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Pharmacogenetics of β_1-Adrenergic Receptor Blockers in Heart Failure Therapy: A Systematic Review

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Abstract

Background: β_1-adrenergic receptor blockers are an important drugs recommended as first-line treatment of Heart Failure (HF) as they improve survival in left ventricular systolic dysfunction due to chronic β_1-Adrenergic Receptor (β_1-AR) activation. However, responses to these drugs are variable among patients due to genetic polymorphism in β_1-AR gene. We conducted a systematic review to summarize all published case-control and prospective studies on pharmacogenetics of β_1-adrenergic receptor blockers (β_1-ARBs) used for the management of HF.

Methods and findings: We performed a systematic search of the literature using Medline (source PubMed, January 1, 1980 to November 30, 2011) with restrictions for English language and polymerase chain reaction assay method of genotyping the receptor polymorphism. Both experimental and observational studies investigating the pharmacogenetics effect of β_1-adrenergic receptor blockers in heart failure were included. The main outcome measure was improvement of HF symptoms which is reflected in a decrease in mortality, hospitalisation and the rate of major clinical events. Of the 30 included studies, 17 articles reporting on effect of genetic polymorphisms of β_1-AR on heart failure, 11 articles reporting on pharmacogenetics of β_1-ARBs in HF, and 2 articles reporting on both β_1-AR gene polymorphisms and pharmacogenetics of β_1-ARBs, were included into the results.

Conclusions: The findings of the current study have shown that β_1-AR polymorphisms have an effect on survival and improvement in left ventricular ejection fraction in HF patients who were Arg389 homozygotes carriers treated with metoprolol and bucindolol. Therefore, the Arg389 of β_1-AR variation alters the β_1-ARBs therapeutic response, and might be used to individualize treatment of HF.

Keywords: Pharmacogenetics, β_1-adrenergic receptor, β_1-adrenergic receptor blockers, Polymorphism, Heart failure

Abbreviations: ACE: Angiotensin Converting enzyme; Arg389: β_1-adrenergic receptor polymorphism with Arginine at amino acid position 389; Arg-Gly: Arginine and Glycine; BEST: Beta-blocker Extends Survival Trial; CAD: Coronary Artery Disease; cAMP: Cyclic Adenosine Monophosphate; CHF: Congestive Heart Failure; CR/XL: Controlled Release/Extended Release; DCM: Dilated Cardiomyopathy; EF: Ejection Fraction; Gly389: β_1-Adrenergic Receptor Polymorphism with Glycine at amino acid position 389; Gly389Arg: Glycine substitution with Arginine at amino acid position 389; Gly49: β_1-adrenergic receptor polymorphism with Glycine at amino acid position 49; HF: Heart Failure; HR: Heart Rate; ICM: Ischemic Cardio Myopathy; LVED: Left Ventricular End Diastolic; LVEF: Left Ventricular Ejection Fraction; LVES: Left Ventricular End Systolic; MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Heart Failure; MI: Myocardial Infarction; NICM: Non-Ischemic Cardio Myopathy; OR: Odds Ratio; PCR: Polymerase Chain Reaction; RCT: Randomized Control Trials; RR: Risk Ratio; Ser49:β_1-AR polymorphism with Serine at amino acid position 49; Ser49Gly: Serine substitution with Glycine at amino acid position 49; SHF: Systolic Heart Failure; SNP: Single Nucleotide Polymorphism; SNS: Sympathetic Nervous System; VO_2: Oxygen consumption; β_1-AR: β_1-adrenergic receptor; β_1-ARBs: β_1-adrenergic receptor blockers; β-AR: β-adrenergic receptor; β-ARBs: β-adrenergic receptor blockers

Introduction

Heart failure (HF) is an important cause of cardiovascular morbidity and mortality [1] that arises from a variety of disorders, the most common of which are ischemic Heart Disease (IHD), hypertension and dilated cardiomyopathy (DCM). HF is characterized by progressive remodelling of the myocardium, accompanied by worsening symptoms, exercise intolerance and fluid accumulation [2].

Patients with HF have poor quality of life [3], and require frequent hospital admissions that accounts for at least 5% in British hospitals [4] and for at least 20 % of all hospital admissions among persons older than 65 in United States [5]. The prevalence of HF is increasing, due to the rise in the number of people living to an old age and an increase in the number of individuals who survive Myocardial Infarction (MI) but are left with Left Ventricular Dysfunction (LVD) [6,7]. Though recent advances in the management of patients with HF, morbidity and mortality rates remain high [8].

In order to develop pharmacologic interventions that might reverse or halt the vicious cycle of HF, different studies have been done to examine the pathophysiologic changes that contribute to the progression of HF. The biologic pathways that were known to protect

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the heart during acute dysfunction were found to be the same pathways that cause progressive deleterious effects with chronic activation of the Sympathetic Nervous System (SNS) and the Rennin-Angiotensin-Aldosterone System (RAAS) [8], resulting in vasoconstriction, sodium and water retention, and ventricular hypertrophy/remodelling [9]. The left ventricular systolic dysfunction is accompanied by the activation of compensatory mechanisms, SNS and RAAS, which improve cardiac function to a normal range and keeping the patient asymptomatic [2,10,11]. However, continued stimulation of these systems leads to further myocardial damage, causing worsening ventricular remodelling and a predictable decline in cardiac performance [10-12].

Beta adrenergic receptor (β-AR) signalling is critical in the progression of HF [2,13]. Antagonism of this pathway by β- adrenergic receptor blockers (β-ARBs) has been shown to produce a clinical improvement in patients with HF together with an improvement in remodelling and pump function [14]. All β-ARBs antagonize the beta1-adrenergic receptor (β_1-AR), and this effect is believed to be responsible for the therapeutic benefit associated with β-ARBs therapy for chronic HF [15]. Conversely, they are all contraindicated in acute HF because of the acute decrease in cardiac output they cause [16]. The β-ARBs commonly used for the treatment of HF are bisoprolol, carvedilol and metoprolol controlled release/extended release (CR/XL) [9]. Chronic β-ARBs therapy reverses left ventricular remodelling, reduces risk of hospitalization, improves survival, reduces risk of sudden cardiac death, improves coronary blood flow to the heart, and protects the heart against cardiotoxic overstimulation by the catecholamines [17]. All of these effects result in a decrease in the oxygen/ energy and metabolic demands of the heart and in an increase in its oxygen/energy supply, thereby improving, in the long-term, left ventricular function and performance [9,11]. They are recommended for all patients with a reduced Left Ventricular Ejection Fraction (LVEF) [9].

The molecular mechanisms underlying for the effects of β-ARBs have been postulated as follows: (1) direct antagonism of catecholaminergic cardiotoxic effects; (2) cardiac β-AR upregulation and restoration of their signaling and function, that is, increase in adrenergic and inotropic reserves of the heart, partly via cardiac GRK2 downregulation; (3) suppression of the elevated cardiotoxic, adverse remodelling–promoting, and proapoptotic neurohormonal systems (RAAS, endothelin); (4) coronary blood flow enhancement (as a result of diastolic prolongation); and (5) restoration of the reflex controls on the heart and the circulation. In addition, restoration of adrenal GRK2–α2AR–catecholamine secretion axis and suppression of norepinephrine release from cardiac SNS endings might contribute to the beneficial effects of β-ARBs in chronic HF, as well [11].

The response to β-ARBs is variable between patients and this may be attributed to polymorphisms in β-AR genes [2,15]. Each of the targets of current pharmacologic therapy has important genetic variations that alter the function of the receptor-mediated signalling pathway both under physiologic conditions and during disease state [8]. Clinical trials assessing the efficacy of drugs used in the treatment of HF have suggested that different populations react differently to the same drug. For example, HF outcomes were found to differ by gender, race, aetiology and environment [18]. According to the American Heart Association in 2005, HF death rates for Caucasian men were 19.4 compared to 21.9 for African American men and 18.2 for Caucasian women compared with 19.4 for African American women [19]. Many of the currently used pharmacological agents for the treatment of HF, chiefly agents that act by modulating the function of the adrenergic receptor-G protein complex [8] mainly the β-AR have demonstrated very different effects in different ethnic or racial groups.

β_1-AR polymorphisms have been concerned with inconsistent results in the pathogenesis, clinical presentation, and prognosis of patients with HF [17]. As a result, the β_1-AR is interesting candidates for pharmacogenetics studies in HF since they mediate the effects of catecholamines in the SNS. These receptors are involved in the progression and treatment of HF diseases with β-ARBs therapy, and have polymorphisms that show altered regulation as compared to their allelic counterparts in recombinant expression systems and genetically modified mice. These results have provoked prospective and retrospective clinical studies examining whether polymorphisms of these genes are risk factors, disease modifiers, or predictors of β-ARBs response in HF. To date, it appears thatβ-AR variants are very likely one genetic component that defines responsiveness to β-ARBs in HF [20].

Several genetic polymorphisms in the gene coding for the β_1-AR have been identified. The Ser49 or Gly49, and Arg389 or Gly389, are the two major Single Nucleotide Polymorphic (SNP) alleles [21-24] most importantly, the Arg-Gly SNP at amino acid position 389 has been associated with cardiac disease [21]. A Ser49Gly variant may be associated with enhanced agonist-induced down-regulation, whereas a Gly389Arg variant was found to bring about a four-fold higher agonist stimulated signal transduction to the G-protein coupled receptor stimulation (Gs) compared with the Gly allele [25].

Recent data have shown that the effects of the β_1-AR polymorphism may differ depending on the specific β-ARBs used [21] and ethnic difference. Genetic variants in the β_1-AR associated with lesser response to β-ARBs are more common in blacks than in whites [26]. There is a clinical data on these β_1-AR polymorphisms and association with response to β-ARBs treatment in HF [23,27]. Therefore, the present study is designed to draw inference about the potentials of β-ARBs for the management of cases of HF, and to evaluate the justifiability of the importance of considering β-AR polymorphisms in the treatment of HF with β_1-ARBs by systematically reviewing the previous researches done on pharmacogenetics of β-ARBs for the management of HF.

Methods

Search strategy

This systematic review follows PRISMA guidelines [28]. We searched the publications listed in the electronic databases Medline (source: PubMed, January 01, 1980 to November 30, 2011) using combination of the following heading terms: pharmacogenetics of beta1-adrenergic receptor blockers, beta1-adrenergic receptor polymorphisms, as well as beta adrenergic receptor blockers for heart failure therapy. Searches were boundless to all study designs: Observational and experimental studies. The references of the initially identified articles, including relevant review papers, were hand searched and reviewed. Citation lists of relevant publications were also searched. Restrictions were applied for both English language and PCR assay method of genotyping the receptor polymorphism.

Study selection

We imposed the following methodological restrictions for the inclusion criteria: (1) Studies published as original articles that were retrospective, prospective, observational, and/or randomised control trial focussing on β_1-ARBs and/or genetic polymorphism in β_1-AR; (2) Studies in which populations were representative of the general population and were all age-, sex- and racial- groups suffering from HF; (3) Studies investigating β_1-ARBs associated with genetic

polymorphisms of β_1-AR, either in monotherapy or in combination with other medication; (4) Studies where control groups received placebo or standard medication regimens for HF (i.e. diuretics, ACE-inhibitors) and also genotyped for β_1-AR; (4) There were no restrictions as to dose, route of application and type of test done (in-vivo, *ex-vivo* and in-vitro); (6) Restriction was designed for method of genotyping the β_1-AR polymorphism [polymerase chain reaction (PCR) with restriction fragment length assay] and for evaluating the pharmacogenetics interactions of β_1-ARBs (standard medication regimens, use of the same β_1-ARBs to all patients, and up-titration of the drug to the maximal possible dose).

Data abstraction

Structured data abstraction form was designed and used to ensure consistency in each study. The following data were abstracted from the included studies: study design, eligibility criteria, intervention (drugs, dose, duration, and method of genotyping), additional medications allowed, methods of outcome assessment, and population characteristics. The main outcome measure was improvement of HF which is reflected in a decrease in mortality, hospitalisation and the rate of major clinical events or expressed by rating systems such as the New York Heart Association Classification [29] (Appendix 1) or standardized assessment by physicians. Specific parameters of cardiac hemodynamics [e.g. echocardiographic evaluation of LVEF] were also compared. Studies for information on acceptability of treatment, physical fitness measures and patient's quality of life were also searched. Where available, basic cardiovascular parameters: Heart Rate (HR) and Blood Pressure (BP) were included.

Data collection and analysis

Data extraction and management: Data were collected and extracted from the included studies with particular focus on the following characteristics: type of study (all types) study population (all age, race, underlying condition, patient number) intervention (β_1-ARBs administered) duration of treatment (minimum of 3 months with the exception of experimental models) and additional information that is relevant and characteristic of the trial.

Data synthesis: Cochrane Review Manager (RevMan 5.1) software was planned to perform data analysis. Wherever possible, data relevant to intention-to-treat analyses has been extracted. For continuous outcomes, mean differences and 95% Confidence Intervals (CI) and for dichotomous outcomes, Odds Ratios (OR) and 95% CI were calculated. However, because data was too heterogeneous, statistical pooling of the results was unsuitable and data were combined in a narrative review.

Results

Study selection

With the search strategy, about 919 articles were initially retrieved. Of these, 184 articles were considered of potential interest. After the abstracts were read 64 full texts was retrieved for further evaluation. Thirty of these 64 articles were finally included in the review (Figure 1).

Study characteristics

Seventeen articles reporting on studies of effect of genetic polymorphisms of β_1-AR on HF [29-48], 11 articles [49-59] reporting on pharmacogenetics of β_1-ARBs in HF (Table 3), and 2 articles [47,48] reporting on both β_1-AR gene polymorphisms and pharmacogenetics of β_1-ARBs in HF, were included into the review. Among the 19 articles comparing the polymorphism of β_1-AR gene in HF, 9 of them were on both Arg389Gly and Ser49Gly and 8 of them were only on Arg389Gly polymorphic allele and 2 of them was only on Ser49Gly. Studies with a sample size greater than 30; the largest being 1348 with all age and racial groups were included with the exception for experimental mice model.

For the purpose of comparing the pharmacogenetics of β_1-ARBs, 13 original articles were included. Of the 13 articles, 4 of them were only for metoprolol; only 2 articles were on three drugs: bucindolol, carvedilol and metoprolol; 2 articles for both carvedilol and metoprolol; 2 articles only for carvedilol; 1 article for both bucindolol and carvedilol; 1 article for both bisoprolol and carvedilol; and only 1 article for atenolol. Studies with a sample size greater than 16; the largest being 2460 (with the exception of experimental mice model) were included. Most studies were in patients with systolic HF. The results of the search are briefly presented in Tables 1-7.

Findings in genetic polymorphisms of β_1-adrenergic receptor (β_1-AR)

Table 1 shows the studies included for the effect of genetic polymorphisms of β_1-AR on HF. The study designs included in this table were 11 prospective cohort, 2 prospective with matched control, 2 experimental mice model and 1 randomized control type. Seven studies directly investigated the association of β_1-AR Arg389Gly with heart function, two of them experimental transgenic mice model [34,47] assessing receptor function and myocardial contractility. The others are on patients with MI and/or DCM [30,32,36,37], and one patients with Systolic Heart Failure (SHF) [40]. Nine studies compared the effect of both β_1-AR Arg389Gly and Ser49Gly polymorphisms on assessing the function of HF symptoms, of which 3 studies enrolled healthy volunteers [31,38,39], 2 were on patients with acute MI and/or idiopathic DCM [41,44] and 4 were on patients with SHF [33,35,42,43].

Effect of genetic polymorphisms of β_1-AR on heart function

There were two most common non-synonymous SNPs in the β_1-AR gene, the Arg389Gly and Ser49Gly, were identified. Table 2 shows evidence for in-vitro and *ex-vivo* study of functional differences in these β_1-AR gene polymorphisms in HF.

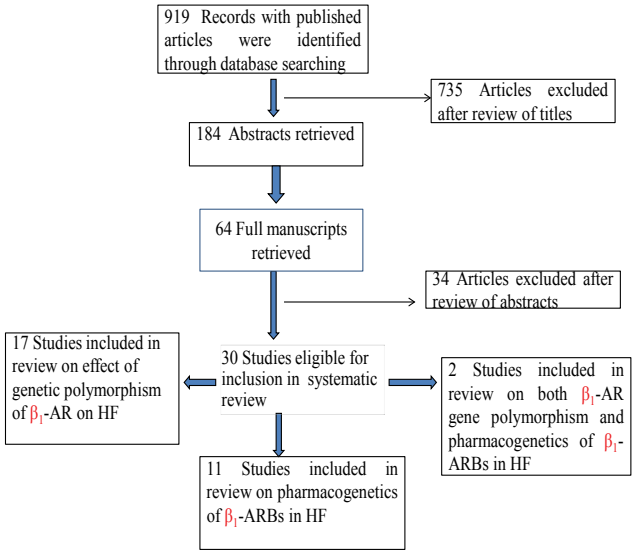

Figure 1: Flowchart of the selection of studies included in systematic review.

Author, Year [Ref]	Study Type	β_1-AR Allele	Number/ Cause of HF	Main Results
Hakalahti AE et al. [30]	P	Arg389Gly	452/ AMI	Arg389 homozygus had a significantly increased LV mass compared to the Gly389 carriers (P=0.023)
Ramu P et al. [31]	P	Arg389Gly Ser49Gly	533/ Healthy	Frequencies of Gly49 and Gly389 alleles were 15.1 and 25.8 % respectively.
Pacanowski MA, et al. [32]	P	Arg389 Gly	628/MI	Gly389 were at higher risk for the composite outcome due to higher rates of MI (adjusted HR= 3.63, 95%CI=1.17–11.28, P=0.03)
Biolo A et al. [33]	RCT	Arg389Gly Ser49Gly	201/SHF and 141/ Healthy controls	389Gly homozyg had significantly less non-sustained VT (17% vs 48% for Arg/Arg patients; P=0.015) and improved HF-related survival,
Akhter SA et al. [34]	Exp	Arg389Gly	Transgenic mice (FVB/N strain)	In 3-month-old mice, there was poor recovery after I/R (~38% vs. ~68% for non-transgenic). At 6 month of age, functional recovery remained severely depressed in Gly389 hearts (~32%) but was similar to non-transgenic for Arg389 hearts (~60%)
Nieminen T et al. [35]	P	Arg389Gly Ser49Gly	890/HF	Arg389Gly affected maximal SAP during exercise (P = 0.04) Arg389 homozyg, were less likely to have ventricular extrasystoles during exercise (OR = 0.68, 95% CI = 0.51–0.91, P = 0.009) than Gly389 carriers (OR = 0.60, 95% CI = 0.42–0.86, P = 0.006).
Sandilands AJ et al. [36]	P	Arg389Gly	83 (MI, or DCM)	Patients with Arg389 homozygous had significantly greater Peak Vo2 and exercise time compared to Gly389 homozygote
Iwai C et al.[37]	P with CC	Arg389Gly	163 DCM and 157-MC	Gly389 allele was more frequent in the VT (MC) group than in the VT(DCM) (0.46 vs 0.24; P= 0.001) OR =0.29 for VT in patients carrying the Gly389 (CI= 0.13-0.64, p=0.002), when compared with the Arg389 homozyg. The Gly389 variant suppressed VT in DCM
Ranade K et al. [38]	P	Ser49Gly Arg389Gly	1348/nuclear family	Ser49Gly polymorphism was significantly associated with RHR (P=0.0004) Arg389Gly variant was not associated (p>0.05)
Mason DA et al. [39]	P	Arg389Arg Arg389Gly	30 normal	Allele frequencies of Gly389 =0.26, Arg389 =0. 74. Arg-389 had slightly higher basal levels of AC activities
Covolo L et al. [40]	P	Arg389Gly	256/HF and 230 normal	Non-significant increase in the risk of HF
Forleo C et al. [41]	P	Ser49Gly Arg389Gly	171/DCM	Gly49 were associated with a lower risk of HF in DCM
de Groote P et al. [42]	P	Ser49Gly Arg389Gly	444/CHF	No polymorphisms were associated with survival.
Borjesson M et al. [43]	P with MC	Arg389Gly Ser49Gly	184/ CHF and 77 age-MC for 5 years	Gly49 allele frequency was 0•13 in MC and 0•18 in CHF (P=0.19). Patients without the mutation had significantly poorer survival compared to those with the mutation, RR=2•34, 95% CI 1•30-4•20, P=0•003.
Wagoner LE et al. [44]	P	Ser49Gly Arg389Gly	263/ I/DCM	Gly389 homozyg had significantly lower peak VO2 compared with those with Arg389 (14.5 ± 0.6 vs 17.7 ± 0.4 mL/kg/min, P = .006). Gly49 carriers had a higher peakVO2 than Ser49 homozygotes
Mialet-Perez J et al. [47]	Exp	Arg389Gly	Mice model	Young Arg389 mice had enhanced receptor function and contractility compared with Gly389 hearts. Arg389 homozyg was associated with improvement in VF during carvedilol treatment in HF.

AC: Adenylyl Cyclase; CC: Case Control; CV: Cardio Vascular; DCM: Dilated Cardiomyopathy; Exp: Experimental Model; Homozyg: Homozygotes; ICM: Ischemic Cardiomyopathy; I/R: Iischemia and Reperfusion; LV: left ventricle; LVEDD: Left Ventricular End-Diastolic Diameter; MC: matched control; SBP: Systolic Blood Pressure; P: Prospective cohort study; p: p-value; OR: Odds Ratio; RR: Risk Ratio; VO2: Oxygen consumption; %VO2--% of maximal predicted VO2; VF: Ventricular Function; VT: Ventricular Tachycardia.

Table 1: Summary of clinical investigation done on the effect of β_1-AR genetic polymorphisms on assessing the function of HF symptoms.

Study Type	β_1-AR gene Polymorphism	Main Results	References
In vitro	Arg389Gly	Human variants recombinantly expressed in rodent cells, the Arg389 receptor had a slightly higher basal and 3-4 fold higher isoprenaline-stimulated AC activity than the Gly389 variant.	[39]
	Ser49Gly	Using rodent models, Ser49 variant being more resistant (in agonist-related down-regulation)	[45]
		Ser49 variant being less active with receptor coupling.	[46]
Ex vivo	Arg389Gly	In human right-atrial preparations, subjects carrying the Arg389 receptor has greater inotropic and cAMP responses to noradrenaline compared to the Gly389 variant	[39]
		On non-failing ventricular tissue, Arg389 tissues having greater contractile responses than Gly389 tissues to isoproterenol	[48]

AC: Adenylyl Cyclase; cAMP: Cyclic Adenosine Monophosphate; Ref: Reference Number from where the result was taken

Table 2: Evidence for functional differences in β_1-AR polymorphisms

B_1-AR Gene Polymorphism	Minor Allele Frequency	Functional Consequences	Ref
Ser49Gly	Indians (15.1%)	Interethnic variation exists	[31]
	Hispanics (20–21%) Asians (14%)	Gly49 allele is more sensitive to the inhibitory effects of metoprolol than Ser49- β_1-AR	[45]
	Caucasians (12–16%) African-Americans (23–28%)	Gly49 allele has greater receptor down-regulation with agonist treatment	[46]
	Indians (25.8 %)	Interethnic variation exists in the polymorphisms of β_1-AR gene	[31]
Arg389Gly	Caucasians (24–34%) African-Americans (39–46%)	Arg389 allele has higher basal and agonist-stimulated Adenylyl cyclase (AC) activity Maximal isoproterenol-stimulated levels were markedly higher for the Arg-389	[39]
	Hispanics (31–33%) Asians (20–30%)	Lower AC activity upon agonist simulation in heart samples from HF patients with Arg389 allele than with Gly389 allele	[47]
Arg-389Arg	White (0.73%) Blacks (0.62%)	38% reduction in mortality (P=0.03), and 34% reduction in mortality or hospitalization (P=0.004) versus placebo	[48]

AC: Adenylyl Cyclase; P: P-value; Ref: Reference Number from where the result was taken

Table 3: Summary of allele frequency and functional consequences of the important genetic polymorphisms of β_1-AR pharmacogenetics in HF.

Author, [Ref]	β_1-ARBs	β_1-AR PA	N	Main Results
Maiet-Perez J, et al. [47]	Carvedilol	Arg389Gly	Mice model	Arg389 homozyg was associated with improvement in VF during carvedilol treatment in HF
Liggett SB et al. [48]	Bucindolol Carvedilol	Arg-389 homozyg	1,040 HF	Allele frequency of 0.73 in white & 0.62 in blacks. 38% reduction in mortality (P = 0.03) and 34% reduction in mortality or hospitalization (P = 0.004) vs. Placebo.
Petersen M et al. [49]	Carvedilol Metoprolol	Arg389Gly	586 CHF	Shorter survival response to carvedilol over a median follow-up period of 6.7 years (P= 0.004). No interaction between genotype and metoprolol (P= 0.61).
Cresci S et al. [50]	Carvedilol Metoprolol	Arg389Gly	2,460(711=AA;1,749=C) HF	Increased survival in C but not AA over 46 months follow-up. Among patients not taking β_1-ARBs , Gly389 was associated with decreased survival in C (HzR=1.98, 95% CI =1.1− 3.7, P =0.03).
Sehnert AJ et al. [51]	Bucindolol Metoprolol Carvedilol	Ser49Gly Arg389Gly	637 HF and LVSD	Significant effect of 4 clinical factors on survival: age (p = 0.006), gender (p= 0.005), EF (p = 0.0002), and hemoglobin (p = 0.00010) over a median follow-up of 1,070 days.
Kurnik D et al. [52]	Atenolol	Ser49Gly, Arg389Gly	165 (92= W;73=B)Healthy	Reduction in exercise HR in W than B (P=0.006). Arg389 was independently associated with a greater reduction in HR (P=0.003).
Lobmeyer M et al. [53]	Metoprolol	Arg389Gly	54 HF	Arg389Arg/deletion-carrier showed the greatest EF increase with metoprolol CR/XL.
Lu C et al. [54]	Carvedilol	Arg389Arg	135 NICMP	After 1.5 years of treatment- improvement in LVEF compared with Gly389 carriers (P<0.001).
De Groote P et al. [55]	Bisoporolol Carvedilol	Gly389Arg Ser49Gly	199 CHF	Significant decrease in HR, significant increase in LVEF (from 30+/-10% to 40+/-13%, P<0.0001). HR and LVEF responses to beta-blockade were not associated with the β_1-AR.
Terra SG, et al. [56]	Metoprolol CR/XL	Arg389Gly Ser49Gly	61 SHF	Arg389Arg - EF increased from 23+/-5 to 29+/-10 (P=0.008). Gly389 carriers no any significant change in EF (P=0.45). Arg389Arg and Gly49 are greater reductions in LV ED/ESD compared to Gly389 carriers and Ser49 homozyg respectively.
Liu J, et al. [57]	Metoprolol	Arg389Gly	16 healthy	Arg389Arg had greater reduction in resting and exercise HR than Gly389Gly:
White HL et al. [58]	Metoprolol CR/XL	Arg389Arg Arg389GlyGly389Gly	600 MERIT-HF	Gly allele was not associated with a significant benefit (P=0.72). Highly significant benefit of Metoprolol CR/XL observed in this sub-study population, RR=0.60; CI, 0.44–0.83 (P=0.002). No effect of the polymorphism was observed on the magnitude of heart rate reduction attained by Metoprolol CR/XL.
Magnusson Y et al. [59]	B-blockers	Ser49Gly Arg389Gly	375 DCM	Ser49Gly has significant association with 5 year survival rate(p=0.014) Lower 5-year mortality rate among Gly49 carriers than Ser49 patients (RR= 0.24; 95% CI= 0.07-0.80; p=0.02)

AA: African Americans, B: Black Population, C: Caucasians, EF: Ejection Fraction; HzR: Hazard Ratio, Homozyg: Homozygotes, LVED/ESD : Left Ventricular end-Diastolic and end-Systolic Diameters, NICM: Nonischemic Cardiomyopathy, PA: Polymorphic Allele, W: White Population.

Table 4: Summary of the findings for the use of β_1-ARBs in HF symptoms improvements.

SP	Study type	B-blocker	N	β_1-ARgene PA	Results	P-value	Ref
SHF	R	Carvedilol	224	Arg389Gly	Greater LVEF improvements in Arg389Arg than Gly389Gly (8.7 ± 1.1 vs. 0.93 ± 1.7%)	0.02	[47]
SHF	P	Bucindolol	1040	Arg389Gly	No associations	NS	[48]
				Arg389Arg	reduction in mortality or hospitalization in placebo	0.004	
CHF	RCT	Carvedilol	586	Arg389Gly withGln27Glu	Patients treated with carvedilol had shorter survival	0.004	[49]
		Metoprolol CR/XL			no interaction between genotype group and metoprolol treatment	0.61 NS	
SHF	R	Metoprolol CR/XL	54	Arg389Gly	Arg389Arg/Del-carrier showed the greatest EF increase with metoprolol	<0.02	[53]
SHF and NICM	R and P	Carvedilol	135	Arg389Arg	Improvement in LVEF compared with Gly389 carriers (Arg389Arg 18.8%; Arg389Gly 9.4%; Gly389Gly 6.0%)	<0.001	[54]
SHF	R	Carvedilol Bisoprolol	199	Gly389Arg Ser49Gly	Significant decrease in HR, a significant increase in LVEF (from 30+/-10% to 40+/-13%).	0.0001	[55]
					HR and LVEF responses to β_1-ARBs were not associated with the β_1-AR	NS	
SHF	P	Metoprolol CR/XL	61	Arg389Gly Ser49Gly	Greater LVEF improvement in Arg389Arg than Gly carriers(From 23 ± 5 to 29 ± 10% vs. from 22 ± 9 to 23 ± 11%)	0.008	[56]
					Gly389 carriers no any significant change in EF	0.45	

CR/XL: Controlled Release/Extended Release; mo: Months; N: Number of Participants; NS: Not Statistically Significant; P: Prospective Cohort; PA: Polymorphic Allele; R: Retrospective Cohort; RCT: Randomized Control Trial; Ref: Reference Number from where the result was taken; SD: Study Duration; SP: Study Population.

Table 5: Pharmacogenetics study of β_1-ARBs evaluating changes in LVEF in HF.

SP	**Study type**	**β_1-ARBs**	**N**	**β_1-AR Gene Polymorphism**	**Results**	**P-value**	**Ref**
HF	P	Atenolol	165	Ser49Gly Arg389Gly	Arg389 was independently associated with a greater reduction in heart rate	0.003	[52]
					Reduction in EHR in whites than blacks	0.006	
CHF	R	Bisoprolol or Carvedilol	199	Gly389Arg Ser49Gly	No significant association between polymorphism and β_1-ARBs	NS	[55]
Healthy	P	Metoprolol	16	Arg389Gly	Arg389Arg had greater reduction in RHR and EHR than Gly389Gly	0.008	[57]
					RHR at 75 mg/day: 6.3 ± 0.8% vs 4.1 ± 0.7%, 150 mg/day: 10.1 ± 1.0% vs 6.2 ± 1.1%, 225 mg/day: 14.4 ± 1.4% vs 10.9 ± 1.3%	0.017	
					EHR at 75 mg/day: 8.9 ± 0.5% vs 6.6 ± 0.7%, 150 mg/day: 14.0 ± 0.9% vs 11.7 ± 1.0%, 225 mg/day: 20.1 ± 1.5% vs 16.4 ± 1.3%	0.72	
HF	RCT	Metoprolol CR/XL	600	Arg389Arg Arg389Gly Gly389Gly	presence of the Gly allele was not associated with a significant benefit RR=0.94; CI=0.69–1.29	0.002	[58]
					Significant benefit of Metoprolol CR/XL observed in this sub-study population, RR=0.60; CI= 0.44–0.83		

CI: 95% Confidence Interval; CR/XL: Controlled Release/Extended Release; EHR: Exercise Heart Rate; mo: Months; N: Number of Participants; NS: Not Statistically significant; P: Prospective Cohort; PA: Polymorphic Allele; R: Retrospective Cohort; RCT: Randomized Control Trial; RHR: Resting Heart Rate; Ref: Reference Number from where the result was taken; RR: Risk Ratio; SP: Study Population

Table 6: Pharmacogenetics studies of β_1-ARBs evaluating changes in heart rate.

SP	ST	β_1-ARB	N	Duration	β_1-AR Gene PA	Results	P-value	Ref
IDCM	P	β-ARBs	171	33 months	Ser49Gly Arg389Gly	Gly49 were associated with a lower risk of HF in idiopathic DCM	--	[41]
CHF	P	β-ARBs	444	41 months	Arg389Gly Ser49Gly	No β_1-AR polymorphisms were associated with survival	NS	[42]
CHF	P/PMC	β-ARBs	184/ 77	60 months	Arg389Gly Ser49Gly	Ser49 homozyg were found to have a RR=2.34 of death or transplantation compared to those with Gly49	<0.003	[43]
MERIT-HF	PCT	Bucindolol (BEST)	1040(525-placebo)	60 months	Arg389Arg	Arg389 homozyg treated with bucindolol significant reduction in mortality or hospitalization compared to placebo [HR=0.62, 95%CI=0.40-.096]	0.03	[48]
						no difference in outcome between Gly389 carriers on bucindolol and those on placebo	NS	
CHF	RCT	Carvedilol Metoprolol	586	80 months	Arg389Gly with Gln27Glu	Patients treated with carvedilol had shorter survival	0.004	[49]
						no interaction between genotype group and metoprolol treatment	0.61	

SHF	P	Carvedilol Metoprolol	2,460	46 months	Arg389Gly	BB treatment increased survival in Caucasians (Log Rank P=0.00038) but not African Americans (Log Rank P=0.327).		[50]
						Gly389 was associated with decreased survival in Caucasians (HR = 1.98, 95% CI = 1.1 − 3.7	0.03	
SHF	P	Bucindolol Metoprolol Carvedilol	637	35 months	Ser49Gly Arg389Gly	No significant effect of the polymorphisms on survival.	0.47	[51]
						no significant association between genotype and survival with metoprolol and carvedilol	0.87	
CHF	P	Bisoprolol Carvedilol	199	3 months	Arg389Arg	better clinical outcomes (survival and hospitalization)	NS	[55]
MERIT-HF	RCT	Metoprolol	600	12 months	Arg389Gly	no survival benefit with presence of the Gly allele RR=0.94; CI=0.69–1.29	0.72	[58]
						significant benefit of metoprolol observed in the sub-study population, RR=0.60; CI= 0.44–0.83	0.002	
DCM	R	β-ARBs	375	60 months	Ser49Gly Arg389Gly	Ser49Gly has significant association with 5 year survival rate	0.014	[59]
						Lower 5-year mortality rate among Gly49 carriers than Ser49 patients RR= 0.24; 95% CI= 0.07-0.80)	0.020	
						Arg389 is not associated	0.08 (NS)	

CI: 95% Confidence Interval; Homozyg: Homozygotes; N: Number of Study Subjects; NS: Not Statistically Significant; PA: Polymorphic Allele; PCT: Placebo Controlled Trial; RR: Risk Ratio; SP: Study Population; ST: Study Type

Table 7: Pharmacogenetics study of β_1-ARBs effects on survival of patients with HF.

Association of the β_1-AR gene polymorphic allele frequency with HF

Table 3 shows the summary of difference in allele frequencies of a functional polymorphism in the β_1-AR gene that might involve in the pathogenesis of HF between different ethnic groups resulted in variable functional consequences. The Gly49 allele frequency in Caucasians (12-16%), in African-Americans (23-28%), Hispanics (20-21%) and Asians (14%) that resulted in greater receptor down-regulation with β_1-AR agonist treatment [46] and also more sensitive to the inhibitory effects of metoprolol than Ser49 β_1-AR [45]. The Arg389Gly and Arg389 homozygotes allele frequency in different racial groups also vary and have different functional consequences. The Arg-389 homozygote allele, its frequency of 0.73 in white & 0.62 in blacks, was associated with a 38% reduction in mortality(p=0.03) and 34% reduction in mortality or hospitalization (p= 0.004) of 1040 HF patients treated with bucindolol when compared with placebo [48].

Findings in pharmacogenetics of β_1-adrenergic Receptor Blockers (β_1-RBs) in HF

Table 4 shows the studies included for findings of pharmacogenetics of β_1-ARBs in HF. The β_1-ARBs commonly used to treat patients with HF and included in this table for the review were β_1-selective blockers (metoprolol, bisoprolol and atenolol) and non-selective β_1- and α_1-AR blockers (carvedilol and bucindolol). Seven studies have investigated the association of β_1-AR gene polymorphism with the improvement of heart function in response to the use of metoprolol therapy among patients with HF [49-51,53,56,58], except one on 16 health subjects [57]. Four studies have compared the association of genetic variation with the effects of carvedilol on patient survival [48,49,51,54]. Another 2 studies were on the mortality benefit of bucindolol for patients with HF [48,51]. 1 study on effect of atenolol on reduction in exercise and resting HR of healthy individuals [52], and another 1 study on bisoprolol pharmacogenetic response for patients with CHF [55].

Hemodynamic response and effect on left ventricular remodeling

Several studies have tested the pharmacogenetics associations between the β_1-AR genes and improvement in LVEF, with mixed results. Table 5 shows effects of β_1-ARBs pharmacogenetics study on the changes in LVEF of patients with HF. To evaluate these responses a minimum study period was 3 months for carvedilol or bisoprolol [55] and a maximum of 80 months [49]. Although LVEF response to a β_1-ARB with regards to the Arg389Gly polymorphism is not associated [48,55,56,58], the study done with respect to the effect on left ventricular remodelling, in 224 patients with HF who were all treated with the carvedilol, Arg389 homozygotes had a greater improvement in LVEF than Gly389 homozygotes [47]. This result was also confirmed by the study done on 135 patients followed for 18 months [54]. Another study of 61 patients with HF, who were on metoprolol, confirmed that the Arg389 homozygotes had a greater improvement in LVEF than Gly389 carriers and also that Gly49 allele carriers had a significantly greater reduction in LVED diameter than Ser49 homozygotes [56]. Additionally in a study of 54 patients with HF, individuals who were Arg389 homozygotes-deletion carriers had a greater improvement in LVEF in response to metoprolol [53]. However, in a cohort study of 199 Caucasians with stable HF who were all treated with either bisoprolol or carvedilol, no association was found between improvement in LVEF and β_1-AR gene polymorphism [55].

Numerous studies have also examined changes in resting and exercise HRs before and after a β-blocker relative to β_1-AR genotypes (Table 6). A prospective study done on different ethnic groups of 165 subjects with HF (92 whites and 73 blacks) resulted in variable response to atenolol sensitivity to exercise-induced tachycardia, and reduction in exercise HR was higher in white than blacks (P=0.006) [52]. Another study on 600 HF patients treated with metoprolol has shown the presence of the Gly allele on β_1-AR gene was not associated with a significant benefit [58]. No association was also reported for 199 patients with CHF treated with bisoprolol [55]. However, in 16 healthy volunteers on metoprolol therapy was associated with greater reduction in both resting HR and exercise HR in Arg389Arg compared with that in Gly389Gly [57].

Effect on patient survival

Table 7 shows the survival rate of patients with an established HF treated with β_1-ARBs. Two Randomized Control Trials (RCT) done on patients with CHF genotyped for Arg389Gly has shown that patients

treated with carvedilol had shorter survival *(p=0.004)* and there was no interaction between genotype group and metoprolol treatment *(p=0.61)* [49] with no survival benefit *(P=0.74)* [58]. The placebo controlled trial of Beta-blocker Extends Survival Trial (BEST) study in a population of 1040 patients followed for up to 5 years: 525 on placebo and 515 on bucindolol therapy has shown Arg389 homozygotes treated with bucindolol had an age-, sex-, and race-adjusted 38% reduction in mortality (*P*=0.03) and 34% reduction in mortality or hospitalization (*P*=0.004) compared with placebo. Arg389Gly polymorphism has no effect on survival or hospitalisation in HF [48]. In another prospective with matched control study of 184 patients with HF genotyped for the β_1-AR Ser49Gly polymorphism and followed-up for 5 years has demonstrated that the Ser49 homozygotes were found to have a risk ratio of 2.34 (p<0.003) of death or transplantation compared to those with Gly49 variants, and after multivariate analysis the risk ratio was reduced to 2.03 with borderline significance (p=0.05) [43]. A univariate analysis in 171 patients with DCM during a median follow-up of 33 months, the β_1-AR Gly49 allele was associated with a lower risk of HF [41]. Associations have also been reported for arrhythmias in HF; in a study of 163 patients with DCM and 157 sex- and age-matched controls, the odds ratio for non-sustained ventricular tachycardia in Gly389 carriers was significantly less (OR= 0.29, 95%CI=0.13-0.64, p=0.002) compared with Arg389 homozygotes [37]. However, a prospective cohort study in 444 patients with HF genotyped for the functional β_1-AR polymorphisms and followed over 41 months has shown that there is no association between the functional β_1-AR polymorphisms and survival in patients with stable CHF [42].

Discussions

Two most common non-synonymous SNPs in the β_1-AR gene, the Arg389Gly and Ser49Gly, were identified and have been studied consistently for their effect on response to HF therapy with β_1-ARBs. These two polymorphic allele have an evedence based functional differences. The Arg389 receptor has a greater coupling and 3-4 fold higher isoproterenol-stimulated adenylyl cyclase activity than the Gly389 variant in transgenic mice model. The *ex-vivo* studies have also shown the same effect. This could lead to a better cardiac performance for patients with Arg389 alleles. Correspondingly, Gly49 homozygotes can be attributed to the in-vitro evidence for more efficient receptor coupling in the Gly49 receptor than the Ser49 variant (which is less active).

The results of this study have also demonstrated that there is a difference in allele frequencies of a functional polymorphism of the β_1-AR gene that might involve in the pathogenesis and progression of HF. The enhanced signalling of the Arg389 variant might increase the risk of HF. In a case-control study involving patients with idiopathic DCM, Podlowski et al. [60] found the Ser49Gly variant more frequently in the group of patients with DCM.

β_1-AR gene polymorphisms were found to predict exercise performance in patients with HF. Among the 3 studies included in the result (Table 1), the Wagoner et al. [44] has shown the Arg389 homozygotes had a significantly higher peak VO2 than Gly389 homozygotes in 263 patients with ischemia or DCM (p = 0.006). This result was supported by Sandilands et al. [17] studied on 83 patients with MI or DCM. Within the Ser49Gly polymorphism, Gly49 carriers had a higher peak VO_2 than Ser49 homozygotes. Haplotype analysis has demonstrated that those who were homozygous for Arg389 and were Gly49 carriers had the highest peak VO_2 than Gly389 and Ser49 homozygotes. This result is similar with a cohort study of 900 patients with coronary heart disease genotyped for β_1-AR polymorphism [61].

For the pharmacogenetics study of $\beta_1$1-ARBs in HF therapy the β_1-AR gene is the primary target. Several studies have tested the pharmacogenetics associations between the β_1-AR genes and improvement in LVEF in response to β_1-ARBs therapy, with mixed results. Although LVEF response to β_1-ARBs with regards to the Arg389Gly polymorphism was not conclusive, the study done with respect to the effect on LV remodelling in 224 HF patients treated with carvedilol, Arg389 homozygotes had a greater improvement in LVEF than Gly389 homozygotes (p= 0.02). Another study on 61 patients with HF, who were on metoprolol therapy, confirmed that the Arg389 homozygotes had a greater improvement in LVEF than Gly389 carriers (p=0.008), and also that Gly49 allele carriers had a significantly greater reduction in LVED diameter than Ser49 homozygotes [56]. Additionally, in a study of 54 patients with systolic HF treated with metoprolol CR/XL and followed for durations of more than 5 months, individuals who were Arg389 homozygotes-deletion carriers had a greater improvement in LVEF in response to metoprolol (p<0.02). The Arg389 homozygotes is also strongly associated with improvement in LVEF in cohort study of 135 HF patients treated with carvedilol (p<0.001). However, in a retrospective cohort study of 199 HF patients who were treated with either bisoprolol or carvedilol, no significant association was found between improvement in LVEF and β_1-AR gene polymorphism although significant increase in LVEF was observed in patients treated with the two β_1-ARBs. No association between genotyping and metoprolol treatment in a RCT study on 586 CHF patients.

Positive associations between β_1-ARBs and β_1-AR gene polymorphism in influencing resting or exercise hemodynamic response have not been reported in patients with HF. A prospective study by Kurnik et al. [26] to examine changes in resting and exercise HR before and after a β_1-ARBs therapy relative to β_1-AR genotypes, has demonstrated the difference in distributions of genetic variants in the β_1-AR in different ethnic groups with HF resulted in variable response to atenolol sensitivity to exercise-induced tachycardia. Higher reduction in exercise HR was observed in white than blacks (p=0.006). All studies have revealed that the Arg389 was associated with a greater reduction in HR response to atenolol and metoprolol, but no association for patients with CHF treated with bisoprolol or carvedilol. Additionally, the presence of the Gly allele on β_1-AR gene in a study of 600 HF patients treated with metoprolol has shown no significant association. However, in 16 healthy volunteers on metoprolol therapy was associated with greater reduction in both resting and exercise HR in Arg389 homozygotes compared with that in Gly389 homozygotes.

β_1-AR polymorphisms have also an effect on survival of patients with HF as persistent β_1-AR signalling contributing strongly to progressive cardiac dysfunction [33]. A RCT done by Petersen et al. [49] on 586 patients with CHF genotyped for Arg389Gly with Gln27Glu (β_2-adrenergic receptor) and followed for 80 months has shown that there was no association between genotype group and metoprolol treatment *(p=0.61)* though patients treated with carvedilol had shorter survival (p=0.004). Another RCT study on 600 patients genotyped for Arg389Gly and treated with metoprolol, significant survival benefit of metoprolol was observed in the sub-study population but no benefit with presence of the Gly allele. The BEST study performed by Liggett et al. [48] in a population of 1040 patients with bucindolol therapy and followed for up to 5 years, the Arg389 homozygotes treated with bucindolol had an age-, sex-, and race-adjusted reduction in mortality (*P*=0.03) and/or hospitalization (*P*=0.004) compared with placebo whereas the Arg389Gly polymorphism has no effect on survival or hospitalisation. Another study on 199 patients with CHF followed

for 3 months also revealed that the Arg389 homozygotes has been associated with better clinical outcomes (survival and hospitalization). However, a prospective cohort study done by de Groote et al. [55] in 444 patients with HF and followed over 41 months has shown that there is no association between the functional β_1-AR polymorphisms and survival in patients with CHF. In another study, after a 5 year follow-up of 184 patients with HF and were genotyped for the β_1-AR Ser49Gly polymorphism, Ser49 homozygotes were found to have a RR of 2.34 (p<0.003) of death or transplantation compared to those with Gly49 variants, and after multivariate analysis the RR was reduced to 2.03 with no statistically significant association (p=0.05). Another study by Forleo et al. [41] demonstrated in a univariate analysis in 171 patients with DCM during a median follow-up of 33 months, the β_1-AR Gly49 allele was associated with a lower risk of HF that shows the Gly49 allele has a cardio-protective effect. Another study that support this result was a retrospective analysis of a case-control study involving 375 patients with DCM receiving β-ARBs and 492 controls, revealed a significant association between 5 year survival rate and the Ser49Gly polymorphism with low mortality rate among Gly49 carriers than Ser49 patients. The same study demonstrated the Arg389 is not associated with survival.

The study by Rochais et al. [21] on the affinity of three β-ARBs (bisoprolol, metoprolol, and carvedilol) to β_1-AR polymorphic allele (Arg389 and Gly389) has shown that, carvedilol had significantly higher degree of inhibitory effects on the activation and cAMP production than the metoprolol or bisoprolol in Arg-389 allele. These data suggest that effects of β-ARBs may differ by 389 allele of β_1-AR and also support to the concept that certain genotypes might respond more or less favourably to certain drugs [21]. Two studies done by Wagoner et al. and Mialet-Perez et al. [44,47] also suggest that β_1-AR Gly389 carriers might respond less favourably to β-ARBs than Arg389 homozygous patients. Based on these results, the therapy targeted at patients with specific genotypes of interest may have better outcomes with bucindolol than the currently used β-ARBs [48].

Study limitations

Although this systematic review has included all relevant published studies, the poor quality and high heterogeneity give inconsistent results and only a qualitative analysis is possible. Many factors may have played a role in producing such inconsistent data summarized in the various tables. Database analysis and various non-statistical factors including differences in study design and population, pharmacologic properties of the drugs, and inaccurate measurement of the phenotype (a combination of genotypes rather than a single genotype are more likely to be related to survival) may also have contributed. Access to full text of some articles also required a subscription that resulted in lacking of an inclusion in this review.

In conclusion, one of the goals of pharmacogenetics research is to provide clinicians with a tool with which to individualize therapy based on a person's genetic make-up. The β_1-ARBs pharmacogenetics literature search has provided hope for the potential clinical utilization of genetic information to individualize β-blocker therapy for HF. The data on the β_1-AR gene are relatively strong but have not been sufficiently consistent with either non-replication or testing in only a single study to date to draw clear messages. The findings have shown bucindolol, metoprolol, carvedilol and bisoprolol, each have differences in β_1-AR subtype specificity and sympatholytic activity. The findings of the current study and the weight of published evidence show β_1-AR polymorphisms has an effect on survival in HF patients treated with metoprolol. Individuals who were Arg389 homozygotes-deletion carriers had a greater improvement in LVEF in response to metoprolol. Additionally, the genotype associated with survival benefit from bucindolol is the same genotype associated with improved LVEF in some studies. The β_1-AR 389 variants alter signalling in multiple models and affect the β_1-ARBs therapeutic response in HF and, thus, might be used to individualize treatment of the case. The study results also suggested that pharmacogenetics studies might help to select the patients who will be more responsive to the drug. Since the β_1-AR gene is highly polymorphic in nature, it should be scrutinly researched from time to time for the effect on drug response. Future extensive research has to be done to use the pharmacogenetics data of β_1-ARBs for patients with HF that might requires large clinical trials for comparative efficacy of these drugs in different subgroups; and those patients whose genotype potentially places them at risk for responding less than optimally or better to the β-ARBs that has an effect on treatment success and patient survival should be identified.

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Author contributions

Contributed to designing the methodology; Takele Beyene Tufa. Contributed to collecting materials: Takele Beyene Tufa and Lidiya Fikirte Melke. Contributed to correcting the methodology and checking up for collected materials: Zelalem Petros. Writing the first draft of the manuscript: Takele Beyene Tufa. Contributed to the writing the manuscript: Takele Beyene Tufa. Agree with the manuscript results and conclusions: Takele Beyene Tufa, Zelalem Petros and Lidiya Fikirte Melke.

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