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# Pharmacogenomics in Heart Failure: Where Are We Now and How Can We Reach Clinical Application

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## Abstract

Heart failure is becoming increasingly prevalent in the United States and is a significant cause of morbidity and mortality. Several therapies are currently available to treat this chronic illness; however, clinical response to these treatment options exhibit significant interpatient variation. It is now clearly understood that genetics is a key contributor to diversity in therapeutic response, and evidence that genetic polymorphisms alter the pharmacokinetics, pharmacodynamics, and clinical response of heart failure drugs continues to accumulate. This suggests that pharmacogenomics has the potential to help clinicians improve the management of heart failure by choosing the safest and most effective medications and doses. Unfortunately, despite much supportive data, pharmacogenetic optimization of heart failure treatment regimens is not yet a reality. In order to attenuate the rising burden of heart failure, particularly in the context of the recent paucity of new effective interventions, there is an urgent need to extend pharmacogenetic knowledge and leverage these associations in order to enhance the effectiveness of existing heart failure therapies. The present review focuses on the current state of pharmacogenomics in heart failure and provides a glimpse of the aforementioned future needs.

### Keywords

pharmacogenetics; pharmacogenomics; personalized medicine; heart failure; polymorphism; beta-adrenergic blocker; angiotensin-converting enzyme inhibitor; angiotensin receptor blocker; diuretic; digoxin

## INTRODUCTION

Heart failure has reached epidemic proportions. Approximately 5 million adults have heart failure in the United States with recent projections suggesting that by 2030, the prevalence

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of this syndrome will increase another 25%. [1] Thus, heart failure has tremendous impact on the health care system and constitutes a major medical and societal burden. Heart failure is characterized by insufficient cardiac performance to meet metabolic requirements or accommodate systemic venous return. [2] The body's neurohormonal system including the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) is activated in order to compensate for these deficiencies [2] but activation of these systems contribute to worsening heart failure, worsened quality of life, and poor outcomes such as the need for a heart transplant, or sudden cardiac death. [3] Evidence-based medical therapies that suppress these responses can substantially reduce the progression of this syndrome. [4–6] Accordingly, comprehensive heart failure management guidelines from both the American College of Cardiology (ACC)/American Heart Association (AHA) and the Heart Failure Society of America (HFSA) recommend specific pharmacological management, mostly focused on neurohormonal suppression, to improve outcomes in all patients with heart failure and reduced ejection fraction. [7,8] β blockers and angiotensin converting enzyme (ACE)-inhibitors are considered the foundation, but evidence has shown important roles for other therapies which help delay progression of heart failure and reduce mortality including angiotensin receptor blockers (ARB)s, aldosterone antagonists, hydralazine/isosorbide combination, and even device therapies such as implanted defibrillators and cardiac resynchronization therapy (CRT). [7,8] In addition, while there is no evidence for mortality benefits with loop diuretics and digoxin, these agents are indispensable, improving symptoms and possibly reducing hospitalizations. [9,10] It is thus evident that heart failure patients are currently subjected to a multiplicity of medications to achieve maximum benefit and optimized outcomes. This polypharmacy in health failure patients is associated with increased risk of toxicity, drug interactions, and poor compliance. [11] Current guidelines do offer some advice regarding tailoring of therapy on clinical grounds; for example, the HFSA guidelines recommend that factors such as age, ethnicity, heart failure severity, renal function, and serum potassium should be used to choose which of the many agents a heart failure patient should receive in his or her regimen. [7] However, even in patients who appear to have similar clinical factors, a great deal of variability exists in response to treatment. [12] Genetic variability in response to heart failure treatment exists [13] and genetic information may complement conventional clinical information in tailoring therapy to an individual patient, ultimately improving outcomes. The present review focuses on available data from pharmacogenomic studies in heart failure medications, particularly focusing on new developments over the past 2 years (earlier literature has been nicely described elsewhere [14,15]), summarized by medication class. Proof-of-principle findings are presented that are important to be aware of, but actionable genetic testing to guide therapeutic choices in heart failure remains limited to date. Thus, the review also shows that further work in this area is needed before the clinical implementation of heart failure pharmacogenomics becomes a reality, and we provide a glimpse of the future needs and directions.

## BETA ADRENERGIC ANTAGONISTS

The role of the adrenergic signaling pathway of the SNS in heart failure is characterized by a vicious cycle in which chronic stimulation of the adrenergic receptor (AR) by circulating catecholamines norepinephrine (NE) and epinephrine promotes cardiac dysfunction that

results in the release of more adrenergic-stimulating catecholamines and further disease progression. [16] While the sub-cellular mechanism of action is not completely elucidated, it is clear that β blockers work by suppression of the adrenergic pathway and interruption of this vicious cycle. [17] Due to evidence of survival benefit, β blockers have been a mainstay of heart failure pharmacotherapy for almost 20 years. [18–20] However, there is great variation in response to β blocker therapy including certain subsets of the heart failure population that do not receive the same mortality and morbidity benefit. [21,22] Single nucleotide polymorphisms (SNPs) in the β1-AR (*ADRB1)*, β2-AR (*ADRB2)*, α2C AR (*ADRA2C)*, and G-protein receptor kinase 5 (*GRK5)* genes of the adrenergic system may partially explain the variable effects received from β blockade. In fact, most of the published pharmacogenomic literature over the past 2 years concerning heart failure has focused on response to β blockers; thus we have given it first and most attention among the drug classes of interest.

β1-AR is the primary pharmacologic target of β blockers. One of the most widely-studied polymorphisms for heart failure in *ADRB1* is the Arg389Gly variant. Arg389 is associated with enhanced adrenergic response to agonist stimulation of β1-AR in vitro [23] and in vivo[24]. Importantly, in a genetic substudy of the β Blocker Evaluation of Survival Trial (BEST), a relationship between $\beta_1$ genotype and mortality response to treatment with the β blocker bucindolol was found.[25] BEST was a large, randomized, clinical trial testing the efficacy of bucindolol in heart failure patients. [26] The trial was terminated prematurely at 2 years due to a lack of mortality benefit, though bucindolol significantly improved mortality in the non-black subset (~75% of the patients).[26] As a result of clinical failure in the overall population, bucindolol was never approved by the FDA for the treatment of heart failure. Notably, bucindolol also acts as a potent sympatholytic in addition to its β blocking properties, reducing circulating NE levels to a much greater extent than the β blockers FDA-approved for heart failure (e.g. carvedilol and metoprolol succinate).[27] This distinct property of bucindolol may have reduced NE to deleteriously low levels thereby abrogating cardiac contractility and negating any beneficial effects realized through β blockade.[25] In the genetic substudy, Arg389 homozygotes were found to have a 34% mortality benefit from bucindolol. [25] A greater survival rate in patients with this genotype was found when NE levels did not decrease compared to baseline, suggesting that an enhanced β blockade affect rather than protection from exaggerated sympatholysis may be responsible for reduced mortality in this population. In contrast, no clinical benefit was observed in carriers of the Gly389 variant. [25] These results were backed up by *ex vivo* and cell data which also showed that enhanced bucindolol response was associated with Arg389. [25] In addition, the results may explain racial differences in bucindolol efficacy, as blacks were less likely to carry Arg389 compared to non-blacks. [25] However the relatively small difference in allele frequencies between racial groups (0.62 in blacks, 0.73 in non-blacks)[25] and contradictory clinical trial data that do not show variation in response to β blocker therapy across race[28], suggest that Arg389 does not sufficiently explain racial disparities in bucindolol response.

In addition to the Arg389Gly polymorphism, a variant at codon 49 also has been found to influence drug response and clinical adverse outcomes in heart failure patients. Specifically in a population of patients with idiopathic dilated cardiomyopathy, Ser49 homozygotes had worsened prognosis (death or cardiac transplantation) compared to Gly49 carriers. [29] This

association remained present among patients who received β blocker therapy (~39% of the population), though the specific β blocker drug patients were taking was not specified. [29] These data were supported by mechanistic follow-up studies where cells transfected with Gly49 had increased sensitivity to metoprolol as well as enhanced catecholamine-induced β1-AR desensitization, which is considered a protective response to heart failure progression. [30] An expanded clinical follow-up confirmed that Gly49 carriers had better survival compared to Ser49 homozygotes, suggesting that higher β blocker doses may be warranted in Ser49Ser patients to achieve optimal survival response. [31]

*ADRB2* has a role in adrenergic signaling in parallel with *ADRB1*. Indeed, clinical trial data from the COMET trial and experimental evidence both suggest that antagonism of $\beta_2$ AR is at least partially responsible for beneficial effects of carvedilol in heart failure. [32,33] *ADRB2* genotype may be important in heart failure pathophysiology and response to β blocker therapy. Kaye et al. were able to show that among heart failure patients receiving carvedilol, the proportion of patients with a favorable EF response to therapy (≥10% improvement in absolute LVEF or ≥5% improvement in absolute FS) was significantly higher in Glu27 carriers compared to Gln27 homozygous patients[34]. These findings were validated in a larger population.[35] Moreover, this effect has been replicated in terms of survival in several subsequent studies. [36–38] For example, in a well-treated cohort of advanced heart failure patients (81% were receiving β blockers), individuals who carried 2 copies of the *ADRB2* Arg16-Gln27 haplotype were more likely to die or require a heart transplant.[38]

The *ADRA2C* gene is responsible for the expression of the $\alpha_{2C}$ AR, an autoreceptor located on presynaptic adrenergic neurons, which limits the release of NE through a negative feedback system. [39,40] Genetic disruption of $\alpha_2$ ARs in mice resulted in elevated NE levels and hearts with significant hypertrophy. [40] The multiple-nucleotide polymorphism $\alpha_{2C}$322–325 deletion (Del) similarly increased risk of developing heart failure in black patients [41], who have a minor allele frequency of 0.4 compared with 0.04 in whites [42]. In a BEST DNA substudy, *ADRA2C* variability surprisingly did not alter baseline levels of NE or the natural course of heart failure progression in placebo-treated patients. *ADRA2C* genotype, however, did affect response to bucindolol treatment. [42] Patients who were carriers of the Del allele had enhanced norepinephrine reduction from bucindolol compared to wild-type patients. Furthermore, bucindolol was found to improve survival only in $\alpha_{2C}$322–325 wild-type homozygotes. [42] Though the precise mechanisms by which *ADRA2C* genotype impacts the ability of bucindolol to reduce NE levels remain unknown, these results are consistent with previous findings[25] that an exaggerated sympatholytic response to bucindolol is associated with reduced survival response to bucindolol.

*GRK5* codes for G-protein receptor kinase 5 which desensitize β AR signaling. [43] Substitution of Gln at the 41$^{st}$ amino acid position with Leu has been found to be a gain-of-function allele resulting in enhanced desensitization, [43] analogous to an endogenous β blocking effect. In a prospective cohort of African American heart failure patients, who have 10-fold higher allele frequencies of this gain-of-function polymorphism than Caucasians, the presence of *GRK5* Leu41 was just as protective in preventing cardiac death or heart transplant as β blocker use. [43] These findings were recapitulated in an expanded population of African American heart failure patients: *GRK5* Leu41 improved survival. [44]

Inconsistencies that contradict the above associations between variants in genes of the adrenergic system and survival response to β blockers exist in the literature. For example, the significant relationship between *ADRB1* Arg389Gly genotype and mortality response to bucindolol is less clear with the β blocker therapies FDA-approved for heart failure[27,45–48]; however, the aforementioned differences in sympatholytic properties among β blockers may explain why the pharmacogenetic association with *ADRB1*Arg389Gly in heart failure patients is inconsistent across members of this drug class. Moreover, De Groote et al. did not find a significant genetic association between any of the five aforementioned adrenergic receptor polymorphisms and survival in β blocker-treated heart failure patients. [49] An investigation in a large registry of heart failure patients with left ventricular dysfunction receiving metoprolol or carvedilol showed that individual variants and haplotypes involving *ADRB1*, *ADRB2*, and *ADRA2C* were not found to have a significant effect on survival.[27] Altogether, these results imply that other factors such as race, disease severity, specific β blocker, and phenotype may interact with pharmacogenomic associations. In addition, SNPs may interact with each other and attenuate the elucidation of these associations.

Despite these challenges (or perhaps because of them), the pharmacogenetics of β blockers in heart failure continues to be an active area of investigation in recent years. Further work has attempted to sort out these inconsistencies, validate findings, and fully characterize the subset of optimal responders to β blocker therapy. An approach that continues to be used to address contradictions in the literature is the investigation of associations between genetic combinations and response to β blocker therapy, rather than individual polymorphisms. [50] This strategy has been adopted by multiple investigators in recent years. Petersen et al. observed that heart failure patients who were homozygous for *ADRB* Arg389 and carriers of *ADRB2* Gln27 in combination received less survival benefit from carvedilol treatment. [51] In contrast, this genotype combination did not impact response to metoprolol, likely due to differences in pharmacological properties. [51] More recently, O'Connor et al. have further elucidated the interaction of multiple adrenergic polymorphisms on β blocker response with another genetic substudy in BEST.[52] In particular they reported an additive loss of bucindolol response in terms of morbidity and mortality in carriers of $\beta_1$ Gly389 and $\alpha_{2C}$322–325 Del alleles, consistent with the effects of the individual SNPs on bucindolol response. [52] And an even more recent BEST substudy shows that genotype combinations determined from $\beta_1$ Gly389 and $\alpha_{2C}$322–325 Del interact with response to bucindolol in terms of its efficacy in preventing ventricular arrhythmias in heart failure patients[53]; this morbidity response to bucindolol is similar to the abovementioned mortality response when using the same SNP combinations. Another important issue that is often overlooked in heart failure pharmacogenomic studies involves the impact of other comorbidities. This issue has been recently explored as well. In a substudy of BEST, atrial fibrillation status did not affect response to bucindolol. $\beta_1$ Arg389 homozygote patients, but not $\beta_1$ Gly389 carriers, had reduced death and hospitalization from bucindolol; which confirms the pharmacogenomic association discovered in the full BEST genetic population. [54] On the contrary, atrial fibrillation history impacted genetic response to β blockers in a population of elderly patients (age > 65) with heart failure. [55] Patients who were $\beta_1$ Arg389 homozygotes and also suffered from atrial fibrillation had blunted heart rate reduction from carvedilol, but not bisoprolol; no attenuation in response to therapy was seen with patients in normal sinus

rhythm regardless of β blocker or genotype [55] demonstrating that comorbidities may interact with pharmacogenetic associations. Indeed β blocker response to adrenergic polymorphisms in acute myocardial infarction patients conflict with those seen in heart failure patients.[56] In addition to these studies which look at the impact of gene-gene interactions and comorbidities on pharmacogenomic associations, investigators continue to report data on individual polymorphisms. In a prospectively recruited population of heart failure patients, Talameh et al. showed that $\beta_1$ Ser49Ser homozygotes, but not Gly49 carriers, had enhanced survival response to β blocker therapy, using a larger population to corroborate previous findings that β blocker therapy has a greater influence on outcomes only in patients with Ser49Ser genotype. [31,57] Another recent genetic substudy looked at the impact of genotype on dose response in heart failure patients receiving metoprolol or carvedilol. [58] $\beta_1$ Arg389 homozygote patients had increased mortality and worsened quality of life from lower β blocker doses, whereas dose did not affect outcomes in Gly389 carriers. [58] This contribution is significant, because few have assessed quality of life outcomes or gene-dose response in pharmacogenomic heart failure studies. [58] Collectively, these recent findings indicate that while progress in this field continues, more work is still needed before clinical utility of β blocker pharmacogenomics can be achieved. At the current rate, this goal does not seem achievable in the near future; a heightened effort is warranted.

## DRUGS TARGETING THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The RAAS also plays a key role during the development and worsening of heart failure. [59] Several classes of agents for heart failure are available that work at different sites within the RAAS to suppress its effects. In particular, ACE inhibitors help to comprise the cornerstone of modern heart failure pharmacotherapy and have compelling evidence of survival benefit in multiple clinical trials. [60,61] ACE inhibitors act by blocking ACE-mediated conversion of angiotensin I to angiotensin II, thereby reducing vasoconstriction, salt-retention, and hypertrophy that occur with this neurohormone. [62] Genetic modifiers of ACE inhibitor effectiveness have been long sought with some early success. An insertion (I)/deletion (D) polymorphism in *ACE* is responsible for half of the variance in systemic ACE levels; the D allele is associated with increased ACE. [63] The presence of this variant is also associated with heart failure incidence and severity. [64,65] Additionally, past research has shown that this polymorphism alters response to ACE inhibitors. Cuoco et al. showed in a population of heart failure patients (90% receiving ACE inhibitors) that carriers of the D allele had significantly improved LVEF compared to wild-type patients after a mean follow-up of ~39 months. [66] In contrast, in a population of patients with left ventricular hypertrophy and hypertension receiving ACE inhibitors, patients with the D/D genotype had less improvement in hypertrophy. [67] In a third study, the presence of the D allele had no impact on mortality in diastolic heart failure patients who received ACE inhibitors. [68] This finding that does not concur with either of the above results, but does agree with an earlier study in systolic heart failure patients that also showed a diminished impact of the polymorphism on outcomes in patients receiving ACE inhibitor therapy, specifically at higher doses. [69]

Currently, the pharmacogenomic impact of *ACE* genetic variation in heart failure remains a controversial subject. In a recent genetic substudy of a randomized trial investigating the impact of pharmacist intervention on outcomes in heart failure patients (68% receiving ACE

inhibitors and 13% receiving ARBs at baseline), the *ACE* I/D polymorphism was not found to be associated with the composite of ED visits and hospitalizations. [70] Further work, including the resolution of the aforementioned conflicting data, is necessary to elucidate the potential application of using of pharmacogenomic information to guide the therapeutic regimen of RAAS drugs in heart failure.

## OTHER HEART FAILURE THERAPIES

Guidelines recommend additional therapy as adjuncts to β blockers and ACE inhibitors for relieving symptoms, delaying the progression of cardiac dysfunction, and improving survival in heart failure patients. [7,8] Among others, adjunct therapies with the most promising pharmacogenetic evidence are digoxin and loop diuretics.

It is fairly well established that digoxin reduces symptoms of heart failure and hospitalizations. [10] Digoxin has been used for centuries in heart failure and continues to be recommended in this population, but only at doses that correlate with relatively low serum levels due to increased mortality at higher levels. [7,71] Given this narrow therapeutic range, factors which impact digoxin concentration may have important clinical implications. P-glycoprotein which is coded by *ABCB1* plays a role in digoxin elimination.[72] The TTT haplotype is a combination of three SNPs (the substitution of thymine at positions 1236, 2677, and 3435) in *ABCB1* that are highly linked and have been found to be associated with digoxin serum levels. [73] In particular, a 2008 study reported that the TTT haplotype was associated with increased digoxin levels in a population of elderly Caucasian patients receiving digoxin. [73] This contrasts an earlier study that evaluated this association in a small population of heart failure patients did not find a significant *ABCB1*effect on digoxin levels, [74] suggesting that further work investigating the pharmacogenetics of digoxin is needed. This area continues to be investigated; a recent study confirms that the *ABCB1* TTT haplotype may be predictive of elevated digoxin concentrations in patients receiving this medication, especially in females. [75] However, similar to the 2008 digoxin report mentioned, this 2012 study did not include a population of exclusively heart failure patients. The negative finding in heart failure patients hint that perhaps clinical or other factors related to the disease state may override any genetic association altering digoxin response. Validation in a larger independent population is necessary to establish if there is a genetic link to digoxin levels and clinical response in heart failure patients receiving digoxin.

Loop diuretics, similar to digoxin, have not been found to have a mortality benefit but are the most common agents used for symptomatic relief due to sodium and water retention. They act by inhibiting sodium-potassium-chloride luminal transporters in the loop of Henle causing an attenuation of the reabsorption of sodium and water. [76] Recently a small study in healthy volunteers suggests that genetics may play a clinically-relevant role in response to loop diuretics. [77] Polymorphisms in *GNB2*, *ANP*, *ACE*, and *ADD1* impacted the excretion amounts of sodium chloride, potassium, and calcium. [77] Similar to the pharmacogenetics of digoxin, further work including confirmation in heart failure patients and a link to clinical efficacy is a necessary fundamental to understand if clinical application is possible.

## FUTURE PROSPECTS FOR PHARMACOGENOMICS

Over the past 15 years the field of pharmacogenetics has spread to include therapy for heart failure. Since the earliest periods of discovery, β blocker pharmacogenomics has been the most heavily explored, however response to other heart failure therapies also have shown the potential to be impacted by genotype. Taken together, the knowledge base summarized above demonstrates that genetic information does have the potential to guide therapeutic regimens for patients with heart failure and to improve outcomes. Despite this wealth of investigation, however, the pharmacogenomics of heart failure therapies still have not reached clinical utility. Additional steps are needed before this can be realized.

First, clarifying the current areas of inconsistency between gene-drug response associations should be a high priority. These inconsistencies suggest that complex genetic and environmental factors play a role. There needs to be a continued focus on the creation of 'polygenic profiles' which serve as novel biomarkers for the response to heart failure medications and allows for the identification of 'full', 'intermediate', and 'non-' responder subsets. Additionally the consideration of comorbidities and other clinical factors are beginning to show utility in predicting which subsets of the heart failure population would respond best to certain agents; these results require further exploration.

Secondly, much emphasis has been placed on genes related to the adrenergic system as expected considering its great promise in predicting response to β blockers in clinical practice. Nonetheless, more attention needs to be placed on emerging pharmacogenetic biomarkers. In addition to the aforementioned pharmacogenetic findings that have been investigated in the past couple years involving ACE inhibitors, digoxin, and loop diuretics, novel genetic biomarkers in the early phases of discovery have potential to determine drug response in the heart failure population. For example, a recent study has shown that variation in genes coding for matrix metalloproteinases may interact with response to therapies altering the risk of heart failure development in hypertension patients. [78] Furthermore, novel genetic biomarkers have the potential to predict response to heart failure therapies beyond pharmacological agents. De Maria et al. recently found that among heart failure patients receiving CRT, those who did not achieve clinically significant reverse remodeling were more likely to have the *NR3C2* minor C allele (rs5522 C/T) compared to patients who achieved reverse remodeling. [79] These data, of course require validation, but overall, support the potential of emerging genetic predictors of response to both pharmacological and non-pharmacological treatment in the early development as well as the advanced progression of heart failure.

Another important step is the continued and expanded use of genetic analyses of heart failure randomized clinical trials (Table). These datasets serve as critical platforms to determine pharmacogenetic associations because they can supply large cohorts in which the impact of the therapy-gene interaction on outcomes can be most clearly demonstrated. Although genetic substudies are limited when the initial intervention has already become standard of care since this may preclude replication in an independent population, alternates for the validation of pharmacogenomic findings exist; these are beyond the scope of this review and are reviewed in great depth elsewhere. [80] Furthermore, these types of studies are

ideal for emerging therapies where they may aid in identifying the best responders to a therapy and reduce the probability of drug development failure in clinical trials. As a result of genetic substudies of BEST that have provided a wealth of knowledge, bucindolol may be the most auspicious candidate to be approved as a heart failure therapy that incorporates a pharmacogenomic-guided strategy. While genetic information is now routinely being collected in clinical trials worldwide [81,82], it is not always being actively utilized or opened for exploration, squandering many great opportunities.

Ultimately randomized clinical studies of pharmacogenomic-guided therapy would be needed to conclusively establish the utility of a pharmacogenomic approach in a clinical setting. The authors feel that one pharmacogenetic clinical trial success in heart failure would invigorate interest and open the flood gates for future studies. On the other hand, while randomized clinical trials represent the definitive proof, it is not a practical endeavor for each genetic variant and drug of potential interest. Indeed efforts to incorporate pharmacogenomic-guided decision making at the bedside at progressive institutions are taking place without the evidence of randomized, prospective trials.[83–85] The medical and scientific community still needs to grapple with and decide on the level of evidence required for universal integration of heart failure pharmacogenomics in clinical practice.

In conclusion, progress in the field of heart failure pharmacogenetics continues, but further research is necessary. A collective and concerted effort between basic, clinical, and translational researchers is merited to achieve its incorporation into guidelines as a standard of clinical care.

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**TABLE**

Recent heart failure pharmacogenomic findings from clinical trials (2012-present)

| Gene (genotype) | Parent trial | Drug | Primary endpoint | Association |
|---|---|---|---|---|
| *ADRA2C* (322–325), *ADRB1* (Arg389Gly) | BEST* [52] | Bucindolol | ACM, ACM or transplant | Carriers of Gly389 and Del in combination had complete loss of bucindolol response in HF patients |
| *ADRA2C* (322–325), *ADRB1* (Arg389Gly) | BEST* [53] | Bucindolol | Incidence of VT/VF | Carriers of Gly389 and Del in combination had complete loss of bucindolol response in HF patients |
| *ADRB1* (Arg389Gly) | CIBIS-ELD† [55] | Bisoprolol, carvedilol | HR | Arg389 homozygotes had reduced carvedilol response in elderly (age > 65) HF patients with AF |
| *ADRB1* (Arg389Gly) | BEST* [54] | Bucindolol | ACM or HFH, CVM or CVH, HR | Arg389 homozygotes had reduced bucindolol response in HF patients with AF (for all endpoints but HR) |
| *ADRB1* (Arg389Gly) | HF-ACTION†† [58] | Any HF β blocker | ACM or ACH | Arg389 homozygotes had reduced β blocker response (low doses) in HF patients |

*Efficacy of bucindolol versus placebo in patients with heart failure

†Efficacy and safety of carvedilol versus bisoprolol in elderly patients with heart failure

††Efficacy of exercise training versus usual care in patients with heart failure

ACM, all-cause mortality; ACH, all-cause hospitalization; AF, atrial fibrillation; CVH, cardiovascular hospitalization; CVM, cardiovascular mortality; HF, heart failure; HFH, heart failure hospitalization; HR, heart rate; VF, ventricular fibrillation; VT, ventricular tachycardia

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