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Single nucleotide polymorphism of *AGT* rs699 in the pathogenesis of hypertension and ACE inhibitors response: a narrative review

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ABSTRACT

Hypertension is a chronic cardiovascular disease that affects more than one billion people in the world. Angiotensinogen in the renin-angiotensin-aldosterone system (RAAS) is the main precursor encoded by angiotensinogen (*AGT*) gene and plays an important role in the development of hypertension. Single nucleotide polymorphism (SNP) of *AGT* gene is thought related to the pathogenesis of hypertension and angiotensinogen levels in plasma that may affect response to ACE inhibitors. This article reviewed the association of SNP *AGT* rs699 with the pathogenesis of hypertension and ACE inhibitors response. A total of 14 articles published from 1995 to 2023 were collected from databases including NCBI, Google Scholar, PubMed and Science Direct. Several studies in different populations have been conducted and showed various results. The T allele or TT genotype of *AGT* rs699 was associated in the pathogenesis of hypertension. However, the association between *AGT* rs699 and ACE inhibitor response shows inconsistent results, thus further research is needed.

ABSTRAK

Hipertensi adalah penyakit kardiovaskular kronis yang mempengaruhi lebih dari satu miliar orang di dunia. Angiotensinogen dalam *renin-angiotensin-aldosterone system* (RAAS) adalah prekursor utama yang dikode oleh gen angiotensinogen (AGT) dan berperan penting dalam perkembangan hipertensi. *Single nucleotide polymorphism* (SNP) gen *AGT* diduga berkaitan dengan patogenesis hipertensi dan kadar angiotensinogen dalam plasma yang dapat mempengaruhi respon terhadap penghambat ACE. Artikel ini membahas kembali hubungan SNP *AGT* rs699 terhadap patogenesis hipertensi dan responnya terhadap penghmbat ACE. Total 14 artikel dari tahun 1995 sampai 2023 diperoleh dari beberapa database yaitu NCBI, Google Scholar, PubMed dan Science Direct. Beberapa penelitian pada populasi yang berbeda telah dilakukan dan menunjukkan hasil yang beragam. Alel T atau genotipe TT dari *AGT* rs699 diketahui memiliki kaitan dalam patogenesis hipertensi. Kaitan antara *AGT* rs699 dengan respon penghambat ACE menunjukkan hasil yang tidak konsisten sehingga diperlukan penelitian lebih lanjut.

INTRODUCTION

Hypertension is the most prevalent cardiovascular disease in the world, characterized by a persistent increase in arterial blood pressure.[1,2] Hypertension is considered as one of the highest causes of death and ranks 6th for non-communicable diseases. The prevalence of hypertension is more than 30% in adults aged 30-79 years worldwide.[3] According to the

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World Health Organization (WHO), an estimated 1.4 billion people worldwide have high blood pressure, but only 14% have it under control.[4] Many factors and mechanisms contribute to the development of hypertension, including genetic and environmental factors, neural, renal, hormonal, and vascular mechanisms. The renin-angiotensin-aldosterone system (RAAS) is one of the main regulators of blood pressure and the most important pathological mechanism in hypertension.[2,5]

Angiotensinogen is a well-known main precursor in RAAS that plays an important role in the development of hypertension. Renin cleaves angiotensinogen to form angiotensin I and then into angiotensin II by angiotensin-converting enzyme (ACE).[6,7] Several studies revealed that increasing plasmatic angiotensinogen levels in circulation have been linked to elevated levels of angiotensin II and hypertension.[8,9] In addition, changes in angiotensinogen plasma levels have been shown to be influenced by single nucleotide polymorphisms (SNP) in the angiotensinogen (*AGT)* gene. The SNP *AGT* rs699 is the most polymorphic *AGT* gene located in exon 2.[9] Several studies reported a correlation between the genetic variations of *AGT* rs699 and a higher risk in developing hypertension.

Besides contributing in the pathogenesis of hypertension, the presence of *AGT* rs699 is also thought to affect the effectiveness of antihypertensive drugs affecting the RAS pathway. The ACE inhibitor as a first-line therapy for hypertension has a mechanism of action targeting the RAS pathway.[1] Previous studies evaluated the possible effect of the *AGT* rs699 polymorphism on the effectiveness of ACE inhibitors in blood pressure reduction. Half of hypertensive patients still fail to achieve blood pressure targets on medication.[10] Variability of the effectiveness of antihypertensive drugs is caused by multifactor. Genetic factors such as SNP can affect pharmacodynamics or pharmacokinetics causing variability in drug response.[11]

Investigation of several target genes in pharmacogenomic studies can contribute knowledge about the allele frequency of the *AGT* rs699 gene variant and its influence on the effectiveness of ACEi therapy in hypertensive patients. In the Health Sector, pharmacogenomic studies, especially the *AGT* rs699 gene, can be taken into consideration in the Health Sector to evaluate recommendations for captopril antihypertensive therapy by considering the *AGT* rs699 gene variant profile in hypertensive patients. This article aimed to review the association of SNP *AGT* rs699 gene to the pathogenesis of hypertension and ACE inhibitors response.

MATERIAL AND METHODS

The Google Scholar, PubMed and Science Direct databases were employed in order to collect the data. The keywords used were "SNP", "*AGT*", "rs699", "Hypertension", "ACE inhibitors", or their combination. All types of open access articles related to this topic were included in this review. Articles without full text or research subjects not hypertensive patients were excluded. A total of 13 original research articles and 1 review article ranging from 1995 to 2023 were obtained. The detailed selection process is presented in FIGURE 1 for reference.

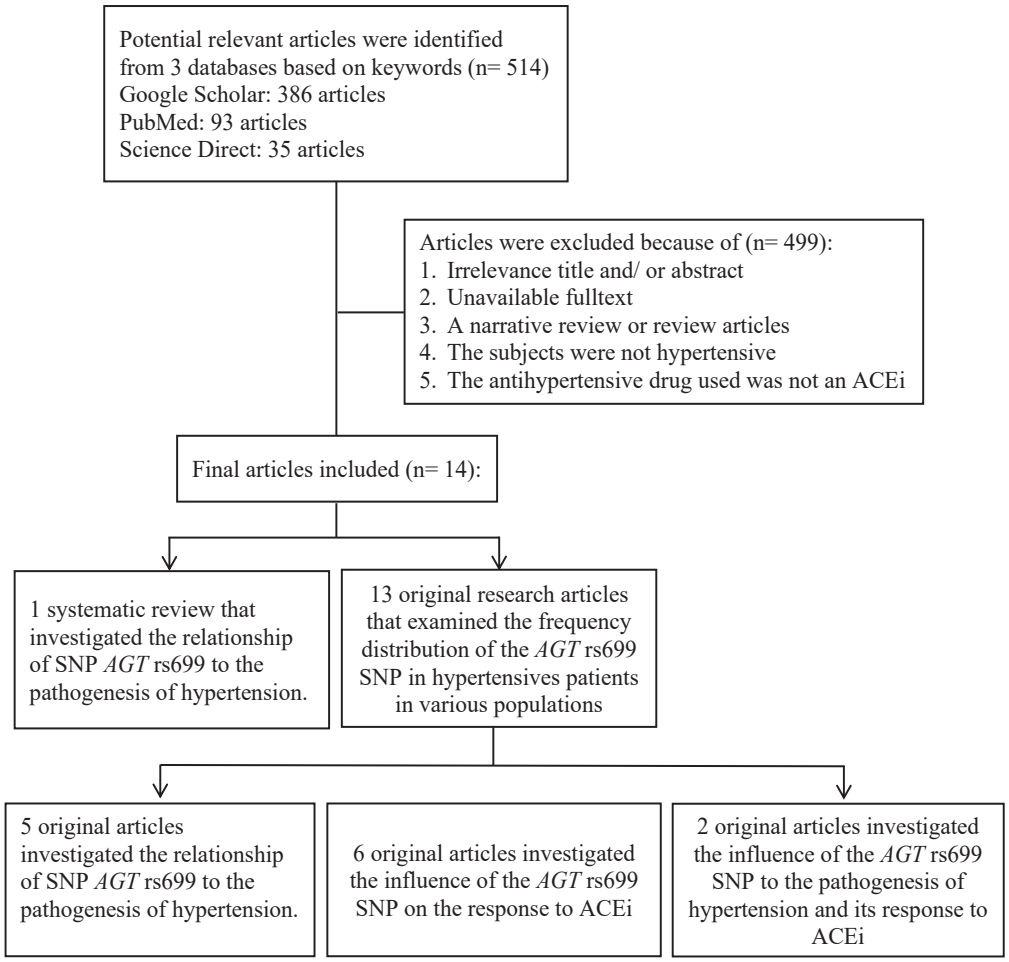

FIGURE 1. A flowchart for eligibility process for this narrative review

RESULTS AND DISCUSSION

The role of angiotensinogen in the pathogenesis of hypertension has been known in some previous studies.[7,12] Angiotensinogen which affects hypertension occurs through sodium homeostasis and regulation of fluid volume. The mechanism is mediated by angiotensin II.[6] In the renin-angiotensin cascade, angiotensinogen is cleaved to angiotensin I by renin, and angiotensin I is cleaved by ACE becomes angiotensin II. Based on these pathological pathways, it can be concluded that angiotensinogen has a fundamental role in the pathogenesis and development of hypertension.[6,7,12]

The ACE inhibitors are medication targeting the RAAS. There are commonly used ACE inhibitors such as lisinopril, captopril, ramipril, enalapril and benazepril.[13] It is used as a one of the first-line agent in the therapeutic management of hypertension. These agents have improved cardiovascular (reduced hospitalizations and cardiovascular mortality) and renal (reduced microalbuminuria and slowing the progression of kidney disease) outcomes.[1,14]

The *AGT* gene is considered as one of the candidate genes in the RAAS. It is the most polymorphic gene located on chromosome 1 at the 1q42 – q43 locus. The *AGT* rs699 is one of the most frequently studied SNPs localized in the 2nd exon.[9,15,16] The *AGT* rs699 is a thymine (T) to cytosine (C) replacement in the 704th position (T704C) at codon 268, that substitution results in the functional replacement from methionine (M) to threonine (T) (M268T).[17,18] The AGT rs699 was previously located at amino acid 235

and it was identified as M235T.[17]

The association of SNP *AGT* rs699 in the pathogenesis of hypertension and the response of antihypertensive therapy is still being studied until now, especially on the pharmacogenomics of ACE inhibitors as antihypertensives that affect RAAS. Recent studies evaluating the distribution of SNP *AGT* rs699 allele and genotype frequencies and their effect on hypertension and ACE inhibitors responses in various races/ ethnicities have been summarized in this review.

The SNP frequency

The distribution of *AGT* rs699 genotype and allele in several hypertensives population are shown in Table 1. The frequency of genotypes variation was obtained based on genotyping results using various polymerase chain reaction (PCR) methods and visualized by electrophoresis.[9] Hardy-Weinberg equilibrium (HWE) is used to estimate allele frequencies in a population based on the number of homozygous and heterozygous variant carriers.[19]

Distribution of genotype and allele frequencies for each population showed various results. The T allele is more frequent in hypertensive Nigerian, Egyptian, Myanmar, South Indian and Ethiopian patients.[15,18,20–23] In contrast, in Northern Indian and Caucasian the M allele is more frequent.[8,24] These variations may be due to several factors in population. Mutations, recombination during reproduction, genetic drift, gene migration, and natural selection are some of the major factors affecting the genetic equilibrium and induce the genetic variability in populations.[25]

TABLE 1. Summary of articles regarding association between single SNP *AGT* rs699 on the pathogenesis of hypertension and ACE inhibitor efficacy.

Population & Sample size	Frequency in hypertensives patient					Frequency in healthy respondent					Association in Hypertension	ACE inhibitor response	Reference & year
	Case group					Control group							
	Genotypes (%)			Alleles (%)		Genotypes (%)			Alleles (%)				
	MM	MT	TT	M	T	MM	MT	TT	M	T			
Caucasian; 410 (control group = 187; case group = 223)	76	107	40	-	-	58	91	38	-	-	-	T allele is correlated with better BP lowering effect in ACE inhibitor treatment.	Hingorani *et al.*, (1996)[26]
Chinese; 732 (hypertensive patient using ACE inhibitor)	67.1	28.9	4.0	-	-	-	-	-	-	-	-	No association with benazepril effect.	Su *et al.*, (2007)[27]
Caucasian; 251 (hypertensive patient using lisinopril)	36.3	46.1	17.6	-	-	-	-	-	-	-	-	No significant association between AGT genotypes and the reduction BP in response to lisinopril.	Dudley *et al.* (1996)[28]
Japanese; 241 (control group = 122; case group = 119)	39		80	-	-	44		78	-	-	-	T homozygotes benefit from effects of quinapril on preventing restenosis after percutaneous coronary intervention (PCI).	Toyofyuku *et al.*, (2002)[29]

TABLE 1. cont.

Population & Sample size	Frequency in hypertensives patient					Frequency in healthy respondent					Association in Hypertension	ACE inhibitor response	Reference & year
	Case group					Control group							
	Genotypes (%)			Alleles (%)		Genotypes (%)			Alleles (%)				
	MM	MT	TT	M	T	MM	MT	TT	M	T			
Caucasian; 309 (control group = 238; case group = 71)	-	54	17	-	-	-	179	59	-	-	-	Greater benefit of ACE inhibitors for patients with TT genotype.	Bis *et al.*, (2003)[30]
Chinese; 251 (Hypertensive patient)	9.2	41.4	49.4	-	-	-	-	-	-	-	-	Influences benazepril responses. Reduction in DBP is significantly greater in geriatric patients carrying the MM compared to TT or MT genotypes	Yu *et al.*, (2005)[31]
North Indian; 500 (control group = 250; case group = 250)	44.8	48	7.2	69	31						T allele is strongly associated with essential hypertension in northern Indians.	TT genotype has higher BP lowering response when treated with Enalapril.	Srivasta *et al.* (2012)[24]
South Indian; 508 (control group = 254; case group = 254)	12.2	11.8	76	18.1	81.9	16.5	38.6	44.9	35.8	64.2	Homozygous TT is independent risk factors for essential hypertension and it has greater effect than other SNP in 2nd exon	-	Karthikeyan *et al.*, 2013)[21]
South Indian; 422 (control group=211; case group= 211)	6.16	38.39	55.45	-	-	14.22	36.97	48.82	-	-	The *AGT* M235T polymorphism influenced the risk of essential hypertension in women.	-	Singh *et al.*, (2014)[32]
Caucasian; 166 (control group = 83; case group = 83)	27.7	51.8	20.5	53.6	46.4	36.1	56.6	7.2	64.5	35.5	*AGT M235T* gene polymorphism is associated with essential hypertension.	*AGT M235T* gene polymorphisms not influence ramipril	Kolovou *et al.*, (2015)[8]
Egyptian; 143 (control group = 60; case group = 83)	14.5	21.7	63.9	25.3	74.7	68.3	23.3	8.3	71.1	28.97	There is a positive risk of developing essential hypertension when having the T allele	-	Shamaa *et al.*,(2015)[20]

TABLE 1. cont.

Population & Sample size	Frequency in hypertensives patient Case group					Frequency in healthy respondent Control group					Association in Hypertension	ACE inhibitor response	Reference & year
	Genotypes (%)			Alleles (%)		Genotypes (%)			Alleles (%)				
	MM	MT	TT	M	T	MM	MT	TT	M	T			
Myanmar; 144 (control group = 72; case group = 72)	2.8	62.5	34.7	34	66	23.61	66.67	9.72	-	-	Plasma angiotensinogen level subjects carrying T allele increased in hyper-than normotensives. Subjects carrying TT genotype possessed 3 folds increased in plasma angiotensinogen level than subjects carrying MM genotype.	-	Sandar *et al.*, (2018)[23]
Ethiopian; 306 (control group = 153; case group = 153)	15.7	28.1	56.2	29.8	70.2	26.1	43.8	30.1	48.1	51.9	TT genotype and the T allele are associated with an increased risk of hypertension.	-	Melake *et al.*, (2023)[15]
Caucasian; 122 (control group = 50; case group = 72)	19	49	10	-	-	15	27	8	-	-	TT genotype carrier is associated with systolic and diastolic BP elevation	-	Repchuk *et al.*, (2021)[33]

Article reviewed	Findings	Reference & year
41 original research articles	T allele of AGT rs699 is associated with increasing the risk of essential hypertension.	Fajar *et al.*, (2019)[9]

*Systematic review/ meta analysis

Gene polymorphism and hypertension

A previous study revealed that the rs699 variant genotype may be linked to the risk of hypertension incidence in several populations (Table 1). Several studies found a significant association between TT genotypes or T allele with essential hypertension in Northern Indian,[24] Southern Indian,[21] Egyptian,[20] Ethiopian,[15] Myanmar,[32] and Caucasian[33] population. In addition, the presence of the T allele (MT and TT genotypes) in Egyptian has a seven-fold higher risk of developing hypertension.[20] In the T allele (TT and MT genotypes), the plasma angiotensinogen level was significantly increased in hypertensives than those of normotensives. Subjects carrying the TT genotype possessed 3 folds increased in plasma angiotensinogen level than subjects carrying MM genotype in essential hypertension.[32] The AGT rs699 polymorphisms were observed to be high risk factors in South Indian females than in males.[21] Previous meta-analysis also revealed that the T allele of *AGT* rs699 was associated with an increased risk of essential hypertension.[9] The polymorphic T allele and TT genotype of *AGT* rs699 were associated with increased serum angiotensinogen levels and the risk of increased blood pressure in hypertension patients.

Polymorphism *AGT* rs699 and ACE inhibitors response

Most studies of genetic variants affecting the pharmacodynamics of ACE inhibitor have looked at ACE inhibitor responses in patients undergoing ACE inhibitor therapy (TABLE 1). The association of *AGT* rs699 variants are contradictory in different populations. A study by Hingorani *et al*. in Caucasian hypertensive patients showed that *AGT* rs699 could independently predict individual response to ACE inhibitors. The results of this study indicate that patients with the T allele have poor ACE inhibitors efficacy.[26] However, a study among hypertensive patients in other races showed different results. In elderly Chinese population showed that the efficacy of benazepril in patients carrying the T allele (MT and TT genotypes) was better than MM genotype.[31] A study on Indian hypertensive patients treated with the ACE inhibitor Enalapril for 6 weeks statistically showed a significant decrease in SBP, DBP, and MAP. Patients with the TT genotype experienced greater reductions in SBP, DBP and MAP compared to patients with the MT and MM genotypes.[24] Toyofyuku *et al*. reported that patients with homozygous TT showed significant improvements in the indices for restenosis after quinapril treatment.[29] The interaction between the *AGT* rs699 and quinapril treatment on restenosis was assessed based on balloon angioplasty and stenting.[29] The findings in the Netherland population suggest greater benefit from ACE inhibitor therapy among individuals with TT genotype. This study was conducted by evaluating blood pressure in control group and case group (stroke and myocardial infarction patients).[30]

In contrast, a study by Su *et al.*[27] in the Chinese population showed that *AGT* SNP rs699 was not associated with blood pressure response to ACE inhibitor benazepril treatment. The results were similar to studies by Dudley *et al.*[28] and Kolovou *et al.*[8] in their finding there is no association between *AGT* rs699 genotype and blood pressure response to the ACE inhibitor lisinopril[28] or ramipril[8] monotherapy.

There may be other genetic candidates or other factors, which influence ACE inhibitor response. That may be due to the differences in the ethnic group background and other characteristics of the study population. There is a possibility that a different study population may reveal different genetic linkage to hypertension and ACE inhibitors response. Further studies are needed to establish whether a similar effect is seen in a large scale and different ethnic groups.

Knowledge of gene-drug interactions can contribute to individualized therapy and increased drug safety. However, the sample size was small and factors influencing the pathogenesis of hypertension (such as physical activity, tobacco use, salt intake, and family history of hypertension or cardiovascular disease) were not controlled in previous studies. Due to these limitations, further studies in other populations and larger sample sizes may be needed to confirm a better association between gene-drug interaction. Further reviews including higher study designs may be required to reach a higher level of evidence.

The limitations in this review are lack of prior research and there is limited current research examine the association between SNP *AGT* rs699 and ACE inhibitor effectiveness, thus original research articles from more than 10 years ago are still included.

CONCLUSION

Our findings based on recent studies have successfully provided evidence that the SNP *AGT* rs699 has a strong influence in the pathogenesis and development of hypertension. Based on these findings, the T allele or TT genotype of *AGT* rs699 was associated with increased serum angiotensinogen levels and the risk of increased blood

pressure in hypertension patients.

Our findings based on recent studies in *AGT* rs699 have shown various outcomes. Several studies found an association between SNP *AGT* rs699 and ACE inhibitors response variability. However, in other studies there is no association.

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