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Pharmacogenetics of antihypertensive treatment: detailing disciplinary dissonance

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Abstract

Hypertension is a common condition associated with increased cardiovascular morbidity and mortality. In the USA only approximately a third of those who are aware of their hypertensive status successfully control their blood pressure. One reason for this is the unpredictable response individuals have to treatment. Clinicians must often rely on empirical methods to match patients with effective drug treatment. Hypertension pharmacogenetics seeks to find genetic predictors of response to drugs that lower blood pressure and to translate this knowledge into clinical practice. To date, around 60 studies have investigated associations between genetic polymorphisms and response to antihypertensive drugs. Here we review 18 studies that have been published since 2005. While consonant findings that are insufficient for clinical translation remain the norm, some consistent findings are emerging with several gene-treatment combinations. Nonetheless, differences in study designs, variable methods for assessing pharmacologic exposures, heterogeneous phenotypes (that is, response variables and outcomes ranging from blood pressure to clinical outcomes) and small sample sizes coupled with a short duration of follow-up in many studies account for a large portion of these inconsistencies. Progress in the future will depend upon our ability to launch large studies using high-fidelity phenotyping with multiple drugs and multiple ethnic groups.

Keywords

antihypertensive; blood pressure; gene; pharmacogenetics; pharmacogenomics

Pharmacogenetics is the study of the association of gene variants with the response to drug treatment. The high prevalence of hypertension [1], its well established association with cardiovascular morbidity and mortality, and the large interindividual variation in response to treatment [2,3] have made antihypertensive drugs a worthy target of pharmacogenetic investigation. Antihypertensive pharmacogenetics (and pharmaco genomics – the whole-genome application of pharmacogenetics) holds the promise of reducing clinicians' dependence on the empirical approach to matching patients with effective treatment while also reducing both adverse effects and the cost of treatment.

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Despite the repeated observation in multiple populations that approximately 50% of the variation in blood pressure is explained by genetic factors, individual genes that account for a large proportion of the variation in blood pressure in the population have yet to be identified. Part of the complexity of the blood pressure phenotype is that alleles at many loci in a number of pathways as well as many environmental factors contribute to its expression. Evidence suggests that the between-person variation in response to blood pressure-lowering drugs is also partially under genetic control [4]. Since the blood pressure response to drugs follows a normal distribution, multiple genetic factors are likely to contribute to treatment response. Indeed, genetic variations observed in blood pressure-regulating drug receptors (e.g., β_1 adrenergic receptors) and receptor response pathways (G-protein β_3 subunit, renin–angiotensin–aldosterone system) have been associated with differential responses to blood pressure-lowering treatment [5–7].

To date more than 60 publications have reported findings from pharmacogenetic studies of antihypertensive drugs. These studies ultimately hypothesize gene variant by treatment interactions, that is, they explore the possibility that populations of individuals with distinct genotypes will show differential response to treatments. This knowledge may someday be clinically useful, allowing clinicians to tailor treatment regimens informed by a patient's genetic profile. Although reviewers remain optimistic about the clinical potential for antihypertensive pharmacogenetics, virtually all agree that, to date, research has produced contradictory findings that are insufficient for translation into clinical practice [8–15]. In this review we discuss the findings of 18 antihypertensive pharmacogenetic studies published in the past 4 years. (For reviews of earlier work, see Arnett *et al.* [16], Johnson and Turner [17], Schwartz and Turner [18]). During this same period, a number of reviews of anti-hypertensive pharmacogenetics have been published; we conclude by offering a meta-review – a review of the reviews, giving special attention to the potential reasons for the dissonant results and possible ways to minimize this discrepencies as the field moves forward.

Recent pharmacogenetic studies of antihypertensive treatment

Overview of recent studies

We made a number of general observations regarding research reported in the past 4 years (see **Table 1**). Study population size ranged from 42 [19] to 38,462 individuals [20]. In approximately a third of the studies, enrollment criteria (for inclusion in a cohort or case group) required participants to have some pre-existing diagnosis other than hypertension (e.g., left ventricular hypertrophy (LVH) [19], coronary heart disease (CHD) [21,22], myocardial infarct (MI)/stroke [23], acute coronary syndrome [ACS] [24]). Nearly 70% of the reviewed studies used blood pressure response (systolic, diastolic or some combination) as the phenotype of interest; other outcomes included hard clinical end points such as CHD, stroke, MI and death. The follow-up period for blood pressure (BP) outcomes ranged from 4 weeks to 6 months or more; in studies of clinical outcomes, patients were followed for 10 or fewer years. Most studies tested associations with one or two variants in one or two genes; however, one study [25] examined 45 polymorphisms in 19 genes and another [4] was a genome-wide association study (GWAS) of 100,000 SNPs. A number of these recent studies

assessed pharmacogenetic associations in genes that have not been previously studied in this context (e.g., *KCNMB1* [26,27], calcium channel, voltage-dependent, l-type, α-1C subunit [*CACNA1C*] [28] and natriuretic peptide precursor type A [*NPPA*] [20]); however, the majority of studies examined genes whose association with antihypertensive treatment has been previously assessed (e.g., *AGTR1* and *ADRB1*). A large percentage of recent studies (nearly 40%) did not report the specific drug or drugs assessed in the pharmacogenetic analysis. (A cursory scan of older antihypertensive pharmacogenetic studies suggests approximately 10% did not specify treatment.) In most of these cases, the drug class or classes analyzed was indicated; however, in one study, all treatments and all combinations of treatment were grouped [29].

Diuretics

Diuretics have served as a mainstay for antihypertensive therapy for years and are currently recommended as a first-line treatment for hypertension [30], although the prevalence of adverse reactions to diuretics has caused some to question this recommendation [31,32]. Diuretics may act at a number of sites, including the proximal tubule, the Loop of Henle, and the distal and collecting tubules. Diuretic treatment initially contracts plasma volume and decreases cardiac output. However, after 1 month of treatment, cardiac output returns to baseline values and neither the initial changes in plasma volume nor changes in cardiac output can account for the long-term effects of diuretics. Diuretics are thought to block sensitivity of blood vessels to catecholamines and reduce peripheral vascular resistance; however, evidence for direct vasodilation therapeutic doses is inconsistent. Diuretics also indirectly activate the renin–angiotensin–aldosterone system. Ultimately, the mechanism by which these drugs effect long-term drops in blood pressure remains largely unknown. However, given the multitude of the effects of this class of drug, a number of genes may predict an individual's response to diuretics. Previously we reported 10 studies that examined inter actions between gene variants and diuretic treatment [16]; here we add three more. Two nested case–control studies both drew their samples from the Genetic Epidemiology of Responses to Antihypertensives (GERA) cohort: one was a study of 19 candidate genes (45 total polymorphisms) [25], the other a 100,000-SNP GWAS [4]. The former study reported variants in sodium channel, nonvoltage-gated 1, γ-subunit (*SCNN1G*) and nitric oxide synthase 3 (*NOS3*) that were associated with differences in diastolic blood pressure (DBP) response after 4 weeks of hydrochlorothiazide treatment. The *SCNN1G* findings were novel; the authors offered no probable mechanism for the observed differences in response, but noted that this gene has been associated with essential hypertension. (Some variants may cause inappropriate sodium reclamation in the distal nephron). The *NOS3* finding was consonant with results from the full GERA cohort [33]. This candidate gene study failed to find evidence of association with a number of variants, including *ADD1* and *GNB3*, implicated in other studies of diuretics. The GWAS study identified SNPs in lysozyme and Yeats domain-containing protein 4 (*YEATS4*), which were associated with response to the diuretic. These findings are consistent with gene-profiling studies [34]. Lynch *et al.* found that C carriers of the *NPPA* T2238C variant had more favorable clinical outcomes when treated with a diuretic whereas individuals homozygous for the T allele responded better to a calcium channel blocker [20]. Manunta *et al.* performed single SNP association analysis and combination analysis on *ADD1* (Gly460Trp), *NEDD4L*

(rs4149601), *WNK1* (5 SNPs) in a 4-week diuretic trial. They found *ADD1* 460Trp carriers had significantly greater BP reduction than Gly460 homozygotes. When considered together, there was a significant trend ($p = 0.008$) in decreases of systolic blood pressure (SBP) (ranging from −3.4 mm Hg to −23.2 mm Hg) for different combinations of genotypes [35].

β-blockers

β-blockers are also a mainstay for antihypertensive therapy, and they are also recommended as a first-line treatment for hypertension [30], although this recommendation has also recently been questioned [32,36]. β-blockers bind to β-adrenergic receptors, thereby antagonizing the binding of endo genous agonists (i.e., norepinephrine and epinephrine). The pharmacogenetics of β-blockers has been intensively studied (we reported 17 studies previously [16]); six new studies have tested gene by β-blocker interactions. Recent studies of β-blockers have tested associations with *ADRB1*, *ADRB2*, *AGT*, *AGTR1* and angiotensin-converting enzyme (*ACE*)variants. Lanfear *et al.* reported that differential survival of ACS patients treated with β-blockers was associated with patients' *ADRB2* Gly16Arg and Gln27Glu genotypes; however, *ADRB1* variants showed no significant associations [24]. Pacanowski *et al.* found no significant interaction (for outcomes of death, MI or stroke in a population with coronary artery disease [CAD]) between atenolol treatment and *ADRB1* or *ADRB2* variants or haplotypes [22]. The case–control study by Lemaitre *et al.* [23] found no significant β-blocker by *ADRB2* interaction in MI and stroke outcomes but did find significant interaction with two SNPs in *ADRB1*. In their study of BP and mean arterial pressure (MAP), Liu *et al.* also reported interactions between *ADRB1* (genotypes and haplotypes) and metoprolol treatment [7]. Finally, the two studies by Schelleman *et al.* reported no β-blocker interactions (for outcomes MI or stroke) variants of *AGT*, *AGTR1* and *ACE* [37,38]. Taken as a whole and placed in the context of previous pharmaco-genetic studies of β-blockers, these newer studies present the familiar mix of concordant and discordant results. (See **Table 1** for details). Given the size and power of a number of these studies reporting significant associations, variants of *ADRB1* and *ADRB2* are worthy of future study.

ACE inhibitors

Angiotensin-converting enzyme inhibitors principally act to prevent the conversion of angiotensin I to angiotensin II in plasma and tissue (especially the vasculature and the kidney) and prevent the degradation of bradykinin. Bradykinin stimulates endothelial-derived relaxing factor (nitric oxide) and perhaps phospholipase A2 and vasodilatory prostaglandin bio-synthesis, resulting in vasodilatation. Clinically, ACE inhibitors reduce peripheral vascular resistance and pulmonary capillary wedge pressure and increase cardiac output and renal blood flow, especially in states of sodium depletion. The acute response to ACE inhibitors is correlated with plasma renin activity. ACE inhibition does not increase resting heart rate, but the postural changes in heart rate and blood pressure are preserved on treatment. Treatment with ACE inhibitors in hypertension has been associated with improvements in vascular compliance, regression of left ventricular hypertrophy, improved systolic and diastolic function, and improvements in insulin sensitivity [39]. ACE inhibitors have been the object of pharmacogenetic studies nearly as frequently as β-blockers. Gluszek

and colleagues' recent small study of BP and ambulatory MAP found no significant interaction between the *AGTR1* variant A1166C and perindo pril treatment [40]. Previous studies of ACE inhibitors and *AGT* variant M235T using BP response as the outcome have been contradictory [41,42]; Bis and colleagues found TT individuals were at lower risk for stroke (but not MI) than M carriers [43]. Schelleman and colleagues' recent cohort study was considerably larger than previous studies, and their finding of increased risk of MI [37] (but not stroke, contra Bis *et al.* [43]) for T allele carriers merits further study. Schelleman and colleagues' study of *AGTR1* (C573T) and *ACE* (ID) reported a novel association between ACE inhibitor therapy and increased MI (but not stroke) risk for carriers of the *AGTR1* C573 allele. They found no significant interaction between ACE inhibitor treatment and *ACE* (ID) alleles for either stroke or MI [38]; this finding is consistent with a previous study [44]. In a four-week trial of fosinopril, Filigheddu *et al.* found no associations between BP response and *ACE* (ID), *AGTR1* (A1166C), *CYP11B2* (−344 C/T), *AGT* (−6 A/G) [45]. Collectively, these data suggest *AGT* and *AGTR1* may warrant more investigation whereas the evidence for a meaningful *ACE* (ID) by ACE inhibitor interaction has grown perhaps more tenuous, a view supported by recent gene-expression studies of *ACE* [46].

Angiotensin II blockers

The spectrum of activity of angiotensin II blockers is very similar to that of ACE inhibitors. The drug binds to angiotensin II receptors, thereby antagonizing the effect of angiotensin II, a potent vasoconstrictor. Previously we reported ten studies that examined interactions between gene variants and angiotensin II blockers treatment [16]; the small study by Kurland *et al.* adds one more [19]. In a study of 42 individuals with hypertension and LVH, Kurland *et al.* reported that after 12 weeks of treatment with irbesartan, plasma concentration of the drug was related to change in systolic BP in TT homo-zygotes of *AGTR1* (C5245T) but not for other genotypes. This is the first investigation of this polymorphism in this pharmacogenetic context.

Calcium channel blockers

Drugs in this class block voltage-gated calcium channels in the heart and vasculature, thereby reducing intracellular calcium. In the heart, this results in decreased cardiac contractility and reduced cardiac output; in the blood vessels, this leads to decreased smooth muscle contraction and peripheral resistance. Calcium channel blockers fall into three subclasses: phenyl alkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem) and dihydropyridines (e.g., amlodipine). Drugs in these subclasses vary in their relative effect on cardiac versus vascular calcium channels, with the dihydropyridines affecting smooth muscle more, phenyl alkylamines relatively selective for the myocardium and benzothiazepines intermediate between the other two. Of all antihypertensive drug classes, calcium channel blockers have seen the greatest increase in pharmacogenetic studies in the past 4 years, and some of these early results are promising. Three SNPs *CACNA1C* had significant associations with treatment in a study of BP lowering with calcium channel blockers [28]. Langaee and colleagues [21] reported suggestive associations between *CYP3A5*3* and **6* variants and verapamil treatment for BP and hypertension risk outcomes in blacks and Hispanics. In their study of two *KCNMB1* variants (Glu65Lys, Val110Leu), Beitelshees and colleagues found that SBP response to verapamil (not necessarily used as

monotherapy) did not differ by genotype for either variant [26]. However, Lys65 carriers achieved earlier BP control and required fewer additional drugs; Leu110 carriers had a reduced risk of death, MI, or stroke. As noted above, Lynch *et al.* found that individuals homo zygous for the T allele of *NPPA* T2238C had more favorable clinical outcomes when treated with a calcium channel blocker whereas C carriers responded better to a diuretic [20]. Pacanowski *et al.* reported that *ADRB1* Ser49–Arg389 haplo type carriers had higher death rates than those with other haplotypes when treated with verapamil [22].

α-blockers

β-blockers bind to α_1-adrenoceptors located on the vascular smooth muscle, thereby blocking the effect of sympathetic nerves on blood vessels. α-blockers dilate both veins and arteries because both contain sympathetic adrenergic nerves; however, the vasodilator effect is more pronounced in the arteries. Only the GenHAT study (reported in Lynch *et al.* [20]) tested pharmaco genetic associations of an α-blocker (doxazosin); this study found no evidence of pharmacogenetic associations with clinical outcomes for chlorthalidone versus doxazosin comparisons with the *NPPA* T2238C or G664 variants.

State of the discipline: a review of recent reviews & commentary

Even a casual review of the recent antihypertensive pharmacogenetics literature reveals a surprising publishing pattern: in the past 5 years, nearly as many reviews of anti-hypertensive pharmaco genetics have appeared in print as primary research articles. The volume of meta-literature likely reflects the perceived potential of a clinical antihypertensive pharmacogenetics. In fact, many reviews are explicitly hopeful about the clinical impact of antihypertensive pharmacogenetics (e.g., ‘there is cause for optimism,’ [15] ‘pharmacogenetics promises to improve safety and efficacy,’ [13] ‘Pharmacogenetics may be the key to individualized treatment,’ [47]). However, some of this self-scrutiny is surely in response to the relative dearth of consonant findings and the fact that antihypertensive pharmacogenetics has not yet found clinical application – points that are also emphasized in nearly every review [8–15]. Some reviewers have usefully moved from summary to synthesis in an effort to identify those factors that may have played a part in producing conflicting findings among studies. Below we summarize these potential reasons for discrepancy.

Studies produce inconsistent findings for two general (and not necessarily mutually exclusive) reasons – because the design and implementation of a particular study is flawed (and has thus produced a spurious result) or because the comparison between or among studies is invalid (i.e., the studies are not truly comparable).

Problematic study design & implementation

Overall study design

Some study designs are more prone to confounding and bias than others [48]. Kurland suggests that an ideal study of the pharmacogenetics of antihypertensive treatment would have the following general characteristics: be prospective, include previously untreated hypertensive individuals, treat with one drug at a time from each drug class on a random,

rotational basis and including a placebo [15]. Every study should be replicated independently. Needless to say, meeting this ideal would be both logistically difficult and costly. (See below for issues related to power and sample size). Treating known hypertensive individuals with a placebo also poses ethical questions.

Sample size & statistical power

Inadequate sample size is cited as a concern by a number of reviewers [48–50], as is the related concern of insufficient statistical power [9,14]. Although adequate sample size and power are of paramount concern in any study, pharmacogenetic studies are especially susceptible to criticisms along these lines for a couple of reasons. First, some studies have observed pharmaco genetic associations only in certain population substrata (e.g., sex and race [51]); significant reductions in power can occur when cohorts are divided for subgroup ana lysis. Second, not only are complex traits, such as blood pressure, likely influenced by a large number of genes and environmental factors, the typical unimodal population response to drugs suggests that pharmacokinetics and dynamics are also influenced by multiple small factors. Flaa and Kjeldsen have suggested that studies have tended to include too few subjects to be adequately powered to detect these small effects [9].

Multiple comparisons

Although this issue could rightly be lumped with more general concerns of statistical power, reviewers have given it special emphasis [48,50]. Given the ascendance of high-throughput and gene-chip methods, proper handling of multiple comparisons is becoming even more imperative. Traditional Bonferroni methods are often ill-suited for genome-wide studies, and newer approaches to deal with multiple testing (false-discovery rate, Bayesian methods) have been developed. See Ziegler *et al.* for a review [52].

Poor participant selection criteria

Manunta and Bianchi and others suggest that some studies have been flawed due to inappropriate selection of study subjects [14,50]. In studies of hypertension and related phenotypes, factors such as age, sex, BMI and ethnicity can be associated with outcomes and must be taken into consideration when, for example, constructing case and control groups. Population admixture should be corrected or controlled [50].

Oversimplification

In a critique that can be seen as a corollary to the previous, Manunta and Bianchi believe many studies have not fully considered the complexity of the blood pressure phenotype, its associated outcomes and its response to pharmacological treatment [14]. As noted above, a complex disease such as hypertension and its response to treatment is likely influenced by many factors. Failure to create realistically complex hypotheses that include genetic, environmental and biological interactions has likely resulted in oversimplified or partial pictures of disease and its response to treatment. Ideal studies should make use of robust microarray technology [15], incorporate haplotype [11,53,54], copy number variation and epigenetic [55] analyses and consider gene by environment interactions beyond that of gene by drug. Researchers should not naively assume that genes that are associated with the

development of hypertension and its sequelae are plausible pharmacogenetic candidates [11]; some pharmacodynamic pathways may be distinct from disease and phenotype pathways. A *priori* biological knowledge must always be brought to bear on the design and interpretation of studies, from the inheritance model used in an analysis [50] to the biological plausibility of candidates identified via genome-wide techniques [12].

Poor communication

Filigheddu identified incomplete and confusing descriptions of methods and results in publications as a possible source of inconsistency [11]. Authors should consult articles in high-impact journals to which their manuscript is likely to be compared and use these as models for content and form. Reviewers should assess pharmacogenetics manuscripts with a special eye on the problem areas outlined here.

Invalid comparisons between & among studies

Differences in study populations

Comparisons between studies with differences in populations (including age, ethnicity, previous hypertension treatment and disease status) are problematic because these factors are known to be associated with the phenotypes of interest [11,48]. Differences between study population, specifically differences in linkage disequilibrium (LD) between populations, can lead to what Filigheddu referred to as ‘accidental association’ [11]. Variants in LD with the causal variant are statistically associated with the phenotype but are not causal (i.e., accidentally associated). Differences in LD between populations means accidental associations may be observed in one population but not in another. LD analysis around variants of interest can help minimize these types of errors [50]. It is important to remember that perfectly valid studies can yield apparently discordant results. In fact, if salient differences between and among populations are well understood, they can increase rather than obfuscate our understanding of antihypertensive pharmaco genetics by suggesting potentially important environmental, demographic, anthropometric and other modifiers of a gene–drug interaction.

Differences in pharmacologic properties of drugs

The various classes of antihypertensive drugs operate and are operated upon by different pharmacodynamic and pharmacokinetic pathways. Even drugs within the same class may have different pharmacologic properties [11,48]. Shin suggested a lack of pharmacokinetic assessment of intervention drugs may have lead to inconsistent results; certainly an understanding of the kinetics of a drug would help study designers choose appropriate drug doses and treatment durations (see below) [48].

Differences in drug dose

Drug dose may be an important variable in pheno type response [56]. As a result, dose must be considered even when comparing studies using the same drug [11].

Differences in duration of washout & drug treatment

When study populations include previously treated hypertensive individuals or if a study employs a crossover design, an adequate washout period is necessary to insure there are no carry over effects from the previous treatments. In pharmacokinetic and equivalency trials, five-times the half-life of the drug is often considered a sufficient washout period. It is possible that some antihypertensive drugs exert influences well beyond this time period [57]; quantifying these long-term carry over effects, however, has proven difficult [58]. Nonetheless, pharmacological washout period should be considered when comparing findings. Drug treatment period must also be considered. Even for intermediate outcomes such as blood pressure, the response-to-drug period in studies has ranged from hours to months. Stabilized response to some classes of antihypertensive drugs can take weeks, and response time can vary among individuals. Therefore, it is feasible that differences in duration of intervention can complicate comparisons between studies.

Differences in phenotypes & differences in measurement of the same phenotype

Although hypertension is associated with hard cardiovascular disease outcomes, increased blood pressure and increased rates of CHD, for example, are not equivalent phenotypes. Given the variety of phenotypes that have been studied, the temptation to elide favorable pheno types into one group to allow comparisons is strong; however, this practice should be avoided [50]. The complexity of hypertension-related phenotypes – even one ostensibly as straightforward as blood pressure [59,60] – demands that care must be taken even when comparing nominally identical phenotypes across studies [11,48]. For example, whether or not a protocol required a drug wash-out period, whether clinical or ambulatory BP measurements were used, and the type of algorithm used to calculate BP response must be considered. The application of ‘phenomics’ and high-fidelity phenotyping will allow more legitimate comparisons between studies [61].

Conclusion

In conclusion, we have summarized the recent pharmacogenetic literature for the major classes of blood pressure-lowering treatment currently in use (i.e., diuretics, β-blockers, ACE inhibitors, angiotensin II blockers, calcium channel blockers and α-blockers). While the pharmaco genetics of hypertension treatment remains a priority area because of the pandemic distribution of the disease and its associated renal and cardiovascular comorbidities, progress towards identification of the genes that contribute to variable treatment response has been slow. Translation of findings into clinical practice remains a distant goal. Multifarious reasons for the slow progress in this complex trait have been identified, and include flaws in study design and implementation as well as invalid comparisons between studies. Progress in the future will depend upon our ability to launch large studies using high-fidelity pheno typing with multiple drugs and multiple ethnic groups.

Future perspective

Although a considerable amount of research has already been conducted in the field of anti-hypertensive pharmacogenetics, the science is still nascent. Basic research in the area will continue to benefit from both techno logical advances in genotyping and better maps of the human genome. The nature of pharmacogenetics research demands that future work be characterized by creative collaboration, close coordination and the establishment of consortia among research groups. Furthermore, given the complexity of cardiovascular phenotypes, their interactions with genes and drugs, and the long-term nature of clinical cardiovascular outcomes, translational research should be initiated and conducted concomitantly with discovery research.

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Executive summary

■ Evidence suggests that the between-person variation in response to blood pressure-lowering drugs is partially under genetic control.

■ Genetic variation observed in blood pressure-regulating drug receptors and receptor response pathways have been associated with differential responses to blood pressure-lowering treatment. This review summarizes the findings of 18 antihypertensive pharmacogenetic studies published in the past 4 years.

■ Although some consistent findings are emerging with several gene-treatment combinations, research in this area continues to be characterized by disparate results.

■ Differences in study designs, variable methods for assessing pharmacologic exposures, heterogeneous phenotypes and small sample sizes coupled with a short duration of follow-up may account for a large portion of these inconsistencies.

■ Progress will depend upon our ability to launch large studies using high-fidelity phenotyping with multiple drugs and multiple ethnic groups.

Table 1

Summary of recent pharmacogenetic studies of antihypertensives by drug class.

First author	Year	Participants	Outcome	Gene (variant)	Treatment	Findings*	Comment
Diuretics							
Maitland-van der Zee *et al.* [25]	2005	195 cases with high DBP, 195 controls with low DBP	DBP at 4 weeks	19 genes (total of 45 polymorphisms)	HCTZ	SNPs *SCNN1G* rs5729, rs5723 and *NOS3* rs1799983 were associated with significant differences in DBP response	*SCNN1G* SNPs have no previously known PGx interactions with diuretics *NOS3* was shown to have PGx association with diuretic [33], however, that was in the full cohort from which these nested cases and controls were drawn
Manunta *et al.* [35]	2008	193 newly diagnosed with HTN	BP at 4 weeks	*ADD1* (Gly460Trp), *NEDD4L* (rs4149601), *WNK1* (5 SNPs)	HCTZ	In single-variant analysis, *ADD1* T carriers had significantly greater BP reduction than GG individuals; no other variants were significantly associated. Individuals carrying specific combinations of alleles of these genes had significantly greater SBP-lowering than other combinations	Single-variant results consistent with a number of other studies [62,63]. The multiple-variant analysis conducted here is novel
Turner *et al.* [4]	2008	194 blacks, 195 whites with HTN from opposite tertiles of DBP response to drug	DBP at 4 weeks	GWAS (100 k SNPs)	HCTZ	SNPs and haplotypes in *LYZ* and *YEATS4* were associated with DBP response to drug	Findings may be consistent with gene-expression profiling study [34]
β-***blockers***							
Lanfear *et al.* [24]	2005	597 with ACS	Time to all-cause 3 year mortality	ADRB1 (Arg389Gly, Ser49Gly), *ADRB2* (Gly16Arg, Gln27Glu)	BB	No associations for *ADRB1* variants. The *ADRB2* Gln27 allele was associated with higher mortality. The *ADRB2* 16Arg allele homozygotes had higher mortality. Risk was maximized when both genotypes were taken into account	Gln27Glu finding consistent with Kaye [64] No reported significant associations with Gly16Arg in this context
Liu *et al.* [7]	2006	61 with HTN	BP and MAP at 4 weeks	ADRB1 (Gly389Arg, Ser49Gly)	Metoprolol	Drop in BP and MAP varied with Gly389Arg genotype. Drop in SBP varied with Ser49Gly genotype 49Ser389Arg/ 49Ser389Arg and 49Ser389Arg/ 49Gly389Arg patients were good responders; 49Ser389Arg/	Ser49Gly findings partially consistent with Johnson [65]. Gly389Arg findings consistent with some studies [65–67] but not others [23] Note,

First author	Year	Participants	Outcome	Gene (variant)	Treatment	Findings*	Comment
						49Ser389Arg patients had a larger SBP drop than 49Ser389Arg/49Gly389Arg patien	Pooled analysis of 49Ser389Arg/49Gly389Arg patien
						49Ser389Arg patients had a larger SBP drop than 49Ser389Arg/49Gly389Arg patien	Study of these 49Ser389Arg/49Gly389Arg patien
						49Ser389Arg patients had a larger SBP drop than 49Ser389Arg/49Gly389Arg patien	Drug combination 49Ser389Arg/49Gly389Arg patien
						49Ser389Arg patients had a larger SBP drop than 49Ser389Arg/49Gly389Arg patien	Pooled population 49Ser389Arg/49Gly389Arg patien
						49Ser389Arg patients had a larger SBP drop than 49Ser389Arg/49Gly389Arg patien	Lack of prevalent 49Ser389Arg/49Gly389Arg patien
						49Ser389Arg patients had a larger SBP drop than 49Ser389Arg/49Gly389Arg patien	Predominantly used 49Ser389Arg/49Gly389Arg patien
							washout protocol for this study hinders comparisons
Lemaitre *et al.* [23]	2008	938 cases with MI or stroke, 2249 controls	MI, Ischemic stroke	*ADRB1* (seven SNPs plus haplotypes), *ADRB2* (five SNPs plus haplotypes)	BBs	Two SNPs In *ADRB1* interacted with treatment for MI and stroke risk BB treatment did not interact with *ADRB2* variants for either outcome	For *ADRB1*, other studies [7,65] reported significant interaction between variants tested here and BB treatment for BP-lowering whereas no interactions were found here. For *ADRB2*, findings agree with previous observations [68]
ACE inhibitors							
Filigheddu *et al.* [45]	2008	191 with HTN	BP at 4 weeks	*ACE* (ID), *AGTR1* (A1166C), *CYP11B2* (-344 C/T), *AGT* (-6 A/G)	Fosinopril	No variants were significantly associated with BP response to fosinopril	Others have found significant associations between fosinopril and *ACE* (ID) for BP response [69]. Findings for these variants with other ACE inhibitors are contradictory
Gluszek *et al.* [40]	2008	64 with essential HTN	BP, ambulatory, MAP at 8 weeks	*AGTR1* (A1166C)	Perindopril	No significant associations	Findings of other studies of this polymorphism with various treatments have been inconsistent; these findings consistent with Hingorani *et al.* (with unspecified ACEI and untreated hypertensives versus this study's mixed treatment, 2-week washout hypertensives) [41]
Angiotensin II blockers							
Kurland *et al.* [19]	2008	42 with HTN and LVH	BP at 12 weeks	*AGTR1* (C5245T)	Irbesartan	Plasma concentration of drug was related to the change In SBP in TT individuals but not for other genotypes	Polymorphism not previously studied in this context/study design
Calcium channel blockers							

First author	Year	Participants	Outcome	Gene (variant)	Treatment	Findings*	Comment
Bremer *et al.* [28]	2006	120 Caucasians	BP at ≥6 mo	*CACNA1C* (62 SNPs)	CCBs	Three SNPs had significant associations with antihypertensive outcomes	This was the earlierst study reporting significant PGx interaction with a CCB and, to date, the only one reporting an association with *CACNA1C*
Langaee *et al.* [21]	2006	537 with CAD and HTN	BP, HTN risk	*CYP3A5* (**3*, **6*)	Verapamil	Alleles marginally associated with treatment outcomes in blacks (p = 0.075) and Hispanics (p = 0.056).	Polymorphisms not previously studied in this context/study design
Beitelshees *et al.* [26]	2007	Overall n = 5979, but n varied by substudy	BP at 6 weeks treatment, time to BP control, number of drugs to control BP, death/MI/stroke	*KCNMB1* (Glu65Lys, Val110Leu)	Verapamil, others as needed	SBP response did not differ by genotype Lys65 carriers achieved earlier control and required fewer drugs Leu110 carriers had reduced risk of death/MI/stroke	Findings consistent with the Kelley–Hedgepeth *et al.* study of BB and this variant [27]; however, incomplete information on previous antihypertensive treatment and washout for these studies hinders comparisons
Multiple drug classes							
Milionis *et al.* [29]	2007	132 untreated with HTN	BP after variable follow-up period	*ACE* (ID), *AGT* (M235T), *AGTR1* (A1166C)	All classes, all combinations	*AGTR1* C allele and AC genotype associated with more BP response, especially in individuals with MetS	Findings of other studies of *AGTR1* A1166C with various treatments have been inconsistent [51,70] Undifferentiated treatment in this study and differences in washout protocols among studies make comparisons difficult
Schelleman *et al.* [37]	2007	4097 with HTN	MI, stroke for approximately 10-year maximum follow-up	*AGT* (M235T)	ACEI, BB	MI risk with ACEI treatment increased for T allele carriers No *AGT*–*ACE*I associations for stroke; no *AGT*–BB associations for MI or stroke	Findings of other studies of this polymorphism with *ACE*Is have been Inconsistent [41,42] for BP lowering; present study is considerably larger and longer-termed than previous and tracks hard outcomes
Kelley–Hedgepeth *et al.* [27]	2008	2594 without CVD	BP	*KCNMB1* (Glu65Lys)	4 HTN drug classes	BB treatment may be responsible for lower BP in Lys65 allele carriers	Findings consistent with those of the Beitelshees *et al.* study of CCB and this variant [26]; however, incomplete information on previous antihypertensive treatment and washout

First author	Year	Participants	Outcome	Gene (variant)	Treatment	Findings*	Comment
							for these studies hinders comparisons for these studies hinders comparisons
Lynch *et al.* [20]	2008	38,462 with HTN	CHD, stroke, all-cause mortality, combined cardiovascular disease outcomes, and 6-month BP changes	*NPPA* (T2238C, G664A)	Chlorthalidone versus amlodipine, doxazosin, lisinopril	Only T2238C variant associated with modification of drug effects on outcomes Minor C allele carriers had more favorable CVD outcomes with diuretic; TT individuals had more favorable outcomes with CCB	Polymorphisms not previously studied in this context/study design
Pacanowski *et al.* [22]	2008	5895 with CAD	death, nonfatal MI, nonfatal stroke for 2.8 year average follow-up	*ADRB1* (Ser49Gly, Arg389Gly, haplotypes), *ADRB2* (Gly16Arg, Gln27Glu, Arg175Arg, haplotypes)	Atenolol, verapami	Ser49-Arg389 haplotype carriers had higher death rates in verapamil but not atenolol group	For *ADRB1*, Ser49-Arg389 haplotype findings consistent with previous BB studies [7,66,71,72]. For *ADRB2*, associations that did not reach significance here did in other studies of BB treatment [24]. These polymorphisms and haplotypes not previously studied in the context of verapamil treatment Incomplete information on previous treatment and washout protocols makes comparisons among studies difficult
Schelleman *et al.* [38]	2008	4097 with HTN	MI, stroke for ~ 10 year maximum follow-up	*AGTR1* (C573T), *ACE* (ID)	ACEI, BB	MI risk with ACEI treatment reduced for *AGTR1* C allele carriers No *AGTR1*–ACEI or BB associations for stroke No *ACE*–ACB or BB associations for MI or stroke	*AGTR1* C573T polymorphism not previously studied in this context *ACE* ID findings consistent with previous study [44]

ACEI: Angiotensin converting enzyme inhibitor; ACS: Acute coronary syndrome; ADD1: α-*adducin gene;* AGT: *Angiotensinogen; BB:* β-*blocker; BP: Blood pressure; CAD: Coronary artery disease; CCB: Calcium channel blocker; CHD: coronary heart disease; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; GWAS: Genome-wide association study; HCTZ: Hydrochlorothiazide diuretic; HTN: Hypertension; LVH: Left ventricular hypertrophy; MAP: Mean arterial pressure; MetS: Metabolic syndrome; MI: Myocardial infarction; NOS: Nitric oxide synthase; PGx: Pharmacogenetic; SBP: Systolic blood pressure.*

*Associations reported here met standards of significance as defined by each study, unless otherwise noted.