ORIGINAL ARTICLE

Frequency of genetic polymorphism for adrenergic receptor beta and cytochrome p450 2D6 enzyme, and effects on tolerability of beta-blocker therapy in heart failure with reduced ejection fraction patients: The Beta GenTURK study

Kalp yetersizliği bulunan ejeksiyon fraksiyonu düşük hastalarda B1 adrenerjik reseptör ve sitokrom p450 2D6 enzimi genetik polimorfizmi sıklığı ve beta bloker tolerabilitesi üzerine etkisi: Beta GenTURK çalışması

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ABSTRACT

Objective: The present objective was to determine frequency of Arginine389Glycine (Arg389Gly) and Cytochrome p450 2D6*10 (Cyp2D6*10) polymorphism in cases of heart failure-reduced ejection fraction (HFREF), and to evaluate the influence of the polymorphisms in response to beta-blocker (BB) therapy.

Methods: A total of 206 HFREF patients and 90 healthy controls were prospectively enrolled. Genotypes for Arg389Gly and Cyp2D6*10 polymorphisms of the healthy controls and 162 of the 206 heart failure (HF) patients were measured, identified by polymerase-chain-reaction- and restriction-fragment-length-polymorphism analysis. HFREF patients and healthy controls were compared regarding Arg389Gly polymorphism. The HFREF patients were separated into 2 subgroups based on achievement of maximal target dose (MTD) of BB.

Results: When comparing frequency of genotype distribution for Arg389Gly polymorphism in HFREF patients to the healthy controls, a statistically significant association was observed with CC genotype and Glisin-Glisin (GG) genotype ($p<0.001$, odds ratio [OR]=16, confidence interval [CI]: 3.8–67.9 and $p<0.001$, OR=0.3, CI: 0.2-0.6). Frequency of genotypes for Arg389Gly and Cyp2D6*10 polymorphism were similar in patients who could or could not achieve BB MTD ($p=0.13$ and $p=0.60$, respectively).

Conclusion: The frequency of Arg389Gly polymorphism in patients with HFREF in the present Turkish population differed from that of the healthy controls. However, neither Arg389Gly polymorphism nor Cyp2D6*10 polymorphism was associated with dose tolerability of BB therapy.

ÖZET

Amaç: Bu çalışmanın amacı, ejeksiyon fraksiyonu düşük olup kalp yetersizliği (KY) bulunan hastalarda Arginine389Glycine (Arg389Gly) ve sitokrom p450 2D6*10 (Cyp2D6*10) polimorfizmi sıklıklarını belirlemek ve bu polimorfizmlerin beta bloker (BB) tedavisi yanıtına etkisini değerlendirmektir.

Yöntemler: Ejeksiyon fraksiyonu düşük olup KY bulunan 206 hasta ve sağlıklı 90 kişilik kontrol grubu ileriye dönük olarak çalışmaya dahil edildi. Kontrol grubunun tümünün, KY'li 206 hastanın ise 162'sinin Arg389Gly ve Cyp2D6*10 polimorfizmi için genotipleri, polimeraz zincir reaksiyon ve restriksiyon fragman uzunluk polimorfizmi analizi aracılığı ile belirlendi. Azalmış ejeksiyon fraksiyonlu KY'li hastalar ve sağlıklı kontroller Arg389Gly gen polimorfizmi açısından karşılaştırıldı. Ayrıca KY'li hastalar en yüksek BB hedef dozuna ulaşıp ulaşamamalarına göre iki gruba ayrıldı.

Bulgular: Azalmış ejeksiyon fraksiyonlu KY'li hastalar ile sağlıklı kontroller arasında Arg389Gly polimorfizmi için genotip dağılım sıklıkları açısından yapılan karşılaştırmada CC ve GG genotipleri ile anlamlı ilişki gözlendi ($p<0.001$, OR=16, CI: 3.8–67.9 ve $p<0.001$, OR=0.3, CI: 0.2–0.6). En yüksek BB hedef dozuna ulaşan ve ulaşamayan hastaların ise Arg389Gly ve Cyp2D6*10 polimorfizmi için genotip sıklıkları benzerdir (sırasıyla, $p=0.13$, $p=0.60$).

Sonuç: Bu seçilmiş Türk popülasyonunda Arg389Gly polimorfizmi sıklığı azalmış ejeksiyon fraksiyonlu KY'li hastalarda sağlıklı kontrol grubundan farklıdır. Ayrıca Arg389Gly ve Cyp2D6*10 polimorfizmi BB tolerabilitesi ile ilişkili değildir.

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Beta-adrenergic receptors (ADRBs) belong to the G protein-coupled receptor family, and are found in the heart in B1, B2, and B3 forms. As the intracellular domain of B1 and B2 receptors interact with G protein, adenylate cyclase becomes active, activating the type-L calcium channel via cAMP signalization, and causing increased cardiac contractility and heart rate. The function of the B3 receptors in the heart has yet to be clarified.[1] In addition, signalizations in ADRBs, and specifically in the B1 receptors, play an important role in the pathophysiology of heart failure (HF).[2]

There are variations in HF patients regarding response to beta-blocker (BB) therapy, and reaching and tolerating the highest target dose recommended in current guidelines.[3,4] Various studies have shown that polymorphism in ADRB1 genes plays an important role in the development of these variations.[5–9] One of the most frequently seen and studied types of polymorphism is B1 Arginine389Glycine (Arg389Gly). Arg389Gly polymorphism results in substitution of the amino acid arginine by glycine at a critical site for G protein coupling. In a previous *in vitro* study, it was found that the arginine form in ADRBs1 causes more cAMP signal generation, in addition to enabling more active receptors, compared with the Glisin form.[10] This suggests that this polymorphism, which changes receptor activity, can also affect pathophysiology of HF and tolerability of BB. Identified for this polymorphism were the homozygote wild genotype, Arginin-Arginin (CC), the heterozygote genotype, Glisin-Arginin (GC), and the homozygote mutant genotype, Glisin-Glisin (GG).[11] The term "wild-type allele" is sometimes used to describe an allele thought to contribute to the typical phenotypic character, as seen in wild populations of organisms. Such a wild-type allele was historically regarded as dominant, common, and normal, in contrast to mutant alleles, which were regarded as recessive, rare, and frequently deleterious. It was once thought that most individuals were homozygous for the wild-type allele at most gene loci, and that any alternative mutant allele was found in homozygous form in a small minority of affected individuals, often as genetic diseases, and more frequently in the heterozygous form in carriers for the mutant allele. It is now understood that most or all gene loci are highly polymorphic, with multiple alleles and with frequencies that vary from population to population. It is also presently understood that a great deal of genetic variation is hidden in the form of alleles that do not produce obvious phenotypic differences.

In addition, the metabolism of BBs may also exhibit changes in individuals. These changes cause differences in drug pharmacokinetics and drug response. Cytochrome p450 2D6 (Cyp 2D6) enzyme plays a role in the metabolism of many BBs, and genes for this enzyme are known to be highly polymorphic. It has been demonstrated in various studies that these genetic variations lead to different responses to BBs. Cytochrome p450 2D6*10 (Cyp2D6*10) polymorphism is one of the most important variants of Cyp2D6. Homozygote wild genotype (CC), heterozygote genotype (CT), and homozygote mutant (TT) genotypes were identified for Cyp2D6*10 polymorphism.[6,12–14]

Abbreviations:

AF	*Atrial fibrillation*
ADRBs	*Beta-adrenergic receptors*
Arginine389Glycine	*Arg389Gly*
BB	*Beta-blocker*
CC	*Arginin-Arginin genotype*
CI	*Confidence interval*
*Cyp2D6*10*	*Cytochrome p450 2D6*10*
EF	*Ejection fraction*
GC	*Glisin-Arginin genotype*
GG	*Glisin-Glisin genotype*
HF	*Heart failure*
HFREF	*Heart failure-reduced ejection fraction*
MI	*Myocardial infarction*
MTD	*Maximal target dose*
NYHA	*New York Heart Association*
OR	*Odds ratio*

By considering the roles of ADRBs1s in the progress and treatment of HF, the frequency of ADRBs1 Arg389Gly polymorphism in patients with heart failurereduced ejection fraction (HFREF) in a selected Turkish population was presently investigated. The effects of ADRBs1 Arg389Gly polymorphism and Cyp2D6*10 polymorphism in the Cyp2D6 enzyme, which plays a role in BB metabolism, was investigated, concerning the effectiveness of BBs and treatment responses in HFREF patients.

METHODS

Study population

A total of 206 patients from 18 centers, with stable HFREF (ejection fraction [EF] ≤45 and New York Heart Association [NYHA] classification; I, II, and III), who were 18 years or older, and who had not undergone BB treatment, were included in the present multicenter, controlled, prospective study between 2009 and 2011. Twenty patients left prior to completion. As a result, a total of 186 patients were monitored for 6 months.

The control group consisted of 90 healthy individuals with no medical condition, and who were not using a BB. Patients with contraindications for BBs were excluded, and these included pregnancy or suspected pregnancy, asthma or severe chronic obstructive pulmonary disease, symptomatic peripheral artery disease, sinus nodal disease or conduction system disease coexisting with bradycardia, severe decompensated HF (class IV) exhibiting with hemodynamic instability hypotension, history of severe depression, and Raynaud phenomenon. Clinical data assessed included systolic blood pressure, heart rate, NYHA classification, body mass index, atrial fibrillation (AF), history of myocardial infarction (MI), and use of cardiovascular medication. However, echocardiographic and laboratory parameters were recorded.

Medications and beta-blocker titration

Maximum recommended target doses were 10 mg/day for bisoprolol, 10 mg/day for nebivolol, 200 mg/day for metoprolol, and 50 mg/day for carvedilol.[15]

Visits were conducted to evaluate whether the patients had reached the maximum recommended target doses of the BBs. Treatment of recommended lowest BB dose for HFREF patients was initiated, and doses were increased at 2-week intervals. Patients were clinically evaluated at 5 visits: once at the beginning, 3 times during possible dose increases, and once at the end of the study. At each visit, patients were evaluated for symptomatic bradycardia, symptomatic hypotension, atrioventricular block, increased dyspnea, weakness, dizziness, decreased libido, and changes in mental status. However, final decision to increase BB dose was left to the doctor who monitored the patient.

Patients with HF were separated to 2 groups: those that achieved the maximal target dose (MTD) recommended in current HF guidelines, and those that did not. Demographic, clinical, and echocardiographic properties were compared between groups, as were genotypic properties concerning Arg389Gly and Cyp2D6*10 polymorphism.

Echocardiographic parameters

Echocardiographic measurements were made according to recent guidelines.[16] EF was calculated using modified Simpson's rule. Left atrium size was measured at end-ventricular systole using M-mode linear dimension, obtained from parasternal long-axis view. Valvular regurgitations were graded into 2 categories (moderate—severe or not) via combination of color flow jet Doppler signal intensity and vena contracta width, according to guidelines.[17]

Genetic analysis

Peripheral blood was obtained for DNA isolation and genotyping. Arg389Gly polymorphisms of the ADRBs1 gene, and Cyp2D6*10 polymorphisms of the Cyp2D6 enzyme gene were analyzed using polymerase-chain-reaction- and restriction-fragment-length-polymorphism.[18,19] Allele frequencies of ADRBs1 gene polymorphism were obtained by direct counting. While genotype frequencies of ADRBs1 polymorphism were not in the Hardy–Weinberg equilibrium, those of Cyp2D6*10 polymorphism were.

Written informed consent was obtained from all patients. The study was performed in accordance with the Declaration of Helsinki for Human Research and approved by the local ethics committee.

Statistical analysis

Variables were investigated using the single-sample Kolmogorov-Smirnov test to determine normalcy of distribution. Continuous variables were expressed as mean±SD or median (min–max) in the presence of non-normal distribution, and categorical variables as percentages. Comparisons were made using chi-squared test for categorical variables, independent samples Student's t-test for normally distributed continuous variables, and Mann-Whitney U test when distribution was skewed. Hardy–Weinberg equilibrium was evaluated using chi-squared test. To examine association of genotypes with HF, logistic regression analyses were performed, and the association was expressed as odds ratio (OR), or risk estimates with 95% confidence interval (CI). All statistical procedures were performed using SPSS software (version 14.0; SPSS Inc., Chicago, IL, USA). A p value of 0.05 was considered statistically significant.

RESULTS

A total of 186 patients with HFREF and 90 healthy controls were evaluated. Mean age of HFREF patients was 61±11 years (25% females), and mean age of healthy controls was 41±8 years (46% females). MTD of BBs was achieved in only 48% of patients. Demographics and clinical data are summarized in Table 1.

Table 1. Comparison of demographic and clinical data according to beta-blocker dose

Characteristic	All patients (n=186)	MTD (+) (n=89)	MTD (–) (n=97)	*p*
Baseline characteristics				
Age (years)	61±11	60±10	62±12	0.143
Women, n (%)	47 (25)	17 (19)	30 (31)	0.092
Body mass index (kg/m^2)	28±6	28±4	29±7	0.367
SBP (mmHg)	123±19	124±20	120±18	0.384
Heart rate (min)	82±14	82±16	81±11	0.701
Atrial fibrillation, n (%)	19 (10)	10 (11)	9 (9)	0.006
NYHA (I/II/III/)	22/76/30	13/41/15	9/35/15	0.811
History of MI, n (%)	39 (21)	25 (28)	14 (14)	0.035
Echocardiographic parameters				
LV ejection fraction (%)	32±8	31±8	32±8	0.494
Left atrial diameter (mm)	44±7	44±7	43±7	0.388
LV diastolic diameter (mm)	59±10	59±9	59±11	0.904
Moderate-severe TR, n (%)	46 (40)	19 (31)	27 (49)	0.075
Moderate-severe MR, n (%)	49 (40)	24 (36)	25 (45)	0.269
Moderate-severe AR, n (%)	6 (6)	4 (7)	2 (4)	0.795
Labaratory parameters				
Creatinine (mg/dL)	1.1±0.6	1.1±0.4	1.2±0.7	0.612
Hemoglobin (gr/dl)	13.5±1.9	13.5±1.8	13.5±1.9	0.873
Nt-pro BNP (pg/ml)	2579 (1200–9520)	3376 (1536–3996)	1855 (1200–9520)	0.286
Medications				
ACEI/ARB (n=123), n (%)	97 (79)	58 (85)	39 (71)	0.085
Antithrombotic (n=124), n (%)	97 (78)	55 (80)	42 (76)	0.654
Statin (n=126), n (%)	64 (51)	37 (53)	27 (48)	0.604
MRA (n=185), n (%)	17 (9)	7 (8)	10 (10)	0.833
Diuretics (n=139), n (%)	75 (54)	35 (48)	40 (61)	0.135
CCB (n=101), n (%)	11 (11)	8 (16)	3 (6)	0.112
Oral nitrat (n=104), n (%)	18 (17)	9 (17)	9 (17)	1.000

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; AR: Aortic regurgitation; BMI: Body mass index; CCB: Calcium-channel blocker; LV: Left ventricle; MI: Myocardial infarction; MTD: Maximal target dose; MRA: Mineralocorticoid-receptor antagonist; Nt-pro BNP: Nt-pro brain natriuretic peptide; SBP: Systolic blood pressure; TR: Tricuspid regurgitation.

Echocardiographic and laboratory parameters did not differ significantly between the groups that reached, or did not, the MTD. There was no statistically significant difference regarding drug use between patients who reached, or did not, the MTD. There was also no statistically significant difference between BB types regarding patients who reached, or did not, the MTD (p=0.094, Table 2). The most frequently existing side effect was weakness, the rate of which was 49% at any single visit. For the 97 patients who did not reach the MTD, reasons were as follows: symptomatic sinus bradycardia in 33 patients, atrioventricular block formation in 20 patients (1st-degree atrioventricular block in 19 patients, 3rd-degree block in 1 patient), symptomatic hypotension in 26 patients, and dyspnea increase in 8 patients. Ten patients did not follow dose increase due to libido decrease (in 5 patients), and weakness (in 5 patients).

Only 162 patients agreed to genetic analysis. When comparing frequency distribution of Arg389Gly poly-

Table 2. Rates of achieving maximal target dose according to beta-blocker type

	Bisoprolol (n=6)	Nebivolol (n=17)	Carvedilol (n=75)	Metoprolol (n=88)	*p*
Maximal target dose of B blocker (+)	3 (50%)	13 (76%)	35 (47%)	38 (43%)	0.094

Table 3. Analysis of Arg389Gly genotypes between patient and control groups

	Study group (n=162)		Control group (n=90)		*p*	OR (95% CI)
	n	%	n	%		
Arg389Gly polymorphism						
Glisin-Glisin	23	14	29	34	<0.001	0.3 (0.2–0.6)
Glisin-Arginin	94	58	55	64	0.385	0.8 (0.5–1.3)
Arginin-Arginin	45	27	2	2	<0.001	16 (3.8–67.9)

CI: Confidence interval; OR: Odds ratio.

Table 4. Arg389Gly and Cyp2D6*10 genotypes according to maximal target dose of beta-blocker

	Target dose (+) (n=82)		Target dose (–) (n=69)		*p*
	n	%	n	%	
Arg389Gly polymorphism					
Glisin-Glisin	10	12	10	14	
Glisin-Arginin	42	51	44	64	0.138
Arginin-Arginin	30	37	15	22	
Cyp2D6*10 polymorphism					
Homozygote wild genotype	58	71	44	64	
Heterozygote genotype	22	27	22	32	0.604
Homozygote mutant	2	2	3	4	

morphism in HFREF patients with that of healthy controls, a significant association was observed with CC genotype and GG genotype (p<0.001; OR=16; CI: 3.8–67.9 and p<0.001; OR=0.3; CI: 0.2–0.6, Table 3). While the rate of CC genotype for Arg389Gly polymorphism was higher in the study group, the rate of GG genotype for Arg389Gly polymorphism was higher in the healthy control group. However, when comparing genotype frequency of GC for Arg389Gly polymorphism in HFREF patients with that of controls, no significant difference was observed (Table 3). Rate of BB MTD achievement did not differ significantly in HFREF patients with different genotypes regarding Arg389Gly polymorphism and Cyp2D6*10 polymorphism (p=0.138, p=0.604, Table 4).

DISCUSSION

Arg389Gly polymorphism, one of the most common polymorphisms in ADRBs1, was presently studied for the first time in HFREF patients in Turkey, revealing a significant difference between patients and healthy controls. It has also been demonstrated that Arg389Gly polymorphism in ADRBs1, and Cyp2D6*10 polymorphism in genes related to the the Cyp2D6 enzyme, did not affect ability to achieve BB MTD in HFREF patients.

The sympathetic nervous system plays a key role in the development and progress of various cardiovascular diseases, particularly HF.[20] It is known that this process is mediated by catecholamines and via ADRBs, leading to neurohormonal effects.[21] ADRBs1 variants, with increased receptor activities due to different genotypic characteristics, may play a role in HF pathogenesis by increasing B-adrenergic signal transfer and reducing stress on the myocardia. Several studies have been conducted in order to evaluate the effects of these polymorphisms on HF pathogenesis. When Arg389Gly polymorphism is investigated by comparing patients with HF, specifically those with dilated cardiomyopathy, to healthy control subjects, no differences are typically determined in the majority of studies.[9,22–24] However, in a limited number of studies, Arg389Gly polymorphism has been determined to differ significantly between patients with HF and healthy control subjects.[25,26]

In various studies conducted in different populations, Arg389Gly polymorphism has not been observed to differ between patients with dilated cardiomyopathy and healthy control subjects, as reported by Paczkowska et al. in a Polish population, Woodiwiss et al. in an African population, and Nonen et al. in a Japanese population.[27–29] Biolo et al. reported no difference in Arg389Gly polymorphism between patients with HF and healthy controls in a Brazilian population.[30] However, in a study by Forleo et al., Arg389Gly polymorphism was found to differ significantly between patients with dilated cardiomyopathy and healthy controls in an Italian population; the rate of homozygous wild genotype CC was higher in patients with dilated cardiomyopathy than in healthy controls.[31] In another study, conducted in a Mexican population, the GC genotype was detected at significantly higher rates in patients with dilated cardiomyopathy. In contrast to the findings of the Italian study, the rate of CC genotype was higher in healthy controls, though the rate of GG genotype did not differ significantly between groups.[25] Similar to the findings of the Italian study, the CC genotype was presently detected at higher rates in HFREF patients, compared to healthy controls. This leads us to consider racial differences with regard to ADRBs1 polymorphism in HF patients. In addition, this suggests that polymorphism can increase susceptibility to development of HF in populations in which differences between HF patients and healthy controls were found.

In the present study, the rate of BB MTD achievement (as recommended in current guidelines) was found to be 47%. BBs act via ADRBs and are the main agents used in the treatment of HF. This rate was reported as 60% in the COPERNICUS study, 68% in SENIORS, and 64% in MERIT-HF.[32–34] The present rates of BB MTD achievement were slightly lower, compared with other large-scale studies, which may be an indication of caution concerning BB dose increase. Although certain standards are followed regarding BB dose increase in HF patients, the main decision is usually left to the doctor who monitors and treats the patient.

When baseline characteristics were examined, no statistically significant differences were noted, excluding AF and MI rates. Rates of patients with AF and MI anamnesis were higher in the group that achieved BB MTD. This result may be linked to a more aggressive approach used by cardiologists for heart rate control in this group. Factors related to BB tolerability have been identified, and include NYHA classification, age, diastolic blood pressure, plasma urea level, EF, presence of obstructive airway disease, and diabetes mellitus.[35,36] Although no statistically significant difference was found between patients who achieved MTD and those who didn't, the fact that mineralocorticoid-receptor antagonist use in all patients was as low as 9% can be explained by the fact that the ESC Acute and Chronic Heart Failure guide was not published in time for our study to be included in its patient population. In addition, the present population included a small number of patients with NYHA classification III, and while calcium-channel blocker use was as high as 10% for HFREF patients, each of these patients took calcium-channel blockers for hypertension, with 7 taking amlodipine, 3 nifedipine, and 1 lercanidipine.

The present rate of BB MTD achievement did not differ among HF patients with different genotypes, regarding Arg389Gly polymorphism in ADRBs1. However, differences in BB tolerability among individuals with different Arg389Gly genotypes have been reported. In a study by Terra et al., HF patients with genotypes homozygous for Arg389 (CC), were shown to better tolerate metoprolol.[6] In a study by Liu et al., metoprolol was shown to cause a more noticeable decrease in heart rate in healthy volunteers with CC genotypes, compared to those with GG genotypes.[37]

According to these results, it may be suggested that ADRBs1s with homozygous wild genotype (CC) may have increased receptor activities, and that those with homozygous mutant genotype (GG) may function as if they were under natural beta blockade. However, findings similar to the present have also been reported, namely that ADRBs1 receptor polymorphism had no effect on BB tolerability. Particularly in studies conducted with hypertensive patients, changes in heart rate following metoprolol treatment were reportedly unrelated to Arg389Gly polymorphism.[38] In a subgroup analysis of the MERIT-HF study, connected to Arg389Gly polymorphism, the effect of metoprolol treatment on heart rate did not differ significantly between HF patients with different genotypes.[39]

The Cyp2D6 enzyme is known to have a function in the metabolism of various BBs, such as metoprolol, carvedilol, bisoprolol, and nebivolol.[12,40] The Cyp2D6 enzyme gene is known to be highly polymorphic, and about 80 of its alleles have been identified. Patients are commonly classified as ultra extensive metabolizers, extensive metabolizers, intermediate metabolizers, or poor metabolizers, based on their number of copies of functional CYP2D6 allele.[41] The Cyp2D6*10 allele is one of the most important Cyp2D6 variants with reduced enzymatic activity, which are referred to as residual functional alleles. As individuals with homozygous mutant genotypes of this allele are usually intermediate or poor metabolizers, it has been suggested that they will be more sensitive to BBs.[42] In addition, it has been indicated that BB tolerability and the development of side effects are not related to Cyp2D6 polymorphism. It has also been reported that different types of polymorphisms affect BB tolerability and the development of side effects.[6,13,14,43,44] However, in the present study, MTD achievement rate did not differ significantly among patients with different Cyp2D6*10 genotypes.

Two primary limitations may have affected the present study: small sample size and inability to achieve Hardy-Weinberg equilibrium for ADRBs1 polymorphism. Hence, the present results cannot be generalized to all Turkish HFREF patients. In addition, genotype distribution may have been affected by gender diversity of the groups. Final limitations included heterogeneity of population regarding BB usage— each drug had its own pharmacokinetics and the possibility to address genetic polymorphisms in different ways— and that the final decision regarding BB dose increase was left to the patient's doctor, as is customary.

In conclusion, the frequency of ADRBs1 Arg-389Gly polymorphism in patients with HFREF in the selected Turkish population differed from that of the healthy control subjects. However, ADRBs1 Arg-389Gly and Cyp2D6*10 polymorphisms did not affect achievement of BB MTD.

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REFERENCES

1. Brodde OE, Michel MC. Adrenergic and muscarinic receptors in the human heart. Pharmacol Rev 1999;51:651–90.
2. Packer M. Neurohormonal interactions and adaptations in congestive heart failure. Circulation 1988;77:721–30. Crossref
3. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation 2005;111:2837–49. Crossref
4. Bristow MR. Treatment of chronic heart failure with β-adrenergic receptor antagonists: a convergence of receptor pharmacology and clinical cardiology. Circ Res 2011;109:1176–94. Crossref
5. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, et al. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. Proc Natl Acad Sci U S A 2006;103:11288–93. Crossref
6. Terra SG, Pauly DF, Lee CR, Patterson JH, Adams KF, Schofield RS, et al. beta-Adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. Clin Pharmacol Ther 2005;77:127–37. Crossref
7. de Groote P, Helbecque N, Lamblin N, Hermant X, Mc Fadden E, Foucher-Hossein C, et al. Association between beta-1 and beta-2 adrenergic receptor gene polymorphisms and the response to beta-blockade in patients with stable congestive heart failure. Pharmacogenet Genomics 2005;15:137–42.
8. Taylor MR, Bristow MR. The emerging pharmacogenomics of the beta-adrenergic receptors. Congest Heart Fail 2004;10:281–8. Crossref
9. Liggett SB, Cresci S, Kelly RJ, Syed FM, Matkovich SJ, Hahn HS, et al. A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure. Nat Med 2008;14:510–7. Crossref
10. Mason DA, Moore JD, Green SA, Liggett SB. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. J Biol Chem 1999;274:12670–4. Crossref

11. Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. N Engl J Med 2002;347:1135–42. Crossref
12. Brodde OE, Kroemer HK. Drug-drug interactions of beta-adrenoceptor blockers. Arzneimittelforschung 2003;53:814–22.
13. Wuttke H, Rau T, Heide R, Bergmann K, Böhm M, Weil J, et al. Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. Clin Pharmacol Ther 2002;72:429–37. Crossref
14. Fux R, Mörike K, Pröhmer AM, Delabar U, Schwab M, Schaeffeler E, et al. Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. Clin Pharmacol Ther 2005;78:378–87. Crossref
15. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847. Crossref
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79–108. Crossref
17. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307–32. Crossref
18. de Groote P, Lamblin N, Helbecque N, Mouquet F, Mc Fadden E, Hermant X, et al. The impact of beta-adrenoreceptor gene polymorphisms on survival in patients with congestive heart failure. Eur J Heart Fail 2005;7:966–73. Crossref
19. Maqbool A, Hall AS, Ball SG, Balmforth AJ. Common polymorphisms of beta1-adrenoceptor: identification and rapid screening assay. Lancet 1999;353:897. Crossref
20. Cody RJ. The sympathetic nervous system and the renin-angiotensin-aldosterone system in cardiovascular disease. Am J Cardiol 1997;80:9–14. Crossref
21. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation 1986;73:615–21. Crossref
22. Tesson F, Charron P, Peuchmaurd M, Nicaud V, Cambien F, Tiret L, et al. Characterization of a unique genetic variant in the beta1-adrenoceptor gene and evaluation of its role in idiopathic dilated cardiomyopathy. CARDIGENE Group. J Mol Cell Cardiol 1999;31:1025–32. Crossref
23. Covolo L, Gelatti U, Metra M, Nodari S, Piccichè A, Pezzali N, et al. Role of beta1- and beta2-adrenoceptor polymorphisms in heart failure: a case-control study. Eur Heart J 2004;25:1534–41. Crossref
24. Metra M, Zani C, Covolo L, Nodari S, Pezzali N, Gelatti U, et al. Role of beta1- and alpha2c-adrenergic receptor polymorphisms and their combination in heart failure: a case-control study. Eur J Heart Fail 2006;8:131–5. Crossref
25. Fragoso JM, Rodríguez-Pérez JM, González J, Cruz D, Pérez-Méndez O, de Jesus García J, et al. Beta1-adrenergic receptor gene polymorphisms in Mexican patients with idiopathic dilated cardiomyopathy. Exp Mol Pathol 2006;80:279–82.
26. Canham RM, Das SR, Leonard D, Abdullah SM, Mehta SK, Chung AK, et al. Alpha2cDel322-325 and beta1Arg389 adrenergic polymorphisms are not associated with reduced left ventricular ejection fraction or increased left ventricular volume. J Am Coll Cardiol 2007;49:274–6. Crossref
27. Paczkowska A, Szperl M, Małek Ł, Mazurkiewicz Ł, Skóra E, Grzybowski J, et al. Polymorphisms of the beta-1 and beta-2 adrenergic receptors in Polish patients with idiopathic dilated cardiomyopathy. Kardiol Pol 2009;67:235–41.
28. Woodiwiss AJ, Badenhorst D, Sliwa K, Brooksbank R, Essop R, Sareli P, et al. Beta1- and alpha2c-adrenoreceptor variants as predictors of clinical aspects of dilated cardiomyopathy in people of African ancestry. Cardiovasc J Afr 2008;19:188–93.
29. Nonen S, Okamoto H, Akino M, Matsui Y, Fujio Y, Yoshiyama M, et al. No positive association between adrenergic receptor variants of alpha2cDel322-325, beta1Ser49, beta1Arg389 and the risk for heart failure in the Japanese population. Br J Clin Pharmacol 2005;60:414–7. Crossref
30. Biolo A, Clausell N, Santos KG, Salvaro R, Ashton-Prolla P, Borges A, et al. Impact of beta1-adrenergic receptor polymorphisms on susceptibility to heart failure, arrhythmogenesis, prognosis, and response to beta-blocker therapy. Am J Cardiol 2008;102:726–32. Crossref
31. Forleo C, Sorrentino S, Guida P, Romito R, De Tommasi E, Iacoviello M, et al. Beta1- and beta2-adrenergic receptor polymorphisms affect susceptibility to idiopathic dilated cardiomyopathy. J Cardiovasc Med (Hagerstown) 2007;8:589–95. Crossref
32. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106:2194–9. Crossref
33. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215,25.
34. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) Lancet 1999;353:2001–7. Crossref
35. Krum H, Ninio D, MacDonald P. Baseline predictors of tolerability to carvedilol in patients with chronic heart failure. Heart 2000;84:615–9. Crossref
36. Krum H, Hill J, Fruhwald F, Sharpe C, Abraham G, Zhu JR,

et al. Tolerability of beta-blockers in elderly patients with chronic heart failure: the COLA II study. Eur J Heart Fail 2006;8:302–7. Crossref

37. Liu J, Liu ZQ, Tan ZR, Chen XP, Wang LS, Zhou G, et al. Gly389Arg polymorphism of beta1-adrenergic receptor is associated with the cardiovascular response to metoprolol. Clin Pharmacol Ther 2003;74:372–9. Crossref
38. Beitelshees AL, Zineh I, Yarandi HN, Pauly DF, Johnson JA. Influence of phenotype and pharmacokinetics on beta-blocker drug target pharmacogenetics. Pharmacogenomics J 2006;6:174–8. Crossref
39. White HL, de Boer RA, Maqbool A, Greenwood D, van Veldhuisen DJ, Cuthbert R, et al. An evaluation of the beta-1 adrenergic receptor Arg389Gly polymorphism in individuals with heart failure: a MERIT-HF sub-study. Eur J Heart Fail 2003;5:463–8. Crossref
40. Van Peer A, Snoeck E, Woestenborghs R. Clinical pharmacokinetics of nebivolol. A review. Drug Invest 1991;3(Suppl. 1):25–30. Crossref
41. Zanger UM, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn Schmiedebergs Arch Pharmacol 2004;369:23–37. Crossref
42. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev 2009;41:89–295. Crossref
43. Lefebvre J, Poirier L, Poirier P, Turgeon J, Lacourciere Y. The influence of CYP2D6 phenotype on the clinical response of nebivolol in patients with essential hypertension. Br J Clin Pharmacol 2007;63:575–82. Crossref
44. Nikolic VN, Jankovic SM, Velickovic-Radovanović R, Apostolović S, Stanojevic D, Zivanovic S, et al. Population pharmacokinetics of carvedilol in patients with congestive heart failure. J Pharm Sci 2013;102:2851–8. Crossref

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