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# Beta-Blocker in Heart Rate Control and Cardio Protection: The Role of ADRB1 Variants and HCN4 Regulation – A Systematic Review

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**ABSTRACT**

Beta-blockers exert cardioprotective effects against heart failure. However, variability in therapeutic responses is associated with ADRB1 variants. ADRB1 variants contribute to rate control and autonomic dysfunction. Persistent hyperadrenergic stimulation contributes to the impairment of the pacemaker (SA node). HCN4 significantly influenced the regulation of heart rate in the pacemaker. Exploring the effect of beta-blockers on pacemaker cells is expanding the view of their cardioprotective effects in heart failure. The objectives of this review were to identify ADRB1 variants affecting heart rate response in heart failure patients receiving beta-blocker treatment and to explore the effect of beta-blockers on HCN4/SA node. A systematic review was performed using three databases (Scopus, PubMed, and Science Direct). The inclusion criteria were English language and original manuscripts with relevant topics. The exclusion criteria were duplication and inaccessibility to the full text. Quality assessment tools were classified based on the use of research subjects and study designs, including NOS (cohort), SYRCLE (animal studies), and SciRAP (*in vitro* studies). Eight of 668 manuscripts were selected. This review found that ADRB1 variants (*A145G*(Ser49Gly) and *C1165G*(Arg389Gly)) can affect heart rate response in beta-blocker-treated heart failure. The percentage of patients with Ser49Ser-Gly389X (67%) who achieved the heart rate target was higher than that of the other haplotypes (48-52%). Among the responders, Arg389Arg required larger carvedilol equivalent daily doses of beta-blockers to reach the identical heart rate target than those with Gly389X (>50% (>25mg) versus ≤50% of the guideline-directed medical therapy (GDMT) target dose (≤25mg), respectively). In addition, this review found that beta-blockers demonstrated beneficial effects in regulating heart rate by inhibiting HCN-gated channels and improving channel regulation in the SA node. In general, this review provides important insights into beta-blockers in treating heart failure, specifically concerning the genetic variability of ADRB1 and the effect of beta-blockers on SA node/HCN4.

**Keywords:** Beta-blocker, ADRB1, HCN4, Heart Failure, Heart Rate

## INTRODUCTION

Elevated heart rates in patients with heart failure are associated with a greater risk of poorer cardiovascular (CV) outcomes, including morbidity and mortality. The underlying pathophysiology of this condition is multifaceted. (Badu-Boateng *et al*., 2018; Bauersachs & Veltmann, 2020; Docherty *et al*., 2020; Hesse, 2022; Vukadinović *et al*., 2017; Vollmert *et al*., 2020). Patients with heart failure tend to have higher resting heart rates due to neurohumoral compensation, which leads to increased sympathetic activity, decreased ventricular efficiency, and exacerbation of heart failure (Badu-Boateng *et al*., 2018; Hesse, 2022).

Heart rate is a strong prognostic indicator of CV outcomes in heart failure (Heidenreich *et al*.,


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2022; Kurgansky *et al*., 2020; Zhang *et al*., 2016). European Society of Cardiology, American College of Cardiology, American Heart Association Joint Committee, and Indonesian Heart Association recommend beta-blockers for controlling heart rate in heart failure. (Heidenreich *et al*., 2022; Hersunarti *et al*., 2020; McDonagh *et al*., 2021). Beta-blockers lower heart rate by decreasing neurohumoral activation, conserving myocardial energy, and lengthening the diastolic filling period (Hesse, 2022). Beta-blockers bind to the Beta1-adrenergic receptor (ADRB1) sites, which are expressed in cardiomyocytes. ADRB1 was dominant in the heart. ADRB1 accounts for approximately 70%, 80%, and 95% of cardiac tissue adrenergic receptors in the atria, ventricles, and sinoatrial (SA) nodes (Chevalier *et al*., 2023; Kelley *et al*., 2018). ADRB1 is crucial for chronotropic inotropic effects and work. ADRB1 regulates the chronotropic-inotropic function and affects cardiac hemodynamic and cardiac ability to tolerate physical activity (Kelley *et al*., 2018; Lymperopoulos, 2013; Muslimova *et al*., 2022; Velmurugan *et al*., 2019).

Beta-blocker is the primary treatment for heart failure, that provides cardiac protection from overstimulation of catecholamine and persistent ADRB signalling. ADRB1 overexpression in the heart causes myocardial hypertrophy, necrosis, and apoptosis. Beta-blockers reduce these negative effects, ultimately improving heart function and reducing the risk of heart failure. Beta-blockers also demonstrate antiarrhythmic effects (Eriksen-Volnes *et al*., 2020; Pathak & Mrabeti, 2021; Shah *et al*., 2017; Velmurugan *et al*., 2019). A lower heart rate (HR) in heart failure reduced ejection fraction (HFrEF) is associated with a better prognosis due to beta-blocker therapy(Hesse, 2022; Velmurugan *et al*., 2019). Achieving heart rate targets is crucial to prevent adverse cardiovascular outcomes. Approximately 19% of patients with HFrEF had higher heart rates and demonstrated a higher risk of hospitalization and mortality in the first six months after diagnosis (Kurgansky *et al*., 2020). However, responses to beta-blockers can vary among individuals (Kurgansky *et al*., 2020; Reddy, 2015; Thomas, 2020).

In heart failure, genetic variability may play a role in different responses to beta-blockers. The variability of the beta-blocker response in heart rate and left ventricular ejection fraction has been associated with single nucleotide polymorphisms (SNPs) (Guerra *et al*., 2022) of ADRB1 genetic variants, which contribute to autonomic dysfunction, arrhythmia, heart rate regulation, and survival (Dumeny *et al*., 2022; Guerra *et al*., 2022; Reddy, 2015; Thomas, 2020). In a failing heart, sustained stimulation of beta-adrenergic receptors can lead to deterioration of cardiac function. Persistent hyperadrenergic stimulation contributes to impairment of the SA node automaticity and depolarization potential (de Lucia *et al*., 2014; Du, 2016; Masarone *et al*., 2021).

The SA node expresses hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, which play a significant role in controlling autonomous rhythm, neuronal excitability, and heart rate (Depuydt *et al*., 2022; Hennis *et al*., 2022; Kashou A.H., Basit H, 2023). The HCN4 isoform has the highest expression level in the SA node compared to the other HCN isoforms. The regulation of the heart rate is significantly influenced by HCN4 (Hennis *et al*., 2022; Xu *et al*., 2018). Recently, a carvedilol derivative (compound 8a (SMU-XY3)) was shown to have an affinity for HCN4 and block HCN (Xu *et al*., 2018). The blockage of the HCN4 channel contributes to a reduction in heart rate (Bueno-Levy *et al*., 2019) Therefore, exploring the impact of beta-blockers on pacemaker cells is expanding the view of their cardioprotective effects on heart failure.

This systematic review aimed to identify ADRB1 genetic variants affecting heart rate response in beta-blocker-treated heart failure. Additionally, this review aimed to gain a comprehensive understanding of how beta-blockers influence the heart rate associated with HCN channels and the function of the SA node within the heart.

## METHODS

Two researchers independently evaluated the manuscript (including screening, assessing the quality of manuscripts, and extracting data). A third researcher was involved when there were discrepancies between the two researchers to reach a consensus for the final decision.

The screening process was used to determine relevant and eligible studies using inclusion-exclusion criteria. Quality assessment is a process used to assess article quality and the risk of bias (ROB). Finally, the data were structurally extracted (Negarandeh & Beykmirza, 2020; Polanin *et al*., 2019; Tawfik *et al*., 2019; Xiao & Watson, 2019).

**Screening for inclusion**

A systematic review of beta-blockers and ADRB1 variant/HCN/SAN was performed according to the PRISMA flowchart of the Proffered Reporting Items for Systematic Reviews and Meta-Analyses (Page *et al*., 2021). Using two PICo frameworks (population/problem (P), phenomena of interest (I), and context (Co)) helped identify the research questions in this review. The first PICo (for the first review objective) was a beta-blocker-treated heart failure (P), heart rate (I), and ADRB1 polymorphism/variant (Co). The second PICo was beta-blocker treatment (P), heart rate (I), and HCN channels/SA nodes (Co).

To obtain relevant publications on these two objectives, we searched three databases (Scopus, PubMed, and Science Direct) using two keywords. The first keywords were (("ADRB1") OR ("B1 ADRENERGIC RECEPTOR POLYMORPHISM")) AND (("BETA BLOCKER") OR ("RATE CONTROL THERAPY")) AND (("HEART RATE") OR ("HEART") OR ("RATE")). The second keywords were (("HCN") OR ("HCN4")) AND (("BETA BLOCKER") OR ("CARVEDILOL") OR ("BISOPROLOL") OR ("METOPROLOL")) AND (("HEART RATE") OR ("RATE") OR ("SINOATRIAL NODE")). Publications were included in the systematic review according to the following inclusion criteria: original manuscripts (published since 2012) written in English, manuscripts about ADRB1 variants influencing heart rate response in beta-blocker-treated heart failure (for the first review objective), and the effect of beta-blockers on heart rate regulation associated with HCN activation/HCN expression/SA node function (for the second objective). The exclusion criteria were duplication/identical manuscripts retrieved from multiple databases and inaccessibility to the full text.

**Quality assessment**

Quality assessment tools were classified based on the research subjects and study designs used in the studies. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used for human subject research with a cohort design. The NOS provided three domains (selection (SB), comparability (CB), and outcome (ED) domains) with nine criteria overall. The NOS-scale was converted to the Agency for Healthcare Research and Quality (AHRQ) standard, which used a rating system of poor, fair, and good quality. According to this rating system, a study was considered of poor quality if it received a rating of ≤2 stars. Specifically, a ≤2-star rating could be due to having 0-1 star in SB, 0 stars in CB, or 0-1 stars in the OD. A study was considered of fair quality if it received a rating of 3-5 stars. This could be due to having 2 stars in SB, 1-2 stars in CB, and 2-3 stars in OD. Finally, a study was considered of good quality if it received a rating of ≥6 stars. Specifically, a study with a rating of ≥6 stars would have 3-4 stars in SD, 1-2 stars in the CD, and 2-3 stars in OD (Ayubi *et al*., 2021; Wells *et al*., 2021).

Animal and *in vitro* studies differ from human studies in many aspects (Hooijmans *et al*., 2014; Tran *et al*., 2021). Therefore, the ROB assessment tool for systematic reviews was adapted. The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) criteria were used to evaluate the ROB in animal studies. The Science in Risk Assessment and Policy (SciRAP) tool was applied to assess the quality of *in vitro* studies (Almeida *et al*., 2021; Hooijmans *et al*., 2014; Roth *et al*., 2021; SciRAP, 2018).

The ROB in the animal study was evaluated using the SYRCLE tool, which consists of seven types of bias, 10 domains, and three judgment criteria. The judgment criteria were "yes" (indicates low ROB), "no"(high ROB), and "unclear"(insufficient details on the manuscript to assess ROB properly)(Hooijmans *et al*., 2014).

SciRAP was used to assess the quality of in the vitro reports (SciRAP, 2018), which consisted of five assessment criteria with 23 checklist topics. The checklist included test compound (1), chemical purity (2), chemical solubility (3), solvent for test solution (4), solvent for control (5), test system (6), source of test system (7), metabolic competence (8), cell line (9), composition of media (10), incubation parameter (11), screening contamination (12), dose/concentration (13), cell density (14), duration of treatment (15), replication (16), analytical method (17), data collection (18), effect of the compound on cytotoxicity (19), result presentation (20), statistical methods (21), funding sources (22), and competing interests (23). The five assessment criteria were test compound (SciRAP topic number 1-5), test system (6-12), administration of the test (13-16), data collection and analysis (17-21), and funding of competing interests (22-23). SciRAP score was indicated as the percentage of fully/partially fulfilled criteria included in the assessment (SciRAP, 2018).

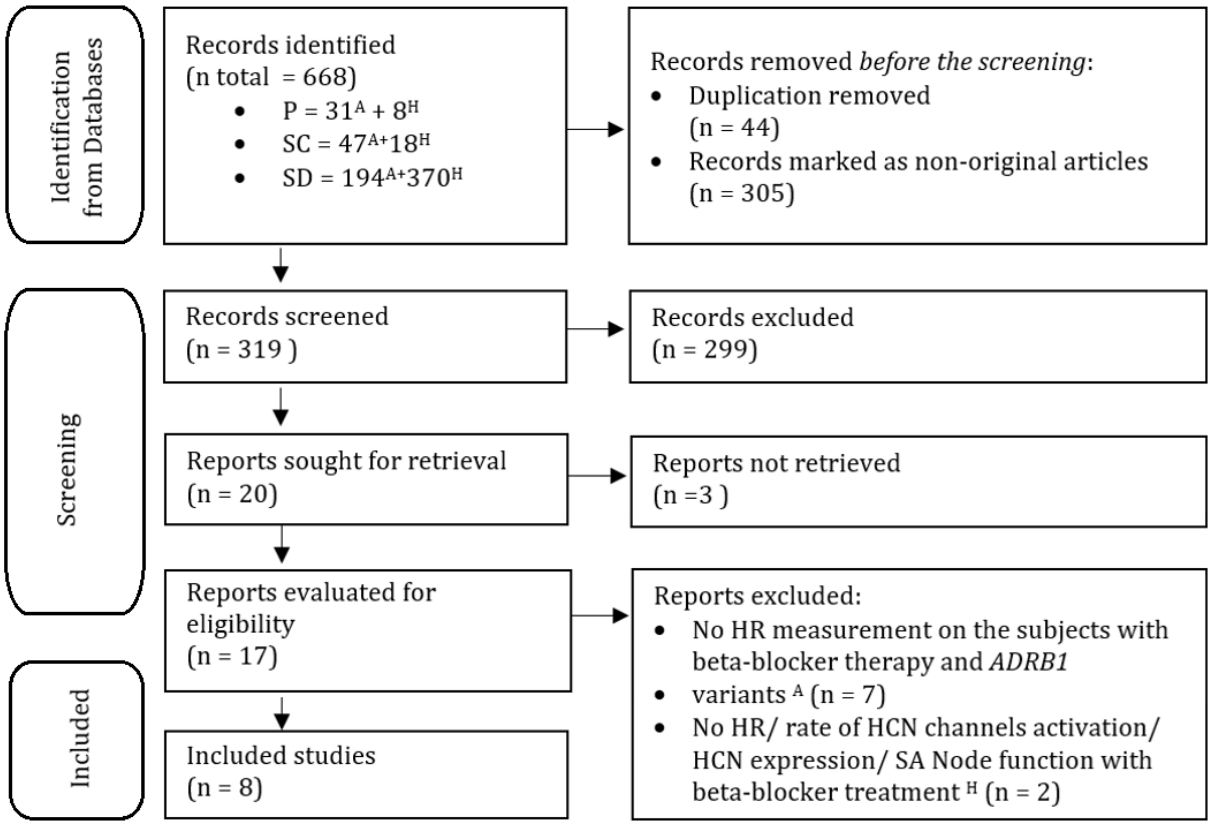


Figure 1. Prisma flowchart.
Note: A = Records/reports based on Beta1-adrenergic receptor (ADRB1) keywords, H= Records based on Hyperpolarization-activated cyclic nucleotide-gated (HCN) keywords, HR = Heart Rate, P= Pubmed, SC= Scopus, SD = Science Direct, SA Node= sinoatrial node

Table I. Quality of cohort studies.

| Study | The quality criteria | | | | | | | | Total NOS Star |
|---|---|---|---|---|---|---|---|---|---|
| | Selection | | | | Comparability | Outcome | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| (Abraham *et al.*, 2022) | * | * | * | * | * | * | * | * | ******** |
| (Aleong, 2013) | * | * | * | * | * | * | * | * | ******** |
| (Fiuzat, 2013) | * | | * | * | * | * | * | * | ****** |
| (Lee, 2016) | * | | * | * | * | * | * | * | ****** |
| (Kao, 2013) | * | * | * | * | * | * | * | * | ******** |
| (Parvez *et al.*, 2012) | * | * | * | * | * | * | * | * | ******** |

Note: The Newcastle-Ottawa Quality Assessment Scale (NOS) criteria: 1=Ensuring that the exposed cohort is representative; 2=Selecting a suitable non-exposed cohort; 3=Accurately identifying exposure; 4=Demonstrating that the outcome of interest was not present at the beginning of the study; 5=Ensuring comparability of cohorts through design or analysis adjusted for confounders; 6=Assessment of outcome; 7= Having a sufficiently long follow-up period for outcomes to occur; 8=Adequacy of follow-up of cohorts.

**Data extraction and analysis**

The data extraction target from each included manuscript was categorized as PICo, which included subject/research characteristics, beta-blocker agents, heart rate, and ADRB1 variant/HCN channel/SA node. To expand the role of beta-blockers, findings related to their cardioprotective effects were also extracted from the included manuscripts. Descriptive analysis was applied in this review.

## RESULTS AND DISCUSSION

Eight of the 668 articles were selected for this systematic review (Figure 1). Six studies were related to ADRB1, and the rest were related to HCN. To expand the view of the beta-blocker effect on the heart rate/HCN channels/SA node, there were no limitations to the research subjects. However, the subjects identified in the six manuscripts (Table I-III) related to ADRB1 were humans ($N_{total}$ =4143). All HF types of heart failure were included in this systematic review. Only non-human subjects were identified in the included studies related to the HCN/SA node (Table IV).

**The quality of included studies**

The outcomes of the quality evaluation (Table I and Figure 2) of the eight included studies. Six included studies (Table I) were cohorts of 4143 human subjects (Abraham *et al*., 2022; Aleong, 2013; Fiuzat, 2013; Kao, 2013; Lee, 2016; Parvez *et al*., 2012). NOS criteria (Ayubi *et al*., 2021; Wells *et al*., 2021) were used to evaluate the quality of the included cohort studies. The rest (Figure 2) were non-human subject research, which included animal research (Du, 2016) and an *in vitro* cell line model (Cao *et al*., 2018).

The quality of the included cohort studies was evaluated using the NOS criteria. Based on the NOS, all included cohort studies had scores of ≥6 (Table I). Three of the six included cohort studies had no placebo-controlled groups (Table II) but compared wild-type and ADRB1 variants (Fiuzat, 2013; Lee, 2016; Parvez *et al*., 2012).

ROB in the included animal study (Du, 2016) was evaluated using the SYRCLE tool. Six domains (sequence generation, allocation concealment, random housing, experimental blinding, random outcome assessment, and blinding outcome) had an unclear risk of bias (Figure 2A). Unclear judgment indicated insufficient details in the manuscript to properly evaluate ROB(Hooijmans *et al*., 2014). The rats were randomized to the treatment group. However, methods for sequence generation, allocation concealment, and random housing were unclear. There was also no evidence as to whether the investigators or assessors had any knowledge of what rat group was the sham-operated control group, heart failure group, or bisoprolol-treated heart failure group (Du, 2016). The remaining domains (baseline characteristics, incomplete outcome data, and selective outcome reporting) had a low risk of bias (Figure 2A). Other sources and problems of bias also have a low risk of bias. However, the research ethics committee's reference number has not yet been reported (Du, 2016).

Five assessment criteria from SciRAP with 23 checklist topics (SciRAP, 2018) were used to assess the quality of the included *in vitro* study (Cao *et al*., 2018), with a SciRAP score of 93,18 (Figure 2B). Item 19 of the 23 topics (impact of the test substance on cytotoxicity), was removed because it was not the focus of this study (Cao *et al*., 2018). With respect to the first criterion (test and control compounds) and the second criterion (test system), the *in vitro* study was assessed under the criteria associated with partially fulfilling the purity of the test compound and unidentified information on the screening of contamination. The remaining assessment elements were fulfilled (Figure 2B).

**ADRB1 and Beta-Blockers**

The choice of beta-blocker agent varied among the included studies. In this systematic review, bisoprolol, carvedilol, atenolol, metoprolol, and bucindolol were used as rate-lowering therapies (Table II). Sympatholytic drugs, such as beta-blockers, bind to ADRB1 sites and inhibit the binding of epinephrine and norepinephrine (NE) to the receptor sites (Farzam & Jan, 2022; Libby *et al*., 2021). ADRB1 is a member of the G protein-coupled receptor (GPCR) family, known as rhodopsin-type (class A). It requires catecholamines such as epinephrine and NE to become activated. (Chen *et al*., 2022; Velmurugan *et al*., 2019). Activation is initiated by the release of epinephrine from the adrenal medulla and NE from cardiac sympathetic nerves (Grandi & Ripplinger, 2019; Oe *et al*., 2020). Activation of GPCRSs initiates the stimulation of adenylyl cyclase (AC), causing an increase in cyclic adenosine monophosphate (cAMP) accumulation, which in turn leads to the activation of protein kinase A (PKA) dependent on cAMP. PKA leads to phosphorylation of phospholamban to accelerate sarcoplasmic reticulum $Ca^{2+}$ uptake.

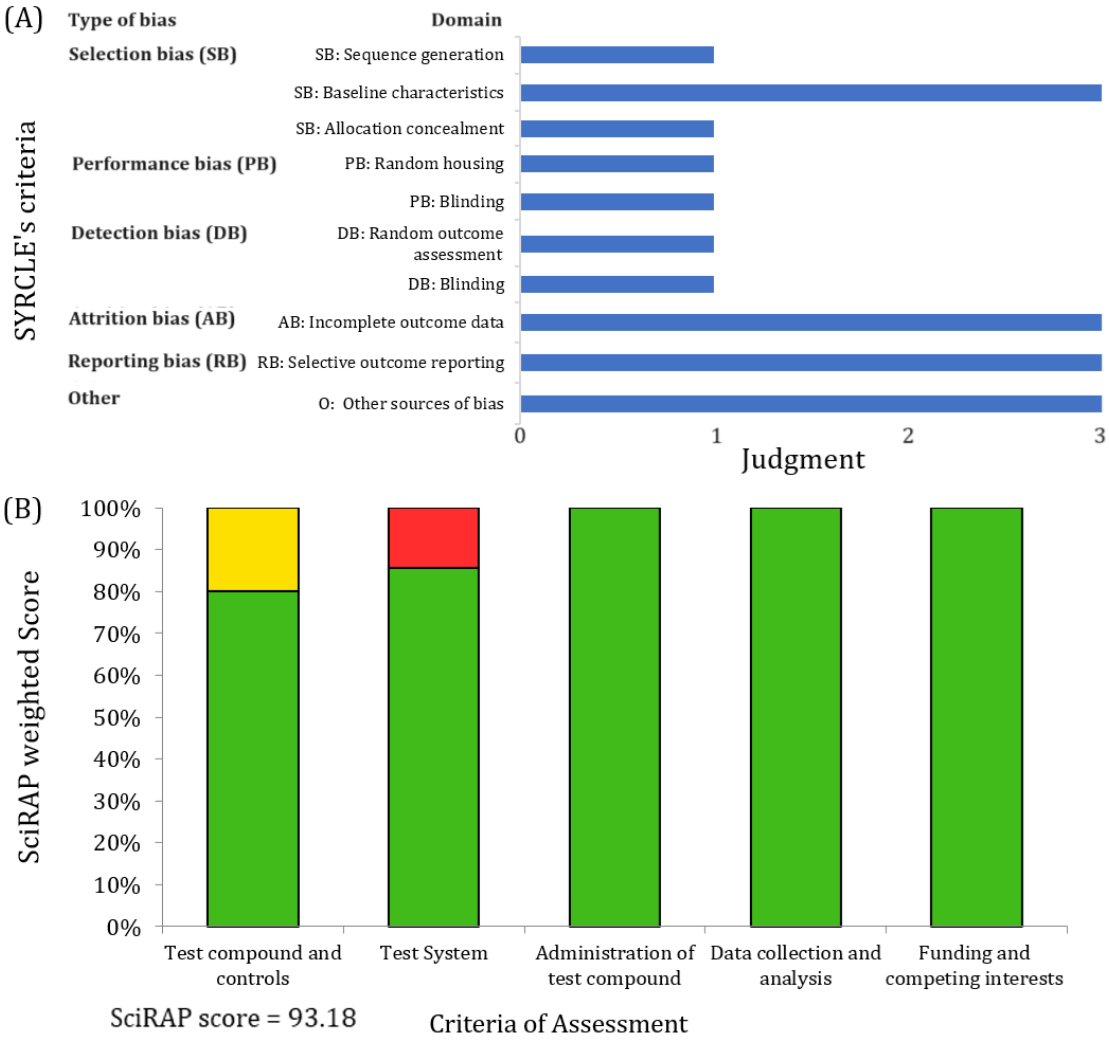


Figure 2. Reporting quality assessment of included studies: (A) SYRCLE, (B) SciRAP

Note: Quallity assessment in the included animal study (Du, 2016) and in vitro study (Cao *et al.*, 2018) consecutively were evaluated using the SYRCLE and SciRAP criteria. SYRCLE judgment was 3= "Yes" indicates a low risk of bias (ROB); 2= "No" shows a high ROB; and 1="unclear" means an unclear ROB. SciRAP weighted score criteria) wa indicated with the color profile (green bar=fulfilled; yellow=partially fulfilled; red=not fulfilled; grey=not determined).

This contributes to an increase in heart rate. Membrane ion channels (including the Na+/Ca2+ exchanger and HCN channels) and spontaneous local Ca2+ release are also required for the PKA-dependent mechanism of the cardiac rhythmic action potential. When the activity of AC in the sinoatrial node increases, it results in a faster heart rate (Behar *et al.*, 2016; Liu *et al.*, 2022). The sympathetic effect of ADRB1 increased heart rate (positive chronotropic effect). Beta-blockers block this pathway, resulting in decreased heart rate (negative chronotropic effect) (Felker & Mann, 2019; Tucker *et al.*, 2023).

Beta-blockers reduced the heart rate and prevented ventricular arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF), in heart failure (Table II). VT/VF are prevalent in patients with chronic heart failure and HFrEF(Aleong, 2013). VT/VF increase the mortality risk and other adverse cardiovascular outcomes (Al-Khatib *et al.*, 2018; Aleong, 2013). Beta-blockers such as bucindolol prevent the incidence of VT or VF in HFrEF (Aleong, 2013). VT is defined as ventricular arrhythmia with ≥ three consecutive beats at a rate of ≥ 100 beats per minutes (bpm) (Foth *et al.*, 2018).

Table II. ADRB1 variants impact on beta-blocker response in human subjects with heart failure($N_{total}$=4143)

| Study, country | N total<br>Subject Characteristic (disease/condition), Beta-blocker agent, Dose***<br>[time to follow up] | ADRB! 389 | ADRB! 49 | Results |
|---|---|---|---|---|
| (Aleong, 2013)<br>USA | N=1040<br>HFrEF<br>Bucindolol<br>Dose in BEST protocol: Initial dose 3 mg, then up-titrated to 200 mg/day (≥75 kg weight) or 100 mg/day (<75 kg)<br>[96 weeks (24 months)] | - Arg 389 Arg<br>- Gly 389 X | N/A | – Basal HR between genotypes was similar (p=0,4). However, bucindolol significantly reduced the risk of VT/VF (hazard ratio, 0.42; P =0.00006).<br>– The incidence of VT/VF was 9.23% in the patients treated with bucindolol.<br>– As compared with a placebo, the bucindolol effect, incidence of VT/VF was significantly modulated by ADRB1 VT/VF Arg389Arg (p=0.00005) in all races, but it was not in ADRB1 389Gly carriers (p=0,085). |
| (Kao, 2013)<br>USA | N=1040<br>HFrEF and AF/SR<br>Bucindolol<br>The mean dose AF:120±69 mg/day and SR:125±64 mg/day (p=0.39)<br>[12 weeks] | - Arg 389 Arg<br>- Gly 389 X | N/A | – The changes in HR between bucindolol and placebo was not significant between genotypes (P= 0.32).<br>– NE levels were signigificanty higher (P , 0.0001), in AF than SR (624+446 vs. 496+320 pg/mL).<br>– Beneficial treatment effects on cardiovascular hospitalization and mortality were significantly observed only in patients with AF and SR who achieved a resting HR ≤80 bpm [hazard ratio 0.79 and 0.61, P<0,05].<br>– HR response was not diminished in Arg389Arg. |
| (Abraham et al., 2022)<br>USA | N=511,<br>HF<br>Metoprolol, Bucindolol<br>Metoprolol GF (SR:169 ± 57 mg/day; and AF:172/day); Bucindolol GF (SR 167±57)mg/day; an AF: 159±55 mg/day); Bucindolol BEST (SR :154±47 mg/day; 157±51 mg/day)<br>[16-17 weeks]] | - Arg 389 Arg | N/A | – The resting HR reduction was significant in the BEST study(p<0.05), but not in the GF study.<br>– BEST had a significantly lower NE level than GF (p<0.05).<br>– Permanent AF, advanced HF, and more severe dysfunction in the left ventricle were associated with higher NE levels.<br>– The NE level was higher in AF than in SR both in GF and BEST |
| (Fiuzat, 2013),<br>Korea | N=957<br>HF<br>Beta-blocker<br>The dose was standardized using CEDB:<br>LD (≤25mg daily)<br>HD (>25 mg daily)<br>[6 weeks]] | - Arg 389 Arg<br>- Gly 389 X | N/A | – HR between genotypes was not different (p<0,99).<br>– HD of CEDB was required to achieve better QOL in Arg389Arg.<br>– Arg389Arg patients with LD CEDB had a higher mortality risk than those who received HD CEDB (p<0.05, hazard ratio=2.09). However, this was not observed in individuals with Gly389X. |
| (Lee, 2016),<br>Korea | N=82<br>Chronic HF, NYHA II-III, LVEF≤ 45<br>Bisoprolol:<br>Initial dose was 1,25 mg, then it was up-titrated to 5.26 ± 2.62 mg (Arg389Arg) vs. 3.96 ± 2.05 mg, (Gly389X), p = 0.022)<br>[52 weeks] | - Arg 389 Arg<br>- Gly 389 X | N/A | – Final HR across genotypes was not significantly different (p=0,022), but Arg389Arg required a significantly bigger dose compared to the Gly389X<br>– HR reduction in Gly389X was higher than the reduction on Arg389Arg (11.9±15.1 bpm vs -8.9±14.8 bpm respectively), but the difference was not statistically significant ($p$ = 0.43) |
| (Parvez et al., 2012), USA | N=513<br>AF and congestive HF<br>Atenolol, Carvedilol, Metoprolol<br>Arg389Gly-Ser49Ser dose vs. other haplotypes= 68 vs. 92 mg (atenolol); 20 vs. 44 mg (carvedilol); 72 vs. 80 mg (metoprolol)<br>[24 weeks] | - Arg 389 Arg<br>- Gly 389 X | - Ser 49 Ser<br>- Gly 49 X | In achieving HR target (set forth by AFFIRM) criteria:<br>– Arg389Arg showed a lower percentage than Gly carriers at 389 (51% vs. 60%, p=0.04).<br>– Ser49Ser showed a lower percentage than Gly carriers at 49 (56% vs. 62%, p>0.05).<br>– Arg389Gly-Ser49Ser haplotype needed the lowest dose compared to other haplotypes (p<0.01)<br>– The percentages of responders vs. non-responders to rate-control therapy based on haplotypes were 48% vs. 52% (Arg389Arg-Ser49Ser), 52% vs. 48% (Arg389Arg-Gly49X), 50% vs. 50% (Gly389X - Gly49X), and 67% vs. 33% (Gly389x-Ser49Ser). The p-value of Gly389x-Ser49Ser was < 0,001. |

Note: ADRB1= beta1-adrenergic receptor; AFFIRM criteria = atrial fibrillation follow-up investigation of rhythm management (AFFIRM); AF= atrial fibrillation; bpm=beats per minute; BEST= beta-blocker evaluation survival trial; Final dose = CEDB (:carvedilol equivalent daily doses of beta-blocker) or bucindolol (:bucindolol final dose); GF= genetic-AF trial; HF= heart failure; HFrEF = heart failure and reduced left ventricular ejection fractions, HR= heart rate; HD= high-dose; LD = low-dose; LVEF= left ventricle ejection fraction; N/A= not available; NE = norepinephrine; NYHA = *new york heart association classification the* stages of heart failure; p value= probability value provided by the included studies; QOL= Quality of life assessment based on Kansas City Cardiomyopathy Questionnaire; SD=standard deviation; SR=sinus rhythm; VF= ventricular fibrillation; VT=ventricular tachycardia; vs. =versus.

A high resting heart rate significantly increases the likelihood of negative outcomes in individuals diagnosed with HFrEF. Patients with HFrEF and sinus rhythm who had heart rates ≥ 70 bpm in the past 6 months exhibited significantly higher rates of hospitalization for heart failure, hospitalization for any cause, and mortality rates of 51%, 25%, and 36%, respectively (Kurgansky *et al*., 2020). Meanwhile, in patients with HFrEF and atrial fibrillation, achieving a resting heart rate of ≤80 bpm significantly reduces the risk of cardiovascular hospitalization and mortality(Kao, 2013). Therefore, achieving a target heart rate is crucial for obtaining beneficial treatment effects, including all-cause hospitalization/mortality (Kao, 2013).

Nevertheless, approximately 50% of patients with congestive heart failure and atrial fibrillation were unable to achieve the heart rate target set by the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) criteria, and approximately 9% of patients with chronic heart failure had a high heart rate associated with VT/VF (Table II). Beta-blocker response variability may be due to genetic factor, medical history, and NE levels (Abraham *et al*., 2022; Parvez *et al*., 2012). Higher NE levels indicate increased sympathetic drive (Borovac *et al*., 2020).

ADRB1 genetic polymorphisms can cause variability in the rate-control response. This systematic review identified two ADRB1 SNPs in cardiomyocytes. These germline genetic variants were *A145G* and *C1165G* (Table II), which resulted in amino acid substitutions of serine for glycine at position 49 (Ser49Gly) and arginine for glycine at position 389 (Arg389Gly), respectively (NCBI, 2022, 2023). The Ser49Gly frequency was 16,45% (Southeastern Europe), 12-16% (Asians and Caucasians), and 13-28% (African-Americans). Arg389Gly frequency was 42,60 % (South-eastern Europe), 24-34% (Asians and Caucasians), and 39-46% (African-Americans) (Katsarou *et al*., 2018; Parvez *et al*., 2012). Allele frequencies in all populations were 16,74% (Ser49Gly) and 30,39 % (Arg389Gly) (Whirl-Carrillo *et al*., 2021).

The reduction in heart rate was greater with Gly389X (Gly389Arg + Gly389Gly). Interestingly, significantly higher carvedilol equivalent doses of beta-blockers (Table II-III) were required to achieve benefits in the Arg389Arg genotype (>50% the guideline-directed medical therapy (GDMT) target dose) than in the Gly389X (Gly389Arg + Gly389Gly) group (≤50% of the GDMT dose). The GDMT dose for carvedilol is either 25 mg twice daily (<85 kg body weight) or 50 mg twice daily (≥85 kg body weight) ((Maddox *et al*., 2021). Glycine substitution for arginine at position 389-position reduced ADRB1 sensitivity. It attenuates receptor function, produces less constitutive activity, decreases the affinity for NE, and results in less responsiveness to sympathetic stimulation. In contrast, ADRB1 Arg389Arg promotes coupling to Gs, accelerates ADRB1 activity, and produces greater sympathetic activity (Filigheddu, 2013; Kao, 2013; Lee, 2016). Hence, administration of a higher dose of beta-blockers to heart failure patients with the Arg389Arg genotype to achieve a response to treatment compared to those with Gly389X (as shown in Table III) was recommended.

Rate-control treatment for heart failure with atrial fibrillation required a higher dose of bucindolol than in those with sinus rhythm (Table II-III, Abraham *et al*., 2022). The discrepancy in the required dose of bucindolol between patients with AF and sinus rhythm could be explained by the difference in baseline norepinephrine (NE) levels (Abraham *et al*., 2022; Liggett *et al*., 2006). NE levels in patients with AF, as shown in Table II, were higher than those in patients with sinus rhythm. However, in another study (Kao, 2013), the dose of beta-blockers administered to patients with sinus rhythm was greater than that administered to patients with AF (Table II-III). This finding is in contrast with that reported by Liggett *et al*. (2006). Therefore, a change in resting heart rate was not significant in patients with HFrEF atrial fibrillation in a study conducted by Kao (2013). NE levels in the body are linked to both the severity of heart failure and degree of left ventricular dysfunction (Borovac *et al*., 2020; Thomas & Marks, 1978; Wu *et al*., 1995). Patients with congestive heart failure had higher plasma NE levels than those without, indicating that their sympathetic nerve activity (SNA) was overactive. In patients with congestive heart failure, the amount of NE spillover in the heart increases significantly, reaching up to 540%, when compared to individuals without heart failure (Borovac *et al*., 2020; Hasking *et al*., 1986). NE levels in severe, moderate, and mild congestive heart failure increased by 3.7, 2.6, and 2.0, respectively, compared with the control (Thomas & Marks, 1978; Wu *et al*., 1995). Increased NE spillover associated with elevated cardiac SNA augments the risk of morbidity and mortality in heart failure (Borovac *et al*., 2020; Ramchandra & Barrett, 2015).

Persistent atrial fibrillation with more severe left ventricle dysfunction and more advanced heart failure is associated with higher NE (Abraham *et al*., 2022).

Patients with heart failure and atrial fibrillation or sinus rhythm showed similar outcomes (Table II). NE levels may be reduced with beta-blocker therapy (Abraham *et al*., 2022; Liggett *et al*., 2006). Beta-blockers attenuated SNA, where beta-blockers reduced plasma NE levels in subjects with LVEF <45% and NYHA class II-IV after one month of therapy (Figueiredo neto *et al*., 2004).

ADRB1 variants at 389 position could be associated with heart rate response to beta-blocker therapy (Table II). However, the results were mixed in heart failure patients, including the pattern of alteration (increase or decrease in heart rate) and the level of significance within a statistical test (p-value). This systematic review also identified ADRB1 variants at 49 position that are associated with the heart rate response in beta-blocker-treated heart failure (Table II). Patients with homozygous Gly389X and Ser49Ser genetic variations appear to have a higher success rate in achieving the heart rate target compared to those with Arg389Arg and Gly49X genetic variations. In atrial fibrillation with hypertension/coronary artery disease/congestive heart failure, a similar pattern was observed in the Ser49Ser-Gly389X haplotype. Among the responder, the percentage of achieving the heart rate target was higher for Ser49Ser-Gly389X (67%) than for the other haplotypes(48-52%). The percentage of patients with the Ser49Ser-Gly389X haplotype that achieved the target heart rate was significantly different from that of the other haplotypes (Parvez *et al*., 2012). Based on an *in vitro* test using HEK 293 cells, the Ser49Ser-Gly389X haplotype showed the lowest cAMP level at baseline and throughout the agonist (isoproterenol)-stimulated response (Sandilands & O'Shaughnessy, 2005).

Achieving a heart rate target is crucial. Without achieving a resting heart rate of ≤80 bpm in heart failure patients with atrial fibrillation, there were insignificant treatment effects on cardiovascular hospitalization and mortality. A similar finding was also observed in sinus rhythm, in which the target rate control was not achieved (Kao, 2013). Younger age, larger body mass index, larger body weight, and lower B-type natriuretic peptide levels were significantly associated with higher carvedilol-equivalent doses (Cohen-Solal *et al*., 2017). The ADRB1 variant is also related to beta-blocker dose requirement. Arg389Arg contributes to significant cardiovascular outcomes. Low dose of beta-blockers for Arg389Arg were related to a two-fold increase in hospital readmission, a double risk of mortality, and a worse quality of life. (Fiuzat, 2013; Parikh, 2018).

**SA Node, HCN and beta-blocker**

A beta-blocker role in the SA node and HCN was identified in two studies (Table IV). Beta-blockers were beneficial for inhibiting HCN-gated channels (Cao *et al*., 2018) and improving ion channel regulation in the SA Node (Du, 2016).

An *in vitro* study in CHO cells demonstrated that carvedilol reduced the elevated heart rate by blocking HCN1, HCN2, and HCN4 channels (Table IV). The effect of carvedilol on HCN4 was not associated with ADRB1 blocking property and cAMP sensitivity. Carvedilol blocks HCN4 expression in cAMP-insensitive mutant channels. The inhibitory effect on HCN4 channels was concentration-dependent. In contrast to ivabradine, carvedilol blocks the HCN-SA Node through a different mechanism (Bucchi *et al*., 2006; Cao *et al*., 2018; Hackl *et al*., 2022). Carvedilol is a direct blocker of HCN channels. It is an HCN channel-negative-gating modulator. Carvedilol reduced the activation rate and accelerated channel deactivation. A threefold decreased activation rate at -120 mV and shifted activation leftwards (-26.8 ± 1.8 mV on HCN4 as compared to control) was demonstrated by carvedilol (Cao *et al*., 2018). Meanwhile, ivabradine lowers diastolic depolarization and heart rate by attaching to the HCN4 channel's internal cavity (Hackl *et al*., 2022; Hennis *et al*., 2021) . Ivabradine is an inhibitor of open-HCN4 channels. As a result, ivabradine has an effect when the channels are opened. In the closed state, ivabradine cannot reach its site of action (Bucchi *et al*., 2006; Cao *et al*., 2018; Hackl *et al*., 2022)). cAMP directly activates HCN channels, whereas PKA promotes HCN4 channel activity (Hackl *et al*., 2022; Kawada *et al*., 2019) .

Bisoprolol demonstrated cardioprotective effects by improving SA-Node function in failing hearts (Table IV). Chronic beta-blocker therapy was beneficial in restoring the cardiac toxic effect upon persistent catecholamine stimulation. Catecholamine is cardiotoxic as it causes myocardial damage (Masarone *et al*., 2021).

Table III. Beta-blockers dose between genotypes

| Study (N Total) | Final Dose (beta- blocker), n (%) | | |
|---|---|---|---|
| | **Arg389Arg** | **Gly389X** | **Result** |
| (Aleong, 2013)<br>• N=1040 | BEST protocol:<br>≥75kg weight: 200mg/day<br><75kg weight:100mg/day<br>(Bucindolol)<br>n=493 (47%) | BEST protocol:<br>≥75kg weight: 200mg/day<br><75kg weight:100mg/day<br>(Bucindolol)<br>n=547 (53%) | At a similar dose, the incidence of high HR associated with VT/VF was higher for Arg389Arg than Gly389X. |
| (Abraham *et al.*, 2022)<br>• N=511 | SR/AF :<br>157.93± 51.00 mg/day<br>(Bucindolol)<br>n=388 (75%)<br>SR/AF :<br>33.59± 11.40<br>mg /day<br>(CEDB)<br>n=123 (24%) | N/A | N/A |
| (Fiuzat, 2013),<br>• N=957 | LD, HD (CEDB)<br>↓<br>There was an interaction between the dose and outcome, therefore HD was recommended.<br>n=439 (46%) | LD, HD (CEDB)<br>↓<br>The interaction between beta-blocker dose and outcome were not observed in Gly389x.<br>n=518 (54%) | To achieve a benefit similar to Gly389x, Arg389Arg requires a higher dose of beta-blockers. |
| (Lee, 2016),<br>• N=82 | 26.30±13.10<br>(CEDB)<br>n=52 (63%) | 19.80±10.25<br>(CEDB)<br>n=30 (37%) | Arg389Arg required a larger dose to achieve similar HR reduction. |
| (Parvez *et al.*, 2012),<br>• N=513 | 27.06±8.73<br>(CEDB)<br>n=270 (53%) | 19.61±2.01<br>(CEDB)<br>n=243 (47%) | Among responders, a higher dose was required for Arg389Arg |

Note : AF= atrial fibrillation; BEST= Beta-Blocker Evaluation Survival Trial(Aleong, 2013; BEST, 1995); Final dose = CEDB (:carvedilol equivalent daily doses of beta-blocker) or bucindolol (:bucindolol final dose); LD-CEDB: = low-dose (≤25mg daily); HD-CEDB=high-dose (>25 mg) daily; HR= heart rate; HD= high-dose; LD = low-dose; SR=sinus rhythm; N/A= not available;

In a failing heart, an increase in catecholamine levels leads to sustained beta-adrenergic receptor stimulation, with consequent dysfunction (Du, 2016; Masarone *et al.*, 2021). The chronic and persistent hyperadrenergic state alters the molecular characterization of the signalling pathway component of the beta-adrenergic receptor, resulting in ionic current remodelling. Impaired SA node automaticity and depolarization potential are contributed by ionic current remodelling in heart failure (Du, 2016).

This systematic review revealed that bisoprolol restored the diminished function of the SA nodes in failing hearts (Table IV). Long-term bisoprolol treatment reversed the downregulation of HCN4 and sodium channels. Bisoprolol protects the beta-adrenergic receptor from overstimulation (Du, 2016). Carvedilol has also demonstrated cardioprotective effects. Chronic carvedilol therapy improves calcium handling in heart failure and restores sodium channel function. Calcium channel dysregulation may be responsible for the decreased sodium current. Carvedilol normalizes calcium regulatory proteins in cardiomyocytes, improves the structure and function of the cardiac calcium-release channel, and decreases calcium influx through L-type calcium channels (Maltsev *et al.*, 2002).

Table IV. *In vitro* and animal study of beta-blocker effect on SA node and HCN4

| Study, Country | Beta blocker, Groups (n), Experimental Approach | Results |
|---|---|---|
| (Cao *et al*., 2018), -China. | - Carvedilol<br>- Three groups:<br>I : HCN1 (6 cells).<br>II : HCN2 (6 cells).<br>III : HCN4 (6 cells).<br>The effects were recorded in the absence (control) and presence (treatment) of carvedilol.<br>- Procedures:<br>a. Transfection: HCN channels cDNAs into CHO cells.<br>b. Whole-cell patch-clamp electrophysiological technique for recording the effect of carvedilol on HCN currents. | *In vitro* study in CHO cells demonstrated that carvedilol blocked HCN1, HCN2, and HCN4 channels by decreasing the channel activation rate and shifting the voltage-dependence of activation leftward ($p<0.05$ vs. control).<br>Therefore, carvedilol reduced the elevated heart rate. |
| (Du, 016), -China. | - Bisoprolol<br>- Three groups of 48 rats:<br>I : Heart failure (16 rats (33%))<br>II : Heart failure with bisoprolol treatment (17 (36%))<br>III : Sham-operated control group (15(31%))<br>- Procedures:<br>a. Intrinsic heart rate and SA node recovery time were recorded using the BL-420s System.<br>b. Laser capture microdissection for isolating SAN cells<br>c. Real-time PCR to quantify mRNA expression of HCN and sodium channels in SA Node | Chronic treatment with bisoprolol in heart failure rats improved the intrinsic heart rate and SA node recovery time ($p<0.01$ vs control).<br>Treatment with bisoprolol restored SA Node function by reversing the downregulation of HCN4 and sodium channels (Nav1.6 and Nav1.1). |

Note: cDNA= complementary DNA; HF = heart failure; HCN= hyperpolarization-activated cyclic nucleotide-gated (subunit HCN1 HCN2, HCN4);SA node= sinoatrial node; mRNa=messenger RNA, vs=versus.

Overall, this systematic review provides important insights into the role of beta-blockers in heart failure treatment, particularly in the context of ADRB1 genetic variability and its impact on the SA node and HCN4 channels. These findings can inform future research and improve our understanding of the mechanisms underlying heart failure and its treatments.

## LIMITATIONS OF THE STUDY

This systematic review study has inherent limitations in measuring the summary effect size. Therefore, a meta-analysis with more comprehensive and homogenous data is required for further exploration. The use of medical subject headings (MeSH) may facilitate the retrieval of relevant manuscripts for meta-analyses.

## CONCLUSION

ADRB1 genetic variants affecting heart rate response in heart failure patients receiving beta-blocker therapy were ADRB1 A145G (Ser49Gly) and C1165G (Arg389Gly). Patients with the Ser49Ser-Gly389X haplotype had a higher probability (approximately 67%) of achieving the heart rate target than those with other haplotypes (48-52%). Among responders, patients with the Arg389Arg genotype required an expanded sum of carvedilol equivalent daily doses of beta-blockers to reach the indistinguishable heart rate target, compared to those with Gly389x (>50% (>25mg) versus ≤50% of GDMT dose (≤25mg), respectively). The necessity of a high-dose beta-blocker for Arg389Arg was demonstrated in all included studies.

Beta-blockers also demonstrated a beneficial effect in regulating heart rate by inhibiting HCN-gated channels and improving ion channel regulation in the SA Node (by reversing the downregulation of the HCN4 and sodium channel).

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## CONFLICT OF INTEREST

The authors declare no conflict of interest in this systematic review

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