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The role of angiotensin I - converting enzyme (*ACE*) insertion/deletion gene polymorphism in hypertension and ACE inhibitor therapy: a narrative review

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ABSTRACT

Primary hypertension is the most prevalent type of hypertension, which is primarily attributed to genetic factors. The angiotensin-converting enzyme (*ACE*) gene has emerged as a prominent candidate among the genetic factors influencing blood pressure regulation. The *ACE* gene encodes the ACE, which plays a crucial role in the renin-angiotensin system. The *ACE* gene insertion/deletion (*I/D*) polymorphism is a variation of the *ACE* gene that affects blood pressure regulation. Individuals with *II*, *ID*, and *DD* genotypes may exhibit distinct ACE plasma concentrations, potentially contributing to variations in blood pressure levels and response to ACE inhibitor therapy. This article aimed to provide a comprehensive overview of the relationship between the *ACE I/D* gene with hypertension and angiotensin-converting enzym inhibitor (ACEI) effectiveness. This article presents a narrative review encompassing relevant studies published between 2013 and 2023. A systematic search was conducted using reputable databases such as PubMed, Science Direct, and Scopus. Inclusion criteria were applied, resulting in the selection of 25 articles that met the predefined criteria. The analysis included 25 studies, comprising 5 articles that investigated the impact of ACEI therapy and 20 articles that examined the *ACE I/D* gene polymorphism in hypertensive populations without ACEI therapy. It can be concluded that compared to the *I* allele, the *D* allele of the *ACE I/D* gene is associated with a higher level of essential hypertension and a reduced ACEI response.

ABSTRAK

Hipertensi primer adalah jenis hipertensi yang paling umum, terutama disebabkan oleh faktor genetik. Gen *angiotensin-converting enzyme* (ACE) merupakan kandidat gen utama di antara faktor genetik yang mempengaruhi pengaturan tekanan darah. Gene ACE mengkode ACE, yang memiliki peran penting dalam sistem renin-angiotensin. Polimorfisme insersi/delesi (*I/D*) gen *ACE* adalah variasi gen *ACE* yang memiliki dampak pada regulasi tekanan darah. Individu dengan genotipe *II, ID,* dan *DD* dapat menunjukkan konsentrasi plasma ACE yang berbeda. Polimerfisme ini berpotensi berkontribusi terhadap variasi tingkat tekanan darah dan respons terhadap terapi penghambat angiotensin-convertinn enzyme (ACEI). Telaah artikel ini bertujuan untuk memberikan gambaran yang komprehensif tentang hubungan antara gen *ACE I/D* dengan hipertensi dan efektivitas ACEI. Artikel ini menyajikan ulasan naratif yang mencakup penelitian relevan antara tahun 2013 dan 2023. Pencarian sistematis dilakukan menggunakan database terkemuka seperti PubMed, Science Direct, dan Scopus. Kriteria inklusi diterapkan, menghasilkan pemilihan 25 artikel yang memenuhi kriteria yang telah ditentukan. Analisis tersebut mencakup 25 penelitian, yang terdiri dari 5 artikel tentang efek terapi ACEI dan 20 artikel tentang polimorfisme gen *ACE I/D* pada populasi hipertensi tanpa terapi ACEI. Dapat disimpulkan bahwa dibandingkan dengan alel *I*, alel *D* dari gen *ACE I/D* terkait dengan tingkat hipertensi esensial yang lebih tinggi dan respons ACEI yang berkurang.

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INTRODUCTION

Hypertension, a medical condition characterized by persistent arterial blood pressure elevation, is a significant health concern. The diagnostic criteria for hypertension entail systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg.[1] This condition poses a substantial risk of developing cardiovascular diseases such as stroke, myocardial infarction, vascular disease, and chronic kidney disease.[2] Etiologically, hypertension can be classified into primary and secondary. Primary hypertension, accounting for over 90% of cases, represents the predominant form observed among individuals.[2] Genetic factors contribute to primary hypertension, influencing critical pathways involved in sodium balance and blood pressure regulation.[2] Numerous genes play a role in the intricate regulation of blood pressure, with the angiotensin I-converting enzyme (ACE) gene being among the most prevalent and impactful in this regard.[3]

The *ACE* gene, responsible for encoding the ACE enzyme, catalyzes the transformation of angiotensin I into angiotensin II. The consequential impact of angiotensin II encompasses the elevation of blood pressure through amplified aldosterone synthesis, enhanced sodium and water reabsorption, heightened blood volume, increased total peripheral resistance, and augmented cardiac output.[2] The *ACE* gene exhibits a diverse range of polymorphisms that intricately influence the activity of the ACE enzyme, thereby instigating variations in blood pressure among individuals. Among these polymorphisms, the *ACE* gene insertion/deletion stands as a frequently studied.[3]

The *ACE* gene insertion/deletion (I/D) polymorphism involves two distinct alleles, the I (insertion) and D (deletion) alleles. The D allele results from deleting 287 base pairs within intron 16, leading to notable differences in ACE production.[4] This polymorphism encompasses three genotypes; II, ID, and DD, leading to distinct plasma ACE concentrations. Genotype II is associated with low ACE enzyme levels, genotype ID demonstrates intermediate concentrations, while genotype DD exhibits high ACE enzyme concentrations in the plasma. The dissimilarity in ACE enzyme concentration results in significant variations in blood pressure profiles within each genotype.[5,6] Studies revealed ethnic-specific differences in the frequency of ACE I/D polymorphism, with a higher prevalence of the D allele observed in Asian, European, and African populations.[7,8]

The ACE enzyme serves as the pharmacological target for ACE inhibitors (ACEI), which are widely used as antihypertensive drugs. The efficacy of ACE inhibitors is expected to be influenced by the concentration of the ACE enzyme. Numerous studies have investigated the impact of the ACE (I/D) polymorphism on the effectiveness of ACEI. Heidari *et al.*[9] reported an association between the D allele of the *ACE* gene insertion/deletion polymorphism and the response of ACE inhibitors in controlling blood pressure among Malay hypertensive patients. Conversely, Schelleman *et al.*[10] reported no impact of the *ACE I/D* gene polymorphism on mean blood pressure in hypertensive patients receiving ACEI. The contradictory findings from these studies pose challenges in predicting the influence of the *ACE I/D* gene polymorphism on the response to ACE inhibitors. Therefore, the purpose of this paper is to investigate the connection between *ACE I/D* polymorphism and the responsiveness to ACEI medication in patients with hypertension.

MATERIAL AND METHODS

This article represents a comprehensive narrative review encompassing the literature search conducted between February and May 2023. Multiple reputable databases, including PubMed, Science Direct, and Scopus, were meticulously explored to acquire relevant publications. The search incorporated various keywords, such as "ace i/d AND hypertension," "ace i/d AND hypertension AND ace inhibitor," "ace insertion/deletion AND ace inhibitor," and "ace insertion/deletion OR ace i/d AND hypertension AND ace inhibitor OR acei". The inclusion criteria for this study encompassed articles published within the last ten years (2013-2023) with case-control, prospective cohort, and randomized control trial (RCT) study designs. The selected primary literature adhered to specific criteria, namely 1) inclusion of subjects who received ACE inhibitor therapy; 2) inclusion of subjects diagnosed with hypertension (stages 1 and 2); 3) inclusion of adult subjects; 4) identification of the ACE I/D gene by the researchers; and 5) publication of original research articles in English between 2013 and 2023. Excluded articles comprised those 1) narrative reviews, systematic reviews, or meta-analyses; 2) studies lacking identification of ACE I/D; 3) articles with inadequate data; or 4) studies duplicating previously included research.

RESULTS

After an extensive literature search, a total of 441 articles were initially identified and subjected to screening based on the specified keywords. Following a rigorous review of titles and abstracts, 416 articles were excluded for various reasons, including their classification as narrative reviews, systematic reviews, or meta-analyses, unavailability of full-text, absence of a control group, the inclusion of non-hypertensive subjects, inadequate genotype data, and duplication of previously included articles. Consequently, a total of 25 studies were ultimately selected for inclusion in this comprehensive narrative review, with five articles investigating the impact of ACE inhibitor (ACEI) therapy intervention and twenty articles focusing on studies without ACEI therapy. The detailed selection process is presented in FIGURE 1.

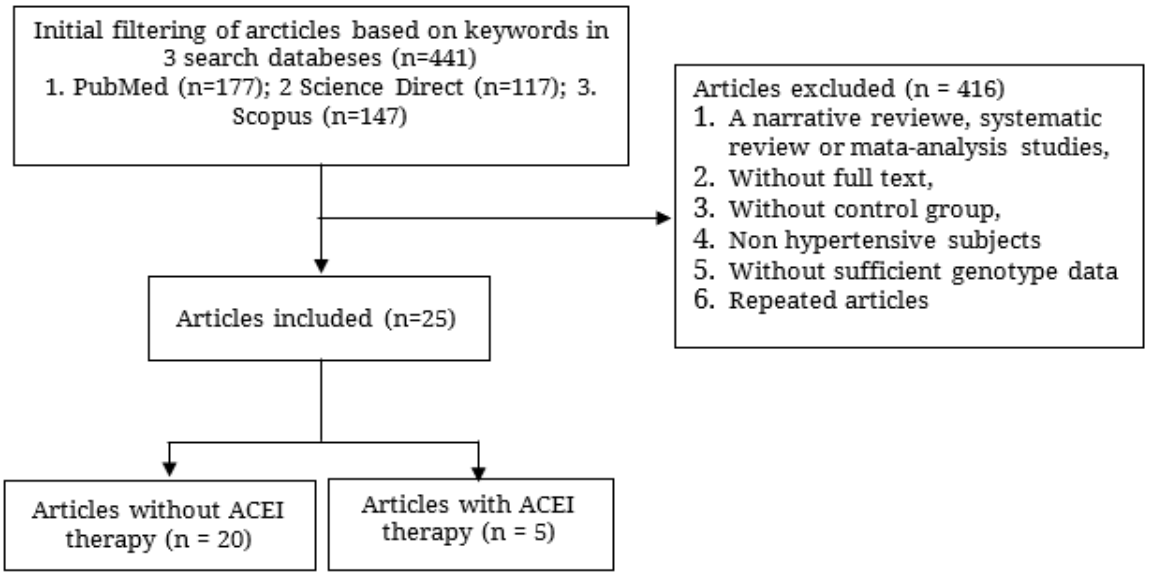

FIGURE 1. Flow diagram of included/excluded studies

TABLE 1 provides a comprehensive summary of each study, outlining essential details such as the first author's name, year of publication, country of origin, association with hypertension, sample size, ACE I/D genotype percentages, and p-values. Additionally, TABLE 2 presents a concise overview of the information relevant to the association between *ACE I/D* polymorphism and ACEI response.

Key finding 1: association between ACE insertion/deletion (I/D) genotype and hypertension

Our review consistently demonstrates a significant association between the *ACE I/D* genotype and hypertension, with multiple studies consistently reporting a higher prevalence of the D allele in hypertensive individuals. These findings indicate that the *ACE I/D* genotype may serve as a genetic marker for increased susceptibility to hypertension.

Key finding 2: ACE I/D genotype and antihypertensive treatment response

Multiple studies consistently indicate an association between *ACE I/D* genotype and antihypertensive treatment response. Individuals with the *DD* genotype exhibit a less favorable response to specific antihypertensive medications, particularly ACE inhibitors, compared to those with *II* or *ID* genotypes. These findings have significant implications for personalized hypertension management.

Summary of key findings are 1) the *ACE I/D* genotype is significantly associated with hypertension, with the D allele being more prevalent in individuals with hypertension; 2) the *ACE I/D* genotype may influence the response to antihypertensive treatment, particularly ACE inhibitors.

TABLE 1. Study search results on the ACE I/D association in hypertensive patients.

Author	Year	Country	Association with hypertension	Sample size	ACE I/D genotypes in hypertensive patients (%)			p
					II	ID	DD	
Kolovou *et al.*[3]	2015	Greece	No	83	13.3	51.8	34.9	0.712
Krishnan *et al.*[11]	2016	South Indian	Yes	208	28.3	32.6	38.9	<0.007
Heidaari *et al.*[9]	2015	Malaysia	Yes	72	5.3	35.3	59.4	0.003
He *et al.*[12]	2013	China	Yes	221	33.0	43.9	23.1	-
Faizal *et al.*[13]I	2013	Indonesia	No	100	48	30	22	-
Shanmuganathan *et al.*[14]	2015	Indian	Yes	30	3.33	80	16.67	0.0002
Assie *et al.*[15]	2021	Iraq	Yes	110	17.14	14.28	68.58	0.022
Singh *et al.*[16]	2016	Indian	Yes	222	31.5	38.7	29.7	<0.001
Birhan *et al.*[17]	2022	Ethiopia	Yes	64	21.9	29.7	48.4	0.005
Mustafa *et al.*[18]	2015	Iraq	Yes	52	11.5	38.5	50	0.02
Kooffreh *et al.*[19]	2014	Nigeria	Yes	612	12	43	45	>0.924
Roger *et al.*[20]	2018	Gabon	No	95	7.4	34.7	57.9	0.368
Tchelougou *et al.*[21]	2015	Africa	Yes	202	13.24	50.98	35.78	<0.05
Patel *et al.*[22]	2022	India	Yes	571	16.48	41.57	41.93	0.064
Pinheiro *et al.*[23]	2019	Brazil	No	240	20.5	54.7	24.8	0.198
Sun *et al.*[24]	2018	China	Yes	2040	25.74	57.62	16.63	<0.0001
Hussain *et al.*[25]	2018	Pakistan	Yes	148	21	61	18	0.005
Rana *et al.*[26]	2018	India	Yes	451	19.7	36.9	43.4	0.015
Hadian *et al.*[27]	2020	Iran	Yes	206	10.8	45.1	44.1	<0.02
Oscanoa *et al.*[28]s	2020	Peru	No	104	47.69	43.08	9.23	0.92

TABLE 2. ACE I/D association with ACE inhibitor effectiveness.

First author	Year	Country	Sample size	ACE inhibitor	Association with hypertension	Results	p
Heidari *et al.*[9]	2015	Malaysia	72	Enalapril, lisinopril	Yes	a high response to the ACEI is strongly associated with the D allele	0.0001
Contini *et al.*[29]	2016	Italy	100	Enalapril	Yes	a low response to the ACEI is associated with the II genotype	<0.01
Gupta *et al.*[30]	2015	India	120	Ramipril	Yes	a low response to the ACEI is associated with the DD genotype	0.028
Heidari *et al.*[31]	2017	Malaysia	142	Lisinopril, enalapril	Yes	a low response to the ACEI is associated with the DD genotype	0.0003
Kolovou *et al.*[3]	2015	Greece	166	Ramipril	No	ACE I/D gene did not influence the blood pressure-lowering efficacy of ACEI	>0.282

DISCUSSION

The ACE gene

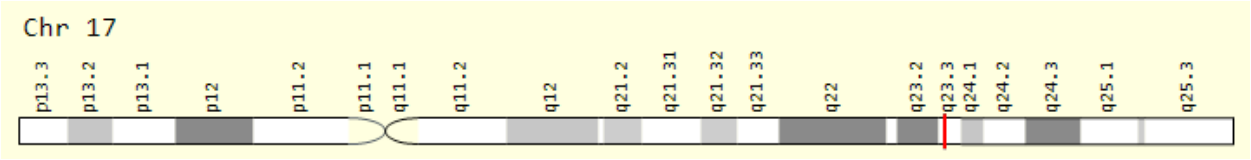

FIGURE 2. Location of the ACE gene in chromosome.[32]

The *ACE* gene, known as the angiotensin-converting enzyme gene, is an essential component of the human genome.[32] It serves as a protein-coding gene and is situated at locus NC_000017, specifically on the long arm of chromosome 17q23.3 (FIGURE 2). Structurally, the *ACE* gene consists of 26 exons and 25 introns, encompassing a total length of 21,320 base pairs.[4,32] This gene exhibits broad and significant expression across multiple tissues within the human body, including the small intestine, duodenum, lung, testis, and various other tissues.[4,32]

The *ACE* gene encodes an ACE, a crucial enzyme in regulating blood pressure and electrolyte balance.[3,32] The *ACE* gene encodes a protein comprising 1306 amino acids, which are responsible for the structural and functional characteristics of ACE.[32] Functionally, ACE catalyzes angiotensin I to angiotensin II, a potent vasopressor that controls blood pressure and electrolyte balance.[2,32] Angiotensin II influences blood pressure by engaging in several physiological mechanisms, including the stimulation of aldosterone synthesis, facilitation of salt and water reabsorption, modulation of blood volume, regulation of total peripheral resistance, and modulation of cardiac output.[2,33]

Individuals exhibit inherent variations in the abundance and

enzymatic activity of ACE attributable to the polymorphism of the *ACE* gene. This gene exhibits a remarkable diversity of more than 160 polymorphic forms, with the majority being single nucleotide polymorphisms (SNPs). Among these polymorphisms, 34 are located within exonic regions, while 18 represent missense mutations.[6] In numerous scientific research, the *ACE* gene insertion/deletion polymorphism (*ACE I/D* gene polymorphism) stands out as one of the most significant and thoroughly examined variants.[4]

The *ACE I/D* gene polymorphism

The *ACE I/D* gene polymorphism, initially discovered in 1990, arises from the presence (insertion/I) or absence (deletion/D) of a 287 base pair segment of Alu from the chromosome.[4,34] Specifically located within intron 16, this polymorphic variation exerts minimal influence on the structural configuration of the resultant enzyme. However, it demonstrates a compelling association with the plasma concentration of ACE, underscoring the substantial impact of the *ACE I/D* gene polymorphism on the regulatory mechanisms governing ACE expression at the systemic level.[6,35-39]

The *ACE I/D* gene polymorphism produces two alleles, namely the insertion allele (I) and the deletion allele (D), resulting in three genotypes: II, ID, and DD. Each genotype is characterized by varying plasma concentrations of ACE, with II exhibiting low levels, ID displaying medium levels, and DD demonstrating high levels.[36-39] This disparity in ACE concentration has been established through Baudin's study, which reported serum ACE concentrations of 240 μg/L, 330 μg/L, and 365 μg/L for genotypes II, ID, and DD, respectively.[35] Interestingly, the concentration of angiotensin II does not align with the ACE concentration, as it measured 11.0, 8.6, and 9.9 μg/L for II, ID, and DD, respectively. The variations in plasma ACE levels observed across different genotypes have significant implications for the risk of hypertension, as ACE plays a pivotal role in regulating blood pressure.[40]

The association of *ACE I/D* gene polymorphism and hypertension

The genetic determinants of hypertension are complex and involve various genes such as renin, angiotensinogen, ACE, and angiotensin II receptors. Among them, the *ACE I/D* gene polymorphism has garnered attention to essential hypertension. The D allele has been linked to increased ACE concentration, thereby facilitating the conversion of angiotensin I to angiotensin II and resulting in elevated levels of angiotensin II, which contribute to the development of hypertension.[8,11,12] Regrettably, investigations examining the *ACE I/D* polymorphism have yielded conflicting findings. Nevertheless, several studies have identified a relationship between the *ACE I/D* gene and hypertension, as summarized in TABLE 1.

The association between the *ACE* gene's *DD* genotype and *D* allele with essential hypertension has been consistently observed in diverse populations. In Indian populations, multiple studies have reported a strong correlation between the *DD* genotype and the *D* allele of the *ACE* gene with essential hypertension.[11,14,16,22,26] Similar results have been observed in hypertensive populations in Malaysia,[31] China,[12,24] Iraq,[15,18] Ethiopia,[17] Nigeria,[19] Africa,[21] Pakistan,[25] and Iran.[27] The frequency of the *D* allele was found to be higher in hypertensive patients compared to normotensive controls. Individuals with the *DD* genotype of the *ACE* gene were approximately three times more likely to develop high blood pressure compared to those with the II genotype.[9,12,17] These findings highlight the critical role of the *ACE* gene in blood pressure regulation, supported by studies demonstrating a genetic linkage between the chromosomal region

encompassing the *ACE* gene and blood pressure.[11] Furthermore, a large-scale study that included 2040 patients from a Chinese hypertensive community found a strong correlation between the risk of hypertension and the *D* allele and *DD* genotype of the *ACE* gene, which was supported by a substantial p (<0.0001).[24] These findings support the hypothesis that the *ACE* gene serves as a promising candidate gene for essential hypertension in humans. Remarkably, the *DD* genotype of the *ACE* gene has been consistently associated with essential hypertension across various ethnic populations, indicating its potential significance in hypertension susceptibility.

Despite the compelling evidence supporting the association between the *DD* genotype and the *D* allele of the *ACE* gene with essential hypertension in various ethnic populations, contradictory findings have also emerged. A study by Faizah[13]I conducted in the Indonesian population showed no significant correlation was found between the *ACE I/D* gene polymorphism and hypertension risk. Surprisingly, this study revealed a higher prevalence of the *I* allele (69%) compared to the *D* allele (31%) among hypertensive patients. Moreover, another study by Hadian *et al*.[27] demonstrated a statistically significant 85% increased risk of hypertension in individuals with the *I* allele compared to those with the *D* allele (p = 0.005). However, out of the 20 studies conducted between 2013 and 2023, only four reported no association between the *D* allele and hypertension, all with relatively small sample sizes of less than 240 patients. Hence, it can state that the *DD* genotype and *D* allele of the *ACE* gene may exhibit an association with essential hypertension in various ethnic populations. Nevertheless, further comprehensive investigations are warranted to unravel the intricate interplay between the *ACE I/D* gene polymorphism and hypertension susceptibility across distinct populations.

The *ACE I/D* gene polymorphism association with ACE inhibitor effectiveness

Antihypertensive therapy represents a crucial intervention to control blood pressure in hypertensive patients. ACE inhibitor are widely recognized as a first-line treatment for hypertension, regardless of complications or the presence of heart failure. It effectively regulates blood pressure by inhibiting angiotensin-converting enzymes, thereby reducing the levels of angiotensin II, a potent vasoconstrictor.[1,2,43] However, the response to antihypertensive therapy can vary considerably among patients, necessitating individualized treatment approaches. Numerous factors, including genetic factors, can significantly influence individual drug responses. Considering an individual's genetic profile and the potential presence of polymorphisms can facilitate the selection of appropriate treatment options tailored to their genetic characteristics. Although the relationship between hypertension and *ACE I/D* polymorphism remains unclear, this genetic variation can potentially influence the response to ACEI. The variations in ACE plasma levels observed among the three genotypes (*II*, *ID*, *DD*) impact the target number of ACEI, which can affect the optimal dosage of ACEI required for effective treatment. Consequently, the response to ACEI may differ among individuals with distinct genotypes.[44,45] Therefore, considering the *ACE I/D* polymorphism and individual genetic characteristics may contribute to selecting the most suitable antihypertensive therapy for hypertensive patients.

A case-control study by Heidari *et al*.[31] in 2017 investigated 142 hypertensive patients who received ACEIs therapy (lisinopril or enalapril) and showed that the *DD* genotype was strongly associated with inadequate treatment response. *ID*

and *DD* genotype frequency was higher in the non-responding treatment group compared to the responding group (p = 0.0003). These findings were consistent with a similar study by Contini *et al.*[29] which focused on heart failure patients treated with enalapril and revealed that the *ACE DD* genotype was associated with an increased vulnerability of the alveolar-capillary membrane to acute fluid overload in patients receiving ACEI. Another study involving 120 essential hypertension patients treated with Ramipril demonstrated a decrease in blood pressure for patients with *DD, ID,* and *II* genotypes of -21.38, -22, and -20.23 mmHg, respectively. These results indicated that patients with II and ID genotypes responded better to ACEI compared to those with *DD* genotypes.[30]

In contrast, an additional study by Heidari *et al.*[9] reported a different and inverse relationship between the *ACE I/D* gene and ACEI response. This study focused on hypertensive patients in Malaysia and found that the *DD* genotype was associated with a better blood pressure reduction response to ACEI. Specifically, the mean arterial pressure (MAP) reduction after ACEI therapy was 2.4 mmHg for the *II* genotype, 5.2 mmHg for the *ID* genotype, and 16.3 mmHg for the *DD* genotype. In contrast, Kolovou *et al.*,[3] stated that the 3 ACE I/D did not significantly affect the effectiveness of the ACEI (ramipril). This conclusion was drawn based on the observation that the reduction in blood pressure among treated patients did not differ significantly between the genotypes (p = 0.282 for systolic and 0.409 for diastolic). TABLE 2 comprehensively summarizes the studies exploring the association between *ACE I/D* polymorphism and ACEI response.

Among numerous studies investigating the relationship of the *ACE I/D* polymorphism with hypertension and the response to ACEI therapy, this study suggests a potential association between the presence of the *D* allele in the *ACE I/D* polymorphism and an increased risk of hypertension, as well as a potential reduction in response to ACEI. The discrepancies in the results could be attributed to genetic and environmental variations across ethnic groups, lifestyle, diet, stress levels, variations in specific ACEI used, and differences in sample size,[41,42] Additionally, the presence of other gene polymorphisms, such as *AGT, AT1*, *AT2*, *ACE2*, among others, should be acknowledged as they can also impact hypertension conditions and drug response in patients.[46]

Notably, research investigating the impact of *ACE I/D* gene polymorphism on the efficacy of ACEI in hypertensive patients remains limited and infrequently conducted. Consequently, the conclusions regarding the relationship between the *ACE I/D* gene and ACEI effectiveness remain conflicting. This narrative review has several limitations, including 1) the scarcity of recent studies examining the correlation between *ACE I/D* and ACEI response; 2) previous studies had a small number of samples included in the analysis, potentially limiting the generalizability of the collected data; and 3) the predominance of studies involving both male and female participants, rendering it unclear whether gender influences the *ACE I/D* gene polymorphism. Thus, future studies with a large number of participants from diverse ethnic populations are necessary to investigate further the correlation between *ACE I/D* gene polymorphism and the effectiveness of ACEI.

CONCLUSION

Our findings demonstrate that the *D* allele of the *ACE I/D* gene is associated with an increased risk of essential hypertension and a diminished response to ACEI compared to individuals carrying the *I* allele. The *ACE I/D* polymorphism serves as a predictor of hypertension, prompting individuals with the *D* allele to maintain their blood pressure vigilantly. Early detection of this genetic variation aids in selecting antihypertensive

therapy. Hypertensive patients carrying the *D* allele may require higher ACEI dosages or alternative antihypertensive medications to attain therapeutic goals. Early detection of this polymorphism benefits hypertension prevention and facilitates appropriate therapy selection.

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