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Pharmacogenomics of Hypertension and Heart Disease

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Abstract

Heart disease is a leading cause of death in the United States, and hypertension is a predominant risk factor. Thus, effective blood pressure control is important to prevent adverse sequelae of hypertension, including heart failure, coronary artery disease, atrial fibrillation, and ischemic stroke. Over half of Americans have uncontrolled blood pressure, which may in part be explained by interpatient variability in drug response secondary to genetic polymorphism. As such, pharmacogenetic testing may be a supplementary tool to guide treatment. This review highlights the pharmacogenetics of antihypertensive response and response to drugs that treat adverse hypertension-related sequelae, particularly coronary artery disease and atrial fibrillation. While pharmacogenetic evidence may be more robust for the latter with respect to clinical implementation, there is increasing evidence of genetic variants that may help predict antihypertensive response. However, additional research and validation are needed before clinical implementation guidelines for antihypertensive therapy can become a reality.

Keywords

Hypertension; Pharmacogenetics; Warfarin; Clopidogrel; Simvastatin

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Introduction

Heart disease remains the leading cause of death in the United States (US), accounting for approximately 610,000 deaths annually [1]. Hypertension is an important risk factor for heart disease and affects more than one billion individuals worldwide and one third of the US adult population [2, 3]. Of concern, only 54 % of hypertensive adults in the US have their blood pressure (BP) controlled [3], and response rates to any given antihypertensive medication are roughly 50 % [4]. Worldwide, BP control rates may be even lower, with only one third of adults achieving target BP despite guideline-driven therapy [5]. Patients typically require antihypertensive medications throughout their lifetime, with the intent of preventing adverse hypertension-related sequelae, such as heart failure, coronary artery disease, atrial fibrillation, ischemic stroke, and peripheral vascular disease, which can result in premature mortality, disability, and significant societal and economic cost [6–8].

Contributors to uncontrolled BP include medication non-adherence, which may be secondary to adverse drug reactions or medication costs, and interpatient variability in drug response secondary to patient-specific factors including genotype [9]. Genotype can affect drug metabolism, transport, and sensitivity to a drug at its target site. Guidelines from expert consensus panels are available for the treatment of hypertension and its sequelae [10–16]. However, guidelines are based on drug efficacy in a clinical trial population as a whole, and there is no assurance that a given treatment will be effective in an individual patient. Pharmacogenetics holds promise for tailoring treatment for each unique patient, who may not fit the mold of the general study population from which evidence-based guidelines are derived.

Accumulating evidence on genetic contributions to drug response led to the establishment of the Clinical Pharmacogenetics Implementation Consortium (CPIC). Formed in 2009, CPIC provides peer-reviewed guidelines to assist with translation of pharmacogenetic test results into actionable prescribing decisions [17]. Currently, CPIC guidelines with strong evidence exist for 13 genes and 36 drugs, including 3 drugs used in the management of cardiovascular disease (clopidogrel, warfarin, and simvastatin) [18]. This review focuses on the pharmacogenetics of cardiovascular medications, particularly on drug–gene pairs addressed in CPIC guidelines or with strong and consistent evidence supporting the potential for clinical implementation. Although the pharmacogenetic evidence is more robust for clopidogrel, statins, and warfarin, emerging evidence on genetic determinants of antihypertensive response is also discussed.

Pharmacogenetics of Antihypertensive Response

Currently, there are no CPIC guidelines addressing antihypertensive medications. While numerous studies show genetic associations with antihypertensive drug response, results across studies are fairly inconsistent and sometimes conflicting. Comparing results across studies is challenging because of dissimilarities in population stratification, sample size, study design, antihypertensive exposure, and methods of assessing blood pressure [19, 20].

The International Consortium for Antihypertensive Pharmacogenomics Studies (ICAPS) was developed in 2012 to assist in discovery of new genetic variants and replication of

previously identified variants that predict response to antihypertensive drugs. ICAPS (<http://icaps-htn.org/>) is comprised of 29 cohorts and over 345,000 total participants from 22 different research groups based in 10 countries. Studies carried out by this consortium include clinical trials and observational studies of BP response, as well as adverse cardiovascular and metabolic outcomes, using both candidate gene and genome-wide association study (GWAS) approaches. A number of reported pharmacogenomic associations remain to be validated. Thus, this section summarizes only the most consistently replicated associations with response to commonly used antihypertensive drugs, in addition to recent promising data in the field. In addition, data pertaining to genetic associations with adverse drug reactions have recently emerged and are briefly discussed at the end of this section.

The most substantiated pharmacogenetic data exist for β -blockers and thiazide diuretics (Table 1). The evidence points to three genes consistently correlated with antihypertensive response across various cohorts: *ADRB1*, *NEDD4L*, and *YEATS4*. The primary target protein of β -blockers, the β 1-adrenergic receptor, is encoded by the *ADRB1* gene. The Ser49Gly (rs1801252) and Arg389Gly (rs1801253) variants are common single nucleotide polymorphisms (SNPs) in the *ADRB1* gene that are by far the most well-studied. The Arg389/Arg389 genotype and the Ser49Arg389/Ser49Arg389 diplotype have both been correlated with greater blood pressure reduction with metoprolol [21, 22]. Evidence suggests that this association is due to genetic effects on adrenergic signal transduction pathways [27]. In a genetic substudy of the International Verapamil SR-Trandolapril Study (INVEST), which compared atenolol versus verapamil sustained-release (SR)-based treatment approaches, investigators found higher mortality rates in carriers of the Ser49Arg389 haplotype [28]. When analyzed by treatment strategy, the increased mortality risk was observed in the verapamil arm, but not in the β -blocker arm [28]. The cumulative data suggest that β -blocker therapy not only effectively lowers blood pressure but also has a protective effect against mortality risk in patients with the *ADRB1* Ser49Arg389 haplotype.

In another INVEST genetic substudy, investigators reported a higher risk score for major adverse cardiovascular events created from SNPs in the *SIGLEC12* (rs16982743), *A1BG* (rs893184), and *F5* (rs4525) genes, which was evident in the verapamil SR treatment arm, but not the β -blocker arm. These findings suggest favorable effects with β -blocker therapy in patients with the higher risk score [29]. A similar, but weak, association with this risk score was observed in the genetic substudy of the Nordic Diltiazem (NORDIL) trial, which compared the effect of diltiazem to that of β -blockers and/or diuretics. The biologic mechanism contributing to treatment-related adverse cardiovascular outcomes with this SNP combination remains to be determined.

In another substudy of the NORDIL trial, the more common G allele of rs4149601 (227G>A) within the *NEDD4L* gene was associated with greater systolic BP (SBP) and diastolic BP (DBP) reduction to β -blockers and diuretics [23]. In an effort to replicate this finding and delineate whether the association was specific to β -blocker or diuretic therapy, rs4149601 was genotyped in participants of the Pharmacogenomic Evaluation of Antihypertensive Responses 1 (PEAR-1) study. The G allele was associated with greater SBP and DBP reduction in Caucasians treated with hydrochlorothiazide (HCTZ)

monotherapy, but not in African Americans. There was no significant association between the rs4149601 genotype and antihypertensive response to atenolol or to HCTZ–atenolol combination therapy [24]. These data suggest that the pharmacogenetic effect seen in the NORDIL study was likely due to treatment with diuretic versus β -blocker therapy. This makes sense physiologically, as *NEDD4L* encodes a protein that regulates expression of the epithelial sodium channel in the distal nephron, which is responsible for sodium reabsorption in the kidneys [30]. Therefore, variants in this gene would be more likely to affect BP response to HCTZ rather than β -blockers, since HCTZ inhibits sodium reabsorption in the distal tubules, promoting increased excretion of sodium and water. The lack of association between rs4149601 and BP response in African Americans may be secondary to the small percentage of African Americans included in the study or the possibility that the associated SNP is not the functional variant. Rather, it may be in linkage disequilibrium with the functional variant in Caucasians, but not African Americans

There is also convincing evidence for the haplotype rs317689/rs315135/rs7297610 on chromosome 12q15 affecting BP response to HCTZ. Turner et al. performed a genome-wide analysis investigating HCTZ response in Caucasians and African Americans from the Genetic Epidemiology of Responses to Antihypertensives 1 (GERA-1) study, observing an association between this haplotype and DBP response to HCTZ in African Americans [25]. They found that the ATC haplotype was more frequent among African American “good” responders to HCTZ, while the ACT and the ATT haplotypes were more frequent among African American “poor” responders [25]. These findings were partially replicated by Duarte et al. in PEAR-1 participants, with the ATT haplotype being significantly more frequent in African American poor responders than good responders to HCTZ [26]. The directionality for the other two haplotype associations was consistent with the findings by Turner et al., though not statistically significant. The investigators hypothesized that this haplotype association was driven by rs7297610, as African Americans with C/C genotypes had greater BP response to HCTZ than T allele carriers [26]. In addition, they proposed that this SNP tags a single, or multiple rare, functional SNP(s), because of its intergenic location and the fact that BP response associations were not observed in Caucasians. Further, the group measured expression of nearby genes in 47 African American PEAR-1 participants to provide insight into this observed pharmacogenomic effect, which revealed that those with the C/C genotype had 22 % higher pre-treatment *YEATS4* expression compared with T carriers ($P=0.024$). After treatment with HCTZ, *YEATS4* expression decreased by 15 % in those with the C/C genotype ($P=0.0088$) [26]. This sort of functional validation offers an additional method to validate pharmacogenomic findings, particularly when large replication populations are not available. While these aforementioned variants appear to hold promise with regard to response to first-line antihypertensive agents, additional evidence is needed before they can be incorporated into clinical implementation guidelines.

Novel genes correlated with BP response were recently identified by several groups within ICAPS. The biological effect of these genes, as well as previously mentioned genes, can be found in Table 2. As part of the Study of the Pharmacogenomics in Italian hypertensive patients treated with the Angiotensin receptor blocker losartan (SOPHIA), a GWAS on BP response was performed in 372 hypertensives treated with losartan for 4 weeks [43•]. Four

SNPs (rs10752271, rs10906202, rs4747995, and rs10737061) in the *CAMK1D* gene were significantly associated with SBP reduction response to losartan ($P < 1 \times 10^{-5}$). The only one of these to reach genome-wide significance ($P = 1.2 \times 10^{-8}$) for SBP response was the imputed SNP rs10752271, with an effect size of -5.5 ± 0.94 mmHg [43•]. This SNP was tested for replication in silico in two independent essential hypertension samples, from the GERA-2 and GENes and Antihypertensive Drug RESponse (GENRES) studies. In GERA-2, rs10752271 was not associated with BP response to candesartan but showed an association to losartan in GENRES with a similar effect size of the G risk allele as seen in SOPHIA [43•]. In a separate GWAS also performed in two Italian hypertensive cohorts (Pharmacogenomics of Hydrochlorothiazide Sardinian Study and the Milan Hydrochlorothiazide study), Chittani et al. searched for variants associated with BP response to treatment with HCTZ for 8 weeks [36]. They identified *TET2* and *CSMD1* as reasonable candidate genes to affect SBP response to HCTZ, although the polymorphisms within those genes showed mixed results in terms of replication (in terms of directionality and response) across the five replication cohorts (GENRES, GERA-1, NORDIL, PEAR-1, CSN-StayOnDiatr) [36]. Potential reasons for inconsistencies in replication for these SNPs include the small effect sizes seen in BP response, study design heterogeneity, and the location of these SNPs (intron or flanking gene regions).

In the GENRES study, a GWAS was performed to identify loci influencing BP response of 228 moderately hypertensive Finnish men to four classes of antihypertensives [41•]. GENRES is unique in that it is a double-blind, placebo-controlled cross-over study where each participant received amlodipine, bisoprolol, HCTZ, and losartan, each as a monotherapy for 4 weeks, in a randomized order. Replication analyses were performed in four studies (PEAR-1, GERA-1 and GERA-2, and SOPHIA). Three SNPs (rs2514036, rs948445, and rs2514037) within the *ACY3* gene showed association with 24-ambulatory SBP response to bisoprolol reaching genome-wide significance in the GENRES GWAS. However, these were not replicated in PEAR-1 using atenolol [41•]. This lack of replication may mean that there may be no real association between SBP response to bisoprolol and these genetic variants, as there are no strong data that link *ACY3* to BP regulation, or perhaps these SNPs are only specific to bisoprolol.

Lastly, an exceptional approach was taken with PEAR-1 data, where genomics, metabolomics, and transcriptomics were integrated to identify novel biomarkers of HCTZ response [39•]. This integrative pathway approach revealed metabolites in the actin nucleation pathway, as well as the Rho Kinase 1 gene (*ROCK1*), as potential factors affecting HCTZ response. Rho-associated protein kinases have shown association with vasoconstriction and elevated BP [38]. *ROCK1* rs8085654 variant allele carriers had a poor SBP and DBP response compared to non-carriers (SBP $P = 5 \times 10^{-5}$ and DBP $P = 9 \times 10^{-4}$). Additionally, *ROCK1* baseline expression levels were significantly different between HCTZ BP responders and non-responders ($P = 0.01$) [39•]. Although this SNP did not reach the standard genome-wide significance in relation to its HCTZ response, its potential functional effect on *ROCK1* gene expression in HCTZ BP responders and non-responders is promising and provides validation that this is likely a real association.

In addition to correlations with antihypertensive drug effectiveness, there is evidence of genetic determinants of antihypertensive-related adverse effects. Several studies show drug-induced blood glucose changes in patients treated with β -blockers and/or thiazide diuretics. Karnes et al. found an association between variation in the *KCNJ1* gene (encoding potassium inwardly-rectifying channel J1) and increased fasting glucose during short-term HCTZ treatment in PEAR-1 African American patients [44]. Further, *KCNJ1* variation was associated with risk of new-onset diabetes during long-term HCTZ treatment in all INVEST race/ethnic groups. Polymorphisms in the *TCF7L2* gene were also associated with new-onset diabetes in HCTZ-treated INVEST participants [45]. In PEAR-1 participants, *PROX1* SNP rs340874 was significantly associated with atenolol-induced glucose change [46]. Identifying susceptibility to these adverse effects is particularly important in patients with cardiovascular disease, as the benefits of BP reduction with these antihypertensive drugs could potentially be offset by the risk related to type 2 diabetes.

Pharmacogenomics in Hypertension Sequelae

Patients with chronic hypertension are at increased risk for acute coronary syndromes (ACS), stroke, atrial fibrillation, and heart failure. Drugs used to treat or prevent these diseases include β -blockers, aspirin, warfarin, statins, and P2Y₁₂ antiplatelet agents. While limited clinically translatable data are available for β -blockers or aspirin, sufficient clinically relevant pharmacogenetic data exist for warfarin, simvastatin, and clopidogrel to support genotype-guided use of these therapies.

β -Blockers

β -Blockers are a standard of care in heart failure for over two decades. As discussed with hypertension above, polymorphisms in the genes encoding the β -adrenergic receptors, particularly Ser49Gly and Arg389Gly, have been top candidates for β -blocker response for nearly as long. There are multiple studies showing mortality risk reduction in Ser49 carriers taking β -blockers for heart failure. One study reported that Ser49 allele carriers on low-dose β -blocker therapy (i.e., <50 % of the target dose) had an increased mortality rate compared to Gly49 homozygotes [47]. This effect was not observed in patients taking higher β -blocker doses, indicating a mortality benefit with target-dose β -blocker therapy in Ser49 carriers. However, other studies have reported no association between mortality and these polymorphisms in patients taking β -blockers [48]. Liggett et al. reported mortality benefit in 389Arg carriers taking bucindolol for heart failure, which was not observed in Gly389 carriers [49]. Interestingly, the same group found that bucindolol decreased both ventricular tachycardia and atrial fibrillation in Gly389 homozygotes, but not in Arg389 carriers [50, 51].

For the Gln41Leu polymorphism in G-protein-coupled receptor kinase 5 (*GRK5*), which is involved in β -receptor signaling, Gln41 homozygotes with heart failure had improved survival on β -blocker treatment [52, 53]. On the other hand, β -blocker associations with the Del322-325 polymorphism in the alpha 2C adrenergic receptor (*ADRA2C*) have been conflicting [48, 54]. Because of contradictory evidence with polymorphisms in the above adrenergic signaling genes, no guidelines currently recommend the use of genetic information to guide β -blocker use in heart failure.

Statins

HMG-CoA reductase inhibitors, or statins, are a mainstay for primary or secondary prevention of MI in patients with multiple risk factors, including hypertension. Pharmacogenomic studies exploring genes associated with statin efficacy (such as *APOE* and *LPA*) have yielded conflicting observations or genetic associations with small effect sizes of unknown clinical significance [55, 56]. While generally well-tolerated, one of the most common adverse effects patients experience with statin treatment is muscle toxicity, which can range from mild myalgias to severe rhabdomyolysis and renal failure.

Strong evidence links a polymorphism in *SLCO1B1* (rs4149056) with increased risk of statin-induced myopathy [57]. This gene encodes the drug transporter OAT1B1, which is known to transport statins (particularly simvastatin) into the liver for metabolism. Higher plasma statin levels and an increased risk for toxicity may result with usual statin doses in patients with reduced hepatic transport. The *SLCO1B1* rs4149056 variant has a minor allele frequency between 5 and 20 %, making it a somewhat common polymorphism. Research suggests that 3 to 18 % of rs4149056 carriers will develop myopathy with simvastatin use [57, 58], and CPIC guidelines are available to guide simvastatin dosing in these patients [58]. In carriers of the variant C allele, lower simvastatin doses or alternative statin therapy is recommended. Pravastatin and rosuvastatin are suggested as alternatives because there is limited evidence that the rs4149056 variant influences risk for myopathy with these statins [59, 60].

Studies examining the association between statin-induced myopathy and other polymorphisms, such as those in *GATM*, have yielded conflicting reports. The *GATM* gene encodes glycine amidinotransferase, an enzyme required for creatine synthesis, and thus polymorphisms responsible for reducing phosphocreatine storage (and cellular energy storage) in the muscles may have a protective effect against cellular stress caused by cholesterol depletion [61]. An initial report included the discovery of differential expression of *GATM* mapped to multiple eQTLs which were then validated in human statin myopathy cohorts [61]. However, two additional groups were unable to replicate these findings in their separate patient populations [62, 63].

Clopidogrel

Clopidogrel is indicated for the treatment of coronary artery disease, cerebrovascular disease, and peripheral vascular disease, all of which are examples of target organ damage from hypertension [64]. Dual antiplatelet therapy with clopidogrel plus aspirin reduces the risk for cardiovascular events after an acute coronary syndrome and the risk for stent thrombosis after percutaneous coronary intervention (PCI) [65–67]. However, there is significant interpatient variability in clopidogrel response, with reduced effectiveness observed in approximately 25 % of patients, which is largely attributed to genetic variability [68].

Clopidogrel is a prodrug that requires biotransformation to its pharmacologically active metabolite, and CYP2C19 is a key enzyme in the bioactivation pathway. Approximately 30 % of Caucasians and African Americans and 60 % of Asians have deficient CYP2C19

activity secondary to genetic polymorphism. The *CYP2C19**2 (splicing defect) and *3 (stop codon) are loss-of-function alleles leading to deficient enzyme activity. Patients with one or two loss-of-function (LOF) alleles are termed intermediate and poor metabolizers (IMs and PMs), respectively. These patients may fail to attain sufficient plasma concentrations of the active metabolite to effectively inhibit platelet activation [69].

Numerous studies have demonstrated an increased risk for major adverse cardiovascular events among clopidogrel-treated patients with a *CYP2C19* LOF allele compared to those without a LOF allele [70]. The data are strongest for patients who undergo PCI. In a meta-analysis of over 9600 clopidogrel-treated patients from nine clinical trials, the hazard ratio for major adverse cardiovascular events (defined as a composite of cardiovascular death, myocardial infarction, or stroke) was 1.6 (95 % confidence interval 1.1 to 2.2) in intermediate metabolizers and 1.8 (1.2 to 2.5) in PMs compared to extensive metabolizers [70]. Among patients who had a PCI, the hazard ratio for stent thrombosis was 2.7 (1.7–4.2) and 4.0 (1.8–9.0) in PMs and IMs, respectively.

The FDA-approved clopidogrel labeling contains a boxed warning of reduced drug effectiveness in PMs and advises consideration of alternative therapy in these patients. Guidelines from CPIC are specific for patients with ACS who undergo PCI and recommend alternative antiplatelet therapy with prasugrel or ticagrelor (which are not affected by the *CYP2C19* genotype) for PMs or IMs, in the absence of contraindications [71]. *CYP2C19* testing to guide antiplatelet therapy has now entered clinical practice. At the University of Florida, *CYP2C19* testing is part of the post-PCI order set, with alternative antiplatelet therapy recommended for patients with a LOF allele, consistent with CPIC guidelines [72]. Some institutions are taking a preemptive approach to testing so that patients' genotypes will be available ahead of time to guide therapy for those requiring dual antiplatelet therapy in the future [73–76].

Aspirin

As with clopidogrel, aspirin is used for prevention and treatment of cardiovascular and cerebrovascular diseases. Two separate studies observed associations between a polymorphism in *PTGS1* (which encodes cyclooxygenase-1) and aspirin resistance, with one study showing increased risk of cardiovascular events in ACS patients with a *PTGS1* variant allele treated with aspirin and clopidogrel [77, 78]. In addition, limited evidence suggests that patients with variation in *LTC4S* (which encodes leukotriene C4 synthase) have an increased risk of urticaria with aspirin [79, 80]. Recently, an association between a polymorphism in *PEAR1* and aspirin response was published [81]. Although the authors were able to replicate this SNP association in an independent cohort, they were unable to definitively determine if it was the causal polymorphism due to a lack of functional data.

Associations in other genes thought to be involved in aspirin's metabolism or mechanism of action have either failed replication or have no replication attempts reported. For example, reports that a polymorphism in *P2RY1* (which encodes the P2Y1 ADP/ATP receptor) was associated with aspirin resistance were later contradicted when a large cohort study found no association with increased risk of cardiovascular events in aspirin-treated MI patients [78, 82, 83]. Because of the limited and sometimes conflicting nature of genetic associations with

aspirin response, no pharmacogenetic tests are recommended to inform aspirin treatment at this time.

Warfarin

Warfarin is widely prescribed for stroke prevention in atrial fibrillation or after cardiac valve replacement and for the treatment and prevention of venous thromboembolism. Genetic variability significantly contributes to warfarin dose requirements and bleeding risk. Specifically, common variations in the *CYP2C9* gene, including the *2, *3, *5, *6, *8, and *11 alleles, reduce the clearance of S-warfarin, lead to lower warfarin dose requirements, and increase the risk for major bleeding with warfarin [84–87]. The *2 and *3 alleles are the pre-dominant variants in European populations, while *5, *6, *8, and *11 occur almost exclusively in those of African descent. The *VKORC1* gene encodes for the primary protein target of warfarin (vitamin K epoxide reductase complex 1), and a single variant, 1639G>A, affects sensitivity to the drug. The GG genotype confers reduced warfarin sensitivity and higher dose requirements, while the AA genotype is associated with increased sensitivity and lower dose requirements [88].

The FDA-approved warfarin labeling includes dose recommendations based on *CYP2C9* and *VKORC1* genotypes, and CPIC guidelines recommend genotype-guided warfarin dosing when genotype is available [89]. Clinical factors, such as age, body size, and concomitant medications, contribute importantly to warfarin response and should also be considered. Dosing algorithms that include both genotype and clinical information are freely available through the www.warfarindosing.org website to assist with personalized warfarin dosing [90]. However, these algorithms were derived from mostly European populations and perform poorly in African Americans. A recent study shows that failure to include the African-specific variants leads to significant over-dosing of warfarin, emphasizing the importance of accounting for such variants when using genotype-guided dosing of warfarin in African Americans [91].

Two clinical trials examining the clinical efficacy of genotype-guided warfarin dosing were published in late 2013. The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial was conducted in a European population and showed greater time in therapeutic anticoagulation range with genotype-guided dosing compared to traditional dosing [92]. In contrast, the Clarification of Optimal Anticoagulation Through Genetics (COAG) trial, which was conducted in a diverse population, showed no benefit of genotype-guided dosing versus dosing based on clinical factors alone. Genotype-guided dosing was worse than clinically based dosing in African Americans who made up 28 % of the study population [93]. Importantly, the trial did not account for African-specific variants (e.g., *CYP2C9**5, *6, *8, *11), which likely contributed to the findings in the African American cohort. Further data are expected from a large ongoing trial that will examine not only anticoagulation control but also the important clinical endpoints of bleeding and thromboembolism [94]. Despite the inconsistent evidence from clinical trials, genotype-guided warfarin dosing has entered clinical practice. Recent preliminary data from the University of Illinois suggest that clinical implementation of a comprehensive pharmacogenetic warfarin dosing service improves anticoagulation-related endpoints (e.g.,

time to therapeutic anticoagulation, risk for over-anticoagulation) compared to historical dosing approaches [95].

Conclusions

Evidence presented herein highlights the paucity of strong pharmacogenetic evidence available for antihypertensive response and reviews recent promising candidate genes that may be further explored. Due to the number and complexity of influential factors on an individual's BP (e.g., genetic variability, diet, and lifestyle) and various methods of BP assessment, antihypertensive response is a particularly difficult phenotype to evaluate, which is further compounded by the differences in the study design of pharmacogenetic trials and the heterogeneity in the underlying mechanism of hypertension. A reliable BP phenotype, albeit more time-consuming and labor intensive to collect than using office or home BP measurements, is the weighted average of BP responses measured by multiple methods. Turner et al. showed in an analysis of data collected from PEAR-1 that a weighted average of office, home, and ambulatory daytime and nighttime BP responses had up to 11-fold signal-to-noise ratios, which provided the greatest power to identify genetic variants for predicting BP response [19]. Perhaps moving forward, alternative approaches to validation of genetic association findings can be emphasized in antihypertensive pharmacogenetic trials, which include functional validation, combined analysis of several populations, and simulation-based methods [96]. With these techniques and the plethora of information within ICAPS, it is inevitable that more genes and genetic variants of antihypertensive response will be recognized and validated moving forward, bringing us closer to building clinical implementation guidelines.

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Table 1

Recent replicated antihypertensive pharmacogenetic associations

Antihypertensive drug class(es)	Closest gene	Genetic variant(s)	Study design	Method of BP measurement	Participants	Results	Strength of Association
β-Blockers	<i>ADRB1</i>	• rs1801252 (Ser49Gly)	• Prospective trial	24-h ambulatory BP	40 (Caucasians, African Americans, Hispanics)	Arg389 homozygotes had nearly three-fold greater DBP reduction compared to Gly allele carriers treated with metoprolol [21].	$P=0.0018$
		• rs1801253 (Arg389Gly)	• Candidate gene study	BP monitoring		Metoprolol-treated patients with the diplotype Ser49Arg389/Ser49Arg389 demonstrated a 14.7-mmHg reduction in DBP compared to a 0.5-mmHg reduction in those with the diplotype Gly49Arg389/Ser49Gly389 [21].	$P=0.006$ (between haplotype groups)
		• rs1801252 (Ser49Gly)	• Prospective trial	Office BP (automatic monitor)	61 Chinese	SBP, DBP, and MAP were significantly reduced in Ser49Arg389/ Ser49Arg389 and Ser49Arg389/ Gly49Arg389 patients treated with metoprolol [22].	$P<0.001$ (for each haplotype)
β-Blockers, thiazide diuretics	<i>NEDD4L</i>	• rs1801253 (Arg389Gly)	• Candidate gene study				$P=0.014$ (SBP, adjusted ADD)
		rs4149601	• Randomized trial	Office BP (manual)	1863 (Swedish; NORDIL participants)	After 6 months of monotherapy with β-blockers or diuretics, the G allele was associated with greater SBP and DBP reduction [23].	$P=0.0001$ (SBP, adjusted DOM)
Thiazide diuretics	<i>NEDD4L</i>		• Candidate gene study				$P=0.015$ (DBP, adjusted DOM)
							$P=0.32$ (DBP, adjusted ADD)
		rs4149601	• Randomized trial	Office ^a , home, and ambulatory daytime/nighttime BP	767 (Caucasians, African Americans; PEAR-1 participants)	G allele was associated with greater SBP and DBP reduction with HCTZ treatment in Caucasians than those with the A/A genotype. No significant association between the rs4149601 genotype and response to atenolol or to HCTZ-atenolol combination [24].	$P=0.0162$ (SBP, adjusted ADD)
		rs292449	• Candidate gene study				$P=0.1112$ (SBP, adjusted DOM)
		GC haplotype					$P=0.0433$ (DBP, adjusted ADD)
		rs4149601- rs292449 GC haplotype				The rs4149601- rs292449 GC haplotype was associated with SBP and DBP reduction only in HCTZ-treated Caucasians [24].	$P=0.0450$ (DBP, adjusted DOM)
							$P=0.0010$ (SBP, adjusted ADD)
	<i>YEATS4</i>	rs317689- rs315135- rs7297610 haplotype	• Randomized trial	Office BP (manual)	195 Caucasians, 194 African Americans (GERA-1 participants)	The rs317689- rs315135- rs7297610 haplotype was associated with DBP response to HCTZ in African Americans [25].	$P=0.0082$ (DBP, adjusted ADD)
			• GWAS				Nominal $P=2.39\times10^{-7}$
							Bonferroni-corrected $P=0.024$
						ATC haplotype was more frequent among African American “good” responders to HCTZ ($P=0.0002$), while the ACT and the ATT haplotypes were more frequent among “poor” responders [25].	$P=0.0018$ (good responders)
							$P=0.0219$ (poor responders)
		rs317689- rs315135-	• Randomized trial	Office, home ^a , and	746 (Caucasians, African	The ATT haplotype was more frequent in African American “poor” responders than “good” responders to HCTZ [26].	$P=0.01$ (ATT haplotype)

Antihypertensive drug class(es)	Closest gene	Genetic variant(s)	Study design	Method of BP measurement	Participants	Results	Strength of Association
		rs7297610 haplotype	• Candidate gene study	ambulatory daytime/ nighttime BP	Americans; PEAR-1 participants)	African Americans who were C/C homozygotes for rs7297610 had greater BP response to HCTZ than T allele carriers [26].	group) P=0.0275 (SBP) P=0.0196 (DBP)

ADD additive model, BP blood pressure, DOM dominant model, DBP diastolic blood pressure, GERA Genetic Epidemiology of Responses to Antihypertensives study, GWA S genome-wide association study, HCTZ hydrochlorothiazide, SBP systolic blood pressure, MAP mean arterial pressure, NORDIL Nordic Diltiazem study, PEAR Pharmacogenomic Evaluation of Antihypertensive Responses study

^aMethod used in this analysis

Table 2

Polymorphisms recently associated with antihypertensive response

Closest Gene	Biological Effect	SNPs	Associated Drugs or Drug Classes
<i>ADRB1</i>	Encodes the (3-1 adrenergic receptor; SNP associations likely due to genetic effects on adrenergic signal transduction pathways [27].	rs1801252 (Ser49Gly) (replicated) [21, 22] rs1801253 (Arg389Gly) (replicated) [21, 22]	metoprolol
<i>NEDD4L</i>	Encodes a protein that regulates expression of ENaC in the distal nephron, which is responsible for sodium reabsorption in the kidneys [30].	rs4149601 (replicated with HCTZ) [23, 24]	Thiazide diuretics and β -blockers
<i>YEATS4</i>	Link to antihypertensive response unclear. <i>YEATS4</i> encodes the protein GAS41, which has a role in chromatin-modification and transcription and is required for repressing the p53 repressor pathway during normal cellular proliferation [31, 32].	rs317689- rs315135- rs7297610 haplotype (replicated) [25, 26]	HCTZ
<i>TET2</i>	Aldosterone-responsive mediator of α ENaC gene transcription [33]. ENaC mediates Na^+ entry across the apical membranes of renal epithelial cells, playing a role in BP and extracellular fluid volume regulation [33–35].	rs12505746 (not replicated) [36]	HCTZ
<i>CSMD1</i>	Link to antihypertensive response unclear. <i>CSMD1</i> was associated with HTN risk per prior case–control studies [37].	rs7387065 (replicated) [36] rs11993031 (not replicated) [36]	
<i>ROCK1</i>	Rho-associated protein kinases have shown association with vasoconstriction and elevated BP [38].	rs8085654 [39•]	HCTZ
<i>ACY3</i>	Link to antihypertensive response unclear. <i>ACY3</i> is abundantly expressed in proximal tubules of the kidney, where it may play a role in deacetylating mercapturic acids [40].	rs2514036 (not replicated) [41•] rs948445 (not replicated) [41•] rs2514037 (not replicated) [41•]	bisoprolol
<i>CAMK1D</i>	Encodes a protein that is part of the regulatory pathway involved in aldosterone synthesis [42].	rs10752271 (replicated) [43•] rs10906202 rs4747995 rs10737061	losartan

ACY3 Aminoacylase 3 gene, *ADRB1* β -1 Adrenergic Receptor gene, *α ENaC* alpha epithelial sodium channel, *BP* blood pressure, *CAMK1D* Calcium/Calmodulin-dependent protein kinase type 1D gene, *CSMD1* CUB and Sushi multiple domains protein 1 gene, *ENaC* epithelial sodium channel, *HCTZ* hydrochlorothiazide, Na^+ sodium, *NEDD4L* Neural precursor cell expressed developmentally down-regulated 4 like gene, *ROCK1* Rho Kinase 1 gene, *SNP* single nucleotide polymorphism, *TET2* Tet methylcytosine dioxygenase 2 gene, *YEATS4* YEATS domain-containing 4 gene