Title: A Physiologic approach to the pharmacogenomics of hypertension

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Introduction

Essential hypertension affects over 40 million Americans and is associated with significant morbidity and mortality. Blood pressure (BP) response to specific antihypertensive agents is highly variable with the mean BP response typically similar to the standard deviation of the response measured. Although physiologic pathways are known that regulate BP and BP response to specific classes of antihypertensive agents, the management of patients with essential hypertension has suffered from a "hit or miss" approach and BP control rates remain low, at approximately 40% in the general population. Demographic characteristics including age, gender, and ethnicity are informative regarding the selection of class of antihypertensive agent; however, other variables (including genotype) that predict BP response are lacking. In part, measures of relative activation of the renin-angiotensin-aldosterone system (RAAS) including plasma renin activity, plasma renin activity/aldosterone ratios, and plasma renin activity indexed for sodium intake have helped to guide selection choice of antihypertensive agent (typically diuretic vs. no diuretic), but significant variation in response to antihypertensive agents exists, even when these characteristics are included when using a specific class of antihypertensive agent.

Hypertension is a multifactorial disease with convergent and divergent physiologic-regulating systems contributing to its presence, severity, and pathways involved in pharmacologically mediated reduction in BP levels. Counter-regulatory systems play a significant role in the development of hypertension as well as response to therapy and establishing genetic predictors of antihypertensive response have been less than ideal. While candidate gene approaches and genome wide association studies are beginning to demonstrate validated genetic predictors of BP response to antihypertensive therapy, it is most likely that yet to be identified significant genetic predictors exist in the form of rare (<1% allele frequency) variants, copy number variation, intronic flanking polymorphisms, RNA variation, and finally that there is a high likelihood that BP response to a given antihypertensive agent is due to polygenic causes. In this review, we have

elected to review in a physiologically guided manner, the pharmacogenomics of hypertension and provide a review of available and published studies, including their findings reproducibility and their limitations (Table 1).

Metabolism polymorphisms

Polymorphisms in genes encoding the enzymes responsible for phase I and phase II biotransformation contribute to inter-individual differences in antihypertensive drug pharmacokinetics. The cytochrome P450 enzymes are part of a microsomal metabolism system in the smooth endoplasmic reticulum that residespredominantly in hepatocytes and in other cells. These enzymes catalyze phase I non-synthetic metabolism of xenobiotics through oxidation, reduction, and hydrolysis. In contrast, phase II synthetic biotransformation enzymes catalyze the conjugation of drugs through glucuronidation, acetylation, sulfation, and methylation. The phase I and phase II metabolism of antihypertensive drugs often lead to their activation or deactivation.

Functional polymorphisms may modify either expression or function of metabolic enzymes that will ultimately influence the parent drug and metabolite concentrations. These concentration changes manifest as alterations in the pharmacogenetic response (BP response to a drug) and in pharmacokinetic parameters such as drug clearance, area under the curve (AUC), or maximum concentration (C_{max}). During drug development, the United States Food and Drug Administration (FDA) provides regulatory guidance to pharmaceutical companies regarding both *in vitro* and *in vivo* drug metabolism and drug interaction studies. As a result, a drug's metabolic enzymes are often known and have received great attention in candidate gene analyses in order to explore relevant genotype-drug interactions.

Metoprolol is predominantly metabolized by CYP2D6. At least 74 variant alleles of CYP2D6 have been described, including non-functional and loss of or reduced function alleles[1]. Individuals who are homozygous for the non-functional alleles are defined as poor metabolizers with a resultant extended half-life of metoprolol. Intermediate metabolizers are heterozygous for non-functional alleles or homozygous for reduced function alleles, while extensive (normal) metabolizers are homozygous or heterozygous for reference functional alleles. The functional

allele frequency for Caucasians is 71%, and for those of African and Asian ancestry is closer to 50%[2]. The FDA label of metoprolol succinate cautions that the CYP2D6 enzyme is absent (poor metabolizer status) in about 8% of Caucasians and about 2% of most other populations. Gene duplication is also not uncommon for CYP2D6, with 12 or more copies previously reported[3]. Individuals with increased CYP2D6 copy number are considered ultra-rapid metabolizers.

Variant alleles in poor and intermediate metabolizers of CYP2D6 have been associated with increased plasma metoprolol levels even after extended year-long dosing. Poor metabolizers also have corresponding changes in their ratio of metoprolol to alpha-hydroxy-metoprolol metabolite[4]. Some small studies have failed to reveal significant adverse events or BP effects associated with metabolizer status, despite changes in pharmacokinetic parameters[5]. However, a prospective, double-blind, longitudinal study of metoprolol use found significant differences in diastolic BP (DBP), QT interval, heart rate, and incidence of bradycardia[6,7]. As such, the Dutch pharmacogenomics working group (DPWG) has endorsed CYP2D6 screening with the use of metoprolol[8]. The group recommends selection of an alternate drug or a 75% dose reduction in poor metabolizers, 50% dose reduction in intermediate metabolizers, and titration up to a maximum of 250% of the normal dose in ultra-rapid metabolizers.

The role of CYP2D6 has been explored with other beta-blockers, including carvedilol. Genotype appears to affect carvedilol clearance and concentration[9,10]. Analogously, genotype is a predictor of drug dose in retrospective analyses[11]. However, alterations in clinical phenotype or therapy response have not been observed[10,11]. Variant alleles in UGT1A1 have also been shown to alter clearance and glucuronidation of carvedilol, without affecting clinical phenotype[12].

Other cytochrome P450 enzymes similarly alter antihypertensive medication metabolism. Losartan is a prodrug metabolized into its active carboxylic acid metabolite by CYP2C9 and CYP3A4. The metabolite is predominantly responsible for the angiotensin II receptor antagonism

of losartan. Losartan's FDA label cautions that in approximately 1% of individuals, minimal conversion of losartan to the active metabolite occurs. *In vitro* studies have suggested CYP2C9 contributes to losartan metabolism to a greater extent than CYP3A4[13]. Candidate pharmacogenomic analyses have illustrated that the CYP2C9*3 reduced function allele is associated with decreased formation of losartan's active metabolite[14,15]. Limited clinical data is available to confirm pharmacodynamic effects. However, associations have been uncovered between the *3 allele and less favorable BP and proteinuria reduction in Caucasians with chronic kidney disease (CKD)[16]. In the Losartan Intervention for Endpoint reduction in Hypertension study, homozygotes with the *2 allele had decreased losartan response; however, this association did not remain significant after adjusting for multiple-testing[17].

Data regarding amlodipine and verapamil is less convincing. These calcium channel blockers are known to be metabolized by CYP3A4 and CYP3A5 through drug interaction data. In a small Korean population, amlodipine concentrations (AUC and C_{max}) were reduced in individuals with a CYP3A5*1/*1 genotype[18]. This data is the opposite of that expected and conflicts with *in vitro* data suggesting amlodipine is primarily metabolized by CYP3A4[19]. CYP3A5 genotypes have not been found to be associated with amlodipine efficacy[18,20]. Similarly, the CYP3A5*3 and *6 alleles were not significantly associated with verapamil response[21]. In contrast, the SNPs rs2740574 and rs2246709 affecting CYP3A4 metabolism were associated with target BP goals in the African-American Study of Kidney Disease and Hypertension Trial[20]. More studies are required to understand the clinical relevance of cytochrome P450 pharmacogenetics in calcium channel blocker metabolism.

Hydralazine undergoes phase II biotransformation by N-acetyltransferase 2. A slow acetylation phenotype is found in 90% of North Africans, 50% of Caucasians, and up to 30% of Asians[22]. The slow phenotype is associated with the NAT2*5, *6, and *7 alleles. The FDA label of hydralazine warns that plasma levels of hydralazine vary widely among individuals. Patients with

*5, *6, and *7 alleles will display higher plasma levels of hydralazine and the drug provides more efficacious BP control in individuals with these slow acetylator genotypes[23]. Currently, it is unclear whether slow acetylator genotypes also predict the development of adverse effects, such as hydralazine-associated systemic lupus erythematosus[24].

Candidate pharmacodynamic polymorphisms of the renin-angiotensin system

In contrast to metabolic variants that affect drug concentration and kinetics, genetic variation in receptors and intracellular targets of antihypertensive pathways mediate pharmacodynamic effects of drugs. These variants alter a compound's effect on a biologic system at a given drug concentration. Candidate variants affecting the signaling of the RAAS have been investigated in detail. However, none of these variants has been endorsed by the Clinical Pharmacogenomics Implementation Consortium (CPIC) or DPWG as ready for broad clinical implementation.

Polymorphisms of the RAAS remain attractive candidates for the study of pharmacogenomics and hypertensive drug response because of their physiologic plausibility. Variants associated with angiotensin-converting enzyme 1 and 2 (ACE1, ACE2), angiotensinogen (AGT), angiotensin II type 1 and 2 receptors (AT1, AT2), and renin (REN) have all been explored to varying extents. The most studied of these variants is rs1799752, an insertion and deletion genetic variant in intron 16 of the *ACE* gene (ACE I/D), with an insertion variant allele frequency of about 40–50%. The insertion variant has been associated with lower serum ACE levels, accounting for 47% of ACE level variance among individuals[25]. As a result, rs1799752 has been evaluated extensively as a predictor of ACE-inhibitor (ACEI) or angiotensin II receptor blocker (ARB) efficacy. Initial candidate studies showed increased ACEI and ARB response in individuals with the II genotype compared with the DD genotype[26-32]. These studies were marked by small sample sizes, significant inter-study heterogeneity, and disparate endpoints as markers of response. These

endpoints have ranged from improvement in measured hemodynamics to reduction in proteinuria to BP response. However, significant conflicting data have since been reported that reveal no association between rs1799752 and ACEI or ARB BP response[17,33-39]. Although evidence does not support the use of rs1799752 as a predictor of ACEI or ARB response, a few studies suggest this SNP may remain a predictor of diuretic response[40-42]. Additional investigation is required to confirm these results.

For variants in *AGT*, *AT1*, and *AT2*, most well-powered studies have failed to show consistent interactions between genotype and antihypertensive response[17,34,35]. In contrast, polymorphisms of *REN* have shown promise in Asian populations. The Renin C-5312T polymorphism was found to be a predictor of valsartan response. While C allele homozygotes do not have altered baseline plasma renin activity, the CC genotype is associated with both improved DBP response to valsartan and lower renal gene expression of *REN*[34,43]. After 5 months of valsartan therapy, a second study revealed reflexive rises in serum renin levels were higher in patients with the CT/TT genotypes[44]. This study also replicated the greater DBP response in C allele homozygotes in the small but independent cohort. An additional variant of *REN*, rs11240688, was associated with HCTZ-induced BP reduction[45]. It remains to be understood whether these results can be extrapolated to populations without Asian ancestry.

Candidate pharmacodynamic polymorphisms of adrenergic response

Beta-adrenergic receptor blockade endures as a mainstay in the treatment of hypertension, congestive heart failure, and cardiac arrhythmia. Adrenoceptor β1 and β2 stimulation increases intracellular cyclic adenosine monophosphate (cAMP) production, augmenting cardiomyocyte contractility and chronotropy. Adrenoceptor β3 stimulation mitigates these effects. These adrenoceptors are G-protein-coupled receptors that initiate intracellular signaling cascades. G-

protein-coupled receptor Kinase 4 (GRK4) mediates phosphorylation of the adrenoreceptors, inhibiting cAMP production. Polymorphisms involved in the signal transduction and receptor antagonism of the adrenergic system have received considerable attention. Variants associated with expression of, function of, or chromosomal proximity to *ADRB1*, *ADRB2*, *ADRB3*, and *GRK4* have all been implicated as predictors of antihypertensive response.

The most studied variant of *ADRB1*, rs1801253, is a missense coding polymorphism that results in a single amino acid substitution of glycine for arginine with the G allele. The SNP has a minor allele frequency of 29.8% for the G allele. In a large dataset of over 86,000 patients, the C allele was associated and replicated with increased baseline systolic blood pressure (SBP) and DBP.[46] The association of this allele with antihypertensive response to beta-blocker therapy is less straight forward. Several small studies have revealed positive results with the C allele corresponding to an improved response to beta-blockade as defined by reduction in BP or heart failure endpoints[47-51]. Studies have also illustrated contradictory results where the G allele is associated with more favorable rate control with verapamil and multiple beta-blockers[52]. However, negative studies, including larger, well-powered investigations, predominate suggesting that rs1801253 cannot reliably predict antihypertensive response, rate control, or heart failure outcomes[11,17,53-58].

Adrenoceptor-β2 agonism is not specific to cardiomyocytes, as its principle effect in bronchial epithelial cells is to facilitate smooth muscle relaxation and bronchodilation. Variants of *ADRB2* have been associated with asthma exacerbations and salmeterol response[59,60]. However, antihypertensive and cardiac investigations of beta-blockers and ACEIs have yielded mixed results of the *ADRB2* variants, rs1042713 and rs1042714, in predicting BP and congestive heart failure responses[10,17,56,57,61-63]. Rs4994, a polymorphism in ADRB3, has been evaluated in hypertensive studies. This variant is associated with essential hypertension in Han Chinese[64],

mean thiazide BP response in Japanese individuals[65], and pulse pressure variation between atenolol and losartan in whites[17]. These associations were not corrected for a multiple testing penalty and have not been replicated. Presently, no variants in *ADRB1*, *ADRB2*, or *ADRB3* have been recommended for routine screening by CPIC or the DPWG.

The adrenergic signaling cascade intermediates, GRK4 and G-protein subunit β3 (GNB3), are promising mediators of antihypertensive response. The SNP rs1024323 is a missense variant of GRK4 with a minor allele frequency of 37%. In the African American Study of Kidney Disease and Hypertension (AASK) trial, the CC genotype of rs1024323 was associated with metoprolol BP response. However, the association was only significant in men who were heterozygous or homozygous for the rs2960306 T allele as well[66]. Significant associations were not found in women or in men homozygous for the rs2960306 G allele. These results have been replicated in a mixed gender population of whites and Hispanics in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) trial and the International VErapamil SR/Trandolapril STudy (INVEST-GENES). These trials similarly found that the haplotype consisting of the C allele of rs1024323 and T allele of rs2960306 were associated with greater atenolol-induced DBP reduction[67]. This haplotype was also associated with improved cardiovascular outcomes independent of the BP effect. These associations were additive and stronger in individuals with the rs1801253 CC genotype of *ADRB1*, supporting the polygenic nature of hypertension.

Several SNPs associated with the G-protein subunit β3 (*GNB3*) have been associated with beta-blocker, clonidine, and diuretic response. A single trial suggested the C allele of variant rs5443 is associated with improved SBP response to atenolol[54]. This trial suggested that two additional SNPs, rs11064426 and rs2301339, were also associated with atenolol response. However, conflicting data have been reported; the T allele of rs5443 was found to be linked to greater heart rate attenuation[68] in a separate study. The T allele was also predictive of net sodium chloride and

calcium excretion in response to loop diuretic use in healthy volunteers[42]. The rs5443 T allele may further predict response to clonidine in cirrhotics and healthy individuals[69,70]; caution should be employed in interpreting these results as the studies were small and employed non-traditional endpoints.

In summary, variants of *ADRB1*, *ADRB2*, *ADRB3,* and *GNB3* have not been reproducibly associated with antihypertensive drug response. Data regarding polymorphisms of GRK4, particularly rs1024323 and rs2960306, are encouraging and warrant further investigation.

Candidate variants contributing to sodium reabsorption

Linkage studies in hypertensive families have vaulted the chromosomal region near the neural precursor cell expressed developmentally downregulated 4-like gene (*NEDD4L*) to candidate gene status[71]. These investigations uncovered a variant (rs4149601) responsible for alternative splicing of *NEDD4L*. The alternative isoform I, from the A allele of rs4149601, led to decreased expression of the distal epithelial sodium channel (ENaC). Furthermore, the A allele was associated with lower DBP compared to the G allele.

Larger candidate gene investigations have both replicated and contradicted these findings. For example, in the Nordic Diltiazem Study (NORDIL), the G allele of rs4149601 was a predictor of thiazide and atenolol response over diltiazem response without consideration of other loci[72]. In contrast, it was the A allele of rs4149601 that was found to predict thiazide responsiveness in a case-control study of hypertensive Chinese subjects[73]. One explanation is that the rs4149601 locus does not fully explain the hypertensive phenotype alone, as additional cotransmitted loci may augment or mitigate the effects observed. In the initial linkage analyses, rs4149601 was only partially causative and the presence of a second intronic variant (rs2288774) was required to

account for significant differences in SBP[71]. In the PEAR and INVEST trials, a haplotype consisting of the G allele of rs4149601 and C allele of a second SNP rs292449 predicted greater BP response to hydrochlorothiazide as well as adverse cardiovascular outcomes in whites not treated by hydrochlorothiazide[74].

Polygenic drug-gene interactions may also be required to explain phenotypic variation. An Italian study evaluated the *NEDD4L* variant in concert with variants of other genes involved in sodium reabsorption, *WNK1* rs880054 and alpha-adducin (*ADD1*) rs4961[75]. The combination of the *ADD1* T allele, the *WNK1* G (T) allele, and the *NEDD4L* A allele was consistently associated with improved BP response to a saline load and greater urinary sodium excretion. As expected, these individuals were also the least responsive to thiazide diuretic-induced BP reduction. The *ADD1* variant rs4961 has been studied extensively on its own. However, results have been conflicting as the T allele has been found to confer increased diuretic efficacy in some studies, but reduced efficacy in others[42,75-84].

Plausible variants uncovered in unbiased analyses

Knowledge of antihypertensive pharmacogenomics has been greatly expanded by candidate gene exploration into the RAAS, adrenergic, and sodium reabsorption pathways. However, the field has been reinvigorated by more recent unbiased investigations in large, hypertensive cohorts. Many of these investigations began as genome-wide association studies (GWAS) that were later replicated or linked to physiologic relevant functional evidence. Several examples of these novel variants are illustrated below.

A GWAS of atenolol and metoprolol BP response was conducted in a cohort of African-American, hypertensive participants from the PEAR studies[85]. Two replicated variants,

rs201279313 in *SLC25A31* and rs11313667 in *LRRC15*, were found to predict improved BP response to β-blocker monotherapy in African Americans. *SLC25A31* encodes a mitochondrial ADP/ATP carriers, while *LRRC15* encodes the leucine-rich repeat containing receptor-like kinase protein 15, whose function is not well characterized. Neither of these variants would have been discovered without an unbiased approach.

Analogously, a GWAS examining atenolol monotherapy was conducted in white participants of the PEAR trials[86]. This analysis identified two polymorphisms, rs12346562 and rs1104514, near the *PTPRD* gene that were associated with improved atenolol BP reduction in whites. *PTPRD* encodes protein-tyrosine phosphatase delta, a signaling molecule that regulates cell growth and differentiation. The significance of rs12346562 was replicated in a cohort of Finnish men from the genetics of drug responsiveness in essential hypertension study (GENRES)[87]. Three other independent groups of hypertensive individuals were examined as part of the replication and validation process. Several other variants of *PTPRD* were identified as significant in these populations, including rs10739150 in black, hypertensive individuals.

An initial GWAS of patient samples from the GERAS trial[88] identified a SNP in *YEATS4*, rs7297610, as a significant predictor of DBP response to hydrochlorothiazide in a mixed population of Caucasians and African Americans[89]. *YEATS4* encodes the YEAT domain-containing protein 4, a transcription factor that aids in gene activation through acetylation of nucleosomal histones H4 and H2A. The association was replicated in the PEAR trial cohort and functional evidence of its direct role in the pathogenesis of hypertension has been proposed[90]. The leukocyte expression of YEATS4 significantly declines following hydrochlorothiazide treatment in African Americans homozygous for the C allele. Baseline YEATS4 expression was also lower in T carriers as opposed to C allele homozygotes. These expression data add functional relevance to the role of rs7297610 as a predictor and mediator of hydrochlorothiazide response.

A combined association study of the PEAR, GERAS, and NORDIL trials highlighted a significant variant of *PRKCA*, protein kinase C alpha, as significantly associated with DBP reduction in response to thiazides[91]. The SNP, rs16960228, was replicated in the GENRES study cohort. Individuals treated with thiazides had a 4.16 mm Hg increased reduction of DBP per A allele.

In summary, these variants identified from unbiased GWAS teach us a great deal about the underlying pathogenesis of hypertension. All of these variants have been replicated and some also have corresponding functional evidence to corroborate their significance. These data reveal a vibrant culture of discovery in the field. Randomized, controlled trials and implementation efforts are now required to translate these innovations into clinical practice.

Implementation

CPIC and DPWG are collaboratives that curate the literature and produce clinical guidelines with information necessary for clinical implementation. These recommendations are available in the Pharmacogenomics Knowledgebase (PharmGKB, www.pharmgkb.org), but significant barriers to the broad adoption of pharmacogenetic testing in clinical practice remain[92]. These barriers include genotyping logistics to provide rapid results; a dearth of prospective, randomized, clinical trials; clinician inexperience with pharmacogenomics; inconsistent reimbursement of pharmacogenomic screening; and a lack of consensus regarding treatment algorithms and professional society recommendations. In order to expend the resources to overcome these obstacles, genetic biomarkers must hold value over and above traditional biomarkers in clinical practice.

The inherent properties of antihypertensive agents magnify some of the obstacles delineated above. These drugs are inexpensive, low in toxicity, frequently titrated, and easily monitored. Traditional biomarkers of efficacy and toxicity such as BP, pulse, and urine output are reliable and readily assessed in clinic. Other adverse events such as hyperuricemia or hypokalemia can be transient and would require serologic monitoring with or without genetic testing. Furthermore, the sheer number of alternative agents allows clinicians the opportunity to optimize a patient's regimen based on trial and error. Although some of the variants discussed in this review are considered of sufficient importance to warrant listing within FDA package inserts, most tests are not routinely reimbursed by the Centers of Medicare and Medicaid Services. Finally, the polygenic nature of hypertension adds complexity to the interpretation of pharmacogenetic testing. These obstacles are reflected in the relative paucity of recommendations for routine use of pharmacogenomic screening in the treatment of hypertension. Presently, CPIC and DPWG have recommended only one genetic screening test for routine use: CYP2D6 screening for metoprolol (DPWG).

Despite these impediments, the opportunity to benefit patients and practitioners is readily apparent. Hypertension is among the most commonly treated diseases worldwide. The American Society of Hypertension has noted that in many communities, fewer than half of all hypertensive patients have adequately controlled BP[93]. For some patients, serial follow-up may be required to develop an adequate regimen. Thus, selecting the right agent first may net cost savings to health systems by decreasing required follow-up and reducing adverse events. Indeed, the emphasis of this review has been on drug efficacy and agent selection. However, there is significant evidence supporting variants predicting adverse events including the hyperuricemia of thiazide use[94], bradycardia associated with β-blockers[5-8,95,96], and ACEI-related cough[97].

Pharmacogenomic implementation efforts are underway at universities across the United States[98-102]; yet, few of these programs place emphasis on translating genetic predictors of antihypertensive drug efficacy or toxicity. Two distinct models of implementation may be discerned from these programs. The first is to implement screening for well-defined CPIC- and/or DPWG-endorsed variants broadly across an entire health care system. Examples include the programs at St. Jude Children's Research Hospital[98] and Indiana University's Eskenazi Health System[102]. Since the genetic test results are available to all practitioners, clear evidence-based dosing algorithms are required to inform clinicians who may have limited prior experience with pharmacogenomic test interpretation. Neither of these programs provides testing for variants with lower levels of evidence. Few variants related to antihypertensive agents meet these evidence thresholds.

An alternative model of pharmacogenomic implementation includes screening for investigational variants, but restricts the results to a small population of physicians with significant understanding of pharmacogenomics. A successful example of this program is found in University of Chicago's "1,200 Patient's Project"[101]. The University of Chicago's open array platform includes screening of variants for hydrochlorothiazide (*REN* and *ADD1*), amlodipine (*CYP3A4* and *CACNA1C*), metoprolol (*ADRB1* and *GRK4*), and atenolol (*LDLR*, *GNB3*, and *AGT*). Most CLIA-approved pharmacogenomic laboratories utilize custom PCR-based OpenArray™ platforms for genotyping. These arrays assess up to 64 variants in a single individual. Given the polygenic nature of hypertension, the using pharmacogenomics as a tool to assist in hypertensive therapy selection lends itself to having a panel of already-available genetic variants in the medical record. The clinical functionality decreases if the genetic screening is prompted by a new antihypertensive agent prescription. Although the cost of genotyping has declined, broad-based genetic screening has not become universal. Until that time, further

randomized, controlled trials are required to validate the utility of genetic variants associated with antihypertensive traits.

Table 1: Description of key pharmacogenomics of hypertension studies by antihypertensive agent.

Class / Drug	Gene	Variant	Allele	Level of Evidence	Clinical Significance	Ref
Hydralazine	*NAT2*	*5,*6,*7,*14		FDA label	Homozygotes for slow acetylation alleles (*5, *6, *7, *14) have greater response to hydralazine.	[23]
Beta-Blockers	*ADRB1*	rs1801253	G > C	Conflicting data	CC genotype may predict increased response to beta-blockers and non-dihydropyridine CCBs	[11,46-55,57,58,103-109]
	GRK4	rs2960306	G > T	Replicated	T allele predicts reduced atenolol and metoprolol efficacy	[66,67]
	GRK4	rs1024323	C > T	Single study data	CC genotype predicts reduced metoprolol efficacy in black males with TC/TT rs2960306 genotype	[66]
	SLC25A31	rs201279313	*del	Replicated	The deletion allele was associated with greater BP reduction after β-blocker treatment	[85]
	LRRC15	rs11313667	*del	Replicated	The deletion allele was associated with better BP response to β-blocker monotherapy	[85]
	PTPRD	rs12346562	A > C	Replicated	A allele associated with improved BP response to atenolol	[86]
Metoprolol	*CYP2D6*	*2,*3,*4, etc.		DPWG guideline	Poor metabolizers require dose reduction and are at risk for bradycardia	[5-8,95,96]
Atenolol	*LDLR*	rs688	C > T	Single study data	TT genotype predicts reduced atenolol efficacy (N = 49)	[110]
	FTO	rs9940629	A > G	Single study data	Caucasians with AA genotype had smaller HDL reductions in response to atenolol (N = 232)	[111]
		rs12595985	C > A	Single study data	African Americans with AA genotype had higher HDL cholesterol with atenolol (N = 152)	[111]
	PLA2G4A	rs1015710	G > C	Single study data	CC genotype predicts higher HDL cholesterol in whites using atenolol (N = 232)	[111]
	PTGS2	rs4648287	A > G	Single study data	GG genotype predicts higher HDL cholesterol in African Americans using atenolol (N = 152)	[111]
	ABCB1	rs3213619	A > G	Single study data	GG genotype of rs3213619 and rs10267099 predict higher HDL cholesterol in African Americans	[111]
	PROX1	*rs340874*	T > C	Single study data	C allele is associated with increased fasting glucose in whites using atenolol	[112]
	GALNT2	rs2144297	T > C	Single study data	TT genotype predicts higher HDL cholesterol in African Americans using atenolol (N = 152)	[111]
	GALNT2	rs2144300	C > T	Single study data	CC genotype predicts higher HDL cholesterol in whites using atenolol (N = 232)	[111]
Carvedilol	*CYP2D6*	*2,*3,*4, etc.		FDA label	Asian poor metabolizers of CYP2D6 have increased concentrations of carvedilol	[8,9,113]

	UGT1A1	*6, *28		Conflicting data	*28 allele predicts increased and *6 predicts decreased glucuronidation of carvedilol	11,12
Angiotensin II Receptor Blockers	*CYP11B2*	rs1799998	A > G	Conflicting data	AA genotype predicts reduced response to candesartan, but increased response to benazepril or imidapril in Asians.	114,115
Losartan	*STK39*	*rs6749447*	T > G	Single study data	TT genotype predicts increased losartan response in whites (N = 202)	116
	CYP2C9	rs1057910	C > A	FDA label	*2 and *3 allele associated with decreased losartan effect, metabolism and metabolite appearance	13,14,17
Irbesartan	*APOB*	rs1367117	G > A	Single study data	AA genotype predicts reduced irbesartan response in whites (N = 48)	110
Valsartan	*REN*	C-5312T	C > T	Replicated	CC genotype predicts improved valsartan response and lower renal expression of *REN*.	34,43,44
ACE Inhibitors	*AGTR1*	rs5182	C > T	Single study data	CC genotype predicts increased cardiovascular event risk with ACEI use (N = 786)	117
	AGTR1	rs5186	A > C	Conflicting data	AA genotype may predict improved ACEI + ARB response and cardiovascular event risk	30,117,118
	BDKRB2	rs1799722	C > T	Conflicting data	TT genotype may confer increased risk of ACEI-related cough in Asians (2 of 4 studies positive) and decreased enalapril response	119-123
		rs8012552	C > T	Single study data	TT genotype confers lower risk of ACEI-related cough (N = 106)	97
	PTGER3	rs11209716	T > C	Single study data	CC genotype confers lower risk of ACEI-related cough (N = 249)	97
	ABO	rs495828	T > G	Replicated	TT genotype predicts development of cough with ACEI treatment	124,125
Enalapril	*VEGFA*	*rs699947*	A > C	Single study data	AA genotype predicts increased response to enalapril (N = 54)	126
	NR3C2	rs5522	C > T	Single study data	TT genotype predicts increased enalapril response in Asians (N = 263)	127
Ramipril	*ACE*	*rs4344*	G > A	Single study data	Homozygosity of either allele predicts increased ramipril response (N = 347)	128
		rs4359	T > C	Single study data	Homozygosity of either allele predicts increased ramipril response (N = 347)	128
Benazapril	*AGT*	rs7079	G > T	Single study data	TT genotype predicts increased benazepril response in Chinese	129
	AGT	*rs4762*	G > A	Single study data	G allele predicts increased benazepril response in Asians	129
	PRCP	rs2229437	T > G, A	Single study data	TT genotype predicts increased benazepril response in Asians (N = 1092)	130
Calcium Channel Blocker	*TANC2*	rs2429427	G > A	Single study data	GG genotype predicts increased BP response to calcium channel blockers in Asians (N = 93)	131
	CACNA1	rs2239128	T > C	Single study data	CC genotype predicts increased calcium channel blocker BP response in whites (N = 120)	132

	C					
		rs2238032	T > G	Single study data	TT genotype predicts increased calcium channel blocker BP response in whites (N = 120)	[132]
Diltiazem	*PLCD3*	Rs12946454	A > T	Single study data	A allele predicts improved BP response for white diltiazem users in NORDIL trial (N = 1990)	[133]
Verapamil	*KCNIP1*	rs2301149	C > G	Single study data	GG genotype predicts increased cardiovascular events with verapamil use compared to CC or CG	[134]
		rs11739136	C > T	Replicated	T allele confers improved BP control with verapamil	[134-136]
	NR1H3	rs2279238	C > T	Single study data	Verapamil use in TT genotype associated with increase in death, myocardial infarction, or stroke	[137]
		rs12221497	G > A	Single study data	Verapamil use in GG genotype associated with increase in death, myocardial infarction, or stroke	[137]
	NOS1AP	rs10494366	T > G	Single study data	GG genotype predicts increased risk of QTc prolongation in whites (N = 7565)	[138]
Amlodipine	*CYP3A5*	rs776746	T > C	Single study data	*1/*1 genotype predicts lower amlodipine AUC and Cmax in Korean males (N = 40)	[18]
	CYP3A4	rs2246709	A > G	Single study data	G allele predicts increased efficacy of amlodipine in African Americans (N = 145)	[20]
		rs2740574	C > T	Single study data	T allele genotype predicts increased efficacy in African American women	[62]
Nifedipine	*SLC14A2*	rs3745009	G > A	Single study data	GG genotype predicts greater BP reduction in Asians using nifedipine (N = 405)	[139]
		rs1123617	G > A	Single study data	AA genotype predicts greater BP reduction in Asians using nifedipine (N = 405)	[139]
Thiazides	*PRKCA*	rs4791040	T > C	Conflicting data	TT genotype predicts reduced thiazide response in NORDIL, but not PEAR and GERA trials	[91]
	TLE1	rs2378479	G > T	Replicated	T allele is associated with BP response in African Americans	**
Hydrochlorothiazide	*KCNJ1*	*rs675388*	G > A	Single study data	A allele predicts increase in fasting glucose during HCTZ use	[140]
		rs658903	T > A	Single study data	TT genotype predicts increased risk of DM in Hispanics (N = 464)	[140]
		rs59172778	A > G	Single study data	AA genotype predicts lower serum potassium	[140]
		rs12795437	G > C	Single study data	CC genotype predicts increased risk of DM in whites and Hispanics (N = 835)	[140]
		rs11600347	C > A	Single study data	AA genotype predicts increased risk of DM in whites and Hispanics (N = 835)	[140]
	PRKCA	rs16960228	G > A	Replicated	AA genotype predicts increased response to HCTZ in whites	[91]
	YEATS4	rs7297610	C > T	Replicated	TT genotype predicts decreased HCTZ response and decreased whole blood YEATS4 expression in African Americans	[89,90]

	WNK1	rs880054	C > T	Single study data	TT genotype predicts decreased SBP response to atenolol (N = 193)	[75]
	LUC7L2	*rs6947309*	C > T	Single study data	T Allele predicts higher uric acid levels with HCTZ use (N = 276)	[94]
	FTO	*rs4784333*	C > G	Single study data	C allele predicts higher uric acid levels with HCTZ use (N = 276)	[94]
	TCF7L2	rs4506565	A > T	Single study data	TT genotype predicts increased risk of DM in whites using HCTZ (N = 1435)	[141]
		rs4132670	G > A	Single study data	AA genotype predicts increased risk of DM in whites using HCTZ (N = 1435)	[141]
		rs7917983	T > C	Single study data	TT genotype predicts increased risk of DM in whites using HCTZ (N = 1435)	[141]
	REN	rs11240688	C > T	Single study data	CC genotype predicts improved response to thiazide diuretics in Asians (N = 90)	[45]
Cross-Class Variants						
Atenolol, ACEI/ARB	*AGT*	rs5051	C > T	Single study data	TT genotype predicts greater atenolol response (white), but reduced ACEI response (Asian)	[142,143]
	AGT	rs699	A > G	Conflicting data	GG genotype may predict greater SBP reduction and LVH decrease with atenolol/ irbesartan, but there is conflicting data for response to ACEI.	[30,129,142, 144-148]
BB, CCB, ACEI/ARB	*AGTR1*	rs5186	A > C	Conflicting data	AA genotype predicts increased response to HCTZ, nitrendipine, and candesartan, but poorer response to perindopril, captopril, irbesartan, and inconclusive results for losartan and quinapril	[30,117,118, 144,146,148 -153]
BB, CCB,ACEI, diuretic	*ADD1*	rs4961	G > T	Conflicting data	T allele confers increased diuretic efficacy in some studies and decreased efficacy in others	ADD1[42 ,75-84]
	ACE	rs1799752	*del	Replicated with conflicting data	del/del genotype predicts increased diuretic response and may decrease RAAS blockade response	[26-42,117,144, 154-165]
	ACE2	rs2106809	A > G	Single study data	GG genotype is associated with increased captopril efficacy, but decreased response to other drugs	[166]
	NOS3	rs2070744	C > T	Replicated	CC genotype predicts resistant hypertension to a variety of drugs	[167,168]
CCB, thiazide	*CLCN6*	rs5065	A > G	Single study data	GG genotype predicts greater thiazide response compared to amlodipine (N = 38,462)	[169]
Atenolol, verapamil	*CACNA1 C*	rs1051375	G > A	Single study data	AA genotype predicts fewer cardiovascular events with atenolol compared to verapamil	[170]
	NR1H3	rs11039149	A > G	Single study data	GG genotype associated with increased cardiovascular events with verapamil or atenolol	[137]
Atenolol, HCTZ	*NEDD4L*	rs75982813	A > G	Replicated	GG genotype predicts improved BP response to atenolol and HCTZ in whites (N = 767)	[74]

	NEDD4L	rs292449	G > C	Single study data	CC + CG genotype predicts improved BP response to HCTZ in whites (N = 767)	[74]
BB, CCB, diuretics	*NEDD4L*	rs4149601	G > A	Replicated	AA genotype predicts adverse cardiovascular events and reduced BP response in whites in PEAR (N = 767), INVEST (N = 1345), and NORDIL (N = 2594) trials, but greater BP response in Asians.	[72-75]
CCB, ACEI	*PTPRD*	rs4742610	C > T	Replicated	TT genotype predicts resistant hypertension in whites and Hispanics	[86]
Thiazide, ACEI	*MMP3*	rs3025058	A > del	Single study data	AA genotype predicts increased stroke risk in ALLHAT study with Lisinopril over chlorthalidone	[171]

Abbreviations: Ref, reference; BP, blood pressure; BB, beta-blocker; CCB, calcium channel blocker; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; AUC, area under curve; Cmax, maximum concentration; HCTZ, hydrochlorothiazide; DM – diabetes mellitus; DPWG, Dutch pharmacogenomics working group recommendation; Replicated, replicated in multiple studies, studies may have large or small effect size. FDA label, pharmacogenomics mentioned in the FDA drug label.

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