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The Pharmacogenomic and Metabolomic Predictors of ACE Inhibitor and Angiotensin II Receptor Blocker Effectiveness and Safety

Hania K. Flaten¹ and Andrew A. Monte^{1,2,3,4}

¹Department of Emergency Medicine, University of Colorado School of Medicine, Leprino Building, 7th Floor Campus Box B-215, 12401 E. 17th Avenue, Aurora, CO 80045, USA

²Center for Bioinformatics & Personalized Medicine, University of Colorado School of Medicine, Aurora, CO, USA

³Skaggs School of Pharmacy, University of Colorado, Aurora, CO, USA

⁴Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority, Denver, CO, USA

Abstract

Hypertension (HTN) is the most common chronic disease in the USA. Hypertensive patients frequently require repeat primary care visits to find an effective drug or drug combination to control their disease. Currently, patients are prescribed drugs for HTN based on race, age, and comorbidities and although the current guidelines are reasonable starting points for prescribing, 50% of hypertensive patients still fail to achieve target blood pressures. Despite numerous strategies to improve compliance, drug effectiveness, and optimization of initial drug choice, effectiveness has remained largely unchanged over the past two decades. Therefore, it is important to pursue alternative strategies to more effectively treat patients and to decrease medical costs. Additional precision medicine work is needed to identify factors associated with effectiveness of commonly used antihypertensive medications. The objective of this manuscript is to present a comprehensive review of the pharmacogenomic and metabolomic factors associated with ACEI and ARB effectiveness and safety.

Keywords

ACE inhibitors; Angiotensin II receptor blockers; Pharmacogenomics; Metabolomics; Precision medicine

Correspondence to: Hania K. Flaten.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

Informed Consent Informed consent is not applicable in this review article.

Introduction

Hypertension (HTN) is the most common chronic disease in the USA. One in three adult Americans [1] and more than one billion people worldwide have high blood pressure [2]. In addition to the high incidence of the disease, half of Americans with HTN do not have the condition well-controlled [1]. Hypertensive patients frequently require numerous primary care visits to find an effective drug or drug combination. Many patients take multiple drugs to control their HTN [3]. Currently, patients are prescribed drugs for HTN based on race, age, and comorbid disease and although the current guidelines are reasonable starting points for prescribing, 50% of hypertensive patients still fail to achieve target blood pressures [1, 4]. The economic burden associated with the management of HTN and the associated secondary comorbidities, such as myocardial infarction, kidney disease, and stroke, are significant. Medication non-compliance contributes to low rates of HTN control but does not account for all the variability seen in response to blood pressure drugs. Despite numerous strategies to improve compliance [5–8], drug effectiveness [9, 10], and optimization of initial drug choice [4], effectiveness has remained largely unchanged over the past two decades [11].

Therefore, it is important to pursue alternative strategies that more effectively treat patients and decrease medical costs. Precision medicine efforts have demonstrated improved outcomes in HTN for drugs such as hydrochlorothiazide and atenolol [12]. However, additional precision medicine research is needed for the most commonly prescribed antihypertensive drugs. The eighth Joint National Committee (JNC-8) evidence-based guideline for the management of HTN lists ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) as first-line therapy for the vast majority of hypertensive patients [4]. Even when ACEIs or ARBs are not recommended as first-line therapy, as in African Americans, they are considered second-line therapy [4]. Like other antihypertensives, ACEIs and ARBs are not 100% effective nor are they 100% safe. It is necessary to first summarize the available precision medicine findings related to ACEIs and ARBs, then examine these associations in large cohorts to improve effectiveness and safety of prescribing practices.

The ultimate goal for providers is to deliver safe and effective treatment to the patient. However, HTN is a complex, polygenic disease [13] and is therefore equally complex to treat. One approach to provide safer and more effective therapies is to guide therapy with genomic and metabolomic analyses [14–16]. Testing each patient for variants in drug targets, metabolic enzymes, and other absorption, distribution, metabolism, and elimination intermediates may allow selection of the most effective drug for each individual. These tests would allow the physician to select a drug for the individual based on specific data, thus obviating numerous follow-up visits to change and adjust prescriptions. Testing for genomic or metabolic markers could also decrease adverse drug events and lead to improved drug safety. In fact, the Precision Medicine Initiative seeks to follow a cohort of one million or more Americans with the goal of improving health outcomes through the development of precise treatments for diseases. A long-term goal of this initiative is to determine the right drug for the right person at the right dose [17].

The objective of this manuscript is to present a comprehensive review of the pharmacogenomic and metabolomic factors associated with ACEI and ARB effectiveness and safety. We will first discuss the mechanisms of action of these medications as a prelude for a review of the precision medicine studies associated with these drugs.

Background

Since their advent in the late 1970s [18], ACEIs have become a commonly prescribed drug. Lisinopril is the most commonly prescribed ACEI in the USA [19]. In 2014, there were 103 million lisinopril prescriptions dispensed, which represents an increase of 90 million prescriptions from 2011 [20]. The first ARB in the USA was approved for use in 1995 [21]. Twenty years after reaching the market, ARBs have risen to a place in the top 20 most commonly prescribed drugs in the USA [19]. In 2014, losartan was prescribed 39.5 million times in the USA [19]. There are many ACEIs and ARBs in use with variable effectiveness and risk of adverse effects (Table 1). Side effects of ACEIs and ARBs include cough, angioedema, hypotension, and hyperkalemia. Patients with these side effects must re-evaluate their treatment with their physician and consider different drugs or altering doses to treat their HTN. Due to near ubiquitous use of ACEIs or ARBs in hypertensive patients, it is important to understand the drugs' mechanisms of action and explain the individualized responses to these commonly prescribed classes of drugs.

Mechanisms of Action

The renin-angiotensin-aldosterone system regulates blood pressure via release of angiotensinogen from the liver into the bloodstream (Fig. 1, no. 1). Angiotensinogen is cleaved by renin to form angiotensin I (Fig. 1, no. 2) which is then converted to angiotensin II via angiotensin converting enzyme, ACE (Fig. 1, no. 3). Angiotensin II promotes constriction of blood vessels leading to an increase in blood pressure (Fig. 1, no. 4). In addition, angiotensin II leads to the formation of aldosterone (Fig. 1, nos. 5 and 6), which increases reabsorption of sodium and water into the blood, resulting in increased blood pressure (Fig. 1, no. 7). ACEIs inhibit ACE from converting angiotensin I to angiotensin II (Fig. 1, no. 8) thus lowering blood pressure by preventing smooth muscle constriction in vasculature and by reducing the release of aldosterone.

Conversion of angiotensin I to angiotensin II is not the sole pathway that produces angiotensin II; trypsin, cathepsin, or the heart chymase all produce angiotensin II leading to inevitable ceiling effect of blood pressure decline [35]. ACEIs are competitive inhibitors and hormone production can be overcome by increasing angiotensin I substrate in vitro [36, 37]. In addition, ACEIs inhibit bradykinin metabolism leading to side effects such as dry cough and angioedema (Fig. 1, nos. 10 and 11).

ARBs target the angiotensin pathway by blocking the angiotensin II receptor (Fig. 1, no. 9). ARBs lower blood pressure with fewer side effects than ACEIs due to their intervening role further downstream in the angiotensin cascade. Angiotensin II type 1 and type 2 (AT1 and AT2) receptors have been described; however, ARBs relax smooth muscle by blocking the interaction of angiotensin II at the AT1 receptor and AT2 plays only a minor role in the antihypertensive effect of the drug class [35]. AT1 receptors are coupled to Gq and IP3

signal transduction pathways which, when stimulated, lead to smooth muscle contraction and increase in blood pressure (Fig. 1, no. 4). ARBs, like ACEIs, are competitive inhibitors; however, the dissociation of ARB from the receptor is exceptionally slow leading to insurmountable antagonism [36, 37]. In addition, ARBs increase salt and water excretion, thus reducing the plasma volume and subsequently, blood pressure (Fig. 1, no. 9) [38].

Demographic and Clinical Associations

Age and race are two clinical factors physicians use to guide prescribing practices. An ACEI or ARB is recommended as first-line therapy for the general population and patients with diabetes or chronic kidney disease [4]. In the general adult black population, ACEIs and ARBs are a second-line treatment due to this population's increased risk of cerebrovascular events [39]. Initial treatment in the black population should include a thiazide-type diuretic or a calcium channel blocker (CCB) [4]. Diuretics and CCBs are generally more effective in the elderly population [40].

Patients with chronic kidney disease, regardless of race or diabetes status, are recommended to begin HTN treatment with an ACEI or ARB to improve kidney outcomes [4]. The FDA classifies ACEIs [41] and ARBs [42] as pregnancy Category C in the first trimester and Category D in the subsequent trimesters.

Genetic Variants Associated with Effectiveness

Several investigators have examined genetic variants associated with ACEI and ARB effectiveness (Table 2). The *ACE* gene has a variant characterized as insertion (I) or deletion (D) of an Alu repeat in intron 16 (17q23.3, rs1799752). Variations at this locus have been associated with myocardial infarction [61, 62] and HTN [63, 64]. In a study of Malay male hypertensive subjects, the D/D genotype conferred a greater blood pressure lowering response to ACEIs (lisinopril and enalapril) [43]. It is hypothesized that ACEIs are particularly effective in patients with the D/D genotype since this genotype has been associated with increased ACE serum levels and higher ACE activity thus leading to more potential for inhibition [44, 45]. There are mixed data regarding the association of angiotensin II levels and ACE I/I, I/D, and D/D genotypes. Studies investigating associations of ACE I/D polymorphism have concluded that although the polymorphism influences the plasma ACE levels, it does not affect angiotensin II or aldosterone production in subjects [65, 66]. However, another study demonstrated that higher plasma levels of angiotensin II were generated in normotensive men with the D/D genotype [67]. A final study concluded that there is a higher level of vascular conversion of angiotensin I to angiotensin II in subjects with the D allele [68]. In the lungs where there is significant excess of ACE, certain ACE genotypes may not affect the net production of angiotensin II.

The I and D polymorphisms have also been studied in the context of ARBs. The Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA) trial made significant advances in identifying single nucleotide variants (SNVs) associated with blood pressure response to ARBs. This trial showed the ARB irbesartan conferred a larger decrease in diastolic blood pressure in I/I genotype compared with D/D or I/D [46], whereas the D/D genotype conferred better response to ACE inhibitors [43].

Renin is the rate-limiting enzyme for the renin-angiotensin-aldosterone system and therefore an important gene to study when considering response to ACEIs and ARBs. A study investigating polymorphisms and response to valsartan demonstrated that CC homozygotes of the *RENC5312T* polymorphism had an increased response to ARBs [60]. The C5312T polymorphism is located in the distal enhancer region of the human renin gene [69] and this polymorphism is hypothesized to increase transcription of renin. Measuring plasma renin can give insight into the etiology of HTN in patients; however, the predictive value of renin status and response to ACEIs and ARBs remains controversial. Renin is known to decrease with age, thus complicating its predictive value when treating HTN [70–73].

Variants in the *CYP11B2* gene (encodes aldosterone synthase) have been associated with variable responses to ARBs. The SILVHIA trial found that subjects with the TT variant at position 344 of *CYP11B2* had a more pronounced response to irbesartan than individuals with TC or CC variants (rs1799998) [48]. The variants at position 344 were not related to the baseline serum aldosterone levels [48]. Another independent study found that the CC variant of *CYP11B2* conferred a greater response to candesartan than the TC or TT variants [49]. Both of these studies were small and require further investigation regarding this variant and response to ARBs.

In addition to polymorphisms within elements of the angiotensin hormone system itself, variants in the drug metabolizing enzymes that interact with ACEIs and ARBs are associated with drug effectiveness. The SILVHIA trial showed the *CYP2C9*2* variant (C430T rs1799853), which predicts less enzymatic activity compared to the wild type *CYP2C9*1*, reduced the metabolism of losartan and thus improved its treatment effect [50]. Enzyme CYP3A4, in addition to CYP2C9, contributes to losartan metabolism and variants of this enzyme may alter ARB effectiveness [74, 75]. Additional variation in drug metabolizing enzymes is likely, such as CES1 which is responsible for conversion of enalapril and ramipril into their active forms, though *CES1* gene variants affecting conversion of ACEIs have not yet been determined.

ARBs conventionally were thought to have shallow dose-response curves. However, these curves were generated using data from both ARB responders and non-responders [76, 77]. For example, patients with the wild type *CYP2C9*1* variant which confers increased enzymatic activity metabolize losartan faster than patients with *CYP2C9*2* variant which confers less enzymatic activity [50]. Thus, the patient with increased enzymatic activity will demonstrate a flat dose-response curve to an ARB, whereas the patient with decreased enzymatic activity may demonstrate a linear dose-response. Further studies investigating the dose-response curve of ARBs by genotype are needed.

SNVs in *ApoA* (A1449G), *EDNRB* (G40A), and *eNOS* (A498G) were predictors of blood pressure reduction with ARB therapy in a group of 97 Swedish patients with HTN [78]. In particular, the association of the SNVA498G in *eNOS* and reduction in blood pressure on ARB therapy suggests the endothelium as a site of action for ARBs. This research suggests that the SNVs studied account for about 50% of the reduction in systolic and diastolic blood pressures in their subjects [78].

The SNV resulting in a missense mutation M235T in the *AGT* gene (coding for angiotensinogen) on chromosome 1 (rs699) may lead to higher plasma levels of angiotensinogen [79]. Carriers of the threonine amino acid change in the angiotensinogen protein had better response to ACEIs in one study [51] but this finding was not successfully replicated in subsequent studies [52].

Finally, *ACE* gene variant rs4329 has been hypothesized to predict effectiveness of ACE inhibition. Patients homozygous with the major allele (AA) at this locus who were treated with ACEIs showed lower levels of aspartylphenylalanine (Asp-Phe) (a by-product of ACE activity on cholecystokinin) when compared to patients homozygous for the minor allele (GG). This finding suggests that ACE is more fully inhibited by ACEIs in patients homozygous for the major *ACE* allele [53].

Genetic Variants Associated with Safety

There are several polymorphisms that have been associated with increased or decreased incidence of common side effects of ACEIs; however, many of these associations are weak and further data are needed to determine their validity. Identifying genomic markers that predict a patient's susceptibility to certain side effects would allow for safer prescribing of ACEIs to hypertensive patients.

As detailed in the previous section, the *ACE* gene I/D polymorphism has been associated with ACEI and ARB effectiveness, however, a meta-analysis found that ACEI-induced angioedema was not significantly associated with the *ACE* gene I/D polymorphism [47].

Cough is the most common side effect of ACEIs. The *SLCO1B1* gene variant T521C (Val174Ala, rs4149056) is known to have a strong association with increased risk of enalapril-induced cough [54]. *SLCO1B1* encodes an organic anion transporter protein, OATP1B1, which is involved in hepatic drug clearance of enalapril [80]. Carriers of T521C variant showed increased plasma concentrations of enalapril. Both ACEIs [80] and ARBs [81, 82] are partly transported into bile and cleared from the plasma by the OATP1B1 transporter. Since enalapril and other ACEIs are cleared less efficiently in individuals with a mutated OATP1B1 transporter, the plasma levels of the drug remain high. High plasma levels of ACEIs lead to increased bradykinin in the blood since bradykinin is broken down into metabolites via ACE (Fig. 1, no. 12). Thus, patients with the T521C variant who are treated with ACEIs are at risk of bradykinin accumulation in plasma and increased incidence of cough (Fig. 1, nos. 10 and 11).

Polymorphisms in the bradykinin receptor *BDKRB2* gene (rs8016905) and *ABO* gene (rs495828) have been associated with ACEI adverse effects [55]. The rs8016905 variant, located in intron 2 of *BDKRB2*, is associated with ACEI-induced cough and thus may implicate this intron in regulatory functions. Alternately, the rs8016905 polymorphism may be in linkage disequilibrium with a yet undescribed functional variant [55].

The *ABO* gene polymorphism rs495828 has been identified as a predictor of ACE activity. ACE activity is a possible predictor of ACEI response [56]. It is hypothesized that this variant in the *ABO* gene may affect aqueous solubility of ACE as well as ACE susceptibility

to proteases. ACE molecules carry ABO antigens and the *ABO* gene encodes glycosyltransferases that transfer monosaccharides to cell surface H antigens. The oligosaccharide moieties are bound to ACE molecules thus affecting the solubility of ACE and ACE susceptibility to proteases. Increased ACE susceptibility to proteases may lead to lower baseline blood pressure or a more effective response to ACEIs at lower doses.

ACE gene variants, rs4459610 and rs4267385, were shown to be protective against ACEI-induced cough [55]. These variants are mapped to the 3' end of the *ACE* gene in intronic regions that are hypothesized to have regulatory functions.

A genome-wide association study (GWAS) has identified additional variants associated with ACEI-induced cough. These include variants in the intron of *KCNIP4* on chromosome 4 (rs145489027, rs16870989, rs1495509, rs1495509) [57]. A major function of the protein KCNIP4 is regulation of Kv4 potassium channels. Problems regulating Kv4 channels due to a mutation in *KCNIP4* gene may lead to stimulation of sensory nerve afferents within the lung that result from accumulation of bradykinin (Fig. 1, no. 11) [83]. Patients with *KCNIP4* variants that induce problems regulating Kv4 channels are thus at higher risk of adverse events attributable to ACEIs since ACEIs prevent the breakdown of bradykinin (Fig. 1, no. 10).

Angioedema is a potentially life-threatening side effect of ACEIs. A GWAS analysis in 2012 found that the variant allele with a T substitution (rs500766) in *PRKCQ* was associated with reduced risk of angioedema, whereas the G allele in *ETV6* (rs2724635) was associated with increased risk of ACEI-associated angioedema [58]. *PRKCQ* and *ETV6* genes are involved in regulation of immune function. An increased risk of angioedema has been noted in specific populations including African Americans [84–86], women [86], and older adults [85]. SNVs associated with angioedema vary between African Americans and European Americans. In African Americans, variant rs989692 in the *MME* gene (which encodes neprilysin) was significantly associated with angioedema [58]. Neprilysin is a secondary mechanism that works with ACE to degrade vasoactive peptides bradykinin and substance P (Fig. 2). Variants in the *MME* gene may result in reduced function of neprilysin which then leads to increased peptide mediators in the plasma in the presence of ACE inhibition. Ultimately, the accumulation of these peptides can result in increased incidence of cough and angioedema (Fig. 2). Patients with decreased neprilysin function are thus at increased risk of ACEI adverse events [58].

Angioedema rates are estimated to be 50% higher in women than those in men [86, 87]. *XPNPEP2* encodes membranous aminopeptidase P (APP) which contributes to inactivation of bradykinin. The C2399A variant (rs3788853) in *XPNPEP2* was shown to be associated with ACEI-induced angioedema in men but not women [59]. While angioedema is more common in women, men may be at higher risk for angioedema when they carry certain variants in the *XPNPEP2* gene since men have only one copy of the gene coding for APP. In contrast, women who carry a variant on *XPNPEP2* may be protected since they carry two copies of the X chromosome (Fig. 3). Race and sex-specific polymorphisms alter the risk of these common and life-threatening adverse drug events.

Metabolomic Associations with Effectiveness and Safety

Metabolomics have the potential to more fully elucidate cellular processes in the human body. ACEI therapy has been associated with increased levels of des-Arg(9)-bradykinin, the active metabolite of bradykinin, and increased HWESASXX, a peptide derived from C3 complement degradation (Table 3) [53, 88]. Bradykinin causes vasodilation and the increased level of bradykinin in patients taking ACEIs is supported by the mechanism of action of the drug class. Excess bradykinin accumulation is associated with ACEI-induced cough and angioedema (Fig. 1, no. 11).

ACEI therapy has been associated with decreased levels of Asp-Phe, the product of cholecystokinin (CCK-8) cleavage by ACE [53] (Fig. 4), and decreased levels of phenylalanylphenylalanine, which is hypothesized to be a product of the cleaving action of ACE [88]. In a study of 448 individuals on ACEIs, investigators found decreased levels of Asp-Phe in patients homozygous for the major *ACE* allele (rs4329, major homozygote AA) and to a lesser extent, in patients heterozygous for the major allele (AG). The Asp-Phe levels did not change in homozygotes for the minor *ACE* allele (GG) on ACEI therapy, which suggests patients with the minor *ACE* allele may not benefit fully from ACEI treatment [53]. In addition Asp-Phe, Leu-Ala, alpha-Glu-Tyr, Phe-Ser, and the unknown metabolite X14086 were present in different concentrations varying with patient *ACE* genotype [53].

Researchers have only begun to examine metabolomic markers of ACEI/ARB drug effectiveness and safety (Table 3) though this approach shows promise for improving drug therapy.

Epigenomics and Proteomics Associated with ACEIs and ARBs

Epigenomics and proteomics are techniques that hold potential for precision medicine. While genomics and metabolomics related to ACEIs and ARBs are emerging in humans, epigenomic and proteomic studies regarding ACEIs and ARBs have advanced further in murine models and may guide precision medicine efforts in humans in the near future.

Stress in utero may increase occurrence of HTN later in life through fetal programming. A murine model showed that maternal low protein diet results in HTN in the offspring. The hypertensive offspring have upregulated expression of AT1b angiotensin receptor gene. Additionally, the AT1b proximal promoter was undermethylated in the offspring. Finally, the hypertensive rats responded well to ACEIs and ARBs indicating the renin-angiotensin-aldosterone system as responsible for the increase in blood pressure [89]. These findings are further supported in humans. Low birth weight children have lower methylation levels of the *ACE* gene promoter, higher ACE activity, and higher systolic blood pressure than normal birth weight children [90].

HTN leads to cardiovascular protein aggregates similar to aggregates found in cardiac aging. Angiotensin II-infused mice showed more complex and diverse patterns of aggregated cardiac proteins when compared to controls. Notably, hypertensive rats and older rats showed alterations in proteins associated in neurodegenerative diseases. These proteins include ApoE, clusterin, complement C3, H1 histones, HSP90 α and β , catalase, and

laminin γ -1. Mitochondrial HSP75 was absent in aged and hypertensive rat hearts [91]. Mitochondrial HSP75 is protective against cardiac hypertrophy and fibrosis [92].

These studies are experimental and researchers can only hypothesize what the findings may mean for humans. Further epigenomic and proteomic exploration is needed in order to develop a systemic biology approach to treating patients.

Future Directions

Given that ACEIs and ARBs are the most commonly prescribed antihypertensive medications, additional GWAS and metabolomics studies examining the effectiveness and safety of these drugs are needed. Moreover, these associations must be examined in large datasets to determine gene-gene interactions and modification of effects amongst those with numerous variants. The identified variants should be incorporated into electronic clinical decision support tools for clinicians to identify patients at risk for adverse drug events and suggest alternative treatments. Guidelines for translation of individual variants associated with actionable pharmacogenomic recommendations will continue to be developed by groups such as the Clinical Pharmacogenomics Implementation Consortium [93]. However, these individual variant associations must be incorporated into the care of the whole patient, utilizing a systems biology approach, in order to improve the predictive values of pharmacogenomics and metabolomic tests. In addition, the Precision Medicine Initiative will present a unique opportunity to examine data from a robust cohort of patients [17]. As personalized medicine becomes more common in the laboratory and at the bedside, we must focus efforts on the common and difficult to treat diseases, such as HTN, which will yield extensive financial and health benefits.

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Definitions

Genomics	The study of genomes and the application of genome variability to various disease states
Pharmacogenomics	The study of the interaction between the genome and drug therapy
Metabolomics	The quantitative measurement of endogenous and exogenous metabolic products to measure metabolic response or predict disease. This sensitive approach may be altered by minute-to-minute changes and accounts for upstream variations in an individual's genome, transcriptome, and proteome
Proteomics	The study of proteins and their variability in human disease states. The proteome may vary between different

	individuals and even different organs and cells within the same individual
Epigenomics	The study of the complete set of epigenetic modifications on the genetic material of a cell or genome
Complex disease	Disease states that are a result of multiple genetic polymorphisms across the entire genome leading to a bell-shaped curve of phenotypic expression. Examples include hypertension, obesity, pain, and heart disease which are affected by numerous genes with allelic heterogeneity resulting in a wide-range disease
Polygenic disease	A disease with multiple genetic mediators of the phenotype. Examples include hypertension, coronary artery disease, and diabetes

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Fig. 1.

ACE inhibitor interaction with the renin-angiotensin-aldosterone system. Angiotensinogen is released from the liver (no. 1) into the blood where it is converted to angiotensin I by renin (no. 2). Angiotensin I is converted to angiotensin II (*ang II*) by angiotensin converting enzyme (*ACE*, no. 3). *Ang II* binds angiotensin receptors which results in increased blood pressure (no. 4). *Ang II* also stimulates the production and release of aldosterone (nos. 5 and 6) which leads to increased blood pressure (no. 7). ACE inhibitors prevent the conversion of angiotensin I to *ang II* (no. 8). Angiotensin receptor blockers (*ARBs*) compete with *Ang II* at angiotensin receptor binding sites and result in decreased blood pressure (no. 9). ACE is an important enzyme for the breakdown of bradykinin (no. 12). In the presence of ACE inhibition, bradykinin accumulates and can lead to adverse effects such as cough and angioedema (nos. 10 and 11)

Fig. 2.

Vasoactive peptide breakdown by neprilysin. Neprilysin breaks down bradykinin, substance P, endothelin, and atrial natriuretic peptide (*ANP*). Mutations in *MME* gene which encodes neprilysin can lead to decreased neprilysin function and accumulation of vasoactive peptides, especially in the presence of ACE inhibition, thus increasing the risk of cough and angioedema

Fig. 3.

XPENPEP2 gene which encodes aminopeptidase P (*APP*) is located on the long arm of the X chromosome, marked *above*. *APP* is an inactivator of bradykinin, and is part of an important alternative bradykinin breakdown pathway in the presence of ACE inhibition. Females have redundancy in the *XPENPEP2* gene due to the possession of two X chromosomes, while males only have one copy of the X chromosome and thus one copy of the *XPENPEP2* gene. Males are likely more susceptible to adverse events during ACE inhibition due to variation in *XPENPEP2* gene than are females

Fig. 4. ACE cleavage of antidiabetogenic cholecystokinin (*CCK-8*) with by-product aspartylphenylalanine (*Asp-Phe*). ACEI therapy leads to decreased levels of *Asp-Phe*. Patients with major *ACE* allele AA at rs4329 have lower levels of *Asp-Phe* indicating ACEI therapy is more effective in patients with this variant

Table 1

Therapeutic dose, data on effectiveness, and incidence of adverse drug events of most frequently prescribed ACE inhibitors and angiotensin II receptor blockers in the USA in 2015

Drug	Dose	Effectiveness	% ADEs
Lisinopril	10–40 mg qd [22]	Decreased pulse pressure by 9.05 mmHg [23].	5.7% discontinued due to adverse experience 5.7% headache 5.4% dizziness 3.5% cough 2.7% diarrhea 2.5% fatigue 0.1% angioedema [22]
Enalapril	2.5–40 mg qd [24]	–14.10/–7.60 mmHg for 10 mg/day group –20.70/–9.60 mmHg for 20 mg/day group [25].	5.2% headache 4.3% dizziness 3.0% fatigue [24]
Ramipril	2.5–20 mg qd [26]	10 mg of ramipril resulted in a mean decrease in systolic blood pressure of 12.2 ± 0.95 mmHg ($P < .001$) [27].	11% hypotension 8% cough increase 4% dizziness 3% angina pectoris [26]
Quinapril	10–80 mg qd [28]	In multiple-dose studies, 10–80 mg per day in single or divided doses lowered systolic and diastolic blood pressure throughout the dosing interval, with a trough effect of about 5–7 mmHg [28].	5.6% headache 3.9% dizziness 2.6% fatigue 2.0% coughing 1.4% N/V 1.0% abdominal pain [28]
Benazepril HCl	20–40 mg qd [29]	Blood pressure lowering effect across this dosage range is –8.70 (95% CI –11.43, –5.97) mmHg for systolic blood pressure and –4.92 (95% CI –6.47, –3.36) mmHg for diastolic blood pressure [25].	6.2% headache 3.6% dizziness 2.4% fatigue 1.6% somnolence 1.5% postural dizziness 1.3% nausea 1.2% cough [29]
Valsartan	80–320 mg qd [30]	Decreased pulse pressure by 9.75 [23].	3% viral infection 2% fatigue 2% abdominal pain [30]
Losartan	25–100 mg qd [31]	Systolic blood pressure decreased 9.8 mmHg. Diastolic blood pressure decreased 6.68 mmHg [23].	8% URI 3% dizziness 2% pain, back 2% nasal congestion [31]
Olmesartan	20–40 mg qd [32]	20 mg qd produces a trough sitting blood pressure reduction over placebo of 10/6 mmHg. 40 mg qd produces a trough sitting blood pressure reduction over placebo of 12/7 mmHg [32].	3% dizziness Other occurred as same rate as placebo [32]
Irbesartan	150–300 mg qd [33]	Irbesartan 150 mg produces a trough sitting blood pressure reduction over placebo of 8/5 mmHg with 56% of patients displaying a favorable response [34].	4% fatigue 3% diarrhea 2% dyspepsia [33]

Table 2

Genetic associations with ACE inhibitor and angiotensin II receptor blocker effectiveness and safety

Gene	Variant	ACEI/ARB association
<i>ACE</i>	Insertion/deletion (I/D) Alu repeat in intron 16 17q23.3, rs1799752	D/D: greater response to ACEI therapy [43] D/D: increased ACE serum levels and higher ACE activity [44, 45] I/I: better response to ARB (irbesartan) [46] Locus not associated with ACEI-induced angioedema [47].
<i>CYP11B2</i>	T or C at position 344, rs1799998	TT: greater response to irbesartan [48] CC: better response to candesartan [49] Note: T and C variants are not associated with baseline serum aldosterone level. Small studies and further research is necessary.
<i>CYP2C9</i>	<i>CYP2C9</i> *2 variant C430T rs1799853	Less enzymatic activity→reduced metabolism of losartan→improved losartan therapy effect [50]
<i>AGT</i>	M235T, rs699	Mixed results in response to ACEIs [51, 52]
<i>ACE</i>	A or G rs4329	AA: lower levels of Asp-Phe when treated with ACEI. Suggests ACEI therapy is more effective in AA variant (major allele) [53]
<i>SLCO1B1</i>	T521C Val174Ala rs4149056	Increased plasma concentrations of enalapril→higher levels of bradykinin→enalapril-induced cough [54]
<i>BDKRB2</i>	rs8016905, intron 2	Associated with ACEI-induced cough [55]
<i>ABO</i>	G > T rs495828	Affect aqueous solubility of ACE and ACE susceptibility to proteases. Increased ACE susceptibility to proteases may lead to lower baseline blood pressure or a more effective response to ACEIs at lower doses [56]
<i>ACE</i>	A > T rs4459610 C > T rs4267385 3' end of <i>ACE</i> gene in intronic regions. May have regulatory function	Protective against ACEI-induced cough [55]
<i>KCNIP4</i>	Intronic regions rs145489027, rs16870989, rs1495509, rs1495509	Associated with ACEI-induced cough [57]
<i>PRKCQ</i>	T substitution, rs500766 Associated with immune function	Associated with reduced risk of angioedema [58]
<i>ETV6</i>	C > G, rs2724635	Associated with increased risk of ACEI-induced angioedema [58]
<i>MME</i>	T > C, rs989692 Gene encodes neprilysin	Associated with angioedema in African Americans [58]
<i>XPNPEP2</i>	C2399A rs3788853 Encodes aminopeptidase P protein which breaks down bradykinin	Associated with ACEI-induced angioedema in men but not women [59]
<i>REN</i>	C5312T Located in distal enhancer region of human renin gene	Associated with increased response to valsartan [60]

Table 3

Metabolomic associations with ACE inhibitor effectiveness and safety

Metabolite	ACEI Association
des-Arg(9)-bradykinin	ACEI therapy is associated with increased des-Arg(9)-bradykinin. Accumulation may lead to adverse events such as angioedema/cough [53, 88].
Aspartylphenylalanine (Asp-Phe)	ACEI therapy is associated with decreased levels of aspartylphenylalanine (Asp-Phe), the product of cholecystokinin (CCK-8) cleavage by ACE [53, 88].
HWESASXX	HWESASXX is a peptide derived from C3 complement degradation. ACEI therapy associated with increased HWESASXX [53, 88].
Aminopeptidase P (APP)	Inactivator of bradykinin. Low levels may increase risk of ACEI adverse drug event [59].