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CYP2D6 Genetic Variation and Beta-Blocker Maintenance Dose in Patients with Heart Failure

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Abstract

Purpose—This study examined whether a *CYP2D6* polymorphism (*CYP2D6**4) was related to beta-blocker maintenance dose in patients with heart failure.

Methods—Logistic regression modeling was utilized in a retrospective chart-review analysis of heart-failure patients (60% Male, 90% of European descent) to assess whether *CYP2D6**4 (non-functional *CYP2D6* allele present in 1 of 5 individuals of European descent) is associated with maintenance dose of carvedilol (n=65) or metoprolol (n=33).

Results—*CYP2D6**4 was associated with lower maintenance dose of metoprolol (OR 0.13 [95% CI 0.02–0.75] p=0.023), and a trend was observed between *CYP2D6**4 and higher maintenance dose of carvedilol (OR 2.94 [95% CI 0.84–10.30] p=0.093). None of the patients that carried *CYP2D6**4 achieved the recommended target dose of metoprolol (50mg/day).

Conclusion—Consistent with the role of *CYP2D6* in the metabolism of metoprolol, the tolerated maintenance dose of metoprolol was lower in *CYP2D6**4 carriers compared to non-carriers. Consistent with the role of *CYP2D6* in activation of carvedilol, tolerated maintenance dose of carvedilol was higher in *CYP2D6**4 carriers compared to non-carriers. Further investigation is warranted to ascertain the potential of *CYP2D6* as a potential predictive biomarker of beta-blocker maintenance dose in heart failure patients.

INTRODUCTION

Heart failure is a major public health problem that impacts nearly 6 million Americans (1). One in five Americans over the age of 40 years will develop heart failure during their lifetime, and one in five heart failure patients will die within 1 year of diagnosis (1). Although heart transplantation is often the only remaining intervention, there is a relative paucity of available donor hearts (<3,000 hearts were donated for transplantation in the United States in 2015) (2). Beta-blockers are one of the few pharmacologic therapies that can significantly prolong survival for patients with heart failure. Accordingly, beta blockers are recommended for all patients with systolic heart failure (unless contraindicated) (3). Unlike other indications for beta-blockers (*e.g.*, hypertension or atrial fibrillation), efficacy has not been consistent among beta-blocker types in heart failure. In the United States, three beta-blockers are recommended for the treatment of heart failure: carvedilol, metoprolol succinate, and bisoprolol (3). While beta-blocker dose is titrated to response (*e.g.*, target blood pressure or heart rate) for beta-blocker indications other than heart failure, the predictive value of these surrogate measures for efficacy in the treatment of heart failure has not been firmly established. In treating heart failure, beta-blockers are titrated, therefore, to a target dose as reflected in the following treatment guideline issued by the American College of Cardiology and the American Heart Association for the treatment of heart failure: Clinicians should make every effort to achieve the target doses of the beta-blockers shown to be effective in major clinical trials (3). The doses shown to be effective were 50, 80, and 200 mg/day for carvedilol, controlled-release carvedilol, and metoprolol succinate or tartrate, respectively (3).

Nearly 85% of heart failure patients achieved recommended doses of beta-blockers in the reported clinical trials of beta-blocker efficacy (3). Only half of patients, however, achieve target doses in clinical practice (4). Dose-limiting adverse effects (*e.g.*, bradycardia, hypotension, or fatigue) are the primary impediment (4). Occurrence and/or severity of adverse effects are likely influenced by altered systemic drug exposure secondary to concomitant medication use, diseased states or genetic polymorphisms. As both metoprolol and carvedilol are metabolized by cytochrome P450 2D6 (CYP2D6) (5–7) and *CYP2D6* is highly polymorphic causing extreme phenotypic variability resulting in CYP2D6 ultra-rapid, extensive, intermediate, and poor metabolizer (UM, EM, IM, and PM, respectively) phenotypes (8), genetic status of *CYP2D6* may be a determinant of beta-blocker tolerability. Importantly, functional polymorphisms in *CYP2D6* are common, with the decrease-of-function *CYP2D6**10 allele present in nearly 40% of patients with Asian ancestry and the *4 non-functional allele present in nearly 20% of patients with European ancestry (8).

Much of the reported research on the effects of *CYP2D6* genetic polymorphisms on beta-blockers was from data collected in late-phase (efficacy) clinical trials (6,9–13) or highly controlled early-phase (pharmacokinetics) clinical studies (5,14–17). The reported findings from those studies, therefore, may not be generalizable to patients under routine clinical care. Moreover, most of the previous research on *CYP2D6* and beta-blockers was not conducted specifically in patients with heart failure. As a result, physiologic changes associated with heart failure (*e.g.*, edema, hepatocellular damage, hypoxia, and elevated levels of pro-inflammatory cytokines) are neglected despite their potential to dramatically

alter beta-blocker pharmacokinetics. Total hepatic cytochrome P450 content is decreased by about 40% (18) and the oral area-under-the-concentration-time curve for many drugs is increased by nearly 50% in patients with heart failure (19). Given these substantial changes associated with heart failure and notable differences between routine clinical practice and controlled clinical trials, this study of the association between *CYP2D6* and beta-blocker maintenance dose in heart failure patients receiving routine clinical care at a large academic medical center is critical to pharmacogenetics and precision medicine research. As this study cohort was comprised largely of patients with European ancestry, this analysis focused on *CYP2D6**4 (the most common non-functional allele in individuals with European ancestry) to assess whether *CYP2D6* is associated with beta-blocker maintenance dose in patients with heart failure. In addition, three *CYP2D6* genotype-metabolizer phenotype classification schemes (based on *CYP2D6**4 status) are presented and compared.

MATERIALS AND METHODS

Patient Data

This study was a retrospective chart review of 102 patients with systolic heart failure that participated in the Ohio State University-Coriell Personalized Medicine Collaborative (OSU-CPMC). The OSU-CPMC has been described in detail previously (20). Briefly, the parent CPMC study sought to understand best practices regarding the use of genomic information in medical settings and in individual health management within three distinct study cohorts: community, cancer, and chronic disease. The community cohort participants were recruited without regard to health status or affiliation with a healthcare institution, while the cancer cohort consisted of participants with a personal history of either breast or prostate cancer. The OSU site within the parent CPMC study specifically focused on the chronic disease cohort. Systolic heart failure and hypertension were the two chronic diseases chosen as foci for the chronic disease cohort. Through the identification of clinical champions, OSU physicians were directly involved in the recruitment of patients from OSU Primary Care Clinics, the Ross Heart Hospital and ambulatory care clinics, and the University Hospital East Cardiology Clinic. For the heart failure cohort, inclusion criteria included a documented age of 18 years or older and documented diagnoses (ICD-9 code in their EPIC[®] electronic medical record, EMR) of systolic heart failure. Dedicated study recruiters worked closely with physicians on the heart failure service at the Ross Heart Hospital to ensure that only patients with systolic heart failure were enrolled. Demographics, vital signs, vital status, diagnosis codes, anthropometric measurements, and detailed medication history including specific drugs, drug doses, dosing frequencies, and drug start/stop dates were collected from the EMR via the OSU Information Warehouse; data was collected for each patient from the first available entry (OSU medical center initiated Epic EMR in 2008) through July 14, 2014.

Medication profiles were reviewed by a board-certified Pharmacotherapy Specialist, and the number of days each patient was prescribed specific beta-blocker doses was counted utilizing the prescription start and stop dates documented in the EMR. For this investigation, beta-blocker maintenance dose was defined as the dose prescribed for the longest period within the available EMR time window, and patients were considered to have reached their

target dose only if their prescribed beta-blocker maintenance dose was at least as high as the guideline-recommended target dose (50, 80, and 200 mg/day of carvedilol, controlled-release carvedilol, and metoprolol succinate or tartrate, respectively) (3). No patients in this study were treated with bisoprolol or other beta-blockers. For this analysis, metoprolol dose was normalized to carvedilol dose by dividing the metoprolol dose by 4. This normalization was based on the mean doses achieved in clinical trials (37 mg/day for carvedilol and 159 mg/day for metoprolol) (3) and is consistent with both the recommended target doses of carvedilol and metoprolol (*i.e.*, the target dose for metoprolol is 4 times greater than for carvedilol) and with the normalization utilized in previous studies comparing carvedilol and metoprolol in patients with heart failure (21). EMRs were also evaluated for the number of concomitant medications known to interact with metoprolol or carvedilol (online supplemental Table V and Table VI, respectively). Medications with potential to increase or decrease beta-blocker exposure or effect (via inhibition or induction of CYP2D6 metabolism, respectively) were tabulated and included in covariate-adjusted models. For clinical characteristics with temporal variation (*e.g.*, body mass index, systolic blood pressure), averages (during the period beta-blocker maintenance dose data were collected) were calculated and included in covariate-adjusted models.

Genotyping and Phenotyping

DNA isolation and genotyping were performed by the Coriell Genotyping and Microarray Center at the Coriell Institute for Medical Research, a Clinical Laboratory Improvement Amendments (CLIA)-certified facility. DNA was isolated from saliva samples per standard protocols and genotyped using the Affymetrix DMET Plus Premier Pack. The Affymetrix DMET Plus Premier Pack covers 31 polymorphisms in *CYP2D6* and translates them into the *star allele nomenclature using standard annotation (specific markers in file version “DMET_Plus.v1.20120731.dc_annot” call *star alleles) detailed at http://www.affymetrix.com/support/technical/byproduct.affx?product=dmet_2). Notably, this method cannot reliably detect increased copy number of *CYP2D6* (*i.e.*, UM phenotype [UM]) or the *5 deletion). The Pharmacogenomics Advisory Group of the CPMC has recommended adding a specific, copy number variation assay to the DMET Plus array, but this assay had not been implemented at the time of this study. *CYP2D6* metabolizer phenotype was estimated from genotypes using three approaches: *4 alone (rs3892097 G>A) and using multiple *star alleles with definitions according to the Pharmacogenomics Knowledgebase (PharmGKB®) (22) and to the Dutch Pharmacogenetics Working Group (DPWG) definition (23). These three approaches are described in Table I. *CYP2D6**4 was the only allele included in this analyses for reasons of logistical simplicity and because it is the most common non-functional *CYP2D6* polymorphism in individuals with European descent. Furthermore, the use of a single genetic variant (*CYP2D6**4) as a predictive biomarker could facilitate more rapid clinical implementation with lower costs compared to multi-variant arrays requiring more complex models (*e.g.*, the PharmGKB® and DPWG models) that still only partially account for *CYP2D6* metabolizer variability. Moreover, *CYP2D6**4 alone identifies the majority of PM (8). Due to its complexity, substrate specificity and current lack of a standard definition, the *CYP2D6* activity score (genotype-based *CYP2D6* phenotype estimates from analyses utilizing probe substrates such as dextromethorphan, codeine and various-depressants) (24) was not used in this analysis.

Statistical Analysis

Continuous variables were summarized by median $\pm$ interquartile range and were compared by the number of *4 alleles using the Kruskal-Wallis test. Categorical variables were summarized by counts and percentages and were compared by the number of *4 alleles using the χ^2 test or Fisher's exact test (when any expected value in the contingency tables was < 5). Hardy-Weinberg equilibrium was assessed with the χ^2 test and the Monte Carlo estimate of the exact p -value using 10,000 permutations. The association between CYP2D6 metabolizer phenotypes (estimated from CYP2D6 genotypes) and beta-blocker maintenance dose was assessed using unadjusted and adjusted ordinal logistic regression models. Linear regression was not appropriate because the maintenance dose variable was not normally distributed (visual inspection of the distribution and Q-Q plots and a failed Kolmogorov-Smirnov goodness-of-fit test). Maintenance dose (in carvedilol dose equivalents) was categorized into 4 levels for ordinal logistic regression modeling: level 1 = 6.25 mg/day ($n = 17$); level 2 = 12.5 mg/day ($n = 18$); level 3 = 20–25 mg/day ($n = 20$); and level 4 = 50 mg/day ($n = 47$). This categorization scheme met the assumption for proportional odds (score test with chi-square distribution $p > 0.05$), and the adjusted models included the following covariates: age, body mass index, gender, self-reported race, and the number of drugs with major interactions with the beta-blocker. Statistical analyses were performed using SAS version 9.3, and $p < 0.05$ was considered statistically significant.

RESULTS

The genotyping call rate for *4 (rs3892097 G>A) was 100% ($n = 102$) and within Hardy Weinberg equilibrium ($p > 0.05$ via χ^2 and exact tests). The minor allele frequencies of *4 were 0.17 and 0.10 in the patients with self-reported European ancestry ($n = 89$) and with self-reported African ancestry ($n = 10$), respectively. These were consistent with the population minor allele frequencies reported in 1000 genomes for European and African populations (0.19 and 0.06, respectively). PharmGKB[®]- and DPWG- defined CYP2D6 metabolizer phenotypes were called in 99% of patients ($n = 101$). The numbers in each CYP2D6 metabolizer phenotype group (categorized according to the three CYP2D6 metabolizer phenotype classification schemes) are presented in Figure 1, and all classification schemes defined the same 2 patients as PM, but the numbers of EM and IM patients differed among the metabolizer classification schemes. The DPWG scheme identified the highest number of patients as IM ($n = 33$), and the PharmGKB[®] definition identified the least IM ($n = 11$). Using *4 alone to classify CYP2D6 metabolizer phenotype status yielded very similar grouping as compared to utilization of the DPWG classification scheme. The numbers of IMs varied by only 5 (28 vs. 33 using *4 alone and DPWG, respectively). The median duration of the EMR time window analyzed was 5.3 years (range 2.0 – 6.3 years). Patient demographics and clinical variables were stratified by number of *4 alleles (Table II), and no significant associations were determined for those variables. Only 23 patients (23%) were prescribed beta-blocker dose(s) higher than the dose determined to be their maintenance dose (*i.e.*, the dose they were prescribed for the longest duration within the time period their EMR was examined), and in those 23 patients the mean duration of treatment at the maximum dose was 348 days compared to 923 days at the dose determined to be their maintenance dose. This relatively low percentage (23%) of patients and the

significantly shorter (3-fold) duration suggest our method for determining maintenance dose was reasonable. The schedule for beta-blocker dose titration utilized in the published clinical trials followed a doubling of the dose every 14 days as tolerated by the patient (25). In clinical practice, however, a 14-day beta-blocker titration is rarely adequate. Fortunately, the lengthy duration of EMR records examined for this study likely provided ample time for multiple dose titrations. No concomitant medications with potential to decrease beta-blocker exposure or effect were identified in any of the patient's medication profiles. The drug-drug interaction variable, therefore, reflected only drug-drug interactions known to increase beta-blocker exposure or effect. Importantly, no individual patient was prescribed more than one interacting concomitant medication during the examined time period of beta-blocker treatment.

Beta-blocker-type (carvedilol and metoprolol) interactions (beta-blocker-type*CYP2D6 metabolizer phenotype) with CYP2D6 metabolizer phenotype were statistically significant ($p = 0.003$ for specific beta-blocker*CYP2D6 phenotype interaction in covariate-adjusted model of *4 alone metabolizer definition, $p = 0.015$ in unadjusted model of *4 alone metabolizer definition, and $p < 0.05$ for PharmGKB® and DPWG metabolizer definitions as well), indicating the effect of *CYP2D6* was significantly different for metoprolol and carvedilol. This was expected given the known roles of CYP2D6 in their metabolism (inactivation of metoprolol and activation of carvedilol) and confirmed that stratification by beta-blocker type was appropriate for subsequent analyses. Patient demographics and clinical variables stratified by specific beta-blocker type are presented in Table III. All patient demographics and clinical variables (Table III) did not vary significantly between carvedilol- and metoprolol-treated groups. However, the following observations were apparent: carvedilol-treated patients reached significantly higher maintenance doses compared to those treated with metoprolol (median normalized dose of 50 mg/day vs. 12.5 mg/day), the duration of treatment at maintenance dose was longer for carvedilol-treated patients compared to those treated with metoprolol (median 3.1 vs. 1.7 years), and the percentage of patients that reached guideline-recommended target maintenance doses was higher in carvedilol-treated patients compared to those treated with metoprolol (70% vs. 12%).

The following relationships (Figure 2) were observed in analyses (co-variate adjusted) of CYP2D6 metabolizer phenotype (defined by *4 alone) and maintenance dose of carvedilol or metoprolol: CYP2D6 metabolizer phenotype was significantly associated with maintenance dose of metoprolol (OR 0.13 [95% CI 0.02 – 0.75] $p = 0.023$) (*i.e.*, metoprolol-treated patients were 7.7 times more likely to be treated with lower maintenance doses of metoprolol for each *CYP2D6**4 allele), and a trend (OR 2.94 [95% CI 0.84 – 10.30] $p = 0.093$) observed between *CYP2D6**4 and higher maintenance dose of carvedilol was observed. Importantly, no metoprolol-treated patients of CYP2D6 IM or PM status (regardless of CYP2D6 metabolizer phenotype classification scheme) reached the guideline-recommended target maintenance dose (50 mg/day). In contrast, all carvedilol-treated patients in each CYP2D6 metabolizer phenotype group (EM, IM, and PM) their recommended target dose. The results were similar for both the PharmGKB® and the DPWG definitions of CYP2D6 metabolizer phenotypes (Table IV and online supplemental Figures 1 & 2). When the PharmGKB® CYP2D6 metabolizer phenotype classification

scheme was utilized, however, no statistically significant association was detected for the metoprolol-treated patients. In adjusted models, *CYP2D6**4 was not significantly associated with duration of treatment with maintenance doses of carvedilol or metoprolol ($p = 0.171$ and $p = 0.252$, respectively).

DISCUSSION

The beta-blocker treatment strategy for patients with systolic heart failure is unique: treatment is titrated to a target dose rather than a target effect. This “one size fits all” treatment strategy (uniform target dose for all patients with systolic heart failure) is inconsistent with the goal of precision medicine (*e.g.*, “the right dose for each individual patient”) (26). In this study, *CYP2D6* metabolizer phenotype was significantly associated with the maintenance dose of metoprolol in patients with heart failure. Regardless of *CYP2D6* metabolizer phenotype classification scheme (*4 alone, PharmGKB®, or DPWG), no patients with *CYP2D6* PM or IM status reached the guideline-recommended (3) target doses of metoprolol. Acknowledging the small sample size and retrospective design of this study, the results suggest potential for a novel implementation of precision medicine: tailoring metoprolol target dose based on *CYP2D6* status. Results from this study were consistent with the known role of *CYP2D6* in the metabolism of metoprolol, suggesting that tolerated maintenance doses may be lower for *CYP2D6* PM or IM compared to EM. Studies in additional cohorts are warranted to substantiate this finding.

As expected, the associations of *CYP2D6* metabolizer phenotype with metoprolol and carvedilol maintenance doses had opposite directions. A decrease in *CYP2D6* metabolic capacity (predicted from *CYP2D6**4 genetic status) was associated with lower maintenance dose of metoprolol ($p = 0.023$), and a trend was observed between *CYP2D6**4 and higher maintenance dose of carvedilol ($p = 0.093$). The different strengths and directions of these associations are consistent with the known differences in *CYP2D6* metabolism of metoprolol and carvedilol. Metoprolol is administered as a racemic mixture of R- and S-enantiomers, both of which are primarily metabolized by *CYP2D6* to inactive metabolites (27). Carvedilol is also administered as a racemic mixture and metabolized by *CYP2D6*. However, *CYP2C9* also plays a major role in the metabolism of carvedilol (28), potentially accounting for the weaker strength of the relationship of *CYP2D6* with carvedilol compared to metoprolol. More importantly, carvedilol is metabolized to active metabolites by *CYP2D6* (including a metabolite that is 13 times more potent than the parent carvedilol) (28), and metoprolol is metabolized to inactive metabolites by *CYP2D6*, accounting for the opposite directions of the observed associations. Patients treated with metoprolol and with decreased *CYP2D6* activity would be expected to have decreased metabolism of the active, parent metoprolol to inactive metabolites, and thus they would have tolerate lower maintenance dose of metoprolol. In contrast, patients treated with carvedilol and with decreased *CYP2D6* activity would be expected to have decreased activation of the parent carvedilol and would, therefore, tolerate higher maintenance dose of carvedilol.

The previous literature supports significant effects of *CYP2D6* genetic polymorphisms on the pharmacokinetics of metoprolol (14) and carvedilol (5,15,17,29–31), but clinical significance has remained uncertain. Although several studies have found a significant

association between *CYP2D6* genetic polymorphisms and beta-blocker dose or patient response to metoprolol or carvedilol (6,10–12,32–40), an almost equal number of studies have reported null findings (9,11,13,33,41–45). Our findings regarding carvedilol dose are consistent with the reported findings of Baudhuin *et al.* (32). They determined that *CYP2D6* PM with heart failure tolerated significantly higher doses of carvedilol than *CYP2D6* EM and IM. Shihmanter *et al.*, however, did not find a significant association between carvedilol dose and *CYP2D6* polymorphisms in their retrospective chart review of patients with heart failure (46). The reasons for discordance among the study results are not clear, but differences regarding the carvedilol doses utilized may have been an important factor. The average treatment dose of carvedilol in this study and in the study reported by Baudhuin *et al.* were about 2-fold higher compared to those in the study reported by Shihmanter *et al.* (45–50 mg/day vs. 22 mg/day). This suggests the effects of *CYP2D6**4 on carvedilol dose may become apparent in only higher dose ranges. Importantly, the higher carvedilol doses in this study and the study reported by Baudhuin *et al.* are more consistent with the guideline-recommended target dose of carvedilol (50 mg/day) (3).

Our findings regarding metoprolol maintenance dose are consistent with conclusions reported in two previous studies. In the prospective, double-blind, longitudinal study reported by Rau *et al.*, metoprolol dose escalation was tolerated in only 6% of *CYP2D6* PM compared to 20% of *CYP2D6* non-PM (6). In the largest study to date of *CYP2D6* genetic polymorphisms and beta-blocker effects (n = 1,533 total with n = 513 metoprolol treated), Bijl *et al.* reported that *CYP2D6* PM were treated with significantly lower doses of metoprolol (39) and that *CYP2D6**4 was significantly associated with heart rate, bradycardia, and diastolic blood pressure in patients treated with metoprolol (39). In contrast to our findings and those reported by Rau *et al.* and Bijl *et al.*, Batty *et al.* did not find a significant association between *CYP2D6**4 and metoprolol dose in their pharmacogenetic sub-study of the MERIT-HF trial (11). As the only study reported on the association of *CYP2D6**4 and clinical outcomes, the study reported by Batty *et al.* did not find significant differences among *CYP2D6**4 genotypes in all-cause mortality or rate of hospitalization (11). The lack of association between *CYP2D6**4 and clinical outcomes reported by Batty *et al.* may have been secondary to an inherent decrease in statistical power (decreased sample size and increased number of comparison groups) characteristic of retrospective genetic sub-study analyses. Less than 10% of the patients from the overall MERIT-HF trial were included in the pharmacogenetic sub-study (n= 313 in the pharmacogenetic sub-study vs. n = 3,991 in the overall trial). Moreover, the randomized clinical trial design does not reflect beta-blocker treatment in routine clinical practice. Approximately 85% of heart failure patients achieved the target doses of beta-blockers in randomized clinical trials (3), but only approximately 50% do in clinical practice (4).

When baseline and clinical variables were stratified by beta-blocker type, carvedilol-treated patients reached significantly higher maintenance doses compared to those treated with metoprolol, the duration of treatment at maintenance dose was longer for carvedilol-treated patients compared to those treated with metoprolol, and the percentage of patients that reached guideline-recommended target maintenance doses were higher in carvedilol-treated patients compared to those treated with metoprolol. Our findings are consistent with a previous study by Pasternak *et al.* (21), in which a higher proportion of carvedilol-treated

heart failure patients reached guideline-recommended target doses than metoprolol-treated patients (52% vs. 12%, respectively) and the duration of treatment with carvedilol was longer than with metoprolol (2.3 years vs. 1.8 years). We speculate that these differences in dose titration and treatment duration may likely have been secondary to differences in the tolerability of carvedilol and metoprolol, potentially related to the larger role of CYP2D6 in the metabolism of metoprolol compared to carvedilol. This study had several strengths and limitations. The small sample size and limited recruitment pool (single academic medical center) as well as the nearly homogenous demographic background (90% of participants with European ancestry) limit the generalizability of our findings. Although focusing on *CYP2D6**4 alone in this study provided several logistic advantages (described in Genotyping & Phenotyping section of Materials and Methods), this was a limitation of the study. Our comparison of three different approaches for defining CYP2D6 metabolizer phenotypes from *CYP2D6**4 genotype was a unique strength of this study, but the *CYP2D6* genotyping platform used in this study was not able to identify gene duplications, the *5 gene deletion, or other functional *CYP2D6* polymorphisms. An additional weakness was that *CYP2C9* genetic status was not accounted for in the analyses of carvedilol-treated patients.

The low number (n = 2) of patients categorized as CYP2D6 PM was another limitation. A strength of this study, however, was the long duration (median 5.3 years of EMR available). The retrospective chart review design was an additional strength because it provided a snapshot in time of real-world patients in routine clinical practice; however, the retrospective chart review design also resulted in additional limitations (*e.g.*, incomplete documentation in EMR, unknown patient compliance, multiple individuals contributing to EMR). As no quantifiable inclusion criteria for heart failure patients were readily available for this study, ICD-9 codes in the EMR along with the clinical expertise of cardiology physician specialists were used to determine eligibility for inclusion in the study. The lack of quantifiable criteria for heart failure represents a weakness of this study. In addition, utilizing EMR data to assess maintenance dose, the primary endpoint, has limitations. Specifically, the EMR shows prescription data and not whether the patients filled the prescription or were adherent to the prescription. Lacking assessment of titration status is another limitation to utilizing the EMR in determining the maintenance dose achieved. Based on our clinical experience and the clinical guidelines (3), beta-blockers are initiated at the lowest dose and then titrated up (as tolerated by patient) to the guideline-recommended target dose. Common dose-limiting side effects include bradycardia, hypotension, or fatigue. Symptoms that would have presumably been related to beta-blocker titration, however, were not available in the EMR. In future studies, a prospective design would allow such data to be collected, providing increased confidence regarding the determination of patient's titration status. Another major limitation of this study was the unavailability of blood samples for measuring concentration levels of carvedilol and metoprolol. Those measurements would have provided an opportunity to validate the assumption that dose requirements were affected by differences in CYP2D6 metabolism. None the less, results of this study demonstrate that associations with *CYP2D6* genotype depend upon the CYP2D6 phenotyping approach (*i.e.*, the association for metoprolol was statistically significant when using the DPWG and *4 alone classification but not when using the PharmGKB® classification) and that *CYP2D6**4 is associated with

tolerated maintenance doses of metoprolol and carvedilol in patients with systolic heart failure.

CONCLUSIONS

The “one size fits all” treatment strategy provided in the current recommendation guidelines for beta-blocker therapy in heart failure patients (the same target dose for all patients) is inconsistent with the tenets of precision medicine. The literature as a whole strongly supports that *CYP2D6* genetic polymorphisms effect the pharmacokinetics of metoprolol and carvedilol, but a consensus has not yet been reached regarding whether those pharmacokinetic effects translate into clinically meaningful differences in clinical outcomes or whether *CYP2D6* may have significant potential as a predictive biomarker for determining a patient’s target beta-blocker maintenance dose. While acknowledging the small sample size and retrospective design, results from this study were consistent with the known role of CYP2D6 in the metabolism of metoprolol and the activation of carvedilol. Although many argue whether prospective, randomized clinical trial validation for every new personalized dosing strategy, especially for drugs already on the market, is feasible or warranted (48–50), results from this study suggest *CYP2D6* may have predictive value regarding tolerable maintenance doses of metoprolol or carvedilol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CLIA	Clinical Laboratory Improvement Amendments
CPMC	Coriell Personalized Medicine Collaborative
CYP2D6	cytochrome P450 family 2 subfamily D member 6
CYP2D6	gene for cytochrome P450 family 2 subfamily D member 6
DPWG	Dutch Pharmacogenetics Working Group
EM	extensive metabolizer
EMR	electronic medical record

IM	intermediate metabolizer
OSU	Ohio State University
PharmGKB	Pharmacogenomics Knowledgebase
PM	poor metabolizer
UM	ultra-rapid metabolizer

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Writing Group Members. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016 Jan 26; 133(4):e38–60. [PubMed: 26673558]
2. U.S. Department of Health and Human Services Organ Procurement and Transplantation Network. National Data. 2016. Available at: <https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/>
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, et al. WRITING COMMITTEE MEMBERS. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013 Oct 15; 128(16):e240–327. [PubMed: 23741058]
4. Porapakkham P, Porapakkham P, Krum H. Is Target Dose of Beta-Blocker More Important Than Achieved Heart Rate or Heart Rate Change in Patients with Systolic Chronic Heart Failure? *Cardiovascular Therapeutics*. 2010; 28(2):93–100. [PubMed: 20398098]
5. Zhou HH, Wood AJ. Stereoselective disposition of carvedilol is determined by CYP2D6. *Clin Pharmacol Ther*. 1995 May; 57(5):518–524. [PubMed: 7768074]
6. Rau T, Wuttke H, Michels LM, Werner U, Bergmann K, Kreft M, et al. Impact of the CYP2D6 genotype on the clinical effects of metoprolol: a prospective longitudinal study. *Clin Pharmacol Ther*. 2009 Mar; 85(3):269–272. [PubMed: 19037197]
7. Horikiri Y, Suzuki T, Mizobe M. Pharmacokinetics and metabolism of bisoprolol enantiomers in humans. *J Pharm Sci*. 1998 Mar; 87(3):289–294. [PubMed: 9523980]
8. Sistonen J, Sajantila A, Lao O, Corander J, Barbujani G, Fuselli S. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. *Pharmacogenet Genomics*. 2007 Feb; 17(2):93–101. [PubMed: 17301689]
9. Sharp CF, Gardiner SJ, Jensen BP, Roberts RL, Troughton RW, Lainchbury JG, et al. CYP2D6 genotype and its relationship with metoprolol dose, concentrations and effect in patients with systolic heart failure. *Pharmacogenomics J*. 2009 Jun; 9(3):175–184. [PubMed: 19365402]
10. Lewis RV, Ramsay LE, Jackson PR, Yeo WW, Lennard MS, Tucker GT. Influence of debrisoquine oxidation phenotype on exercise tolerance and subjective fatigue after metoprolol and atenolol in healthy subjects. *Br J Clin Pharmacol*. 1991 Apr; 31(4):391–398. [PubMed: 2049246]
11. Batty JA, Hall AS, White HL, Wikstrand J, de Boer RA, van Veldhuisen DJ, et al. An investigation of CYP2D6 genotype and response to metoprolol CR/XL during dose titration in patients with heart failure: a MERIT-HF substudy. *Clin Pharmacol Ther*. 2014 Mar; 95(3):321–330. [PubMed: 24193112]
12. Hamadeh IS, Langaee TY, Dwivedi R, Garcia S, Burkley BM, Skaar TC, et al. Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate. *Clin Pharmacol Ther*. 2014 Aug; 96(2):175–181. [PubMed: 24637943]
13. Wu D, Li G, Deng M, Song W, Huang X, Guo X, et al. Associations between ADRB1 and CYP2D6 gene polymorphisms and the response to beta-blocker therapy in hypertension. *J Int Med Res*. 2015 Jun; 43(3):424–434. [PubMed: 25823457]
14. Blake CM, Kharasch ED, Schwab M, Nagele P. A meta-analysis of CYP2D6 metabolizer phenotype and metoprolol pharmacokinetics. *Clin Pharmacol Ther*. 2013 Sep; 94(3):394–399. [PubMed: 23665868]

15. Honda M, Nozawa T, Igarashi N, Inoue H, Arakawa R, Ogura Y, et al. Effect of CYP2D6*10 on the pharmacokinetics of R- and S-carvedilol in healthy Japanese volunteers. *Biol Pharm Bull.* 2005 Aug; 28(8):1476–1479. [PubMed: 16079496]
16. Takekuma Y, Takenaka T, Kiyokawa M, Yamazaki K, Okamoto H, Kitabatake A, et al. Evaluation of effects of polymorphism for metabolic enzymes on pharmacokinetics of carvedilol by population pharmacokinetic analysis. *Biol Pharm Bull.* 2007 Mar; 30(3):537–542. [PubMed: 17329852]
17. Giessmann T, Modess C, Hecker U, Zschiesche M, Dazert P, Kunert-Keil C, et al. CYP2D6 genotype and induction of intestinal drug transporters by rifampin predict presystemic clearance of carvedilol in healthy subjects. *Clin Pharmacol Ther.* 2004 Mar; 75(3):213–222. [PubMed: 15001973]
18. Lambert C, Halpert JR, Rouleau J, Jutras L, Leroyer V, du Souich P. Effect of congestive heart failure on the intrinsic metabolic capacity of the liver in the dog. *Drug Metab Dispos.* 1991 Sep-Oct; 19(5):985–989. [PubMed: 1686247]
19. Ogawa R, Stachnik JM, Echizen H. Clinical pharmacokinetics of drugs in patients with heart failure: an update (part 2, drugs administered orally). *Clin Pharmacokinet.* 2014 Dec; 53(12): 1083–1114. [PubMed: 25248847]
20. Sweet K, Gordon ES, Sturm AC, Schmidlen TJ, Manickam K, Toland AE, et al. Design and implementation of a randomized controlled trial of genomic counseling for patients with chronic disease. *J Pers Med.* 2014 Jan 8; 4(1):1–19. [PubMed: 24926413]
21. Pasternak B, Svanstrom H, Melbye M, Hviid A. Association of treatment with carvedilol vs metoprolol succinate and mortality in patients with heart failure. *JAMA Intern Med.* 2014 Oct; 174(10):1597–1604. [PubMed: 25173681]
22. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther.* 2012 Oct; 92(4): 414–417. [PubMed: 22992668]
23. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther.* 2011 May; 89(5):662–673. [PubMed: 21412232]
24. Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther.* 2014 Apr; 95(4):376–382. [PubMed: 24458010]
25. MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999 Jun 12; 353(9169):2001–2007. [PubMed: 10376614]
26. Peck RW. The right dose for every patient: a key step for precision medicine. *Nat Rev Drug Discov.* 2016 Mar; 15(3):145–146. [PubMed: 26669674]
27. U.S. Food and Drug Administration. Metoprolol prescribing information. 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019962s0441bl.pdf
28. U.S. Food and Drug Administration. Carvedilol prescribing information, 2015. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020297s0371bl.pdf
29. Takekuma Y, Takenaka T, Kiyokawa M, Yamazaki K, Okamoto H, Kitabatake A, et al. Evaluation of effects of polymorphism for metabolic enzymes on pharmacokinetics of carvedilol by population pharmacokinetic analysis. *Biol Pharm Bull.* 2007 Mar; 30(3):537–542. [PubMed: 17329852]
30. Seht D, Meineke I, Tzvetkov M, Gultepe S, Brockmoller J. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. *Pharmacogenomics.* 2011 May 23.
31. Saito M, Kawana J, Ohno T, Hanada K, Kaneko M, Mihara K, et al. Population pharmacokinetics of R- and S-carvedilol in Japanese patients with chronic heart failure. *Biol Pharm Bull.* 2010; 33(8):1378–1384. [PubMed: 20686235]
32. Baudhuin LM, Miller WL, Train L, Bryant S, Hartman KA, Phelps M, et al. Relation of ADRB1, CYP2D6, and UGT1A1 polymorphisms with dose of, and response to, carvedilol or metoprolol

- therapy in patients with chronic heart failure. *Am J Cardiol*. 2010 Aug 1; 106(3):402–408. [PubMed: 20643254]
33. Nozawa T, Taguchi M, Tahara K, Hashimoto Y, Igarashi N, Nonomura M, et al. Influence of CYP2D6 genotype on metoprolol plasma concentration and beta-adrenergic inhibition during long-term treatment: a comparison with bisoprolol. *J Cardiovasc Pharmacol*. 2005 Nov; 46(5): 713–720. [PubMed: 16220080]
34. Wuttke H, Rau T, Heide R, Bergmann K, Bohm M, Weil J, et al. Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther*. 2002 Oct; 72(4):429–437. [PubMed: 12386645]
35. Lennard MS, Silas JH, Freestone S, Ramsay LE, Tucker GT, Woods HF. Oxidation phenotype--a major determinant of metoprolol metabolism and response. *N Engl J Med*. 1982 Dec 16; 307(25): 1558–1560. [PubMed: 7144837]
36. McGourty JC, Silas JH, Lennard MS, Tucker GT, Woods HF. Metoprolol metabolism and debrisoquine oxidation polymorphism--population and family studies. *Br J Clin Pharmacol*. 1985 Dec; 20(6):555–566. [PubMed: 2868742]
37. Kirchheiner J, Heesch C, Bauer S, Meisel C, Seringer A, Goldammer M, et al. Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther*. 2004 Oct; 76(4):302–312. [PubMed: 15470329]
38. Koytchev R, Alken RG, Vlahov V, Kirkov V, Kaneva R, Thyroff-Friesinger U, et al. Influence of the cytochrome P4502D6*4 allele on the pharmacokinetics of controlled-release metoprolol. *Eur J Clin Pharmacol*. 1998 Aug; 54(6):469–474. [PubMed: 9776437]
39. Bijl MJ, Visser LE, van Schaik RH, Kors JA, Witteman JC, Hofman A, et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. *Clin Pharmacol Ther*. 2009 Jan; 85(1):45–50. [PubMed: 18784654]
40. Goryachkina K, Burbello A, Boldueva S, Babak S, Bergman U, Bertilsson L. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. *Eur J Clin Pharmacol*. 2008 Dec; 64(12):1163–1173. [PubMed: 18648788]
41. Rau T, Heide R, Bergmann K, Wuttke H, Werner U, Feifel N, et al. Effect of the CYP2D6 genotype on metoprolol metabolism persists during long-term treatment. *Pharmacogenetics*. 2002 Aug; 12(6):465–472. [PubMed: 12172215]
42. Fux R, Morike K, Prohmer 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 Oct; 78(4):378–387. [PubMed: 16198657]
43. Zineh I, Beitelshes AL, Gaedigk A, Walker JR, Pauly DF, Eberst K, et al. Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther*. 2004 Dec; 76(6):536–544. [PubMed: 15592325]
44. Clark DW, Morgan AK, Waal-Manning H. Adverse effects from metoprolol are not generally associated with oxidation status. *Br J Clin Pharmacol*. 1984 Dec; 18(6):965–967. [PubMed: 6335664]
45. 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 Mar; 77(3):127–137. [PubMed: 15735607]
46. Shihmanter R, Nulman I, Goland S, Caspi A, Bar-Haim A, Harary I, et al. Variation in the CYP2D6 genotype is not associated with carvedilol dose changes in patients with heart failure. *J Clin Pharm Ther*. 2014 Aug; 39(4):432–438. [PubMed: 24673480]
47. Sachse C, Brockmoller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet*. 1997 Feb; 60(2): 284–295. [PubMed: 9012401]
48. Luzum JA, Lanfear DE. Pharmacogenetic Risk Scores for Perindopril Clinical and Cost Effectiveness in Stable Coronary Artery Disease: When Are We Ready to Implement? *J Am Heart Assoc*. 2016 Mar 28; 4(3):e003440.
49. Gillis NK, Innocenti F. Evidence required to demonstrate clinical utility of pharmacogenetic testing: the debate continues. *Clin Pharmacol Ther*. 2014 Dec; 96(6):655–657. [PubMed: 25399714]

50. Ratain MJ, Johnson JA. Meaningful use of pharmacogenetics. Clin Pharmacol Ther. 2014 Dec; 96(6):650–652. [PubMed: 25399712]

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Figure 1.

Numbers of CYP2D6 metabolizer phenotypes identified according to the following three definitions (detailed definitions in Table I): *4 (rs3892097 G>A) alone, and using multiple *star alleles with the Pharmacogenomics Knowledgebase (PharmGKB®) definition (22) and the Dutch Pharmacogenetics Working Group (DPWG) definition (23). EM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer.

Figure 2.

Associations of CYP2D6 metabolizer phenotype (defined by *4 [rs3892097 G>A] alone) with maintenance doses and the achievement of guideline-recommended target doses for carvedilol (left) and metoprolol (right) in $n = 98$ patients with systolic heart failure. Each circle represents an individual patient. Open circles are patients that were still alive at follow-up, and red circles are patients that were deceased at follow-up. Bolded p-values are statistically significant ($p < 0.05$). Gray area in plot indicates the range of guideline-recommended target doses (≥ 50 mg). An "X" indicates the mean maintenance dose. EM = extensive metabolizer (zero *4 alleles); IM = intermediate metabolizer (one *4 allele); OR = odds ratio; PM = poor metabolizer (two *4 alleles)

Table 1

Three approaches used to define CYP2D6 metabolizer phenotypes.

Allele definitions			
Functional	*1, *2		
Decreased function	*9, *10, *17, *18, *29, *41		
Non-functional	*3, *4, *6, *7, *8, *11, *12, *14, *15, *19, *20, *21, *38, *40, *42		
Phenotype definitions			
	EM	IM	PM
*4 alone (rs3892097 G>A)	zero *4 alleles	one *4 allele	two *4 alleles
PharmGKB®	2 functional alleles 1 functional + 1 decreased function allele 1 functional + 1 non-functional allele	2 decreased function alleles 1 decreased function + 1 non-functional allele	2 non-functional alleles
DPWG	2 functional alleles 1 functional + 1 decreased function allele	2 decreased function alleles 1 decreased function + 1 non-functional allele 1 functional + 1 non-functional allele	2 non-functional alleles

DPWG = Dutch Pharmacogenetics Working Group; EM = extensive metabolizer; IM = intermediate metabolizer; PharmGKB® = The Pharmacogenomics Knowledgebase; PM = poor metabolizer
Bolded entries highlight the difference between the PharmGKB® and DPWG definitions.

Table II

Patient demographics and clinical variables overall and stratified by the number of *CYP2D6**4 alleles.

	Overall (n = 102)	Number of <i>CYP2D6</i> *4 alleles			p-value
		0 (n = 72; 71%)	1 (n = 28; 27%)	2 (n = 2; 2%)	
Age (years)	63 ± 17	63 ± 18	63 ± 16	74 ± 12	0.278
Females	40 (40%)	29 (40%)	11 (39%)	0 (0%)	0.757
African-Americans	10 (10%)	8 (11%)	2 (7%)	0 (0%)	0.921
Body mass index (kg/m ²)	30 ± 9	30 ± 8	30 ± 10	26 ± 3	0.548
Systolic blood pressure (mmHg)	113 ± 15	112 ± 16	114 ± 17	121 ± 13	0.552
Diastolic blood pressure (mmHg)	68 ± 9	67 ± 11	74 ± 8	74 ± 8	0.516
Heart rate (beats per minute)	76 ± 11	76 ± 11	72 ± 9	72 ± 9	0.704
Carvedilol	62 (61%)	43 (60%)	18 (64%)	1 (50%)	0.894
Carvedilol controlled-release	3 (3%)	2 (3%)	1 (4%)	0 (0%)	
Metoprolol succinate	32 (31%)	22 (31%)	9 (32%)	1 (50%)	
Metoprolol tartrate	1 (1%)	1 (1%)	0 (0%)	0 (0%)	
No beta-blocker treatment	4 (4%)	4 (6%)	0 (0%)	0 (0%)	1.000
Deaths	8 (8%)	6 (8%)	2 (7%)	0 (0%)	
* Normalized beta-blocker maintenance dose per day (mg)	25 ± 37.5	25 ± 37.5	37.5 ± 37.5	28.1 ± 43.8	0.925
Duration of treatment with beta-blocker maintenance dose (years)	2.6 ± 3.1	2.4 ± 3.2	2.6 ± 3.3	4.1 ± 3.3	0.444
Years of medical records available	5.3 ± 1.3	5.3 ± 1.4	5.3 ± 1.0	5.5 ± 0.4	0.641
Number of patients with beta-blocker dose at guideline-recommended target dose	48 (48%)	33 (47%)	14 (50%)	1 (50%)	0.912
Number of patients taking a drug that interacts with their maintenance beta-blocker	28 (27%)	20 (28%)	8 (29%)	0 (0%)	1.000

* metoprolol ÷ 4 = carvedilol

Continuous variables were summarized by the median ± interquartile range and compared by the number of *4 alleles using the Kruskal-Wallis test. Categorical variables were summarized by counts and percentages and compared by the number of *4 alleles using the χ^2 test (or Fisher's exact where necessary).

Table III
Patient demographics and clinical variables overall and stratified by specific beta-blocker treatment.

	Overall (n = 102)	Carvedilol (n = 65; 64%)	Metoprolol (n = 33; 32%)	** No Beta-Blocker (n = 4; 4%)	p- value
Age (years)	63 ± 17	63 ± 18	63 ± 17	56 ± 27	0.893
Females	40 (40%)	26 (40%)	12 (36%)	2 (50%)	0.879
African-Americans	10 (10%)	7 (11%)	3 (9%)	0 (0%)	0.180
Body mass index (kg/m ²)	30 ± 9	30 ± 10	30 ± 6	30 ± 7	0.644
Systolic blood pressure (mmHg)	113 ± 15	114 ± 14	112 ± 21	112 ± 12	0.931
Diastolic blood pressure (mmHg)	68 ± 9	67 ± 8	69 ± 10	66 ± 4	0.686
Heart rate (beats per minute)	76 ± 11	76 ± 10	76 ± 12	78 ± 5	0.758
Deaths	8 (8%)	7 (11%)	1 (3%)	0 (0%)	0.471
<i>CYP2D6</i> *4 frequency	0.16	0.16	0.17	0.00	0.595
PharmGKB® EM/IM/PM	88/11/2 (87%/11%/2%)	56/7/1 (88%/11%/2%)	28/4/1 (85%/12%/3%)	4/0/0 (100%/0%/0%)	1.000
DPWG EM/IM/PM	66/33/2 (65%/33%/2%)	41/22/1 (64%/34%/2%)	21/11/1 (64%/33%/3%)	4/0/0 (100%/0%/0%)	0.598
* Normalized beta-blocker maintenance dose per day (mg)	25 ± 37.5	50 ± 25	12.5 ± 18.75	0 ± 0	<.001
Duration of treatment with beta-blocker maintenance dose (years)	2.6 ± 3.1	3.1 ± 2.9	1.7 ± 1.4	0 ± 0	<.001
Years of medical records available	5.3 ± 1.3	5.5 ± 1.1	5.0 ± 1.3	5.3 ± 1.2	0.043
Number of patients with beta-blocker dose at guideline-recommended target dose	48 (48%)	44 (70%)	4 (12%)	0 (0%)	<.001
Number of patients taking a drug that interacts with their maintenance beta-blocker	28 (27%)	13 (21%)	13 (39%)	0 (0%)	0.101

* metoprolol ÷ 4 = carvedilol

** Only patients treated with beta-blockers were included in the pharmacogenetic analyses

CYP2D6 = gene for cytochrome P450 family 2 subfamily D member 6; DPWG = Dutch Pharmacogenetics Working Group; EM = extensive metabolizer; IM = intermediate metabolizer; PharmGKB® = The Pharmacogenomics Knowledgebase; PM = poor metabolizer

Bolded entries indicate p < 0.05. Continuous variables were summarized by the median ± interquartile range and compared by the number of *4 alleles using the Kruskal-Wallis test. Categorical variables were summarized by counts and percentages and compared by the number of *4 alleles using the χ^2 test (or Fisher's exact where necessary).

Table IV

Summary of associations of CYP2D6 metabolizer phenotype (defined by *4 (rs3892097 G>A) alone, the PharmGKB[®], and the DPWG) with maintenance doses of carvedilol and metoprolol in patients with systolic heart failure.

carvedilol (n = 65)				
CYP2D6 metabolizer phenotype definition	Model	OR	95% CI	p-value
*4 alone	adjusted	2.9	0.84–10	0.09
*4 alone	unadjusted	1.8	0.60–5.5	0.3
PharmGKB [®]	adjusted	3.4	0.46–25	0.2
PharmGKB [®]	unadjusted	3.6	0.49–26	0.2
DPWG	adjusted	2.9	0.83–10	0.09
DPWG	unadjusted	1.5	0.53–4.1	0.5
metoprolol (n = 33)				
CYP2D6 metabolizer phenotype definition	Model	OR	95% CI	p-value
*4 alone	adjusted	0.13	0.02–0.75	0.023
*4 alone	unadjusted	0.18	0.04–0.75	0.019
PharmGKB [®]	adjusted	0.19	0.02–1.58	0.12
PharmGKB [®]	unadjusted	0.37	0.08–1.73	0.207
DPWG	adjusted	0.14	0.03–0.66	0.014
DPWG	unadjusted	0.27	0.08–0.96	0.044

Adjusted models included the following covariates: age, gender, body mass index, self-reported race, and drug interactions. Bolded values indicate statistical significance ($p < 0.05$).