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Pharmacogenomic studies of hypertension: paving the way for personalized antihypertensive treatment

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Abstract

Introduction—Increasing clinical evidence supports the implementation of genotyping for anti-hypertensive drug dosing and selection. Despite robust evidence gleaned from clinical trials, the translation of genotype guided therapy into clinical practice faces significant challenges. Challenges to implementation include the small effect size of individual variants and the polygenetic nature of antihypertensive drug response, a lack of expert consensus on dosing guidelines even without genetic information, and proper definition of major antihypertensive drug toxicities. Balancing clinical benefit with cost, while overcoming these challenges, remains crucial.

Areas covered—This review presents the most impactful clinical trials and cohorts which continue to inform and guide future investigation. Variants were selected from among those identified in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR), the Genetic Epidemiology of Responses to Antihypertensives study (GERA), the Genetics of Drug Responsiveness in Essential Hypertension (GENRES) study, the SOPHIA study, the Milan Hypertension Pharmacogenomics of hydro-chlorothiazide (MIHYPHCTZ), the Campania Salute Network, the International Verapamil SR Trandolapril Study (INVEST), the Nordic Diltiazem (NORDIL) Study, GenHAT, and others.

Expert Commentary—The polygenic nature of antihypertensive drug response is a major barrier to clinical implementation. Further studies examining clinical effectiveness are required to support broad-based implementation of genotype-based prescribing in medical practice.

Keywords

Antihypertensive; blood pressure; pharmacogenomics; implementation; precision medicine

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Declaration of Interest

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1. Introduction

Implementation of pharmacogenomics is underway across the developed world [1–5]. Thought leaders from the Clinical Pharmacogenomics Implementation Consortium (CPIC) and Dutch Pharmacogenomic Working Group (DPWG) continue to distill abundant pharmacogenomic evidence into actionable recommendations for clinicians [6,7]. Despite a lack of widespread adoption by payers, institutions such as universities, health systems, pharmacies, and private enterprises have driven pharmacogenomics into the clinical sphere because each finds value in implementing personalized medicine for patients.

The National Human Genome Research Institute's 'Implementing Genomics in Practice' (IGNITE) initiative aims to incorporate genomic information into clinical care [8]. Several network members have succeeded in enabling genotype-guided dosing for clopidogrel, warfarin, antidepressants, and pain medications within their health systems [3,9,10]. Although the prevalence of hypertension exceeds 34% (85 million) of the U.S. adult population [11], implementation of genotype-guided dosing for antihypertensive agents has not been prioritized. The opportunity to improve control of hypertension persists, as the number of individuals with treatment-resistant hypertension has steadily increased to 13.7% of the general population and its cardiovascular consequences are significant [11].

Challenges must be overcome in order to realize personalized antihypertensive therapy. Given the enormous prevalence of hypertension, a propensity exists to approach hypertension treatment algorithms on a population-based level. Indeed, the Eighth Joint National Committee (JNC 8) simplified and relaxed therapy targets based on evidence produced from the ACCORD trial [12,13]. Many of the disease-specific blood pressure (BP) thresholds present in prior JNC iterations were removed. Subsequently, the SPRINT trial has again prompted reassessment of BP targets in individuals at high risk [14]. Based on data from SPRINT, tighter BP goals have been adopted by the American College of Cardiology/American Heart Association Task Force [15]. In terms of agent selection, JNC 8 recommended only four classes of first-line medications: thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). Personalization was essentially limited to the prioritization of ACEI and ARB use in those with chronic kidney disease, and the converse in those older than 75 years of age and individuals of African-American (AA) descent – with race perhaps serving as a surrogate for genetic indicators of antihypertensive class response.

In contrast to the prevailing population-based algorithms, the Pharmacogenomics Research Network, International Consortium for Antihypertensive Pharmacogenomics Studies (ICAPS), and other contributors have generated robust evidence demonstrating the interaction of genotype with antihypertensive agent response [16]. The identified variants can be used to predict an individual's response to a given BP medication or class. However, on balance, these interactions have failed to meet the evidentiary standards of CPIC. For most agents, expert consensus on dosing guidelines has not been achieved. Contributing factors include the small effect size of individual variants, population heterogeneity, population size, polypharmacy, a relative lack of major antihypertensive drug toxicities, varying clinical trial designs with relatively small patient populations, and the polygenic

nature of antihypertensive drug response. Overcoming nonadherence to therapy [17], great inter- and intra-patient BP variability [18,19], and differences in BP measurement strategies [20,21] may be of equal or greater importance in improving clinical effectiveness than genotype-guided prescribing. Provider inertia is an additional barrier due to a lack of familiarity with pharmacogenomics [22,23]. With an extensive arsenal of antihypertensive agents available, clinicians may feel they have 'personalized' antihypertensive therapy long before genotype–phenotype associations were identified. As such, the translation of pharmacogenomic data into hypertension therapy has been relegated until further replication and validation is conducted.

Nonetheless, this report seeks to evaluate relevant genomic studies of hypertension with their identified variants that portend the highest likelihood of clinical translation. The prevalence of hypertension is considerable and the associated cardiovascular consequences are severe [11], so the improvement in clinical effectiveness provided by pharmaco-genotyping is welcome and important. We now focus our attention on studies affording differential antihypertensive agent selection. Genomic predictors of incident hypertension fall outside the scope of this report. The ensuing review delineates the studies, variants, and related genes with the greatest evidence for clinical utility.

2. Body

A broad range of genetic variants and loci have been identified as predictors of hydrochlorothiazide (HCTZ) response (Table 1), beta-blocker response (Table 2), and response to CCBs or rennin-angiotensin system inhibitors (Table 3). Evidence for these associations was provided by a number of pharmacogenomic cohorts and trials including the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR), the Genetic Epidemiology of Responses to Antihypertensives (GERA) study, the Genetics of Drug Responsiveness in Essential Hypertension (GENRES) study, the SOPHIA study, the Milan Hypertension Pharmacogenomics of hydrochlorothiazide (MIHYPHCTZ), the Pharmacogenomics of Hydrochlorothiazide Sardinian Study (PHSS), the Campania Salute Network (CSN), the International Verapamil SR Trandolapril (INVEST) Study, the Nordic Diltiazem (NORDIL) Study, and GenHAT. The polygenic nature of anti-hypertensive efficacy significantly complicates efforts to implement genetic testing for these agents in clinical practice. To date, a complete multigene model has not been developed to guide dosing or drug selection for these drugs. Further, the partial models that are available often do not account for environmental factors such as sodium intake or biochemical markers like renin activity levels. The evidence supporting these predictors is outlined below.

2.1. Pharmacogenomic Evaluation of Antihypertensive Responses

The first Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR1) study was a prospective cohort study which sought to evaluate genetic predictors of HCTZ and atenolol response in 768 subjects [24]. The Caucasian (N = 461) and AA (N = 298) populations were analyzed separately. After antihypertensive drug washout, subjects were initially prescribed either HCTZ or atenolol monotherapy for 9 weeks. The alternate drug was added if BP control (<120/ 70 mm Hg) was not obtained after titration of the initial drug which occurred

in over 90% of participants. PEAR1 compared home BP response to genotype in 37 candidate single nucleotide polymorphisms (SNPs) which were selected from previously published SNPs associating with BP traits in large epidemiologic studies with tens of thousands of patients [25–29]. These traits included cross-sectional systolic blood pressure (SBP) and diastolic blood pressure (DBP), but the investigations had not specifically evaluated BP change in response to an antihypertensive agent.

PEAR1 assessed BP response to monotherapy after 9 weeks. At the conclusion of the study, no variant met Bonferroni-corrected statistical significance [30]. However, a three SNP model composed of rs1458038 (*FGF5*), rs3184504 (*SH2B3*), and rs4551053 (*EBF1*) explained 4.3% and 5.3% of the SBP and DBP response, respectively, to HCTZ monotherapy in Caucasians. None of these SNPs were similarly correlated in the AA population. In fact, the SNP in *SH2B3* was nominally associated with HCTZ response with the opposite direction of effect in AAs.

A second model of HCTZ response was facetted by uniting metabolomics and genomics approaches. Three novel variants, rs2727563 in *PRKAG2*, rs12604940 in *DCC*, and rs13262930 in *EPHX2* were uncovered in a genome-wide analysis of the Caucasian PEAR1 cohort, with replication in the GERA cohort (described below) [31]. The metabolomics profiling identified 13 molecules associated with HCTZ monotherapy SBP and DBP responses, which were enriched for interaction with netrin signaling. Three SNPs in the model were selected after a round of replication because of their association with the arachidonic acid metabolic pathway. The crafted model is additive; individuals with only 1 BP lowering allele had an average change in SBP and change in DBP of −1.5 and 1.2 mmHg, respectively. In contrast, individuals with 6 BP lowering alleles had more remarkable reductions in SBP and DBP at −16.3 and −10.4 mmHg, respectively. The model was able to account for 11–12% of the variability in HCTZ BP response. Although both the *FGF5/SH2B3/EBF1* and the *PRKAG2/DCC/EPHX2* models show promise, a combined six-gene model evaluating the independent contribution of all of these variants has yet to be reconciled.

Analogous to the HCTZ models, PEAR1 sought to establish predictive model of atenolol monotherapy response in Caucasians. A four SNP model was derived and is listed in Table 2. rs1458038 in *FGF5* is common to both the atenolol and HCTZ models, but with the C allele favoring atenolol efficacy and the T allele associated with HCTZ response. This SNP may prove to be a useful marker in BP agent selection. Again, these variants failed to replicate in the AA population. The authors concluded that there was insufficient evidence to suggest the genetic scores for either atenolol or HCTZ BP lowering alleles in Caucasians were associated with BP response in AAs – even when index SNPs were evaluated in flanking regions of the initial candidate variants. While PEAR1 was underpowered to identify a single variant strongly predictive of BP response, important insights were gleaned into the pharmacology of these drugs. When analyzed in conjunction with other BP response studies, additional associations have been identified which are discussed below.

To demonstrate the importance and the power of combining study cohorts, the PEAR1 study participants were analyzed in conjunction with the GENRES and INVEST cohorts

(described below). Although not part of the above model, variants in *PTPRD* were found to be significantly associated with atenolol monotherapy response, with the opposite direction of effect noted for HCTZ [32]. Using a genome-wide association study (GWAS) analysis, several SNPs near *PTPRD* correlated with BP response to atenolol and HCTZ therapy. The *PTPRD* gene encodes for protein tyrosine phosphatase receptor D which is important in malignant glioma. Two SNPs, rs12346562 and rs1104514, are located upstream of *PTPRD* gene on chromosome 9p23 and were associated with favorable DBP to atenolol and unfavorable DBP response to HCTZ in Caucasians. A different SNP, rs10739150, was located downstream of the *PTPRD* gene on chromosome 9p23 and was associated with favorable DBP to atenolol in the AA population. Finally, two additional SNPs, rs4742610 and rs324498, located in intron of *PTPRD* gene were associated with resistant hypertension in patients with coronary artery disease. Since the SNPs near the *PTPRD* gene are predictors of the responses to atenolol and HCTZ with the opposite directional effects, these mutations could prove important in tailoring initial antihypertensive therapy, much like rs1458038 in *FGF5*.

The second iteration of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR2) study assessed class effects of thiazides and B-blockers and studied chlorthalidone and metoprolol response in 457 AAs and Caucasians. CYP2D6 metabolizer status was identified as a predictor of metoprolol response [33]. This drug–gene pair now has formal allele-based dosing recommendations outlined by the DPWG. Subjects receiving chlorthalidone in PEAR2 served as a replication cohort for PEAR1 to help identify an expression quantitative trait locus, rs10995, near the gene vasodilator-stimulated phosphoprotein (*VASP*). rs10995 was associated with improved systolic and diastolic BP response, as well as *VASP* mRNA expression [34].

In a combined meta-analysis of the first PEAR1 and PEAR2 cohorts, the association of β-blocker BP response with genotype was investigated in the AA population [35]. A total of 459 individuals (150 treated with atenolol alone, 168 treated with metoprolol alone, and 141 treated with atenolol and HCTZ) were included in the analysis. The variant rs201279313, characterized by the deletion of a TTA in the intronic region of *SLC25A31*, was associated with favorable DBP response to atenolol at a Bonferroni-corrected significance in the meta-analysis. The *SLC25A31* gene encodes a membrane transporter involved in the exchange of ADP and ATP across mitochondrial membranes which maintains mitochondrial membrane potential.

A second associated variant, rs11313667, is characterized by an insertion/deletion variant (C/−) in the intronic region ofleucine rich repeat containing 15 (*LRRC15*) gene. This SNP was associated with favorable SBP response in the AA population. It is important to note that platelet glycoprotein 5 present in the intronic region of the *LRRC15* gene is associated with thrombosis and is elevated in hypertensive patients. In the β-blocker monotherapy group, a third SNP variant, rs1367094 present in the intronic region of the gene *ZMAT4*, was also associated with better DBP response at genome-wide significance. The effect size of the three variants was robust with per allele β values of −4.42 (rs201279313), −3.65 (rs11313667), and −5.34 (rs1367094) mmHg. The SNPs discovered in this genomic wide meta-analysis warrant further investigation.

2.2. Genetic Epidemiology of Responses to Antihypertensives

The Genetic Epidemiology of Responses to Antihypertensives (GERA1 and GERA2) studies were the earliest pharmacogenetics study in antihypertensive agents and are a set of multi-ethnic prospective cohort studies examining the interindividual variability of response to antihypertensive agents [36,37]. After a 4 week washout, GERA1 evaluated response to 4 weeks of HCTZ monotherapy in 505 individuals (280 Caucasian and 225 AA). GERA2 assessed candesartan monotherapy response in 439 individuals of White and AA descent. The GERA cohorts have been employed in both discovery and replication analyses. Since many of the primary cohort studies involved multiple drugs or subjects from multiple racial backgrounds, pooling these studies has proven essential for increasing the sample size to enable discovery and improve generalizability of any identified variants.

For example, in a meta-analysis of over one million variants in the GERA1 and PEAR study cohorts, two variants were identified in HCTZ-exposed Caucasians at nearly genome-wide significance [38]. The two cohorts had similar demographics except that the PEAR enrollees were older and had higher pretreatment BPs. However, GERA1 assessed BP in a clinical research center, as opposed to the home BP responses measured in PEAR. The most significant association with HCTZ BP response was rs16960228, an intronic SNP located in *PRKCA* (encoding protein kinase Cα) which met genome-wide significance. This drug–gene interaction was replicated in the GENRES and NORDIL studies, but did not reach significance in the MIHYPHCTZ study (trials described below). A second variant, rs2273359 near the *GNAS-EDN3* gene regions, was nearly genome-wide significant. The association was replicated in the NORDIL study, but genetic data were unavailable for this variant in the GENRES and MIHYPHCTZ studies.

In AAs, the strongest signal identified for HCTZ response was found in *YEATS4* (YEATS domain containing 4) related to rs7297610 [39]. This SNP was independently associated with DBP response in both the GERA1 and PEAR 1 cohorts. rs7297610 belongs to a haplotype consisting of two additional variants on chromosome 12 – rs317689 near *LYZ* (lysozyme) and rs315135 near *FRS2* (fibroblast growth receptor substrate 2). The variant rs7297610 was found to be an expression quantitative trait locus of *YEATS4*, as baseline leukocyte mRNA expression varied across genotypes [40]. Expression of *YEATS4* was reduced post-treatment in those with the CC genotype, providing mechanistic insight into the relevance of this variant.

The GERA2 study identified genes relevant to angiotensin II receptor blockade. One sub-investigation identified 273 polymorphisms which predicted candesartan response, but held the opposite direction of effect for associations with HCTZ response [41]. The SNP rs11020821 near *FUT4* (fucosyltransferase 4) was the most highly associated variant in Caucasians. A second SNP near *FUT4*, rs16924603, was nominally significant and maintained the same direction of effect in AAs. These variants may prove important in the selection of a diuretic or angiotensin II receptor blocker as initial antihypertensive therapy.

2.3. Genetics of Drug Responsiveness in Essential Hypertension and Losartan Intervention For Endpoint Reduction in Hypertension

The GENRES study was a single center, placebo-controlled crossover study. Subjects included 228 Finnish men who received monotherapy of amlodipine, bisoprolol, HCTZ, or losartan in a sequential, but randomized order [42]. The study differed from PEAR and GERA in that neither home nor office BP was measured; instead, 24 h ambulatory BP monitoring was employed. The GENRES study importantly identified the missense variant rs3814995 in nephrin (*NPHS1*), which is enriched in the Finnish population associated with losartan response [43]. This variant was first replicated in the GERA2 and SOPHIA cohorts, and later in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, an additional Finnish cohort study (including men and women) which examined atenolol and losartan response in 927 subjects [44]. As opposed to GENRES, LIFE did not include an a priori pharmacogenomic outcome and this information was retrospectively acquired.

By co-examining the bisoprolol arm of the GENRES study with the atenolol arm of LIFE, rs2514036, a SNP in ACY3, was found associated with beta-blocker response. However, rs2514036 was not found to be predictive of atenolol response in the PEAR cohort. Two additional HCTZ response SNPs were uncovered near the *ALDH1A3* (rs3825926) and *CLIC5* (rs321329) genes, which maintained the same direction of effect in the PEAR and GERA1 cohorts.

2.4. The Italian cohorts

Four Italian studies have contributed considerable evidence for novel pharmacogenomic predictors of BP response: SOPHIA, the PHSS, the MIHYPHCTZ, and the CSN. The SOPHIA study specifically assessed losartan response in 372 hypertensive individuals. The study initially enrolled 722 hypertensive subjects with a systolic BP between 140 and 179 mmHg and DBP between 90 and 109 mmHg [45]. Clinic visit BP response was utilized as the primary outcome after 4 weeks of losartan therapy. A number of issues affected the sample size in this investigation. For example, 25.3% of the cohort had normalization of their BP during an 8-week run-in period which required enrollees to meet dietary sodium and potassium restrictions. These subjects, as well as those with prior BP treatment (N = 106), were excluded from the final analysis. Finally, the genotyping of 124 individuals failed to meet quality control. In the 372 remaining individuals, four SNPs (rs10752271, rs10906202, rs4747995, and rs10737061) in the *CAMK1D* gene were significantly associated with losartan SBP response. The gene is relevant to the aldosterone synthesis pathway. An intronic SNP of *CAMK1D*, rs10752271, reached Bonferroni significance and was replicated in the GENRES cohort. Whether this variant can be extrapolated as a predictor of response to other ARBs remains to be seen since the SNP was not associated with candesartan response in the GERA2 study.

Two Italian cohorts evaluated HCTZ response in individuals without prior treatment. The MIHYPHCTZ enrolled 142 newly diagnosed individuals with hypertension and the PHSS contributed an additional 343 individuals who had not undergone prior treatment for hypertension [46]. All participants were Caucasian with an office SBP > 140 mmHg and a DBP > 90 mmHg (MIHYPHCTZ allowed either SBP or DBP as entrant criteria). Both

studies maintained similar protocols. The MIHYPHCTZ study required a 4-week run-in period to standardize sodium and potassium intake, followed by an 8-week total treatment period. This interventional period consisted of 12.5 mg daily of HCTZ for 4 weeks and then 25 mg daily of HCTZ for the final 4 weeks. The PHSS study used an 8-week run-in period, followed by an 8-week intervention trial of 25 mg daily of HCTZ without titration. Subjects in the PHSS cohort were older with higher BMIs and pretreatment SBPs. The GENRES, GERA1, NORDIL, and CSN served as replication cohorts.

The GWAS in these two Italian cohorts revealed six variants predictive of SBP response and five variants predictive of DBP. No SNPs were significant for both phenotypes. The most highly associated variants with SBP response were found in the introns of two genes, *TET2* or Tet methylcytosine dioxygenase 2 (rs12505746) and *CSMD1* or CUB and Sushi multiple domains protein 1 (rs7387065 and rs11993031). Two SNPs, rs12505746 in *TET2* and rs7387065 in *CSMD1*, were replicated in the GENRES cohort, but not in the GERA1, NORDIL, PEAR, or CSN groups. Both genes appear to have plausible mechanisms as *TET2* is a mediator of αENaC gene transcription in the renal collecting duct and *CSMD1* is a member of the vacuolar-protein-sorting-13 family that has been associated with peripheral artery disease, metabolic syndrome, and risk of hypertension. One SNP identified in MIHYPHCTZ and PHSS, rs9590353 in *UGGT2*, was associated with HCTZ DBP response and was replicated in the CSN cohort. *UGGT2* encodes a glycoprotein without a clear mechanistic role in hypertension.

The CSN is an Italian network consisting of thousands of individuals with hypertension [47]. These individuals are followed longitudinally by general practitioners near Naples. The network has evaluated the interaction of hypertension with renal function [48], obesity [49], left ventricular hypertrophy [50], and many other relevant phenotypes. This cohort has contributed important data detailing the role of a Gln27Glu variant (rs1042714) in the Beta2-adrenergic receptor *ADRB2* gene that mediates differential effects on left ventricular hypertrophy in those treated with atenolol [51]. The authors conclude that individuals with the Glu27 allele are more likely to benefit from enalapril therapy as opposed to atenolol. Of note, the opposite conclusion was reached in an Australian cohort where Gln27 homozygotes showed less improvement in LVH in response to carvedilol [52].

2.5. International Verapamil SR Trandolapril Study

The INVEST Study is a multinational, open label study of 22,576 patients with hypertension and coronary artery disease [53]. The study aimed to compare morbidity and mortality outcomes in individuals randomized to receive verapamil or atenolol. Subjects were co-treated with trandolapril and/or HCTZ to achieve adequate BP control. The study concluded that the calcium antagonism strategy was as effective as the β-blockade strategy in achieving BP goals and preventing adverse events. A subset of individuals was genotyped as part of the INVEST-GENES study, enabling a number of important BP response variants to be uncovered. Many of the studies discussed in detail above were specifically developed with a primary endpoint of BP response; in contrast, INVEST was different as its primary outcome was related to cardiovascular events including all-cause death, nonfatal MI, and nonfatal stroke.

Since the study involved a CCB arm, it follows logically that several of the genes uncovered in INVEST are related to calcium transport or sensitivity. One such gene, *KCNMB1* [54], was relevant for verapamil response in 5979 INVEST patients with White, Black, or Hispanic ancestries. *KCNMB1* encodes the β1 subunit of the BK channel. Decreased function of this protein is associated with decreased calcium sensitivity, elevated BP, and cardiac hypertrophy. Two nonsynonymous polymorphisms in the *KCNMB1* gene, Glu65Lys (rs11739136) and Val110Leu (rs2301149), contribute to the inter-patient variability in verapamil BP response. Lys65 variant carriers achieved BP targets faster than individuals who were homozygous for Glu65. The Leu110 allele correlated with protection from nonfatal myocardial infarction in patients treated with verapamil, but not those treated with atenolol.

Mirroring these results, important variants in the calcium channels themselves have been identified which may aid in the differential selection of a CCB or β-blocker. The variants tested were uncovered through candidate association studies, not genome-wide tests. *CACNA1C* encodes the alpha1c-subunit of the L-type calcium channel. In a candidate SNP nested case-control study, eight SNPs in *CACNA1C* were screened for an interaction between treatment effect of verapamil or atenolol with the primary outcomes of death, myocardial infarction, and stroke. Among those randomized to verapamil SR treatment, rs1051375 allele status correlated strongly with outcome. The AA genotype was associated with a reduction in the primary outcome (odds ratio 0.54, 95% confidence interval or CI 0.32–0.92), while the GG genotype was associated with an increased risk of the composite primary outcome in those taking verapamil (odds ratio 4.59 95% CI 1.67–12.67) [55]. A second calcium channel, *CACNB2* encoding the regulatory β2 subunit of the voltage-gated calcium channel, was associated with cardiovascular outcomes in individuals randomized to the verapamil arm [56]. The GG genotype of a promoter SNP (rs2357928) was associated with an increased risk of the primary outcomes in Whites, Blacks, and Hispanics in the verapamil arm as compared to the atenolol arm. A second SNP, rs11014166, was also similarly associated with outcomes in those of Hispanic ancestry as compared to Whites or Blacks. *CACNA1C* and *CACNB2* remain mechanistically plausible genes that may aid in the selection of a CCB or beta-blocker.

The large sample size of INVEST-GENES facilitated the replication of commonly studied variants. For example, the influence of *ADRB1* on hypertension and β-blocker response is well-documented, but inconsistent [57–61]. In INVEST, the Ser49-Arg389 *ADRB1* haplotype was associated with a significant mortality risk (odds ratio 3.66, 95% CI 1.68–7.99) – whether 1 or 2 alleles were present [62]. This haplotype consists of a two SNP model: rs1801253 (Arg389Gly) and rs1801252 (Ser49Gly). The mortality risk was more pronounced in individuals treated with verapamil and nonsignificant in those individuals receiving atenolol. This finding would suggest that those with the Ser49-Arg389 should preferentially receive β-blocker therapy as it attenuates the risk mortality risk of the Ser49-Arg389 *ADRB1* haplotype. INVEST did not necessarily conclude the converse, i.e. that Gly49 individuals should preferentially receive CCB therapy. However, this recommendation would be corroborated by recent results from the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, in which individuals with the *ADRB1* Gly49 allele

who were treated with atenolol were at higher risk for major adverse cardiovascular events (hazard ratio 2.03; 95% CI 1.20–3.45) [63].

Of note, additional variants relevant to adrenergic signal transduction have been assessed. Polymorphisms in G protein–coupled receptor kinase 4 (*GRK4*) interrupt adrenergic signaling by leading to phosphorylation of the adrenoreceptors and inhibition of cyclic adenosine monophosphate production. GRK4 polymorphisms were identified in the PEAR and INVEST cohorts which both impact atenolol mediated BP reduction and cardiovascular outcomes [64].

While the INVEST cohort reinforced the association of the *ADRB1* haplotype with β-blocker response phenotypes, the study had the opposite effect on another well-chronicled variant, rs4961 in the α-adducin gene (*ADD1*). The T allele of this SNP is a nonsynonymous Gly460Trp mutation in *ADD1*. It has been associated with salt sensitivity, conferring increased diuretic efficacy in some studies, but not others [65–68]. A meta-analysis of four studies and more than 1000 patients ultimately found a small but significant effect of the GG genotype on increased HCTZ BP response [69]. However, the results of INVEST suggest the T allele is associated with increased cardiovascular risk, but not HCTZ response as measured by either 1) DBP change or 2) total number of antihypertensive agents required for BP control [70].

To develop clinically useful recommendations from a vast quantity of genetic data – facilitating selection of either β-blocker or CCB therapy – the INVEST group built a genetic risk score model [71]. The most highly associated nonsynonymous SNPs in the White and Hispanic ethnic groups were tested and later validated in the NORDIL study. Three variants were selected for inclusion in the model: rs16982743 in *SIGLEC12*, rs893184 in *A1BG*, and rs4525 in *F5*. A genetic risk score ranging from 0 to 3 is assigned based on the number of variant alleles present with one point applied for each genotype that confers increased risk in the verapamil arm over the atenolol arm. In individuals with a risk score of 0 or 1, CCB therapy was associated with lower odds of meeting the cardiovascular endpoint (odds ratio 0.60, 95% CI 0.42–0.86), while those at higher risk with a score of 2 or 3 were more likely to meet a cardiovascular endpoint higher risk (odds ratio 1.31, 95% CI 1.08–1.59) on verapamil and should receive a β-blocker instead.

2.6. Nordic Diltiazem

The NORDIL Study is a prospective, randomized study which enrolled over 10,000 subjects aged 50–74 in Norway and Sweden [72]. The cohort was composed of individuals with an initial diastolic BP exceeding 100 mmHg. Individuals were randomized to receive diltiazem, a diuretic, a β-blocker, or both a diuretic and a β-blocker. The study concluded that diltiazem was as effective as diuretics, beta-blockers, or both in preventing cardiovascular adverse events. An additional outcome of the study was the identification of rs13333226, a SNP in the uromodulin gene (*UMOD*) [73]. While this SNP was not associated with response to an antihypertensive agent, it was independently associated with a risk of hypertension and reduced urinary uromodulin excretion. The variant's renal etiology provides a plausible mechanism for mediating sodium homeostasis.

NORDIL contributed a couple of very important pharmacogenomic predictors of drug response. First, in a sub-study of 1990 diltiazem treated individuals, genotyping was completed for rs12946454, an intronic SNP of *PLCD3*. *PLCD3* encodes a Phospholipase C enzyme, essential for calcium release in smooth muscle and maintaining vascular tone. The T allele of *PLCD3* was associated with both increased systolic and diastolic BP response to diltiazem [74].

A second major contribution of the NORDIL study was to help identify a polymorphism in *NEDD4L* (the neural precursor cell–expressed developmentally downregulated 4-like) gene as a mediator of HCTZ response [75]. This SNP leads to alternative splicing and varying expression of the C2 domain in its host gene and related protein [76]. NEDD4-2 assists in the regulation of cell surface expression of the epithelial sodium channel (ENaC) in the principal cell of the collecting duct. The G allele of this SNP is associated with higher ENaC expression and higher baseline BP. This allele also predicted greater response to HCTZ and atenolol in the NORDIL study, without an effect on diltiazem efficacy, a finding that was replicated in both the PEAR and INVEST studies [77].

2.7. GenHAT

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a large study of over 40,000 individuals that reached completion in 2002. The study randomized patients aged 55 or older with at least one cardiovascular risk factor to chlorothalidone, atenolol, doxazosin, lisinopril, or amlodipine therapy. BP response and cardiovascular outcomes were assessed. As an ancillary study to ALLHAT, GenHAT included 39,114 individuals and examined several candidate hypertension-related genes to determine if variants in the six genes interacted with antihypertensive drug response.

The *ACE* gene regulates the renin-angiotensin system and promotes conversion of angiotensin I to angiotensin II. Previous studies had identified an interaction between ACE-inhibitor response and the insertion/deletion (I/D) polymorphism in the *ACE* gene (rs1799752) that accounts for variation in circulating levels of the angiotensin converting enzyme. GenHAT rather definitively showed that the DD genotype does not influence BP reduction or cardiovascular outcomes in patients on ACE-inhibitor therapy, as compared to the I/D and II alleles [78]. Although the investigators noticed differences in the prevalence of myocardial infarction and left ventricular hypertrophy, the rates of death during 5-year follow-up did not differ for the various ACE I/D genotypes. Some of the reasons for the observed difference in BP independent effects in ACE I/D genotype groups might be related to variation in circulating ACE levels. Although the ACE DD genotype was not associated with ACE-inhibitor response, an additional meta-analysis did find a small but significant association with HCTZ response [69].

GenHAT is one of the larger genetic studies of hypertension. Its cohort was sufficient to enable primary discovery in the AA population. A sub-study assessed the contribution of genetics to interindividual variability in response to chlorothalidone, doxazosin, lisinopril, and amlodipine in AAs. Thirty-five candidate genes involved in the regulation of salt-water balance, the renin-angiotensin system, coagulation, and tissue modeling were interrogated in

1131 participants to determine BP response to each medication [79]. No variants reached Bonferroni-corrected significance.

Despite this, several variants were identified at suggestive levels of significance which can differentiate response to the various BP agent pairings. For example, SNPs in *AGTR1* (rs275653), *F7* (rs6046), *F13* (rs5985), *MMP3* (rs3025058), and *REN* (rs6681776) were able to assist in distinguishing predicted chlorthalidone efficacy from amlodipine or doxazosin. Variants in *AGT* (rs5051), *F7* (rs762637), and *REN* (rs6681776) were useful in predicting lisinopril utility over that of chlorthalidone. It is interesting to note that the *F7* and *MMP3* genes were associated with both cardiovascular outcomes and BP response to medications.

2.8. International Consortium for Antihypertensive Pharmacogenomics Studies

The ICAPS (http://icaps-htn.org) is a multinational collaboration of at least 29 cohorts with over 300,000 participants. All of the studies and trials described above are included among its associated groups. ICAPS states its goal is to advance pharmacogenomic discovery and find definitive evidence to inform the use of genetic information to guide antihypertensive treatment decisions.

The power of this collaborative approach is illustrated in a recent meta-analysis of HCTZ BP response [80]. This study included individuals from the GENRES, GERA1, MIHYPHCTZ, NORDIL, PEAR1, and PHSS studies. Caucasians were used as the discovery cohort and the AA population was examined for replication. The meta-analysis identified two regulatory regions *GJA1* (Gap Junction protein Alpha 1 gene) and *FOXA1* (Forkhead box A1 gene) using a GWAS. *GJA1* was associated with SBP response to thiazides in the caucasian population (rs11750990). *GJA1* encodes for Connexin-43, a gap junction protein, which is present in myocardial smooth muscles and regulates cell-to-cell communication, elasticity and contractibility of vascular wall. In the replication cohort, a similar association was found in a second *GJA1* variant, rs10499113, in the AA population.

The second locus near *FOXA1* was associated with DBP response to HCTZ in both Caucasians (rs177848) and AAs (rs177852). *FOXA1* is expressed in the collecting duct of the kidney and it appears to be a transcription factor, binding to the promoter regions of the vasopression receptor, Na+-K+ ATPase, and E-cadherin genes. Although none of the four SNPs in *GJA1* and *FOXA1* met genome-wide significance, all of the associations were suggestive. Adjunctively, the investigators performed a functional GWAS, using a gene-expression-based filtering of the variants. In the meta-analysis approach, the *HSD3B1* gene (Hydroxyl-delta-5-steroid-dehydrogenase, 3 beta and steroid delta-isomerase 1) was identified and found to influence BP response to thiazides in the Caucasian population. *HSD3B1* is associated with aldosterone and ouabain synthesis; genetic variation in this gene has been associated with BP variation. The three gene loci that were identified influence the BP response to thiazide diuretics. Future research should be focused on reconciling these associations with the many other predictors of thiazide response, building the most complete model possible.

2.9. Pharmacogenomic studies in Asian cohorts

A number of excellent cohort studies have examined variants predictive of antihypertensive response in Asian populations. In a Chinese prospective cohort called the Chinese Community-Based Comprehensive Prevention and Control of Hypertension project, candidate gene variants were assessed in an analysis of 1447 individuals. A SNP (rs7079) in *AGT* was found to be nominally associated with DBP reduction during benazepril therapy [81]. In a smaller cohort of 265 Japanese individuals (part of the HOMED-BP-GENE study) six SNPs were identified at nominal significance as associated with BP response of CCBs, ACE-inhibitors, and angiotensin II receptor blockers [82]. It is well known that amlodipine is metabolized by the CYP3A4 and CYP3A5 enzymes. In a study of hypertensive Chinese patients after renal transplantation, significant associations were found that the efficacy of amlodipine in CYP3A5*3 homozygotes was significantly higher than that in patients with other CYP3A5 genotypes [83].

2.10. Biologically attractive variants

The associations discussed in the preceding sections have been uncovered through either carefully selected candidate variant studies or unbiased whole genome approaches. Biologic plausibility is readily understood for candidate variants in genes of BP pathways such as the renin-angiotensin-aldosterone system, adrenergic signaling, or sodium reabsorption pathways. For example, rs4149601 in NEDD4L impacts expression of ENaC in the collecting duct, driving sodium reabsorption. The locus for this SNP was first found in a linkage analysis and then the actual SNP was confirmed to impact BP in additional cohorts [76,84,85]. Subsequently, the G allele of this SNP was found to be associated with higher ENaC expression, higher baseline BP, and improved response to diuretics [75]. Although the NORDIL study identified an association between the G allele of rs4149601 and diuretic response, the effect size was greatest among the 258 individuals on a potassium-sparing diuretic (β: 9.0 ± 3.4 mmHg in the dominant model) such as amiloride which directly blocks ENaC – speaking to the biologic relevance of this variant.

Other biologically attractive candidate variants include the GenHAT variants in angiotensinogen (rs5051) and renin (rs6681776). These SNPs offer credible targets for discrimination between lisinopril and chlorthalidone efficacy [79], possibly acting as surrogates for renin activity. Analogously, the *CACNA1C* (encoding a subunit of the L-type calcium channel) variant from INVEST (rs1051375) aids in differential selection of a β-blocker or CCB [55]. Further corroborating their role, variants in *CACNA1C* and *AGT* were also discovered to predict incident hypertension in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium [26]. These studies indicate that several gene loci that predict the development of hypertension and cardiovascular outcomes also influence the response to anti-hypertensive medications.

In contrast, rs7297610 in *YEATS4* is a less obvious biologically attractive candidate. *YEATS4* is a transcription factor that is involved in acetylation of nucleosomal histone proteins. The SNP was initially identified as part of a GWAS [39]. In order to enhance the plausibility of its relationship to HCTZ response, the investigators showed that the variant

allele impacted expression of its host gene and that expression was associated with a HCTZ response phenotype [40].

Ten Genome wide association studies have revealed a great deal about the underlying biology of hypertension. To this end, a number of variants and genes identified in 10 of the largest incident hypertension GWAS trials [25–29,86–90] were cross-referenced with the pharmacogenomic predictors discussed above. Since the variants from genes discovered in the disease association studies served as candidates for some of the pharmacogenomic studies, overlap did exist. As discussed above, SNPs from *FGF5, SH2B3*, and *EBF1* were associated with both HCTZ response in PEAR and incident hypertension in the CHARGE consortium [29,30]. SNPs in *PLCD3, CACNA1C*, and *ADRB1* were similarly found to impact incident BP in the CHARGE and Global BPgen Consortiums [26,29]. The majority of variants and genes that overlap with pharmacogenomic variants were identified from disease association studies published prior to 2015. It is possible that the variants in newer GWAS studies [86–90] will ultimately associate with antihypertensive drug efficacy, but these studies have not been conducted yet.

Pharmacogenomic Predictors of Toxicity—Much of the discussion above has centered on variants associated with BP drug efficacy; however, variants associated with pharmacogenomic predictors of toxicity have also been uncovered – with the strongest evidence found in the HCTZ studies. For example, the GERA and PEAR studies have identified genetic variation underlying HCTZ-induced hypertriglyceridemia, elevated uric acid levels, and hypokalemia. Two variants in NELL1, rs12279250 and rs4319515, were found to be associated with a significant change in fasting serum triglyceride levels in AAs [91]. In both AAs and Caucasians, several loci were identified that predicted elevations in uric acid [92]. In the PEAR and GERA cohorts, two SNPs near the HEME binding protein 1 gene (rs10845697) and the Mitoferrin-1 gene (rs11135740) were found to be significant predictors of hypokalemia in a mixed analysis of Caucasians and AAs [93].

Variants have also been identified that are predictive of HCTZ-induced new-onset diabetes or elevated fasting plasma glucose in the INVEST-GENES study. In the INVEST and PEAR cohorts, variants predictive of elevating fasting blood sugar or new-onset diabetes have been investigated. Studies have identified SNPs associated with the development of HCTZ-induced new-onset diabetes [94–96]. A risk allele, rs7917983 in *TCF7L2*, yielded an odds ratio of 1.53 (95% CI 1.04–2.25) for the development of diabetes in response to HCTZ use. The opposite allele held a protective effect, as it decreased the odds of diabetes development to 0.48 (95% CI 0.27–0.86) in individuals never treated with HCTZ [94]. In a candidate association study, *KCNJ1* was assessed because of the suspected relationship between HCTZ-induced hypokalemia and blood sugar. *KCNJ1* encodes a potassium channel which has been associated with changes in fasting plasma glucose in response to HCTZ treatment. During a combined analysis of INVEST and PEAR, over 10 SNPs were found to be significantly associated with new-onset diabetes during HCTZ therapy. Haplotypes were constructed for the AA, Hispanic, and Caucasian populations [95] which are predictive of diabetes development. Although the odds ratio of new-onset diabetes is above 2 when risk alleles are present, it is clear a multivariant predictive model is required should this information be translated into clinical practice.

3. Conclusion

In summary, we present an overview of the most impactful pharmacogenomic studies of antihypertensive agent response. A prodigious wealth of information has been derived from the efforts of those involved in PEAR, GERA, GENRES, SOPHIA, MIHYPHCTZ, the CSN, INVEST, NORDIL, GenHAT, ICAPS, and others. This knowledge has increased our appreciation of the underlying pathophysiology of hypertension as well as the pharmacodynamics of commonly used drugs. High evidence variants relevant to HCTZ, β-blockade, calcium channel antagonism, and renin-angiotensin antagonism are presented and summarized.

It is most likely that polygenic models will be needed to inform clinical behavior in an additive fashion. A sophisticated computational analysis will be required to build clinical recommendation sets from the polygenic architecture that has been discovered. As we move into the next phase of pharmacogenomic discovery and application, randomized controlled trials should, to the extent possible, standardize genotyping platforms, define precise phenotypes and outcomes, and employ common BP measurement techniques. Clinical effectiveness trials may be entertained which examine panels of genes in a real-world setting of polypharmacy. The incredible diversity of genes and variants uncovered presents both an obstacle and an opportunity for future clinical translation.

4. Expert commentary

The promise of discovery using GWA Studies for complex medical disorders has been significantly underappreciated. As this review shows, multiple SNPs in genes with biological plausibility for a role in hypertension, BP response and/ or alternatively cardiovascular and mortality risk have been identified. Given that only rare variants would have a large effect size, it is not surprising that the platforms used in the pharmacogenetics studies reported in this review would not capture these variants given that all required a minor allele frequency of > 0.05. This review substantially supports the value of multiple SNPs in combination providing significant measures of the interindividual variability of BP response to multiple classes of antihypertensive agents. In addition, although evidence for adverse events related to antihypertensive therapy is now forthcoming, it is highly likely that many more issues related to the genetic prediction of safety of antihypertensive medications will be coming forward.

Power and replication continue to be the biggest barriers to identifying genetic predictors of BP response. Combined cohorts, as mentioned in this report, are limited primarily in heterogeneity in study design that impacts patient characteristics, methods of pre-study medication withdrawal, and duration and dosing of study medication. Despite these differences, consistent genetic signals are emerging, which should, if they play a predictive role in BP response to a particular agent or class of agent. This suggests then, that despite heterogeneity of study populations and study design, the same answer should be obtainable.

Implementation science is now required to best take these findings forward in a way that is clear, easy to use and overcomes the potential clinician inertia that may be present due to

lack of formal education in genetics, familiarity with the available pharmacogenomic evidence, and a computer decision support (CDS) system which efficiently filters drug dose and class recommendations in the clinic. Before this translation can be realized, consensus guidelines will be required which delineate the variants relevant to each drug, in each population.

5. Five-year view

There are key barriers to implementing pharmacogenomic-based prescribing in the treatment of hypertension. Two notable issues include the polygenic nature of BP response and the relatively small contribution of any single variant to the BP response phenotype. The authors speculate that even advances in technology will be unable to overcome these impediments over the next several years. Many electronic medical record systems contain CDS to aid clinicians in dosing medications. The authors believe it is more likely that a clinical bioinformatics model of antihypertensive drug-dosing and titration will be implemented before a genomic model. Factors such as age, demographics, race, ethnicity, drug– drug interactions (DDIs), and plasma renin activity are stronger predictors of antihypertensive response than most of the genetic variants discussed in this review [97]. A CDS algorithm that incorporates these clinical predictors, DDIs, and plasma renin activity is a more cost-effective and evidence-based approach to optimizing antihypertensive response. Additional implementation science studies are required to confirm if genetic variants of antihypertensive response add value over a clinical algorithm.

From an investigational standpoint, whole exome (or genome) sequencing is likely to become more common place in clinical studies of genetics. In some cases, this sequencing data will move into the clinical sphere as part of implementation science; however, it is more likely to be applied to disease prediction or pharmacogenomic prediction with large effect sizes. The genetic data will continue to trend toward increasing complexity and even greater individualization. Algorithm development will prove essential to afford rapid translation of polygenic data into a single, sometimes binary, clinical recommendation. The implementation of these algorithms will also rely upon CDS to move complex genetic matrices into the clinical setting. Complex risk scores will be calculated behind the scenes and clinicians will use these risk scores to inform their prescribing habits.

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Key issues

- Hypertension is a major risk factor for cardiovascular disease and blood pressure control remains sub-optimal in the United States. Treatment-resistant hypertension exceeds 13% of the general population. Present guidelines provide little guidance on personalization of antihypertensive regimens.
- Pharmacogenomic markers have been identified that predict the blood pressure lowering response to commonly used antihypertensive agents.
- The major trials and cohorts providing the strongest level of evidence for genomic predictors of hypertension drug response are described. These studies are quite heterogeneous in their populations, outcomes, variants assessed, drugs utilized, and measurement of blood pressure. As such, the identified variants may replicate in some, but not all studies. Genetic interactions with blood pressure response have failed to meet the evidentiary standards of the Clinical Pharmacogenomics Implementation Committee.
- Barriers persist which limit clinical translation. To date, few drugs have expert consensus on pharmacogenomic dosing guidelines. Further, the small effect size of some variants, frequent polypharmacy, and polygenic nature of antihypertensive drug response must be addressed and overcome in future studies.
- In order to accomplish clinical translation, multiple studies with large sample sizes, well defined populations, and standardized blood pressure phenotypes are required. Replication is essential. The development of multi-gene models and computer decision support algorithms will further assist in this endeavor.

Table 1

Studies identifying variants and loci of thiazide-type diuretic response.

Study	Gene	Variant(s)	Population	Phenotype	MAF	Notes	Reference
PEAR1	*FGF5*	rs1458038	Caucasians	SBP (β: −2.48 mmHg, $p = 0.0067$) and DBP (β: −1.42 mmHg, $p = 0.02$) response to HCTZ	0.23 (0.27)	A 3 SNP model predicted HCTZ response. SBP ($p = 0.0006$); DBP ($p = 0.0003$)	[30]
	SH2B3	rs3184504	Caucasians	SBP (β: −1.73 mmHg, $p = 0.02$) and DBP (β: −1.28 mmHg, $p = 0.013$) response to HCTZ	0.15 (0.45)		
	EBF1	rs4551053	Caucasians	SBP (β: −1.56 mmHg, $p = 0.05$) and (DBP β: −1.28 mmHg, $p = 0.02$) response to HCTZ	0.22 (0.32)		
PEAR	*PRKAG2*	rs2727563	Caucasians	SBP and DBP response to HCTZ ($p = 2 \times 10^{-5}$)	0.23 (0.45)	An additive 3 SNP model based on arachidonic acid metabolism explains SBP (11.3%, $p = 1 \times 10^{-5}$) and DBP (11.9%, $p = 3 \times 10^{-9}$) response.	[31]
	DCC	rs12604940	Caucasians	SBP ($p = 0.003$) and DBP ($p = 2 \times 10^{-5}$) response to HCTZ	0.13 (0.11)		
	EPHX2	rs13262930	Caucasians	SBP ($p = 0.003$) and DBP ($p = 0.002$) response to HCTZ	0.46 (0.24)		
PEAR2	*VASP*	rs10995	Caucasian	SBP (ΔSBP: −12.3 v −6.8 mmHg, $p = 3 \times 10^{-4}$) and DBP (ΔDBP: −8.2 v −3.5 mmHg, $p = 5 \times 10^{-5}$) response to thiazides	0.22 (0.32)	SNP is an eQTL of *VASP*.	[34]
GERA1, PEAR1	*PKCa*	rs16960228	Caucasians	DBP response to HCTZ (β: −4.16 mmHg, $p = 6.03 \times 10^{-8}$) response	0.16 (0.04)		[38]
	GNAS-EDN3	rs2273359	Caucasians	SBP response to HCTZ (β: 8.15 mmHg, $p = 5.54 \times 10^{-8}$)	0.05 (0.02)		
GENRES, PEAR1	*ALDH1A3*	rs3825926	Caucasians	HCTZ 24-H Ambulatory BP Response. SBP β: 7.3 mmHg, $p = 1.0 \times 10^{-5}$. DBP β: 3.8 mmHg, $p = 6.6 \times 10^{-4}$.	0.03 (0.004)		[43]
GERA1, PEAR1	*NELL1*	rs12279250	African Americans	HCTZ-induced hypertriglyceridemia (rs12279250 β: 28 mg dl^{-1}, $p = 6.6 \times 10^{-9}$ and rs4319515 β: 27 mg dl^{-1}, $p = 4.05 \times 10^{-8}$)	0.28 (0.16)		[91]
		rs4319515			0.28 (0.12)		
GERA1, PEAR1	*YEATS4*	rs7297610	African Americans	DBP response to HCTZ (Haplotype $p = 2.39 \times 10^{-7}$)	0.12 (0.26)	rs7297610 is an eQTL of *YEATS4*. rs317689 and rs315135 are part of the same CHR12 locus with rs7297610.	[39]
	LYZ	rs317689	African Americans	DBP response to HCTZ (Haplotype $p = 2.39 \times 10^{-7}$)	0.22 (0.18)		
	FRS2	rs315135	African Americans	DBP response to HCTZ (Haplotype $p = 2.39 \times 10^{-7}$)	0.05 (0.11)		
PEAR, GERA	*HEBP1*	rs10845697	Black, white	HCTZ-induced hypokalemia (Bayes factor = 5.56)	0.50	A Bayes factor > 5 was genome wide significant.	[93]
PEAR, GERA	*MFRN1*	rs11135740	Black, white	HCTZ-induced hypokalemia (Bayes factor = 5.258)	0.33		
GENRES, PEAR1, GERA1	*CLIC5*	rs321329	Caucasians	HCTZ 24-H Ambulatory BP Response (SBP (β: −2.2 mmHg, $p = 1.2 \times 10^{-4}$) & (DBP β: −1.7 mmHg, $p = 1.1 \times 10^{-5}$)	0.34 (0.42)		[43]

Study	Gene	Variant(s)	Population	Phenotype	MAF	Notes	Reference
MIHYPHCTZ, PHSS	*TET2*	rs12505746	Caucasians	SBP response to HCTZ (β: −5.4 mmHg, $p = 9.4 \times 10^{-6}$)	0.12 (0.07)		[46]
	CSMD1	rs7387065	Caucasians	SBP response to HCTZ (rs7387065 β: −3.5 mmHg, $p = 1.71 \times 10^{-6}$, rs11993031 β: −3.4 mmHg, $p = 7.65 \times 10^{-6}$.	0.25 (0.31)		
		rs11993031			0.35 (0.5)		
	UGGT2	rs9590353	Caucasians	DBP response to HCTZ (β: −4.63 mmHg, $p = 5.39 \times 10^{-6}$)	0.12 (0.08)		
INVEST	*TCF7L2*	rs7917983	Multiple	HCTZ-induced diabetes mellitus (OR 1.53, $p = 0.03$)	0.37		[94]
INVEST, PEAR	*KCNJ1*	Multiple	Multiple	HCTZ-induced diabetes mellitus	-		[95]
INVEST, others	*a-adducin*	rs4961	Multiple	Cardiovascular outcomes and BP response to HCTZ	0.21	Conflicting data	[69,70]
INVEST	*SIGLEC12*	rs16982743	Caucasians, Hispanics	Cardiovascular outcomes in response to verapamil and atenolol (OR 1.98, $p = 0.0032$)	0.18 (0.19)	A 3 SNP model informed choice of verapamil or atenolol, $p = 2.39 \times 10^{-5}$	[71]
	A1BG	rs893184	Caucasians, Hispanics	Cardiovascular outcomes in response to verapamil and atenolol (OR 5.08, $p = 0.0029$)	0.15 (0.05)		
	F5	rs4525	Caucasians, Hispanics	Cardiovascular outcomes in response to verapamil and atenolol (OR 2.65, $p = 0.0242$ in hispanics)	0.26 (0.27)		
NORDIL, others	*NEDD4L*	rs4149601	Caucasians	SBP response to HCTZ and atenolol (ΔSBP: 19.5 v 15.0 mmHg, $p < 0.0001$) and DBP (ΔDBP: 15.4 v 14.1 mmHg, $p = 0.015$) response	0.28 (0.35)	SNP leads to alternative splicing of *NEDD4L*	[75,76]
ICAPS	*GJA*	rs11750990	Caucasians	SBP response to HCTZ (β: 2.44 mmHg, $p = 8.11 \times 10^{-6}$)	0.04 (0.04)	A meta-analysis of 6 clinical trials.	[80]
	GJA	rs10499113	African Americans	SBP response to HCTZ (β: 3.14 mmHg, $p = 3.46 \times 10^{-3}$)	0.40 (0.41)		
	FOXA1	rs177848	Caucasians	SBP response to HCTZ (β: −0.6 mmHg, $p = 5.81 \times 10^{-6}$)	0.38 (0.50)		
	FOXA1	rs177852	African Americans	DBP response to HCTZ (β: −2.95 mmHg, $p = 1.43 \times 10^{-3}$)	0.22 (0.10)		

MAF – Minor Allele Frequency, SNP – Single nucleotide polymorphism, SBP – systolic blood pressure, DBP – diastolic blood pressure, 24-H – 24 h, eQTL – expression quantitative trait locus. OR – Odds Ratio. For minor allele frequency, global MAF from the 1000 genomes cohort is provided first, followed by population specific frequency in parentheses; CEU was used as the Caucasian reference population, ASW for African Americans (or YRI if ASW unavailable), MEX for Hispanics, HCB for Chinese, and JPT for Japanese. Global MAF is only given when SNPs are relevant to multiple populations.

Table 2

Studies identifying variants and loci of Beta-Blocker response.

Study	Gene	Variant	Population	Phenotype	MAF	Notes	Reference
PEAR1	*FGF5*	rs1458038	Caucasians	SBP (β: −2.48 mmHg, $p = 0.0067$) and DBP (β: −1.42 mmHg, $p = 0.02$) response to atenolol	0.23 (0.27)	A 4 SNP model predicted atenolol response. *FGF5* predicted the opposite direction of atenolol response as compared to HCTZ (SBP: $p = 3.3 \times 10^{-6}$, DBP: $p = 1.6 \times 10^{-6}$)	[30]
	CHIC2	rs871606	Caucasians	SBP (β: −3.23 mmHg, $p = 0.017$) and DBP (β: −2.57 mmHg, $p = 0.0037$) response to atenolol	0.21 (0.13)		
	MOV10	rs2932538	Caucasians	DBP (β: −1.84 mmHg, $p = 0.005$) response to atenolol	0.17 (0.27)		
	HFE	rs1799945	Caucasians	SBP (β: −3.38 mmHg, $p = 0.02$) response to atenolol	0.07 (0.18)		
PEAR2	*CYP2D6*	*2,*3,*4,*6, *10,*17, *41	All	Pulse response to metoprolol (β: 2.1, $p = 0.004$)	Allele dependent		[33]
PEAR1, PEAR2	*SLC25A31*	rs201279313	African Americans	DBP response to atenolol (β: −5.13 mmHg, $p = 1.1\times10^{-7}$)	0.09*	rs201279313 is an Indel. * = MAF is obtained from the reference ($P < 5*10^{-7}$)	[35]
	LRRC15	rs11313667	African Americans	SBP response to atenolol (β: −4.9 mmHg, $p = 1.49\times10^{-7}$)	0.41 (0.74)*		
	ZMAT4	rs1367094	African Americans	DBP response to atenolol (β: −5.34 mmHg, $p = 2.8\times10^{-8}$)	0.03 (0.5)		
GENRES LIFE	*ACY3*	rs2514036	Caucasians	Bisoprolol (SBP β: −5.4 mmHg, $p = 2\times10^{-8}$, DBP β: −3.1 mmHg, $p = 1.4\times10^{-6}$) response and atenolol (SBP β: −1.3 mmHg, $p = 0.005$ in men) response	0.2 (0.18)	Not replicated in PEAR	[43,44]
CSN	*ADRB2*	rs1042714	Caucasians	Glu27 decreases LVH hypertrophy regression in atenolol treated individuals ($p = 0.003$).	0.2 (0.47)	Opposite effect seen in an Australian cohort	[51,52]
INVEST	*ADRB1*	rs1801253	Black, white, hispanic	Ser49-Arg389 haplotype predicts mortality benefit for atenolol over verapamil (HR: 8.58, $p = 0.0003$)	0.3		[62]
		rs1801252			0.18		
INVEST, PEAR	*GRK4*	rs1801058	Black, white, hispanic	486V allele increased cardiovascular events, atenolol mitigating these effects. (OR 2.29, $p = 0.0002$)	0.30	Increased CV risk still present with verapamil	[64]
INVEST, PEAR	*GRK4*	rs1024323	Black, white, hispanic	SBP and DBP reduction with atenolol (ΔSBP: −9.5 v −4.7 mmHg, $p = 0.0204$ and ΔDBP: −9.1 v −5.3 mmHg, $p = 0.0088$ in participants with 0 and 2 copies of 65L-142V)	0.37	Number of 65L-142V copies impacts response	
		rs2960306			0.31		
NORDIL, others	*NEDD4L*	rs4149601	Caucasians	SBP response to HCTZ and atenolol	0.28 (0.35)	Same SNP as in Table 1	[75,76]

Study	Gene	Variant	Population	Phenotype	MAF	Notes	Reference
PEAR, INVEST	*PTPRD*	rs12346562	Caucasians	Predicts improved SBP response (β: −3 mmHg, $p = 2.7\times10^{-4}$) to Atenolol	0.17 (0.27)	Directionally opposite association for response to HCTZ for these SNPs.	[32]
	PTPRD	rs1104514	Caucasians	Predicts improved DBP response (β: −2.29 mmHg, $p = 5.9\times10^{-6}$) to Atenolol	0.38 (0.27)		
	PTPRD	rs10739150	African American	Predicts improved SBP response to Atenolol (β: −4.7 mmHg, $p = 8.2\times10^{-6}$)	0.35 (0.48)		

MAF: Minor Allele Frequency; SNP: single nucleotide polymorphism; SBP: systolic blood pressure; DBP: diastolic blood pressure; HCTZ: hydrochlorothiazide; CV: cardiovascular; OR: odds ratio; HR: hazard ratio; For minor allele frequency, global MAF from the 1000 genomes cohort is provided first, followed by population specific frequency in parentheses; CEU was used as the Caucasian reference population, ASW for African Americans (or YRI if ASW unavailable), MEX for Hispanics, HCB for Chinese, and JPT for Japanese. Global MAF is only given when SNPs are relevant to multiple populations.

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Table 3

Studies identifying variants and loci of anti-hypertensives targeting calcium channel blockade, renin-angiotensin Inhibition, or alpha-inhibition.

Study	Gene	Variant	Population	Phenotype	MAF	Notes	Reference
GENRES, LIFE, GERA2, SOPHIA	*NPHS1*	rs3814995	Caucasians	Losartan response SBP (β: 7.1 mmHg, $p = 0.03$) and DBP (β: 5.9 mmHg, $p = 0.02$)	0.29 (0.32)		[43,44]
GERA2	*FUT4*	rs11020821	Caucasians	SBP and DBP ($p = 8.98 \times 10^{-7}$) candesartan response	0.26 (0.32)	Opposite direction of effect for HCTZ response	[41]
	FUT4	rs16924603	African American	SBP and DBP ($p = 1.52 \times 10^{-2}$) candesartan response	0.16 (0.1)		
SOPHIA, GENRES	*CAMKW*	rs10752271	Caucasians	SBP response to losartan (β −5.5 mmHg, $p = 1.2 \times 10^{-8}$)	0.16 (0.05)		[45]
INVEST	*KCNMB1*	rs11739136	Black, white, hispanic	Glu65 improves rate of BP control and need for additional antihypertensives with verapamil (OR: 0.43, CI 0.19–0.95)	0.09		[54]
	KCNMB1	rs2301149	Black, white, hispanic	Leu110 protects from MI in verapamil treated patients (HR: 0.68, CI 0.47–0.998)	0.12		
INVEST	*CACNA1C*	rs1051375	Black, white, hispanic	A allele protects from death, MI, and stroke in verapamil treated patients ($p = 0.0001$)	0.47		[55]
INVEST	*CACNB2*	rs2357928	Black, white, hispanic	GG genotype increases cardiovascular risk in verapamil treated patients ($p = 0.002$)	0.42	rs11014166 held similar effects in Hispanics	[56]
NORDIL	*PLCD3*	rs12946454	Caucasians	Diltiazem response for SBP (β: −1.53 mmHg $p = 0.010$) and DBP (β: −0.73 mmHg $p = 0.014$)	0.21 (0.25)		[74]
GenHAT	*REN*	rs6681776	African American	AA genotype predicts better response to chlorthalidone over doxazosin ($p = 0.02$) or Lisinopril (0.04)	0.14 (0.18)		[79]
	F7	rs762637 rs510317	African American	AA predicts improved response to doxazosin (ΔSBP: −21.2) and lisinopril (ΔSBP: −22.5) as compared to chlorthalidone (ΔSBP: 15.7). $p = 0.01$ and 0.02	0.23 (0.14)	These SNPs have merged	
	F7	rs6046	African American	AA predicts reduced response to amlodipine (ΔSBP: −6.7) compared to chlorthalidone (ΔSBP: −20.7, $p = 0.03$)	0.14 (0.18)	All of these SNPs predict relative BP response to chlorthalidone.	
	AGTR1	rs275653	African American	GG genotype predicts reduced response to amlodipine compared to chlorthalidone (β: 3.44 mmHg, $p = 0.02$)	0.19 (0.28)		
	AGT	rs5051	African American	GG genotype predicts reduced response to lisinopril compared to chlorthalidone (β: 5.38 mmHg, $p = 0.04$)	0.29 (0.26)		
CCBCPCH	*AGT*	rs7079	Chinese	DBP response to benazepril ($p = 0.001$)	0.19 (0.20)		[81]
HOMED-BP	*PICALM*	rs588076	Japanese	SBP ($p = 0.0015$) and DBP ($p = 0.0024$) response to CCBs	0.22 (0.27)	These studies used home BP monitoring.	[82]
	TANC2	rs2429427	Japanese	SBP response to CCBs ($p = 0.013$)	0.28 (0.14)		
	NUMA1	rs10898815	Japanese	DBP response to CCBs ($p = 0.0004$)	0.28 (0.14)		
	APCDD1	rs564991	Japanese	DBP response to CCBs ($p = 0.0002$)	0.43 (0.44)		
	ABCC9	rs1283807	Japanese	SBP ($p < 0.0001$) and DBP ($p = 0.0004$) response to ARBs	0.39 (0.20)		

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Study	Gene	Variant	Population	Phenotype	MAF	Notes	Reference
	YIPF1	rs6588492	Japanese	DBP response to ARBs ($p = 0.0008$)	0.31 (0.09)		
Huang et. al.	*CYP3A5*	*3 allele	Chinese	DBP response to amlodipine ($p < 0.05$)	0.65	renal transplant patients	[83]

MAF: Minor allele frequency, SNP: single nucleotide polymorphism; SBP: systolic blood pressure; DBP: diastolic blood pressure; HCTZ: hydrochlorothiazide; CCB: calcium channel blocker; ARB: angiotensin II receptor blocker; OR: odds ratio; HR: hazard ratio. For minor allele frequency, global MAF from the 1000 genomes cohort is provided first, followed by population specific frequency in parentheses; CEU was used as the Caucasian reference population, ASW for African Americans (or YRI if ASW unavailable), MEX for Hispanics, HCB for Chinese, and JPT for Japanese. Global MAF is only given when SNPs are relevant to multiple populations.