European Journal of Heart Failure (2013) **15**, 258–266
doi:10.1093/eurjhf/hfs175

Association between adrenergic receptor genotypes and beta-blocker dose in heart failure patients: analysis from the HF-ACTION DNA substudy

Mona Fiuzat[1]*, Megan L. Neely[1], Aijing Z. Starr[1], William E. Kraus[1], G. Michael Felker[1], Mark Donahue[1], Kirkwood Adams[2], Ileana L. Piña[3], David Whellan[4], and Christopher M. O'Connor[1]

[1]Duke University and the Duke Clinical Research Institute, Durham, NC, USA; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3]Montefiore Einstein Center for Heart and Vascular Care, Bronx, NY, USA; and [4]Thomas Jefferson University, Philadelphia, PA, USA

Received 6 July 2012; revised 20 August 2012; accepted 21 September 2012; online publish-ahead-of-print 31 October 2012

Aims Beta-blockers reduce morbidity and mortality in chronic heart failure (HF) patients with reduced ejection fraction. However, there is heterogeneity in the response to these drugs, perhaps due to genetic variations in the β1-adrenergic receptor (ADRβ1). We examined whether the Arg389Gly polymorphism in ADRβ1 interacts with the dose requirements of beta-blockers in patients with systolic HF.

Methods and results HF-ACTION was a randomized, multicentre trial of ambulatory HF patients with systolic dysfunction who were randomized to exercise training or usual care. A subset of patients provided DNA. The relationships among beta-blocker dose, ADRβ1−389 genotype, and outcomes were assessed using the Cox proportional hazards regression model. The interaction between beta-blocker dose and the ADRβ1−389 genotype was tested. DNA information was available for 957 patients. The alleles did not deviate from Hardy−Weinberg equilibrium. Patients with the ADRβ1−389 Arg/Arg genotype receiving low-dose beta-blockers had a two-fold increase in the risk of death compared with those receiving a high dose (hazard ratio 2.09; $P = 0.015$); this was not conferred in Gly carriers. There was also an interaction between improvements in Kansas City Cardiomyopathy Questionnaire score and beta-blocker dose by genotype, suggesting that higher doses of beta-blockade might be needed to achieve benefit in Arg/Arg genotype patients.

Conclusion There was a gene−dose interaction with the ADRβ1−389 Arg/Arg vs. Gly carrier genotype and beta-blocker dose, suggesting that patients with the Arg/Arg genotype might require a higher dose of beta-blockade to achieve a treatment response similar to that of Gly carriers.

Keywords Adrenergic receptor polymorphisms • Genotypes • Heart failure • Beta-blockers • Dose

Introduction

Heart failure is a global public health problem accounting for > US$30 billion in total costs annually, and > 550 000 new cases are diagnosed each year in the USA alone.[1–5] Beta-blockers have been shown to improve survival and reduce morbidity in patients with heart failure; however, there is heterogeneity in the response to these drugs.[6–8] One potential explanation for this is that genetic variations in an individual patient's profile may contribute to the variability of response to beta-blockade.[9–17] The β1-adrenergic receptor (AR) gene (ADRβ1) has a single nucleotide polymorphism (SNP) encoding an arginine (Arg) or a glycine (Gly) residue at position 389, which has been shown to alter the molecular interaction of the β-receptor with the regulatory guanine nucleotide-binding proteins (G-proteins) and acts as a gain-of-function polymorphism.[18,19] Specifically, the Arg389

* Corresponding author. DUMC Box 3356, Durham, NC 27710, USA. Tel: +1 919 613 5619, Fax: +1 919 681 7755, Email: mona.fiuzat@duke.edu

version of the human β1 AR is markedly different from the Gly version; it has three to four times greater signal transduction capacity and higher probability of being constitutively active, and it may be more sensitive to the effects of inverse agonists.[8,9,18,20,21] Given the data suggesting that genetic polymorphisms in the ADRβ1 gene may explain differences in individual beta-blocker therapeutic responses, a critical question remains as to whether these genetic variations may also influence the dose requirements of patients.

In the only study prospectively designed to test dose–response relationships with the beta-blocker carvedilol, Bristow *et al.* reported dose-related improvements in left ventricular ejection fraction (LVEF) and survival.[22] In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) substudy, no dose–response relationship was observed for the overall cohort, but a wide variation in dose response was observed in patients.[23] Few studies have evaluated a relationship between genetic variations and beta-blocker dose requirements. One study by McNamara *et al.* evaluated the angiotensin-converting enzyme deletion allele variant and beta-blocker dose.[24] In our study, we aimed to assess whether a gene–dose interaction exists between beta-blockers and the ADRβ1–389Arg/Gly gene variant.

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial was the largest study to test the effects of exercise training vs. usual care in heart failure patients with systolic dysfunction.[25] HF-ACTION investigators collected DNA from ~ 1000 patients with thorough phenotypic characterization. This provided a large, well-treated contemporary heart failure population in which to explore the relationship between genetic variation and beta-blocker response. We examined whether a pharmacogenetic interaction between the ADRβ1–389 polymorphism and dose requirements of beta-blockers exists in patients with systolic heart failure. Because the ADRβ1–389 Arg/Arg receptor has demonstrated increased adrenergic activity, we hypothesized that patients with the Gly variant would require lower doses of beta-blockers to achieve similar beneficial outcomes.

Methods

Study cohort

The HF-ACTION trial design and outcomes have been described previously.[25] Briefly, HF-ACTION was a multicentre, randomized, controlled trial testing the long-term safety and efficacy of aerobic exercise training plus evidence-based medical therapy vs. evidence-based medical therapy alone in ambulatory outpatients with left ventricular systolic dysfunction (LVEF <35%) and New York Heart Association (NYHA) class II–IV heart failure. Although not mandated, enrolment criteria included patients who were on optimal heart failure therapy according to American College of Cardiology/American Heart Association and Heart Failure Society of America guidelines (including treatment with beta-blocker therapy) or patients with a documented rationale for variation (including intolerance, contraindication, patient preference, or personal physician's judgement). Patients were prescribed a stable dose of beta-blocker for ≥ 6 weeks. Exclusion criteria included an inability to exercise, regular aerobic exercise (more than once per week), and a major cardiovascular event in the previous 6 weeks. The primary endpoint was the composite of all-cause death or all-cause hospitalization. All-cause death was a pre-specified secondary endpoint. Patients were randomly assigned to usual care alone (optimal medical therapy and a recommendation for regular physical activity) or usual care plus a prescription of 36 sessions of supervised aerobic exercise training at 60–70% of heart rate reserve three times per week, followed by home-based training at the same intensity five times per week. Patients were followed for a median of 2.5 years. Approximately 95% of patients were on a beta-blocker.

Events were adjudicated by an independent clinical events committee. This study complied with the Declaration of Helsinki; the relevant institutional review boards, research ethics boards, and ethics committees of participating centres approved the study; and the coordinating centre approved the protocol. An independent data and safety monitoring board appointed by the trial sponsor (the National Heart, Lung, and Blood Institute) reviewed the protocol. All participants provided informed consent.

A subset of patients enrolled in the HF-ACTION study agreed to participate in the DNA substudy and provided blood collection at randomization. Samples were stored at the Duke Center for Human Genetics. Genomic DNA was isolated from whole blood using an automated extractor (Qiagen Autopure). SNP genotyping was performed using commercially available assays and kits (Applied Biosystems TaqMan®).

Statistical methods

Baseline characteristics were summarized by counts and percentages for categorical variables and by medians with interquartile ranges for continuous variables. Characteristics were compared between the overall HF-ACTION cohort and the DNA cohort, and then between Gly carriers (patients with the Gly/Gly or Gly/Arg genotype at the ADRβ1–389 receptor SNP) and Arg homozygotes (patients with the Arg/Arg genotype at the ADRβ1–389 receptor SNP) among patients in the DNA cohort. For continuous variables, differences between Arg homozygotes and Gly carriers were tested for significance using the analysis of variance (ANOVA) *F*-test when the assumption of normality was satisfied; otherwise, the non-parametric (NP) Kruskal–Wallis test was used. For categorical variables, the χ^2 test was used when the cell frequency was sufficient; otherwise, exact tests (EXs) were used. A *P*-value ≤ 0.05 was considered statistically significant for all analyses.

The primary endpoint was all-cause mortality or all-cause hospitalization, and a secondary endpoint was all-cause mortality. The relationship between these endpoints and beta-blocker dose and the ADRβ1–389 genotype was assessed using the Cox proportional hazards regression model. Hardy–Weinberg equilibrium was assessed for the candidate SNP using the χ^2 test. Due to evidence that pathophysiology differs among Arg homozygotes vs. Gly carriers,[18,19] the analysis was conducted using a dominance model for the Gly allele. Beta-blocker dose at baseline was standardized using carvedilol equivalents and analysed discretely as low-dose (1–25 mg daily) vs. high-dose (>25 mg daily) groups. Patients with zero dose or missing data were excluded. To determine whether the impact of beta-blocker dose differed among Gly carriers and Arg homozygous patients, the interaction between beta-blocker dose and the ADRβ1–389 genotype was tested. For each endpoint, the regression analysis was adjusted for clinical risk factors. Adjustment models were built using the approach described by O'Connor *et al.*[26] but with a larger set of candidate variables.[26] The clinical adjustment model for the primary endpoint included Weber class, Kansas City Cardiomyopathy Questionnaire (KCCQ) symptom stability, blood urea nitrogen, region (USA vs. non-USA), LVEF, sex, mitral regurgitation (severe vs.

non-severe), and ventricular conduction. The clinical adjustment model for the secondary endpoint of all-cause mortality included exercise duration, body mass index, creatinine, sex, loop diuretics dose, LVEF, Canadian Cardiovascular Society angina classification, and ventricular conduction. Because the ADRβ1−389 genotype frequencies were found to differ significantly by race, we also adjusted for self-reported race. Adjusted Kaplan−Meier curves were plotted for each endpoint by the ADRβ1−389 genotype. If the interaction was significant, the plots were examined for low vs. high beta-blocker dose separately.

Another secondary endpoint was quality of life, measured by changes in KCCQ score at 3 and 12 months. For each time point, the change in KCCQ score was summarized by medians with interquartile ranges. Differences in KCCQ score change were compared for the low vs. high beta-blocker dose groups using the rank sum test. This comparison was performed overall and then among the ADRβ1−389 genotypes separately.

Additional analyses were conducted to examine the effects of another common SNP in the β1 receptor, the Ser49Gly polymorphism (referred to here as ADRβ1−49). The analyses described above were conducted with the substitution of ADRβ1−49 to test whether there was an interaction of this polymorphism with beta-blocker dose.

Statistical analysis was performed by the Duke Clinical Research Institute using SAS software version 9.2 (SAS Institute, Cary, NC, USA).

Results

Evaluable DNA information was available for 957 patients. Of those, 55 patients were not on a beta-blocker or did not have dose information available; therefore, 902 patients were included in this analysis. The alleles did not deviate from Hardy−Weinberg equilibrium ($P = 0.82$). Baseline characteristics are shown in *Table 1*. There were no significant differences in clinical characteristics between the Arg homozygous patients and Gly carriers except for race ($P < 0.01$). The proportion of Gly carriers was higher among black patients (22.8% Arg vs. 37.4% Gly) but lower among white patients (73.5% Arg vs. 57.1% Gly). Overall, the ADRβ1−389 allele frequencies were 0.68 (Arg) and 0.32 (Gly), with 0.72 (Arg) and 0.28 (Gly) in whites and 0.59 (Arg) and 0.41 (Gly) in blacks. These are consistent with previous studies showing ADRβ1−389 Arg allele frequencies of ∼0.73 in whites and 0.58 in blacks.[27]

There was an equal distribution of Arg homozygous patients and Gly carriers in the beta-blocker high-dose and low-dose groups, and the median dose was the same in both genotypes (38 mg carvedilol equivalents daily). For the primary endpoint of all-cause mortality or all-cause hospitalization, there was no significant interaction between the ADRβ1−389 genotype and beta-blocker dose ($P = 0.29$). However, for the secondary endpoint of all-cause mortality, there was a significant interaction between the ADRβ1−389 genotype and beta-blocker dose in the model ($P = 0.04$). As shown in *Table 2*, patients with the ADRβ1−389 Arg/Arg genotype receiving low-dose beta-blockers had a two-fold increase in the risk of death compared with those receiving a high dose, after adjusting for other important clinical variables [hazard ratio (HR) 2.09; $P = 0.015$]. There was no significant difference in risk between patients receiving low- vs. high-dose beta-blocker (HR 0.91; $P = 0.73$) among the Gly carriers. The adjusted Kaplan−Meier curves for the two endpoints are shown in *Figures 1* and *2*. Among the four genotype−dose groups, Arg/Arg patients on low-dose beta-blocker had the highest event rate, which increased over time. Specifically, the adjusted Kaplan−-Meier event rate at 2 years for Arg/Arg patients on low-dose beta-blockers was 14.4% vs. 9.1% for those on a high dose.

Because the effect of the ADRβ1 genotype on the outcome could be confounded by differences in allele frequencies among race, the analysis was repeated by race to determine if the findings were consistent across populations. Although the interaction between the ADRβ1−389 genotype and beta-blocker dose was no longer significant [probably due to the substantial decrease in sample size for each subgroup analysis ($P = 0.06$ for whites and $P = 0.16$ for blacks)], the pattern of results remained—we observed an increased risk of death for Arg homozygous patients on low- vs. high-dose beta-blockers and the ratio of HRs between Arg homozygous patients and Gly carriers remained relatively constant.

There was no significant difference in KCCQ score change at 3 and 12 months between low- and high-dose beta-blocker groups in the overall cohort of patients in this analysis. However, Arg homozygotes on high-dose beta-blockers experienced a significant improvement in their KCCQ scores at 3 months compared with those on low-dose beta-blockers ($P = 0.04$). Although the median change in KCCQ score at 12 months in patients with Arg homozygotes was higher for those on high-dose vs. low-dose beta-blockers, the difference was no longer statistically significant.

Unlike the ADRβ1−389 analysis, the results of the ADRβ1−49 analysis were non-significant. Specifically, the *P*-value for the interaction between the ADRβ1−49 genotype (Ser homozygotes vs. Gly carriers) and beta-blocker dose (low vs. high) was 0.87 for the primary endpoint of all-cause mortality or all-cause hospitalization and 0.69 for the endpoint of all-cause mortality. Similar results were seen when repeating this analysis by race (*P*-values = 0.98 and 0.91 for whites and *P*-value = 0.08 and 0.75 for blacks).

Discussion

There were several important findings from this analysis. First, for patients on beta-blockers, there was a gene−dose interaction with the ADRβ1−389 genotype (Arg homozygous patients vs. Gly carriers) and beta-blocker dose (≤ 25 mg vs. >25 mg carvedilol equivalents daily), suggesting that Arg homozygotes might require a higher dose of beta-blockade to achieve a mortality risk reduction similar to that of Gly carriers. In addition, there was an interaction between improvements in KCCQ score at 3 months and beta-blocker dose by genotype, suggesting that higher doses of beta-blockade might be needed to achieve benefit in Arg homozygotes.

Our study showed that there was a genetic interaction with beta-blocker dose when analysing the outcome of all-cause mortality. Several studies report differential response to beta-blocker therapy based on the ADRβ1−389 genotype for endpoints such as exercise capacity, initial tolerability during beta-blocker titration, changes in LVEF, and changes in left ventricular remodelling.[9,11,12,28−30] Most of these studies had several limitations,

Table 1 Baseline characteristics by DNA cohort and by ARDβ1–389 genotype

Parameter	HF-ACTION cohort (n = 2331)	Total DNA cohort (n = 957)	ARDβ1 genotype		
			Arg/Arg (n = 439)	Gly carriers (n = 518)	P-value[a]
Age, years[b]	2331, 59.3 (51.1, 68.0)	957, 58.7 (50.5, 67.5)	439, 59.7 (51.0, 67.9)	518, 58.0 (50.1, 67.0)	0.29 NP
Female sex, *n* (%)	661 (28.4)	284 (29.7)	118 (26.9)	166 (32.0)	0.08
Race, *n* (%)					<0.01
Black	749 (32.6)	290 (30.7%)	99 (22.8)	191 (37.4)	
White	1426 (62.1)	611 (64.7)	319 (73.5)	292 (57.1)	
Other	121 (5.3)	44 (4.7)	16 (3.7)	28 (5.5)	
History of diabetes, *n* (%)	748 (32.1)	289 (30.2)	126 (28.7)	163 (31.5)	0.49
History of MI, *n* (%)	979 (42.0)	392 (41.0)	190 (43.3)	202 (39.0)	0.23
History of hypertension, *n* (%)	1388 (59.9)	574 (60.2)	268 (61.0)	306 (59.4)	0.41
Smoking status, *n* (%)					0.50
Never	866 (37.3)	350 (36.8)	156 (35.7)	194 (37.7)	
Current	388 (16.7)	168 (17.6)	73 (16.7)	95 (18.4)	
Past	1066 (45.9)	434 (45.6)	208 (47.6)	226 (43.9)	
HF hospitalizations in previous 6 months, *n* (%)					0.60
0	1701 (73.6)	696 (73.3)	317 (72.9)	379 (73.7)	
1	464 (20.1)	192 (20.2)	86 (19.8)	106 (20.6)	
2	94 (4.1)	43 (4.5)	24 (5.5)	19 (3.7)	
3 +	52 (2.3)	18 (1.9)	8 (1.8)	10 (1.9)	
HF aetiology, *n* (%)					0.09
Ischaemic	1197 (51.4)	486 (50.8)	236 (53.8)	250 (48.3)	
Non-ischaemic	1134 (48.6)	471 (49.2)	203 (46.2)	268 (51.7)	
NYHA class, *n* (%)					0.65 EX
II	1477 (63.4)	635 (66.4)	298 (67.9)	337 (65.1)	
III	831 (35.6)	317 (33.1)	139 (31.7)	178 (34.4)	
IV	23 (1)	5 (0.5)	2 (0.5)	3 (0.6)	
Mitral regurgitation, *n* (%) (moderate or severe)	256 (12.0)	115 (13.0)	55 (13.4)	60 (12.6)	0.70
Systolic BP, mmHg[b]	2327, 111.0 (100.0, 126.0)	956, 112.0 (1.00.0, 126.0)	438, 114.0 (102.0, 127.0)	518, 110.0 (100.0, 126.0)	0.16
Diastolic BP, mmHg[b]	2326, 70.0 (60.0, 78.0)	956, 70.0 (62.0, 78.5)	438, 70.0 (60.0, 78.0)	518, 70.0 (62.0, 80.0)	0.99 NP
Heart rate, b.p.m.[b]	2326, 70 (63.0, 77.0)	957, 70.0 (64.0, 77.0)	439, 70.0 (64.0, 77.0)	518, 70.0 (63.0, 77.0)	0.99 NP
Body mass index[b]	2324, 29.9 (26.0, 35.1)	957, 29.9 (26.2, 35.2)	439, 29.6 (25.8, 34.9)	518, 30.3 (26.5, 35.4)	0.08 NP
LVEF, %[b]	2327, 24.7 (20.0, 30.1)	956, 24.8 (20.2, 30.1)	438, 24.9 (20.5, 30.0)	518, 24.6 (20.0, 30.2)	0.93 NP
Rest ECG ventricular conduction, *n* (%)					0.84
Normal	979 (43.1)	379 (40.2)	170 (39.1)	209 (41.2)	
LBBB	379 (16.7)	166 (17.6)	81 (18.6)	85 (16.8)	
RBBB	85 (3.7)	27 (2.9)	14 (3.2)	13 (2.6)	
IVCD	292 (12.9)	142 (15.1)	68 (15.6)	74 (14.6)	
Paced	536 (23.6)	228 (24.2)	102 (23.4)	126 (24.9)	

Continued

Table I *Continued*

Parameter	HF-ACTION cohort ($n = 2331$)	Total DNA cohort ($n = 957$)	ARDβ1 genotype		
			Arg/Arg ($n = 439$)	Gly carriers ($n = 518$)	*P*-value[a]
Creatinine, mg/dL[b]	2091, 1.2 (1.0, 1.5)	874, 1.2 (1.0, 1.5)	395, 1.2 (1.0, 1.5)	479, 1.2 (1.0, 1.5)	0.98 NP
BUN, mg/dL[b]	2028, 20 (15.0, 28.0)	858, 20.0 (15.0, 27.2)	388, 20.0 (15.0, 29.0)	470, 20.0 (15.0, 27.0)	0.33 NP
Haemoglobin, g/dL[b]	1763, 13.5 (12.3, 14.6)	745, 13.5 (12.3, 14.6)	332, 13.6 (12.3, 14.5)	413, 13.5 (12.3, 14.6)	0.62
NT-proBNP, pg/mL[b]	1383, 815.0 (340.5, 1805.0)	718, 821.3 (344.2, 1805.0)	338, 814.0 (345.8, 1793.0)	380, 827.7 (343.2, 1808.0)	0.57 NP
CPX test duration, min[b]	2309, 9.6 (6.9, 12.0)	953, 10.0 (7.4, 12.4)	438, 10.0 (7.7, 12.5)	515, 10.0 (7.0, 12.1)	0.06
Peak VO_2, mL/kg/min[b]	2275, 14.4 (11.5, 17.7)	947, 14.8 (11.9, 17.9)	436, 15.1 (12.1, 18.0)	511, 14.5 (11.6, 17.8)	0.11 NP
6MWT distance, min[b]	2280, 370.6 (298.7, 435.0)	926, 374.9 (300.0, 440.4)	421, 381.0 (300.0, 450.0)	505, 371.2 (300.0, 432.8)	0.09 NP
Beta-blocker dose, n (%)					0.67
High dose	1155 (52.9)	486 (53.9)	221 (53.1)	265 (54.5)	
Low dose	1028 (47.1)	416 (46.1)	195 (46.9)	221 (45.5)	

BP, blood pressure; BUN, blood urea nitrogen; CPX, cardiopulmonary exercise test; ECG, electrocardiogram; HF, heart failure; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro brain natriuretic peptide; RBBB, right bundle branch block; VO_2, oxygen consumption. 6MWT, 6 min walk test.
[a]*P*-value comparing Arg/Arg vs. Gly carriers. Non-parametric Kruskal–Wallis tests (NP) were used for continuous variables. Exact tests (EX) were used for categorical variables.
[b]Data are presented as *n* (non-missing), median (Q1, Q3).

primarily their limited power due to small sample sizes. One study by Sehnert *et al.* of 637 patients on carvedilol or metoprolol showed no differential effect by ADRβ1−389 genotype on the endpoint of transplant-free survival.[28] Two large heart failure trials with beta-blockers, MERIT-HF and the Beta-Blocker Evaluation of Survival Trial (BEST), included DNA substudies that examined the ADRβ1−389 Arg/Gly polymorphism and clinical outcomes.[9,31] The MERIT-HF trial's DNA substudy of 600 patients showed that morbidity or mortality were not differentially affected by treatment with metoprolol CR/XL (controlled release/extended release) by ADRβ1−389 genotype. In contrast, the BEST trial DNA substudy of 1040 patients showed that the ADRβ1−389 genotype signifianctly affected treatment response to the beta-blocker bucindolol. However, bucindolol may have a specific pharmacological profile, which confers a unique association of the ADRβ1−389 polymorphism with treatment response in heart failure.[8,32]

The evidence for a dose−response relationship for cardiovascular drugs has been limited. The Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) trial was the only study to examine prospectively dose−response with beta-blockers in heart failure; it demonstrated a positive dose−response relationship between beta-blocker dose and LVEF improvement, as well as an improvement in survival.[22] However, given the small sample size, the survival findings were difficult to interpret. We recently showed that in the HF-ACTION trial there was a significant relationship between beta-blocker dose and outcomes.[33] In the current study, there did not appear to be a relationship between the genetic polymorphism and the beta-blocker dose requirement in terms of the primary combined endpoint of all-cause mortality or all-cause hospitalization. However, when examining mortality alone, Arg homozygotes had worse outcomes than Gly carriers on lower doses of beta-blockade ($P = 0.015$), but the benefit was not different with higher doses of beta-blockade ($P = 0.17$). This may, in part, be explained by varied pharmacological activity of the receptor in those patients with this genotype, given the increased signalling capacity and higher probability of being constitutively active than the Gly variant. Because of the mechanism of action of metoprolol and carvedilol (neutral antagonists),[8] it could be postulated that a higher dose is needed to achieve antagonism. Adjusted Kaplan−Meier event rates were 14% for Arg/Arg patients on low-dose beta-blockers vs. 9% for those on a high dose at 2 years. The clinical implications could be substantial considering the difference in the risk of events when higher doses are used with genotyping for Arg homozygotes.

Another unique finding of this study that has not previously been shown is the association of genetic variation and quality of life, relative to beta-blocker dose. Beta-blockers have been shown to improve quality of life,[34] but the interaction between genotype and beta-blocker dose has not been examined. Our study suggests that in patients who are Arg homozygous, there may be a greater improvement in quality of life with higher doses of beta-blockade, compared with lower doses.

Limitations

Our findings should be considered in the context of several limitations. First, the DNA substudy represents a subgroup of the entire

Table 2 Relative risk of events for low- vs. high-dose beta-blocker by ADRβ1–389 adrenergic receptor genotype

Outcome	Total DNA cohort			White cohort			Black cohort		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
All-cause hospitalization or mortality[a]									
Interaction[b]			0.292			0.553			0.146
All-cause mortality[c]									
Interaction[b]			0.036			0.058			0.162
β1–389 AR genotype									
Arg/Arg	2.09	1.16–3.78	0.015	2.50	1.26–4.93	0.008	4.81	0.71–32.70	0.108
Gly carrier	0.91	0.52–1.58	0.729	0.74	0.35–1.60	0.448	1.32	0.49–3.56	0.586

AR, adrenergic receptor; Arg, arginine; CI, confidence interval; Gly, glycine; HR, hazard ratio for low- vs. high-dose beta-blocker.
[a]Adjusted for Weber class, Kansas City Cardiomyopathy Questionnaire symptom stability, blood urea nitrogen, region (USA vs. non-USA), left ventricular ejection fraction, sex, mitral regurgitation (severe vs. non-severe), ventricular conduction, and race (only in the total DNA cohort).
[b]β1–389 adrenergic receptor genotype by beta-blocker dose.
[c]Adjusted for exercise duration, body mass index, creatinine, sex, loop diuretics dose, left ventricular ejection fraction, Canadian Cardiovascular Society angina classification, ventricular conduction, and race (only in the total DNA cohort).

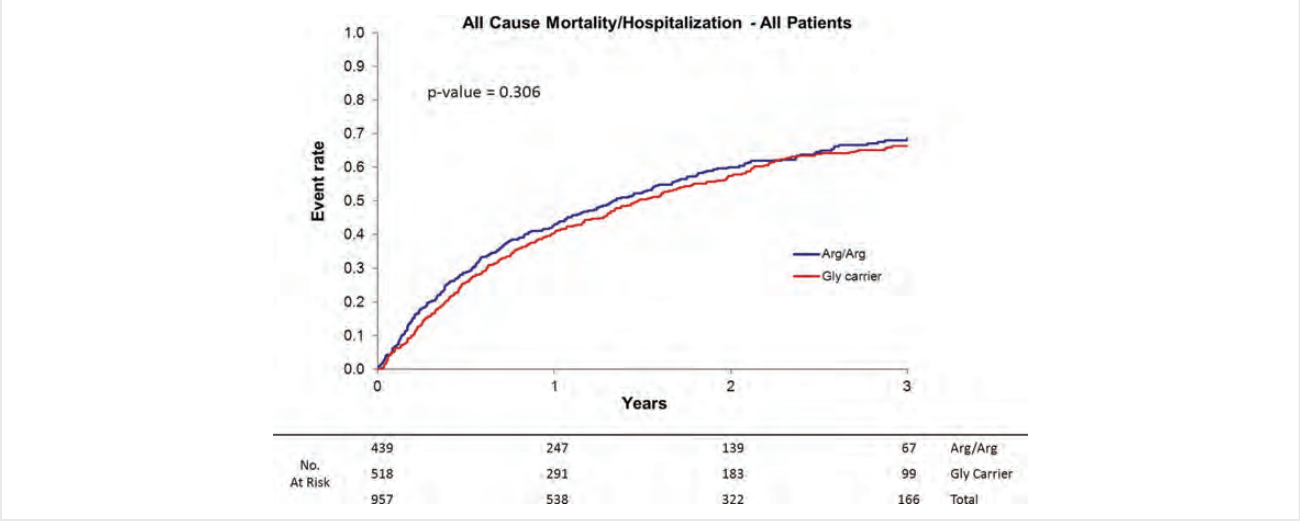

Figure 1 Adjusted Kaplan–Meier curves for primary endpoint by ADRβ1–389 genotype. Adjusted for Weber class, Kansas City Cardiomyopathy Questionnaire symptom stability, blood urea nitrogen, region (USA vs. non-USA), left ventricular ejection fraction, sex, mitral regurgitation (severe vs. non-severe), ventricular conduction, and race.

patient cohort; however, this subpopulation was similar to the overall HF-ACTION study cohort in terms of clinical characteristics, and is one of the largest DNA substudies of ambulatory patients with heart failure and reduced ejection fraction. Secondly, this study analysed a patient population in which the majority of patients received carvedilol or metoprolol. Our findings may not apply to different types of beta-blockers used to treat patients with heart failure. The current study was not a prospective evaluation of beta-blocker dosing; thus, sicker patients may have received lower doses due to an inability to tolerate higher doses. Although we adjusted for numerous known predictors of adverse outcomes, the possibility of important unidentified prognostic indicators must be considered. Finally, although we examined the most common coding SNP in the ADRβ1 gene, we cannot exclude the possibility that other SNPs in non-coding regions or more extensive haplotypes not tested in this study may be associated with beta-blocker response in heart failure.

Conclusions

Our study suggests there may be a differential dose requirement of beta-blockers based on the ADRβ1–389 Arg/Gly polymorphism. Clinically, this could be used to identify patients who may require titration to higher doses of beta-blockade. This supports the concept of clinical trials and clinical practice moving from a 'one-size-fits-all' framework to individualized treatment based on

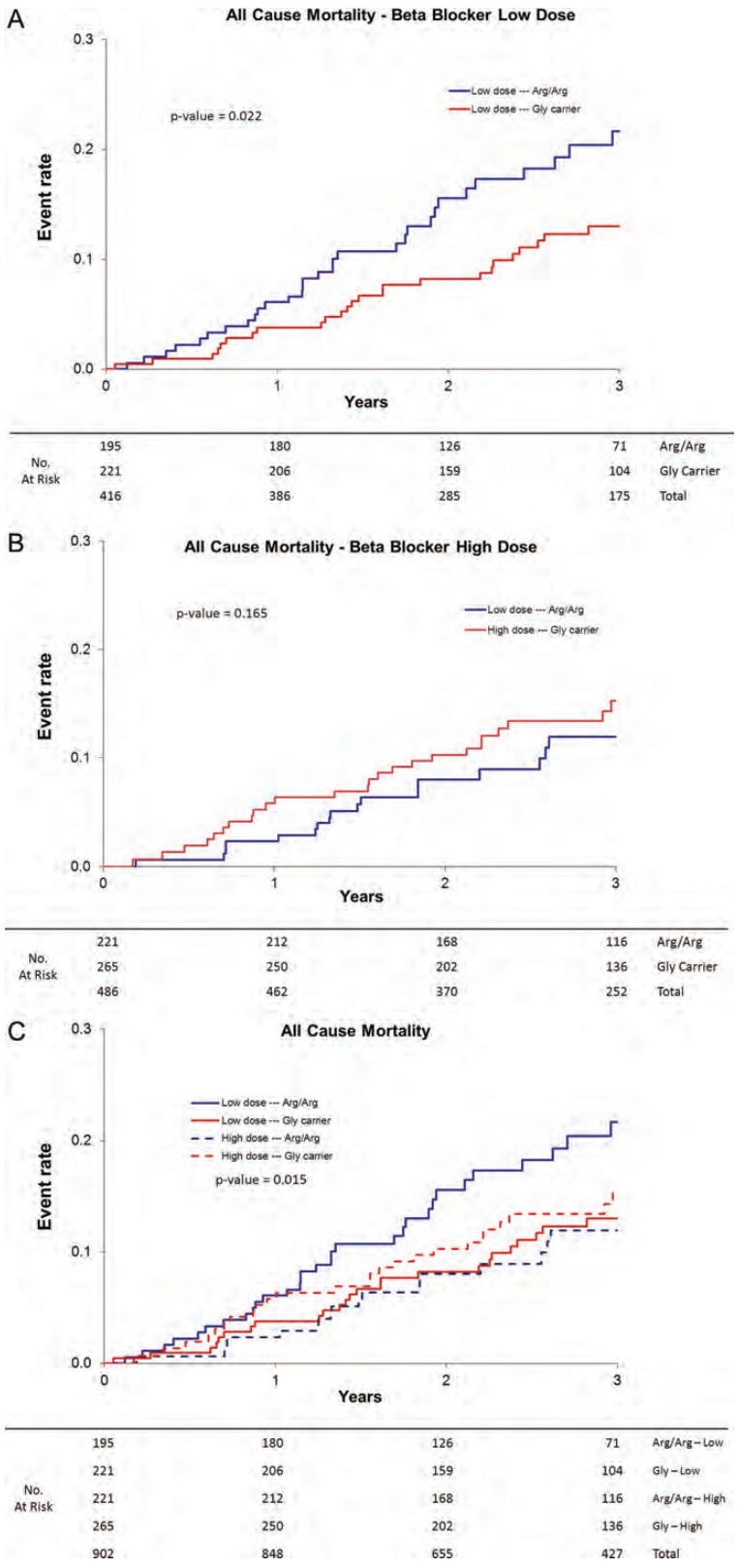

Figure 2 (*A*) Adjusted Kaplan–Meier curves for all-cause mortality for (*A*) low-dose beta-blocker and (*B*) high-dose beta-blocker by ADRβ1–389 genotype. (*C*) Adjusted Kaplan–Meier curves for all-cause mortality by beta-blocker and ADRβ1–389 genotype. Adjusted for exercise duration, body mass index, creatinine, sex, loop diuretics dose, left ventricular ejection fraction, Canadian Cardiovascular Society angina classification, ventricular conduction, and race.

genotyping. The ability to target appropriate doses of an agent could improve outcomes while avoiding adverse events, allowing optimization of the risk–benefit ratio for individual patients.

Funding

The HF-ACTION trial was supported by the National Heart, Lung, and Blood Institute, Bethesda, MD.

Acknowledgments

We would like to thank Carol Haynes, Albert Sun, and Karen Abramson for their help with the genotyping, and Morgan deBlecourt for her help with editing the manuscript as part of her regular duties as an editor employed by the Duke Clinical Research Institute.

Conflict of interest: M.F. is a shareholder of ARCA biopharma. All other authors have no conflict of interest to declare.

References

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics— 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;**119**:480–486.
2. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW; American College of Cardiology Foundation; American Heart Association. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009; **53**:e1–e90.
3. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, Harjola VP, Drexler H, Dickstein K, Tavazzi L, Nieminen M. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J* 2009;**30**:478–486.
4. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2012;**33**:1635–1701.
5. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J* 2012;**33**:1058–1066.
6. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;**101**:558–569.
7. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation* 2005;**111**:2837–2849.
8. Bristow MR. Treatment of chronic heart failure with beta-adrenergic receptor antagonists: a convergence of receptor pharmacology and clinical cardiology. *Circ Res* 2011;**109**:1176–1194.
9. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, Nelson B, Morrison J, Domanski MJ, Wagoner LE, Abraham WT, Anderson JL, Carlquist JF, Krause-Steinrauf HJ, Lazzeroni LC, Port JD, Lavori PW, Bristow MR. 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 USA* 2006;**103**:11288–11293.
10. Liggett SB. Pharmacogenetics of beta-1- and beta-2-adrenergic receptors. *Pharmacology* 2000;**61**:167–173.
11. Terra SG, Pauly DF, Lee CR, Patterson JH, Adams KF, Schofield RS, Belgado BS, Hamilton KK, Aranda JM, Hill JA, Yarandi HN, Walker JR, Phillips MS, Gelfand CA, Johnson JA. Beta-adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. *Clin Pharmacol Ther* 2005;**77**:127–137.
12. de Groote P, Helbecque N, Lamblin N, Hermant X, Mc Fadden E, Foucher-Hossein C, Amouyel P, Dallongeville J, Bauters C. 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**:137–142.
13. Taylor MRG, Bristow MR. The emerging pharmacogenomics of the beta-adrenergic receptors. *Congest Heart Fail* 2004;**10**:281–288.
14. Liggett SB, Cresci S, Kelly RJ, Syed FM, Matkovich SJ, Hahn HS, Diwan A, Martini JS, Sparks L, Parekh RR, Spertus JA, Koch WJ, Kardia SL, Dorn GW 2nd. A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure. *Nat Med* 2008;**14**:51–57.
15. O'Connor CM, Fiuzat M, Carson PE, Anand IS, Plehn JF, Gottlieb SS, Silver MA, Lindenfeld J, Miller AB, White M, Walsh R, Nelson P, Medway A, Davis G, Robertson AD, Port JD, Carr J, Murphy GA, Lazzeroni LC, Abraham WT, Liggett SB, Bristow MR. Combinatorial pharmacogenetic interactions of bucindolol and β1, α2C adrenergic receptor polymorphisms. *PLoS One*; in press.
16. Bristow MR, Murphy GA, Krause-Steinrauf H, Anderson JL, Carlquist JF, Thaneemit-Chen S, Krishnan V, Abraham WT, Lowes BD, Port JD, Davis GW, Lazzeroni LC, Robertson AD, Lavori PW, Liggett SB. An alpha2C-adrenergic receptor polymorphism alters the norepinephrine-lowering effects and therapeutic response of the beta-blocker bucindolol in chronic heart failure. *Circ Heart Fail* 2010;**3**:21–28.
17. Magnusson Y, Levin MC, Eggertsen R, Nyström E, Mobini R, Schaufelberger M, Andersson B. Ser49Gly of beta1-adrenergic receptor is associated with effective beta-blocker dose in dilated cardiomyopathy. *Clin Pharmacol Ther* 2005;**78**: 221–231.
18. 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**:12670–12674.
19. Mialet Perez J, Rathz DA, Petrashevskaya NN, Hahn HS, Wagoner LE, Schwartz A, Dorn GW, Liggett SB. Beta 1-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure. *Nat Med* 2003;**9**: 1300–1305.
20. Dorn GW 2nd, Tepe NM, Lorenz JN, Koch WJ, Liggett SB. Low- and high-level transgenic expression of beta2-adrenergic receptors differentially affect cardiac hypertrophy and function in Galphaq-overexpressing mice. *Proc Natl Acad Sci USA* 1999;**96**:6400–6405.
21. White HL, Maqbool A, McMahon AD, Yates L, Ball SG, Hall AS, Balmforth AJ. An evaluation of the beta-1 adrenergic receptor Arg389Gly polymorphism in individuals at risk of coronary events. A WOSCOPS substudy. *Eur Heart J* 2002;**23**: 1087–1092.
22. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996;**94**: 2807–2816.
23. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J, Wedel H; MERIT-HF Study Group. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002;**40**:491–498.
24. McNamara DM, Holubkov R, Postava L, Janosko K, MacGowan GA, Mathier M, Murali S, Feldman AM, London B. Pharmacogenetic interactions between angiotensin-converting enzyme inhibitor therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure. *J Am Coll Cardiol* 2004;**44**:2019–2026.
25. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
26. O'Connor CM, Whellan DJ, Wojdyla D, Leifer E, Clare RM, Ellis SJ, Fine LJ, Fleg JL, Zannad F, Keteyian SJ, Kitzman DW, Kraus WE, Rendall D, Piña IL, Cooper LS, Fiuzat M, Lee KL. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail* 2012;**5**:63–71.
27. Moore JD, Mason DA, Green SA, Hsu J, Liggett SB. Racial differences in the frequencies of cardiac beta(1)-adrenergic receptor polymorphisms: analysis of c145A>G and c1165G>C. *Hum Mutat* 1999;**14**:271.

28. Sehnert AJ, Daniels SE, Elashoff M, Wingrove JA, Burrow CR, Horne B, Muhlestein JB, Donahue M, Liggett SB, Anderson JL, Kraus WE. Lack of association between adrenergic receptor genotypes and survival in heart failure patients treated with carvedilol or metoprolol. *J Am Coll Cardiol* 2008;**52**: 644–651.
29. Terra SG, Hamilton KK, Pauly DF, Lee CR, Patterson JH, Adams KF, Schofield RS, Belgado BS, Hill JA, Aranda JM, Yarandi HN, Johnson JA. Beta1-adrenergic receptor polymorphisms and left ventricular remodeling changes in response to beta-blocker therapy. *Pharmacogenet Genomics* 2005;**15**:227–234.
30. Cresci S, Dorn GW 2nd, Jones PG, Beitelshees AL, Li AY, Lenzini PA, Province MA, Spertus JA, Lanfear DE. Adrenergic-pathway gene variants influence beta-blocker-related outcomes after acute coronary syndrome in a race-specific manner. *J Am Coll Cardiol* 2012;**60**:898–907.
31. White HL, de Boer RA, Maqbool A, Greenwood D, van Veldhuisen DJ, Cuthbert R, Ball SG, Hall AS, Balmforth AJ; MERIT-HF Study Group. 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**: 463–468.
32. Fiuzat M, Bristow MR. Pharmacogenetics in heart failure trials. *Heart Fail Clin* 2011; **7**:553–559.
33. Fiuzat M, Wojdyla D, Kitzman D, Fleg J, Keteyian SJ, Kraus WE, Piña IL, Whellan D, O'Connor CM. Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. *J Am Coll Cardiol* 2012;**60**:208–215.
34. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vítovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;**283**:1295–1302.