. To standardize the analysis approach, Linear Mixed Models were additionally employed to support the findings across all comparisons. Categorical variables were compared using chi-square or Fisher's exact tests, as appropriate, to assess proportions across the four defined groups, as no ordinal trend was assumed in their categorization. Baseline characteristics associated with LVRR were first identified using univariate logistic regression. The relationship between the achieved heart rate at 1 year and LVRR was then evaluated using multivariable logistic regression analysis. Baseline variables with a *P* value < 0.10 in the univariable analysis were included as covariates in the multivariable model to adjust for potential confounders. Multicollinearity was assessed by variance inflation factor and no multicollinearity existed. Moreover, to assess the association between HR and

LVRR, three multivariate models were constructed as part of sensitivity analysis: Model 1 included baseline covariates and HR reduction from baseline (per 10 bpm); Model 2 included baseline covariates and baseline HR (per 10 bpm); and Model 3 included baseline covariates and achieved HR < 70 bpm as a categorical variable. Ivabradine continuation was included as an independent covariate in all models. To assess the risk of clinical events, including HF re-hospitalization and cardiovascular death, according to the achieved heart rate at 1 year, survival curves for each group were generated using the Kaplan–Meier method. The comparison between the groups was conducted using the log-rank test. The index time for this analysis was defined as the moment when the follow-up echocardiography at 1 year was conducted. All statistical analyses were performed using R software, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and all tests were two sides assuming $P < 0.05$ being statistically significant.

Data availability

The data generated in this study is available from the corresponding author(s) upon reasonable request.

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Author contributions

Conceptualization: Oh J, Kang SM; Data curation: Lee J, Oh J; Investigation: Oh J, Ha J, Lee CJ, Kang SM; Resources: Oh J, Kang SM; Software: Lee J, Oh J; Supervision: Oh J, Kang SM; Writing—original draft: Lee J, Oh J; Writing—review & editing: Lee J, Oh J, Kang SM. All authors reviewed and approved the manuscript, and its submission to *Scientific Reports*.

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Declarations

Competing interests

The authors declare that they have no conflict of interest and declare no financial or non-financial competing interests.

Additional information

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