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**RESEARCH ARTICLE**

## Distribution of Genetic Polymorphisms of the *Agt M235t* Gene in Hypertension Patients Taking Angiotensin-Converting Enzyme Inhibitor (ACEi) Drugs in Indonesia

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**ABSTRACT**

The condition of high blood pressure is characterized by a systolic pressure (TDS)  $\leq 140$  mmHg and a diastolic pressure (TDD)  $\geq 90$  mmHG. The M235T gene polymorphism inside the AGT gene has the potential to serve as a biomarker for the early identification and detection of hypertensive disease. The presence of the TT genotype and the T allele in the AGT M235T gene is associated with an increased susceptibility to hypertension. Furthermore, the study revealed a notable disparity in the occurrence of the AGTM235T variant (rs699) between individuals with hypertension and the control group. The objective of the study is to see the distribution of genetic polymorphism of AGT M235T gene in hypertensive patients taking Angiotensin-Converting Enzyme Inhibitor (ACEi) drugs. This study used the Narrative Review Method with a comprehensive systematic review of articles that have been published from 2013 to 2023 in English using the MEDLINE (PubMed), Google Scholar, and Cochrane Library databases. The AGT M235T polymorphism has been found to have a significant association with the use of ACEi medications in individuals diagnosed with hypertension, as indicated by several investigations. This study exhibits certain limitations and needs additional prospective investigations to corroborate the findings. In some studies, AGT M235T polymorphism in hypertension patients has a strong correlation with ACEi drugs.

**KEYWORDS**

Hypertension; Polymorphism; AGT; Gene *AGT M235T*; ACEi

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**1. Introduction**

Hypertension is recognized as one of the cardiovascular disorders that significantly contributes to mortality rates within the global population. Hypertension is defined as a condition characterized by blood pressure readings of systolic (TDS)  $\leq 140$  mmHg and diastolic pressure (TDD)  $\geq 90$  mmHg, as determined through two separate blood pressure tests (Jabani et al., 2021). According to data provided by the World Health Organisation (WHO) from 2015 to 2020, it has been observed that around 1.13 billion individuals worldwide are affected by hypertension. This indicates that one out of every three individuals globally has been diagnosed with hypertension (Mills et al., 2016). According to estimates, by the year 2025, over 1.5 billion individuals are projected to experience the effects of hypertension. Furthermore, it is anticipated that on an annual basis, 9.4 million individuals will succumb to hypertension and its associated problems (Deasy, 2018). Hypertension, a cardiovascular condition, is associated with the aging process, as it is characterized by a decline in arterial wall elasticity and altered systemic blood vessel behaviour. Consequently, these age-related changes in the cardiovascular system contribute to the vulnerability of the elderly population to hypertension (Nuraini, 2015).

The renin-angiotensin cascade is considered the primary mechanism behind hypertension. Based on the aforementioned data, it is widely acknowledged that angiotensinogen (AGT) is widely acknowledged as the principal precursor having a pivotal role in the pathogenesis of hypertension and its related comorbidities. In summary, the process involves the cleavage of angiotensinogen

(AGT) by renin, resulting in the formation of angiotensin I. Subsequently, angiotensin I is converted into angiotensin II through the action of the angiotensin-converting enzyme (ACE). Angiotensin II assumes a substantial role in the initiation of hypertension and associated hypertensive disorders via many mechanisms (Lu et al., 2016). Multiple investigations have demonstrated a positive correlation between elevated levels of angiotensinogen (AGT) in the bloodstream and higher amounts of angiotensin II, leading to the onset of hypertension (Kooffreh et al., 2013). Furthermore, previous studies have provided evidence indicating that changes in plasma angiotensinogen (AGT) levels are impacted by specific variations in the genetic sequence known as single nucleotide polymorphisms (SNPs) located in exon 2 of the AGT gene. The AGT M235T single nucleotide polymorphism (SNP) located in exon 2 has been subject to intense investigation. This particular SNP involves the substitution of methionine with threonine at position 235.

In a study on the pharmacogenetics of antihypertensive drugs, it was found that genetic variations that interact with medication can cause differences in the response to treatment given to each individual (Cabrera et al., 2015). This pharmacokinetic adaptation of the drug will provide significant benefits. The immediate reaction to ACE inhibitors exhibits a correlation with plasma renin activity. The action of ACE inhibitors hinders the synthesis of angiotensin II, a molecule that plays a significant role in the Renin-Angiotensin System (RAS) (Kooffreh et al., 2013).

The renin-angiotensin-aldosterone system (RAAS) is an essential component in the control of blood pressure, maintenance of electrolyte equilibrium, and adjustment of vascular tone. The functioning of this system leads to the synthesis of angiotensin II, a substance that elicits vasoconstriction, increased aldosterone secretion, and fluid retention, hence playing a significant role in the pathogenesis of hypertension (Jefri Pratama Susanto, 2015). Angiotensinogen (AGT) assumes a crucial role as a fundamental component inside the renin-angiotensin-aldosterone system (RAAS) effector. The development of essential hypertension has been associated with the existence of genetic polymorphisms in components of the renin-angiotensin-aldosterone system (RAAS), specifically AGT M235T (Raygan et al., 2016). The angiotensinogen (AGT) molecule undergoes a process of conversion, resulting in the formation of angiotensin I. This angiotensin I molecule is then further changed into angiotensin II, a vasoconstrictor of significant potency, by the catalytic activity of the enzyme angiotensin-converting enzyme (ACE). The AGT gene is accountable for regulating the transcription of angiotensinogen, a polypeptide mostly produced by the hepatic cells (Raharjo, 2020). The cleavage of the angiotensinogen molecule by renin, leading to the liberation of angiotensin I, is subsequently succeeded by the conversion of angiotensin I to angiotensin II via the enzymatic activity of the angiotensin-converting enzyme. The substance indicated above exhibits a strong attraction to its specific receptors, which triggers physiological reactions that affect the balance of sodium in the body and the resistance of blood vessels. As a result, it plays a crucial role in regulating blood pressure (Fajar et al., 2019).

Genetic polymorphism pertains to the presence of genetic diversity within the human genome arising from disparities in DNA sequences among distinct populations (Shahid et al., 2022). This phenomenon can arise as a result of the existence of multiple alternative allelic forms inside the genome of each individual, encompassing single-nucleotide polymorphisms, repetitive DNA and RNA sequences, and genetic material interchange. Furthermore, it is worth noting that genetic mutations can give rise to polymorphisms, which arise from alterations in nucleotide sequences and lead to the manifestation of distinct phenotypes within a given population. The M235T gene polymorphism represents a genetic variation observed in the angiotensinogen (AGT) gene in humans. The phenomenon of polymorphism is observed at nucleotide position 235 when the nucleotide adenine (A) undergoes substitution with thymine (T). The aforementioned differences have the potential to impact the expression and function of AGT, hence potentially affecting the regulation of blood pressure and susceptibility to cardiovascular disease. Angiotensinogen (AGT) functions as an intrinsic substrate of the renin-angiotensin system (RAS) and is mostly generated in hepatic tissue (Kolovou et al., 2015). There are variations in the association between these variants observed across different groups. The AGT gene is located at the chromosomal locus q42-43 and consists of five exons and four introns, with a total length of 13 kilobases (Kolovou et al., 2015). Considering the strong correlation seen between plasma angiotensinogen (AGT) levels and blood pressure [13], it is justifiable to regard the AGT gene as a credible contender for the regulation of blood pressure. Numerous polymorphisms within the AGT region have been detected, with a specific focus on two particular polymorphisms, namely M235T (rs699) and T174M (rs4762), which are situated in exon 2 (Kolovou et al., 2015).

## **2. Objective**

This article briefly presents the distribution of genetic polymorphisms of the AGT M235T gene in hypertensive patients taking ACEi drugs in Indonesia.

## **3. Method**

A comprehensive systematic review of articles published from 2013 to 2023 in English using the MEDLINE (PubMed), Google Scholar, and Cochrane Library databases using the following keywords and search terms: Hypertension, AGT polymorphism, AGT M235T gene, ACEi was done.

## 4. Result and Discussion

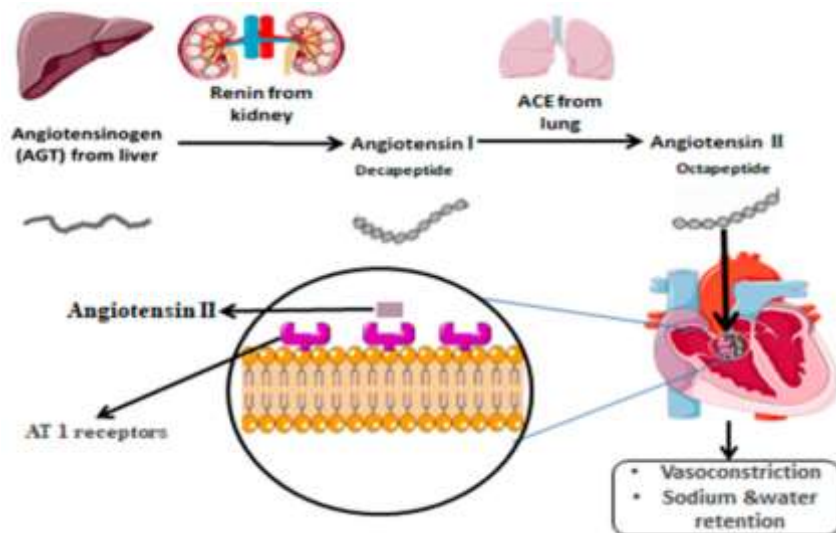
### 4.1 Angiotensin-converting enzyme Inhibitors (ACEi)

Angiotensin-converting enzyme inhibitors (ACEi) are commonly utilized in the treatment of hypertension, serving as a pharmacological class of drugs. The mechanism of action is the suppression of the angiotensin-converting enzyme (ACE), which is a vital constituent of the renin-angiotensin-aldosterone system (RAAS) (Purwaningtyas & Barliana, 2021). The Renin-Angiotensin-Aldosterone System (RAAS) is an endocrine system that plays a crucial role in maintaining blood pressure and fluid balance inside the human body. The enzymatic conversion of angiotensin I into angiotensin II is impeded by the suppression of ACE. Angiotensin II is a highly effective vasoconstrictor, leading to the constriction of blood vessels and, therefore, raising blood pressure (Ferrari, 2013). ACE inhibitors exert their pharmacological effects through the inhibition of angiotensin II production, thereby eliciting vasodilation and facilitating the relaxation of blood vessels, finally culminating in a reduction in systemic blood pressure. In addition to their antihypertensive activities, angiotensin-converting enzyme (ACE) inhibitors demonstrate various advantageous effects. One strategy entails the inhibition of aldosterone release, a hormone that has a role in increasing fluid retention, hence allowing the reduction in fluid volume and concomitant decrease in blood pressure. The utilization of angiotensin-converting enzyme inhibitors (ACEi) has been observed to augment endothelial function, alleviate inflammation, and demonstrate features that protect the heart (Y. Li, 2012). Several ACE inhibitor medications that are commonly administered encompass lisinopril, enalapril, ramipril, and captopril. Angiotensin-converting enzyme inhibitors (ACEi) are frequently employed as the initial treatment for hypertension, particularly in individuals who have specific comorbidities such as diabetes, heart failure, or chronic renal disease (Ella et al., 2021). Furthermore, healthcare professionals can recommend its usage in conjunction with other antihypertensive medications, such as diuretics or calcium channel blockers, to enhance the management of blood pressure. In general, ACE inhibitors have demonstrated efficacy and favorable tolerability as pharmaceutical agents for managing hypertension, with supplementary advantages that extend beyond the mere decrease of blood pressure (Ella et al., 2021).

The angiotensin-converting enzyme inhibitor (ACEi) is a vital zinc metalloenzyme found in the renin-angiotensin system (RAS) and is widely distributed in renal tissue (Kolovou et al., 2015). The main function of angiotensin-converting enzyme (ACE) is to catalyze the conversion of angiotensin I to angiotensin II, a biologically active peptide that plays a crucial role in the regulation of electrolyte balance and blood pressure (Kolovou et al., 2015). The ACEI/D gene polymorphism is characterized by the presence (insertion) or absence (deletion) of a 287 base pair AluYa5 fragment located within intron 16. The association between the existence of this genetic variation and a heightened vulnerability to essential hypertension has been established (He et al., 2013). Certain pharmacological agents, such as ramipril, which fall under the category of angiotensin-converting enzyme (ACE) inhibitors, are utilized to manage hypertension and congestive heart failure. The therapeutic effects of these drugs are achieved through targeted modulation of the renin-angiotensin system (RAS) pathway (Zivko et al., 2013).

### 4.2 AGT M235T Gene

The human angiotensinogen (AGT) gene is classified under the serpins gene superfamily. The genetic sequence under consideration exhibits a cumulative length of approximately 12 kilobases (kb) and is comprised of a total of 5 exons and 4 introns. The gene is located on chromosome 1, precisely at the 1q42-q43 locus (Y. Y. Li et al., 2021). Alpha-1 antitrypsin (AGT) is found in several tissues, such as the liver, adipose tissue, heart, blood vessel walls, brain, and kidney, exhibiting a constant cellular specificity (Shahid et al., 2022). The angiotensin peptides can be attributed to their source, angiotensinogen (AGT), which is a protein comprising 485 amino acids, encompassing a signal peptide containing 33 amino acids. The enzymatic action of renin facilitates the hydrolysis of a specific set of ten amino acids located at the N-terminus of mature angiotensinogen (AGT), a protein synthesized by hepatocytes. This process leads to the production of angiotensin I (Ang I). Angiotensin I functions as a precursor for many physiologically active angiotensin peptides (Lu et al., 2016). Renin is a crucial component of the Renin-Angiotensin-Aldosterone System (RAAS) and is produced and secreted by juxtaglomerular cells. The enzymatic reaction between renin and angiotensinogen (AGT) is widely recognized as the stage that determines the rate at which the renin-angiotensin-aldosterone system (RAAS) cascade proceeds. The cascade described in this context is of significant importance in the regulation of plasma angiotensinogen (AGT) levels, and it is essential for the proper maintenance of blood pressure (Purkait et al., 2017). The central peptide of the renin-angiotensin-aldosterone system (RAAS) is angiotensin II, which is produced via the enzymatic activity of angiotensin-converting enzyme (ACE) following the hydrolysis of the angiotensin-I decapeptide by renin. To carry out its physiological function, angiotensin II engages in interactions with G-protein-coupled receptors that are situated on the cellular membrane. The angiotensin II receptor, known as AT1R, is expressed inside the human body and has a crucial function in the regulation of electrolyte balance and blood pressure (Shahid et al., 2022). Within the renal system, there exists a presence of two discrete angiotensin-II receptors, namely AT1R and AT2R. The receptors under consideration are comprised of 359 and 363 amino acids, respectively, and have a 30% overlap in their amino acid sequence (Rianto et al., 2021). Furthermore, these receptors can be detected in various anatomical sites within the human body, such as the brain, heart, adipose tissue endothelium, adrenal glands, and vascular smooth muscle (Shahid et al., 2022).



**Picture 1.1** AGT M235T Process (Shahid et al., 2022)

**Table 1.1** Research study on the distribution of AGT M235T gene polymorphism

Researcher	Year	Research Subject	Result
Dodik Tugasworo, Retnaningsih, Aditya Kurnianto, Suryadi, Dani Rahmawati, Rahmayanti, Jethro Budiman (Tugasworo et al., 2023)	2023	The Neurology polyclinic of Dr. Kariadi Semarang handled 72 ischemic stroke patients from January to December 2013. The Diponegoro National Hospital CEBIOR laboratory extracted research volunteers' DNA from January to March 2020. It was amplified by PCR. RFLP-based PCR product digestion.	The study included 72 ischemic stroke patients treated at Dr. Kariadi Semarang's neurology polyclinic from January to December 2013. The Diponegoro National Hospital CEBIOR laboratory extracted research volunteers' DNA from January to March 2020. It was amplified by PCR. RFLP-based PCR product digestion.
Apriliani Nur Puspita Sari1, Tiar M. Pratamawati2, Ahmad Fariz Malvi Zamzam Zein (Nur et al., n.d.)	2022	An analytical cross-sectional research at Plumbon Health Centre comprised 50 participants. PCR-RFLP and total blood count were used to collect data.	The M235T polymorphism (94%) and vascular inflammation (66%) were found in most study participants. Vascular inflammation and the AGT gene M235T polymorphism were not statistically significant ( $p = 0.218$ ). However, the prevalence ratio showed that essential hypertension patients had a significant prevalence.
Sapto Raharjo*1, Agus Cahyadi2, Aulia Fadhilah3, Tien4, Andi Noor Kholidha5, SjarifSubijakto (Raharjo et al., 2017)	2017	Research participants numbered 61. On 45-65-year-old hypertensives, total sampling was used. All 53 patients had blood pressure > 140 mmHg, whereas 8 had normal blood pressure.	Ethnic Southeast Sulawesi had no connection between the M235T polymorphism and essential hypertension. The Tolaki ethnicity has higher TT and MT genotypes than Muna and Buton.

Kolovou V, Lagou E, Mihas C, Vasiliki G, Katsiki N, Kollia A, Triposkiadis F, Degiannis D, Mavrogeni S, Kolovou G (Kolovou et al., 2015)	2015	The study genotyped 166 adults (83 hypertension and 83 normotensives) for AGTM235T (rs699) and AGTT174M (rs4762).	These findings suggest that essential hypertension and AGTM235T gene polymorphisms are connected due to significant genotype and allele distribution differences. AGTM235T, AGTT174M, and ACEI/D did not influence ramipril efficacy.
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Recent research has shown evidence that genetic variants play a substantial role as a risk factor in certain diseases. The enzyme angiotensinogenase (AGT) holds significant importance within the physiological system known as the renin-angiotensin-aldosterone system (RAAS) (Shahid et al., 2022). The critical role of its involvement in the synthesis of angiotensin I and II can be linked to its impact on the regulation of blood pressure. Multiple different variants of angiotensinogen (AGT) are present, which exert an influence on the concentrations of AGT within the circulatory system (Zhai et al., 2019). The AGT M235T variation exerts a notable influence on the pathogenesis and advancement of several diseases. These two variants are commonly observed and have been associated with a higher prevalence of diseases in comparison to other AGT variants. Various disorders are associated with different variants of AGT (Shahid et al., 2022). The AGT M235T variation is linked with hypertension, pre-eclampsia, diabetic nephropathy, obesity, depression, and many cardiovascular diseases. The medical ailment known as cirrhosis of the liver does not exhibit any association with the M235T polymorphism. Nevertheless, previous studies have provided evidence indicating a significant association between the presence of the A-6G and A-20C polymorphisms and the onset of this particular ailment. While it has been observed that all of these polymorphisms lead to elevated blood levels of AGT, there is currently no evidence to suggest that variants other than M235T are linked to any specific diseases (Shahid et al., 2022). The prevalence of these polymorphisms varies across different populations, with M235T being observed as more prevalent (Shahid et al., 2022).

In Kolovou Journal (Kolovou et al., 2015), The research conducted two distinct meta-analyses on Chinese populations, both of which provided confirmation that the T allele of the AGTM235T polymorphism is really associated with essential hypertension (Xi et al., 2012). However, Niu et al. found no statistically significant association between essential hypertension and the AGT M235T polymorphism. This lack of linkage remained consistent even after accounting for variables such as age, sex, and disease severity. In a similar vein, Caulfield et al. reported a lack of statistically significant association between the AGT M235T gene polymorphism with the studied condition. In contrast, Mohana et al. demonstrated an increased vulnerability to hypertension only among women possessing the AGT M235T polymorphism, exhibiting an odds ratio of 2.82 (95% confidence interval: 1.22-6.49;  $p=0.012$ ). Therefore, specific studies provide evidence supporting the association, while others present conflicting findings (Rotimi et al., 1994). The current study demonstrated a notable disparity in the prevalence of the TT genotype of the AGTM235T gene polymorphism between the hypertension group and the normotensive control group. Specifically, the hypertension group exhibited a considerably higher prevalence, about three times more than that reported in the normotensive control group ( $p=0.042$ ) (Kolovou et al., 2015).

There are just a few studies that have looked at the relationship between ACEI/D, AGTT174M, and AGTM235T gene polymorphisms and ramipril's hypotensive effects (Zivko et al., 2013). In a group of sixty-six hypertensive patients, the study found no statistically significant correlation between the ACEI/D gene polymorphism and the ramipril-induced reduction in blood pressure. In a similar vein, the present study did not yield any noteworthy disparities in blood pressure alterations about the insertion/deletion polymorphism. In contrast, a study conducted by Gupta in 2015 and documented in Kolovou (Kolovou et al., 2015) revealed that there was a notable disparity in the response rates to ramipril medication between patients with genotype II and those with genotype ID, with a much larger number of responders observed in the former group. The current state of research on the impact of this polymorphism on ramipril-induced blood pressure variations is characterized by conflicting data, leading to an uncertain conclusion (Raharjo et al., 2017).

## 5. Conclusion

Numerous studies have shown compelling evidence of a substantial correlation between the AGT M235T polymorphism and the utilization of ACEi medicines among hypertensive persons. In many scholarly publications, it has been observed that the AGT M235T gene, specifically in individuals with the TT genotype and T allele, has a significant correlation with an elevated susceptibility to hypertension. Nevertheless, this value remains well below the established norm. The M235T gene variant of the AGT gene has the potential to serve as a biomarker for the early identification and detection of hypertension. However, further investigation using larger sample sizes is necessary to fully understand the correlation between the AGT gene and hypertension. Moreover, a significant discrepancy in the frequency distribution of AGTM235T (rs699) was detected in persons with hypertension compared to the control group. Additional research is required to ascertain an association between these variables in larger and more comprehensive sample sizes. The present study demonstrates various limitations and calls for further prospective investigations to validate the results.

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