Pharmaceutical and Clinical Journal of Nusantara (PCJN)
Volume 03, No. 02, July 2025, Page 94-100
E-ISSN 2985 – 4040 (Online Media)
https://nusantarascientificjournal.com/index.php/pcjn/index
https://doi.org/10.58549/pcjn.v3i02.113

Pharmacogenomic and Bioinformatic Insights into ACE Gene Variants and Their Influence on ACE Inhibitor Response in Hypertension

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Abstract

Response to angiotensin-converting enzyme inhibitors (ACEIs)-based antihypertensive therapy varies between individuals, which is largely influenced by genetic factors. The ACE gene has several polymorphisms that can affect enzyme levels and therapeutic efficacy. This study aims to explore the relationship between genetic variations in the ACE gene and response to captopril, lisinopril, ramipril, and enalapril in hypertensive patients. This study used a bioinformatics and pharmacogenomics approach by analyzing data from PharmGKB, Ensembl, and GTEx Portal. Genetic polymorphisms were analyzed to evaluate their association with ACEI efficacy using a descriptive statistical approach. Results: Four single nucleotide polymorphisms (SNPs) in the ACE gene were found to be associated with response to ACEI. Variants rs4291 and rs1799752 were associated with captopril efficacy, where the AA genotype showed a decrease in the severity of renal failure. The rs1799752 variant was also associated with lisinopril and enalapril, with the DD genotype providing greater blood pressure reduction. In addition, rs4359 and rs4344 were correlated with the efficacy of ramipril, especially in the CC+TT and AA+GG genotypes. Genetic variation in the ACE gene plays a role in determining the response to ACEI therapy. Pharmacogenetic approaches have the potential to improve the efficacy and safety of antihypertensive treatment.

Keywords: ACE, genetic polymorphism, pharmacogenomics, ACE inhibitors, hypertension

Abstrak

Respons terhadap terapi antihipertensi berbasis angiotensin-converting enzyme inhibitors (ACEIs) bervariasi antar individu, yang sebagian besar dipengaruhi oleh faktor genetik. Gen ACE memiliki sejumlah polimorfisme yang dapat memengaruhi kadar enzim dan efektivitas terapi. Penelitian ini bertujuan mengeksplorasi hubungan antara variasi genetik pada gen ACE dan respons terhadap kaptopril, lisinopril, ramipril, dan enalapril pada pasien hipertensi. Penelitian ini menggunakan pendekatan bioinformatika dan farmakogenomik dengan menganalisis data dari PharmGKB, Ensembl, dan GTEx Portal. Polimorfisme genetik dianalisis untuk mengevaluasi keterkaitannya dengan efektivitas ACEI menggunakan pendekatan statistik deskriptif. Empat polimorfisme nukleotida tunggal (SNP) pada gen ACE ditemukan berasosiasi dengan respons terhadap ACEI. Varian rs4291 dan rs1799752 dikaitkan dengan efikasi kaptopril, di mana genotipe AA menunjukkan penurunan keparahan gagal ginjal. Varian rs1799752 juga terkait dengan lisinopril dan enalapril, dengan genotipe DD memberikan penurunan tekanan darah yang lebih besar. Selain itu, rs4359 dan rs4344 berkorelasi dengan efektivitas ramipril, terutama pada genotipe CC+TT dan AA+GG. Kesimpulan: Variasi genetik pada gen ACE berperan dalam menentukan respons terhadap terapi ACEI. Pendekatan farmakogenetik berpotensi meningkatkan efikasi dan keamanan pengobatan antihipertensi.

Keywords: *ACE, polimorfisme genetik, farmakogenomik, inhibitor ACE, hipertensi*

Received: 21 June 2025 *Revised: 03 July 2025* *Accepted: 07 July 2025* *Publish: 09 July 2025*

INTRODUCTION

Hypertension is one of the main risk factors for cardiovascular disease that contributes to global morbidity and mortality[1,2]. Hypertension management often requires pharmacological therapy tailored to the characteristics of each patient to achieve optimal efficacy and reduce the risk of side effects [3]. One group of drugs that are often used in hypertension therapy are angiotensin-converting enzyme inhibitors (ACEIs) which work by inhibiting the conversion of angiotensin I to angiotensin II, thereby reducing vasoconstriction and lowering blood pressure [4]. The response to ACEIs such as captopril, lisinopril, ramipril, and enalapril can vary between individuals, mostly due to genetic factors[5]. The gene encoding the angiotensin-converting enzyme (ACE) has polymorphisms that can affect enzyme levels and response to ACEI therapy[6]. The most studied polymorphism is the insertion/deletion (I/D) in intron 16 of the ACE gene, which is associated with the level of enzyme activity in the circulation. Individuals with the DD genotype have higher ACE levels compared to individuals with genotype II or ID which has

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implications for the pharmacological response to drugs in the ACEI group [7]. Several studies have shown that ACE genotype can affect the effectiveness and safety of ACEIs in hypertensive patients. For example, patients with the DD genotype tend to have a lower response to ACEIs which may require higher doses or combination therapy with other antihypertensives. Therefore, understanding the effect of ACE genotype on the response to captopril, lisinopril, ramipril, and enalapril is important in efforts to personalize hypertension therapy[8].

This study aims to explore the relationship between ACE gene polymorphisms and pharmacological responses to various ACEIs used in hypertension therapy. By understanding the specific effects of ACE genotype on these drugs, it is hoped that pharmacogenetic approaches can be improved in the management of hypertension and optimize patient therapy more individually.

METHODOLOGY

This study employed a pharmacogenomics-based bioinformatics approach to explore the relationship between ACE gene polymorphisms and the effectiveness of ACE inhibitors (captopril, lisinopril, ramipril, and enalapril). [9,10]. Data were obtained from various bioinformatics databases, including PharmGKB, Ensembl, and GTEx Portal [11,12].

Genetic Data Collection

Genetic variations in the ACE gene will be obtained from the Ensembl database to identify the most relevant polymorphism[13]. ACE gene expression data in various tissues will be obtained from the GTEx Portal to understand the correlation with enzyme activity [14,15].

Pharmacogenetic Analysis

Information on the interaction between genetic variants and response to captopril, lisinopril, ramipril, and enalapril will be obtained from the PharmGKB database[16,17]. The relationship between ACE genotype and pharmacological response will be analyzed using a statistical approach [18]. The results of this study are expected to provide new insights into the personalization of pharmacogenomic based antihypertensive therapy, thereby increasing the effectiveness and safety of ACEI use in hypertensive patients [19,20].

RESULTS AND DISCUSSION

The results of this study found that there are four SNPs in the ACE gene that are associated with the response to therapy using ACEI, namely captopril, lisinopril, ramipril, and enalapril. In (Table 1) it can be seen that the rs4291 and rs1799752 variants in the ACE gene are associated with the response to captopril. Patients with the AA genotype at rs4291 experienced a decrease in the severity of kidney failure when treated with captopril compared to the AT+TT genotype (p=0.029). Likewise, patients with the AA genotype at rs1799752 showed a positive response with decreased blood pressure and improved total vascular resistance (p=0.01).

The results of the study on the relationship between the ACE gene variant genotype and lisinopril therapy can be seen in (Table 3) which shows that the rs1799752 variant is also associated with the response to lisinopril, where individuals with the del/del genotype have greater clinical benefits with a more significant decrease in blood pressure compared to other genotypes (p = 0.0001).

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Table 1. Four *ACE gene variants* associated with response to therapy using ACEIs

Gene	SNP	Drug	Phenotype Category
ACE	rs4291	Captopril	Effectiveness
ACE	rs1799752	Captopril, Lisinopril and Enalapril	Effectiveness
ACE	rs4359	Ramipril	Effectiveness
ACE	rs4344	Ramipril	Effectiveness

Table 2. Relationship of *ACE* gene variants with captopril therapy

Variants	Gene	Association	P-Value	Phenotype Category
rs4291	*ACE*	The AA genotype is associated with decreased severity of Kidney Failure when treated with captopril in people with Alzheimer's Disease compared with the AT + TT genotype.	0.029	Effectiveness
rs1799752	*ACE*	The AA genotype is associated with decreased severity of Kidney Failure when treated with captopril in people with Alzheimer's Disease compared with the AT + TT genotype.	0.01	Effectiveness

Table 3. Relationship of *ACE* gene variants with lisinopril therapy

Variants	Gene	Association	p-value	Phenotype Category
rs1799752	*ACE*	DD genotype is associated with increased clinical benefit of enalapril or lisinopril in men with hypertension	0.0001	Effectiveness

Table 4. Association of ACE gene variants with ramipril therapy.

Variants	Gene	Association	p-value	Phenotype Category
rs4359	*ACE*	The CC + TT genotype is associated with an increased response to ramipril in people with hypertension compared with the CT genotype.	0.003	Efficacy
rs4344	*ACE*	The AA + GG genotype is associated with an increased response to ramipril in people with hypertension compared with the AG genotype.	0.03	Efficacy

Research results of the relationship between ACE gene genotype variants and ramipril therapy can be seen in (Table 4) which describes the relationship between rs4359 and rs4344 variants and response to ramipril. Patients with CC + TT genotypes at rs4359 and AA + GG at rs4344 showed a faster response in achieving blood pressure targets compared to heterozygous patients ($p = 0.003$ and $p = 0.03$, respectively).

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Table 5. Relationship of ACE gene variants with enalapril therapy.

Variants	Gene	Association	p-value	Phenotype Category
rs1799752	*ACE*	The DD genotype is associated with increased clinical benefit of enalapril or lisinopril in men with hypertension.	0.0001	Efficacy

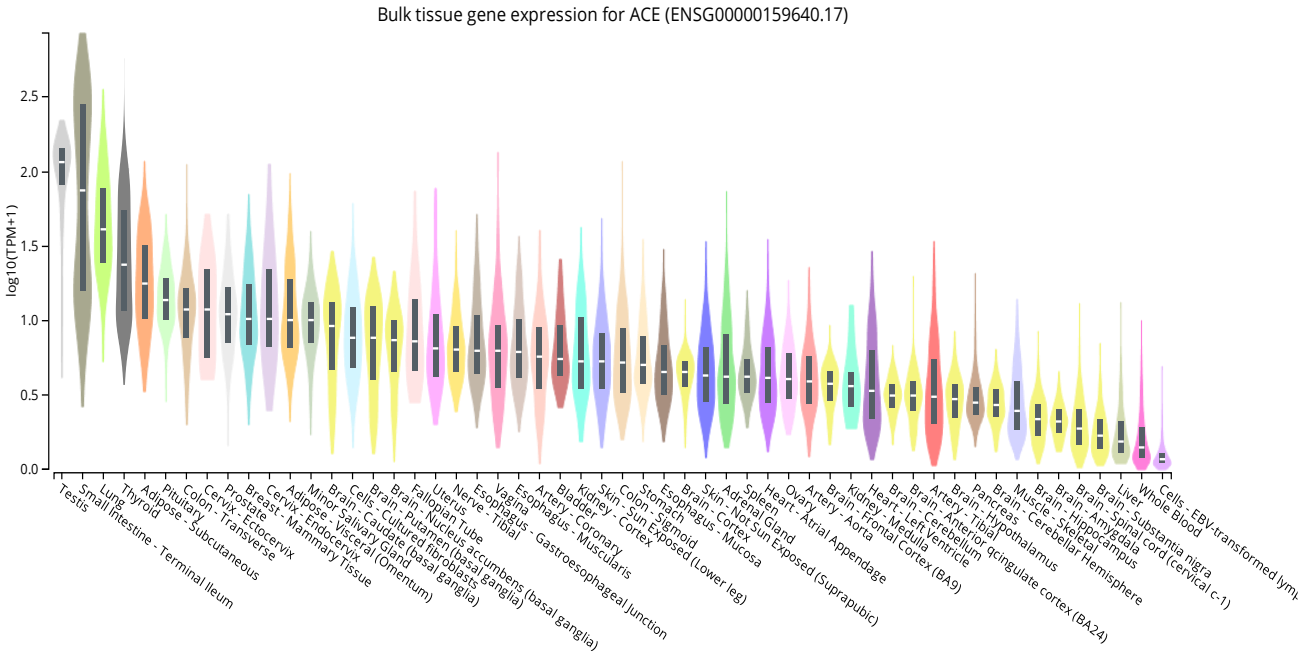

Figure 1. Bulk tissue gene expression for ACE (ENSG00000159640.17)

The results of the study The relationship between the genotype of the ACE gene variant and enalapril therapy can be seen in (Table 5) which shows that the rs1799752 variant again plays a role in the response to enalapril. Patients with the del/del genotype experienced a greater decrease in blood pressure compared to other genotypes (p = 0.0001.)

The Angiotensin-Converting Enzyme (ACE) gene shows significant expression levels in several extravascular tissues, including the terminal ileum of the small intestine. In this tissue, ACE plays a role in the processing of active peptides such as angiotensin I to angiotensin II, as well as the degradation of bradykinin and other peptides involved in the regulation of vascular tone and local inflammatory processes. Expression of ACE in the terminal ileum suggests that the Renin-Angiotensin System (RAS) has a paracrine/autocrine role in modulating intestinal mucosal function, fluid and electrolyte homeostasis, and mucosal immune responses. In the context of therapy, high expression of ACE in the intestine may affect the bioavailability and pharmacological efficacy of ACEi, especially oral ACEi that must pass through the gastrointestinal system. On the other hand, exposure of ACEi in the intestinal lumen or mucosa may also decrease the local conversion of angiotensin I, potentially affecting mucosal microcirculation and intestinal motility. Although the direct influence of ACE expression in the ileum on

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the systemic effectiveness of ACEi is still not fully understood, this expression remains important because it may contribute to individual variability in drug response, particularly regarding absorption and gastrointestinal side effect.

The results of this study confirm that genetic variations in the ACE gene have a significant impact on the pharmacological response of hypertensive patients to ACE inhibitors (ACEIs) such as captopril, lisinopril, ramipril, and enalapril. In the context of cardiology and genetics, the relationship between genetic polymorphisms and the efficacy of antihypertensive therapy further strengthens the importance of personalized medicine in the management of hypertension [21]. One of the main findings of this study is the role of the rs1799752 variant which shows that individuals with the DD genotype tend to experience a greater decrease in blood pressure compared to individuals with the ID genotype[22].

Mechanistically, the DD genotype is associated with increased expression of the ACE enzyme which causes increased angiotensin II levels, which in turn increases blood pressure [23]. Therefore, patients with the DD genotype are more responsive to ACEIs because ACE inhibition directly decreases angiotensin II production, thus providing a more significant antihypertensive effect [23]. Clinically these findings confirm that patients with the DD genotype may derive greater benefit from ACEIs compared to patients with genotype II who may require alternative therapies such as angiotensin receptor blockers (ARBs) [23].

In addition, the rs4291 variant was associated with decreased severity of renal failure in captopril-treated patients [24]. This may be related to differences in the regulation of ACE expression in the kidney where the A allele has a protective effect against elevated creatinine and long-term renal dysfunction. From a clinical perspective, patients at high risk of developing hypertensive nephropathy may benefit more from ACEI-based therapy if they have this variant. Therefore, genetic screening may help in determining more optimal therapeutic options, especially in hypertensive patients with renal comorbidities. In ramipril treatment, SNPs rs4359 and rs4344 also play a role in modulating patient response to therapy. Patients with the CC + TT genotype at rs4359 and AA + GG at rs4344 reached target blood pressure faster[25] This suggests that these variants may affect the interaction of ACE with its substrates or the renin-angiotensin signaling pathway as a whole which may have implications for higher drug efficacy. From a clinical perspective patients with this genetic profile may be given lower doses or monitored more closely on ACEI therapy to avoid potential side effects due to too rapid a response to the drug [24].

In addition, it should be noted that not all hypertensive patients will provide an optimal response to ACEI based on genetic factors alone. Other factors such as age, race, lifestyle, and the presence of comorbidities such as diabetes mellitus or heart failure also play a role in determining the effectiveness of antihypertensive therapy [26]. Patients with genotypes that show a suboptimal response to ACEI can be directed to combination therapy with ARB or diuretics to achieve better blood pressure control. The application of genetic screening in the management of hypertension still faces challenges, especially related to the availability of technology and costs [27].

However, with the development of pharmacogenomics and bioinformatics,

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genetic screening can become part of the standard of hypertension therapy in the future. By integrating genetic analysis in the selection of antihypertensive therapy, it is expected to increase the effectiveness of treatment, reduce unwanted side effects and improve the long-term prognosis of hypertensive patients [28]. Therefore, further research is needed to strengthen clinical evidence and develop guidelines for the use of ACEI based on the patient's genetic profile [29]. Overall, this study highlights the importance of genetic analysis in determining the effectiveness of antihypertensive therapy [22]. The implementation of genetic screening in clinical practice could be a step forward in a more precise therapeutic approach, which could ultimately improve the quality of life of hypertensive patients and reduce the risk of long-term cardiovascular complications. This study was based entirely on publicly available bioinformatics databases and did not include clinical patient data. Therefore, findings may not directly reflect population-wide effects without further validation. Future studies involving clinical trials or observational cohorts are necessary to validate the pharmacogenetic associations observed in this analysis and to confirm their applicability in diverse patient populations.

CONCLUSION

The results of the study showed that genetic variants rs1799752, rs4291, rs4359, and rs4344 in the ACE gene have a significant effect on the effectiveness of ACE inhibitor (ACEIs) therapy. Therefore, further research is needed to ensure the application of genetic screening as part of a more appropriate and evidence-based antihypertensive drug therapy strategy.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest in the scientific article written.

ETHICAL STATEMENT

This study did not involve any human participants, animal experiments, or the use of clinical data. All data used in this research were obtained from publicly available bioinformatics databases (PharmGKB, Ensembl, and GTEx Portal). Therefore, ethical approval was not required.

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