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Review

RAAS genetic polymorphism and individualized treatment in essential hypertension

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Abstract. . The renin-angiotensin-aldosterone system (RAAS) is involved in the pathogenesis of essential hypertension (HTN). Essential HTN is a complex polygenic disease. The genes encoding RAAS components are involved in the regulation of blood pressure (BP). Although there is currently no indication for the genetic testing of HTN in the routine clinical evaluation of patients, an increasing number of studies support the relationship between the effects of antihypertensive medication and RAAS genetic polymorphisms. RAAS suppression through angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) is the treatment strategy for the control of increased BP values and the prevention of HTN complications. The aim of this article is to synthetically present the role of genetic polymorphisms in relation to the therapeutic control of essential HTN with ARBs and ACEIs.

Key Words: renin-angiotensin-aldosterone system polymorphism, essential hypertension, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers

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Introduction

Essential hypertension (HTN) uncontrolled by drugs is the main cause for cardiac and cerebrovascular ischemic events (Oparil et al 2019, Cozma et al 2018). In the pathophysiology of essential HTN, a number of environmental, molecular and genetic factors play a role. The renin-angiotensin-aldosterone system (RAAS) is one of the important etiological factors for HTN (Yu et al 2014). Several studies have identified a transmission rate of essential HTN of about 50% in the families of hypertensive patients. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the most widely used classes of hypertensive drugs, with a similar efficacy on major cardiovascular events and mortality (Kjeldsen et al 2018).

1) RAAS

RAAS includes the following components: angiotensinogen (AGT), renin (REN), angiotensin I (AngI), angiotensin II (AngII), angiotensin-converting enzyme (ACE), AngII type 1 receptor (R1 AngII), AngII type 2 receptor (R2 AngII), and aldosterone. RAAS has effects on water and sodium homeostasis, causing an increase in blood pressure (BP) values. RAAS is involved in a chain of events that contributes to the pathogenesis of cardiovascular diseases, including cardiac remodeling (Ferrario et al 2016).

REN is synthesized in juxtaglomerular epithelioid cells, its synthesis being triggered by hypovolemia, hypotension, hyponatremia and sympathetic stimulation (Gong et al 2019).

AGT is a protein synthesized in the liver, being located in the myocytes of the ventricles, in the proximal and distal renal collecting tubules (Ferrario et al 2016). AGT interacts with REN and produces AngI, while ACE converts AngI to AngII. ACE is a metallopeptidase, which is distributed on the surface of endothelial and epithelial cells (Emdin et al 2015).

AngII is a potent vasoconstrictor, influences water retention by stimulating the synthesis of antidiuretic hormone (ADH). It also stimulates the release of norepinephrine, metanephrine and aldosterone (Emdin et al 2015). In hypertensive patients, plasma AGT and AngII concentrations are higher compared to normotensive subjects (Ferrario et al 2016, Gong et al 2019). HTN and DM are risk factors that can stimulate AngII production (Ferrario et al 2016). The effects of AngII and aldosterone are cardiac and vascular remodeling, vascular endothelial dysfunction, glomerular dysfunction. These effects are presented in Figure 1.

2) RAAS inhibition

AngII has endocrine, paracrine and autocrine functions. It acts on R1 and R2 of AngII (Ferrario et al 2016, Gong et al 2019,

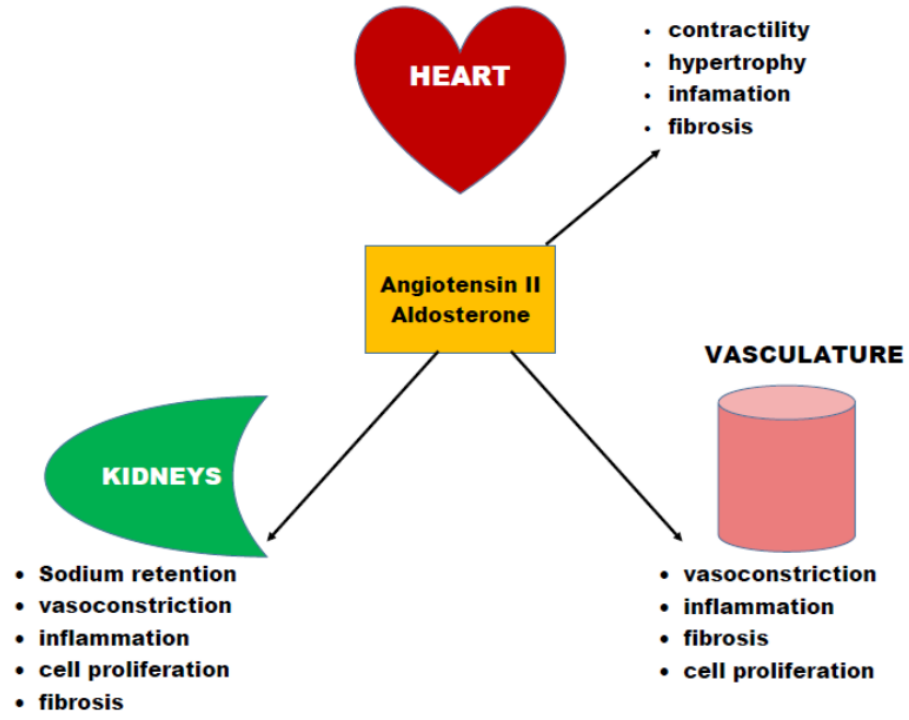

Figure 1. Angiotensin II and aldosterone effects in the heart, kidneys and vasculature

Emdin et al 2015). AngII receptors are located in the vascular smooth muscles, in the adrenal gland cortex, in the heart, kidneys, etc. (Gong et al 2019).

R1 AngII promotes cell growth, plays a role in the synthesis of growth factors, aldosterone, mediates the atherogenic effects of AngII (Emdin et al 2015). Activated R1 AngII may contribute to cardiac remodeling even in the absence of AngII (Yasuda et al 2012). Binding angiotensin II to R1 AngII triggers stages in the development of cardiac hypertrophy, such as: fibrosis through collagen synthesis by fibroblasts and myocyte hypertrophy (Ferrario et al 2016).

R2 AngII counters the effects of R1 AngII. R2 AngII has an anti-inflammatory, antifibrotic and vasodilator effect, inhibits the cell hypertrophy process in the vascular smooth muscles and cardiomyocytes (Emdin et al 2015).

RAAS activation can lead to an increase in reactive oxygen species production and induces oxidative stress. By activating oxidative stress, RAAS plays a role in the pathogenesis and progression of HTN, contributes to inflammatory processes in the vascular wall and vascular remodeling. Preventing inflammation and oxidative stress can be an important therapeutic strategy.

Personalized antihypertensive treatment can benefit the patient by controlling BP values and preventing complications (Do et al 2014). The response to antihypertensive treatment is individualized and variable (Woodiwissa et al 2006). The RAAS blockers presented in this article are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Clinical studies have demonstrated that RAAS blockers can alter the cardiac remodeling process, through LVH regression, being beneficial in reducing morbidity and mortality (Ferrario et al 2016, Yasuda et al 2012).

ACEIs and ARBs have a protective role by decreasing BP values and preventing the HTN-mediated involvement of the target organ (Inaba et al 2011). Treatment with RAAS blockers is beneficial for hypertensive patients who present cardiac and metabolic complications (Yasuda et al 2012).

The two classes of ACEIs and ARBs have common mechanisms of action that contribute to inhibiting the effects of AngII (Messerli et al 2018, Jaźwiec et al 2018). In studies comparing the therapeutic effect of ACEIs and ARBs in hypertensive patients with DM without heart failure, no statistically significant superiority regarding the decrease in the risk of death from myocardial infarction (MI) and stroke was reported (Messerli et al 2018).

The common adverse effects of ACEIs and ARBs are hypotension, hyperpotassemia and aggravation of nitrogen retention (Mirabito et al 2019).

a) Angiotensin-converting enzyme inhibitors

According to therapeutic guidelines, ACEIs are the first choice in antihypertensive treatment, and ARBs are considered as a therapeutic alternative for patients with ACEI intolerance (Messerli et al 2018). ACEIs inhibit AngII formation and reduce the effects of R1 AngII. ACEIs inhibit vasoconstriction, water retention and activation of the sympathetic system. Compared to ARBs, ACEIs do not inhibit bradykinin, which is involved in the pathogenesis of cough and angioedema, explaining the intolerance of patients to ACEIs treatment. Another disadvantage would be continuous AngII production, despite ACE inhibition (Messerli et al 2018).

The response to ACEIs treatment is variable and heterogeneous, can be influenced by race, genotype and body mass index (BMI). Some studies report that the therapeutic effect of ACEIs in hypertensive patients of African origin was weaker compared to Caucasians (Woodiwissa et al 2006).

Studies have demonstrated that ACEIs monotherapy has a favorable effect in hypertensive female patients with a high body mass

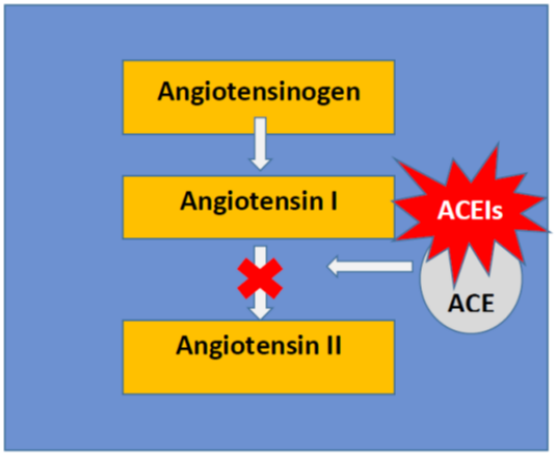

Figure 2. The mechanism of action of angiotensin-converting enzyme inhibitors (ACEIs)

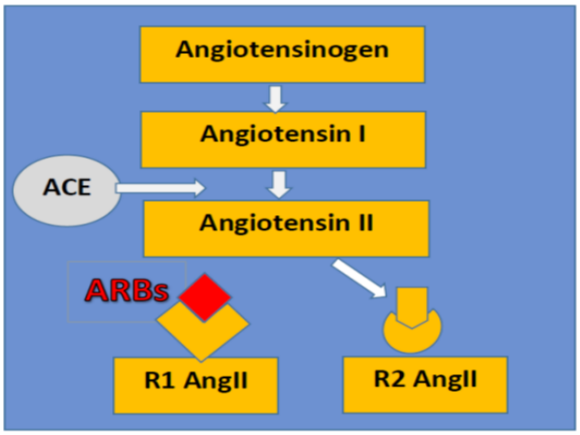

Figure 3. The mechanism of action of angiotensin receptor blockers (ARBs)

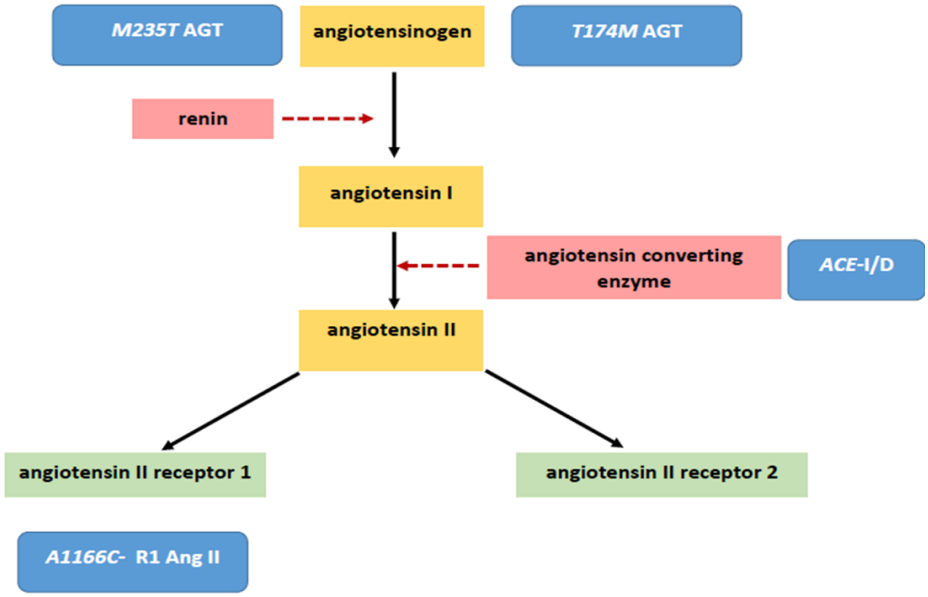

Figure 4. The renin-angiotensin-aldosterone system polymorphism

index (BMI), and this response is due to the AGT genetic variation. The mechanism of action of ACEIs is shown in Figure 2.

b) Angiotensin receptor blockers

ARBs inhibit AngII that act on R2 AngII, and the therapeutic effect of decreasing BP values occurs by vasodilation and natriuresis (Messerli et al 2018). In studies conducted on animal models, it was demonstrated that the beneficial effect of ARBs in preventing vascular remodeling is due to the reduction of oxidative stress and inflammation in the vascular wall, through reactive oxygen species inhibition (Inaba et al 2011). The mechanism of action of ARBs is shown in Figure 3.

3) Genetic variations

HTN is a polygenic disease. HTN treatment might be personalized depending on the patient's genotype. This would allow reducing hospitalization costs related to HTN complications (Gong et al 2019). Specific RAAS genotypes can predict the response to antihypertensive treatment (Gong et al 2019, Inaba et al 2011).

M235T AGT and T174M AGT genetic polymorphism

The AGT gene is located on chromosome 1q42-q43. The AGT genetic polymorphism was described for the first time in 1992, in twins with HTN, who had high AGT values (Jeinmaitre et al 1992). The AGT genetic polymorphism comprises the *M235T* and *T174M* AGT genetic variations (Do et al 2014).

The *M235T* AGT genotype represents the substitution of methionine by threonine at position *235* of AGT (Procopciuc et al 2019). The *M235T* genetic variation is found in Chinese, African and Caucasian hypertensive subjects (Gong et al 2019). Homozygous carriers of the T allele have high AGT concentrations (Emdin et al 2015).

T174M AGT is a point mutation by which thymine is replaced by cytosine in nucleotide *521 (T521C)*, exon 2 of the AGT gene (Chr 1q42-q43), through which threonine is replaced by methionine at position 174 of AGT (Thr174Met-T174M) (Yuan et al 2009).

The AGT genetic polymorphism can be considered a risk factor in hypertensive patients for ischemic cardiac and cerebrovascular disease (Procopciuc et al 2019). The AGT genetic variants can be associated with ischemic cerebrovascular and cardiac events. Hypertensive patients carrying the T allele for the M235T genetic variant had a higher risk for MI and stroke (Do et al 2014).

ACE-I/D genetic polymorphism

ACE-I/D is the gene located on chromosome 17q23, representing the insertion (I)/deletion (D) of a fragment of the ACE gene of Ang I to Ang II (Chr 17q23.3), which induces an increase in plasma ACE level and activity. Allele distribution is differentiated depending on ethnicity, so that the I allele is more frequent in the Asian and Mongoloid population, and the D allele is more frequent in American and European Caucasians (Singh et al 2016). The DD genotype is associated with increased plasma ACE and AngII values compared to the II genotype (Emdin et al 2015).

A1166C-R1AngII genetic polymorphism

The R1 AngII genetic polymorphism is located on chromosome 3q21-3q25, where adenine is replaced by cytosine in nucleotide *1166* of the gene. The *A1166C*-R1 AngII genetic polymorphism is associated with HTN (Emdin et al 2015).

4) Influence of genetic variants on treatment with ACEIs or ARBs

Genetic factors can influence the response to antihypertensive treatment (Yu et al 2014). There are few and contradictory data regarding the influence of genetic variations on antihypertensive response to RAAS blockers (Gong et al 2019).

ACEIs and M235T AGT and T174M AGT genetic polymorphism

A number of studies have assessed the impact of the AGT gene on the response to antihypertensive treatment with ACEIs; data are contradictory and vary depending on the race and genotype. Some studies maintain that Chinese and African hypertensive patients carrying the AGT genotype had a favorable response to ACEIs treatment (Sue et al 2007, Woodiwissa et al 2006, Yu et al 2014). Hypertensive women of African origin with a high BMI, carrying the AGT genotype had a favorable response to ACEIs treatment regarding the control of BP and pulse pressure (PP) values (Woodiwissa et al 2006; Yu et al 2014).

PP is an indirect marker for the evaluation of arterial stiffness and the risk for ischemic cardiovascular and cerebrovascular events. The reduction of PP values after 6 weeks of ACEIs treatment was favorable in patients carrying AGT genetic variations (Yu et al 2014).

Hypertensive patients carrying the TT and MT genotype for the *M235T* AGT genetic polymorphism had a better antihypertensive response to ACEIs compared to patients carrying the MM genotype (Srivastava et al 2012; Hingorani et al 1995). Another study evidenced that ACEIs treatment in carriers of the TT genotype protected against cerebrovascular accidents, but not ischemic cardiac events (Bis et al 2003; Maitland-Van Der Zee et al 2011). Homozygous carriers of the *M235T* AGT and *T174M* genotype had controlled BP values under ACEIs treatment compared to negative patients (Charita et al 2012).

In contrast, another study showed that the *M235T* AGT genetic variation did not influence the response to ACEIs treatment (Taverne et al 2010).

ACEIs and ACE-I/D genetic polymorphism

Studies published so far report contradictory results regarding the therapeutic control of ACEIs in HTN. The heterogeneity of the response is due to the ACE-I/D genetic polymorphism; the genetic variant differs depending on sex and race (Heidari et al 2015).

Some studies show that the response to antihypertensive ACEIs treatment is influenced by the ACE- I/D genetic variation (Heidari et al 2017).

Hypertensive patients on treatment with ACEIs, carrying the I/I and I/D genotype had a better therapeutic control of BP values compared to the D/D genotype (Haas et al 1998, O'Toole et al 1998, Suwelock et al 2002). Other studies reported that the D/D genotype had a favorable influence on the response to ACEIs treatment compared to I/I (Stavroulokis et al 2000, Lix et al 2003). PP was significantly reduced under ACEIs treatment in patients carrying the DD genotype compared to ID heterozygotes (Głuszek et al 2008).

Other studies report a similar response to ACEIs treatment for DD, ID and II genotypes (Emdin et al 2014).

Hypertensive male patients carrying the DD genotype had increased serum ACE values compared to hypertensive patients carrying the II genotype. For patients carrying the DD genotype, the response to ACEIs treatment was weaker compared to carriers of the II genotype (Hristova et al 2019).

ACEIs and *A1166C*-R1 AngII genetic polymorphism

The published studies are contradictory regarding the impact of the *A1166C*-R1 AngII genetic polymorphism in hypertensive carriers treated with ACEIs. According to a study, ACEIs treatment had a protective role for MI through the control of BP values in patients carrying the AC and AA genotype (Maitland-Van Der Zee et al 2011).

An observational study reported that Caucasian carriers of the *A1166C*-R1 AngII genotype showed no better control of BP values when treated with ACEIs (Taverne et al 2010). Also, there was no relationship between the AA or AC genotype and the reduction of BP values in hypertensive patients on ACEIs treatment (Yan et al 2011, Gluszek et al 2008).

ARBs and *M235T* AGT and *T174M* AGT genetic polymorphism

Studies conducted so far have shown that the M235T-AGT genetic polymorphism was not associated with the control of increased BP values under ARBs treatment (Taverne et al 2010, Gong et al 2019).

ARBs and ACE- I/D genetic polymorphism

Most of the studies found no statistical correlation between the response to antihypertensive ARBs treatment and the ACE-I/D genetic variation.

Few studies have reported that homozygous carriers of the D/D genotype had a better therapeutic control of essential HTN compared to carriers of the I/I and I/D genotypes (Emdin et al 2014). High diastolic BP values improved after ARBs treatment in patients carrying the D allele; this can be explained by the fact that the D allele is associated with increased ACE and Ang I concentrations (Taverne et al 2010).

Table 1. Pharmacogenetic effects of ACEIs and ARBs

Gene	Genotype	Drug class	Effect	References
AGT		ACEIs	Favorable therapeutic response, control of BP values	Do et al 2014, Woodiwissa et al 2006 Yu et al 2014
M235T	TT and MT	ACEIs	Idem	Srivastava et al 2012, Heidari et al 2017
	TT	ACEIs	Protective role against stroke and MI	Heidari et al 2017, Maitland-Van Der Zee et al 2011
T174M and M235T	TT, MT	ACEIs	Favorable therapeutic response, control of BP values	Heidari et al 2017, Maitland-Van Der Zee et al 2011
M235T		ACEIs	Did not influence treatment response	Taverne et al 2010
M235T		ARBs	Did not influence treatment response	Taverne et al 2010, Gong et al 2019
ACE-*I/D*		ACEIs	Favorable therapeutic response, control of BP values	Heidari et al 2017
ACE-*I/D*	I/I and I/D	ACEIs	Idem	Heidari et al 2017
	D/D	ACEIs	Idem	Heidari et al 2017
	I/I and I/D D/D	ACEIs	Idem	Emdin et al 2014
	D/D	ACEIs	Did not influence treatment response	Hristova et al 2019
	D/D	ARBs	Favorable therapeutic response, control of BP values	Emdin et al 2014, Taverne et al 2010
***A1166C*-R1 AngII**	AC and AA	ACEIs	Protective role against stroke and MI	Maitland-Van Der Zee et al 2011
	AC and AA	ACEIs	Did not influence treatment response	Taverne et al 2010, Głuszek et al 2008, Yan et al 2011
	C	ARBs	Favorable therapeutic response, control of BP values	Maitland-Van Der Zee et al 2011

AGT - angiotensinogen; ACE - angiotensin-converting enzyme; R1 AngII - angiotensin II type 1 receptor; I/D - insertion/deletion; ACEIs – angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers

ARBS and A1166C-R1 AngII genetic polymorphism

The response to antihypertensive ARBs treatment was favorable for patients carrying the C allele for the *A1166C*-R1 AngII genotype compared to carriers of the A allele (De Denus et al 2018). The therapeutic action of ARBs was favorable because the C allele is associated with low aldosterone and renin concentrations (Maitland-Van Der Zee et al 2011).

An observational study reported that Caucasian carriers of the *A1166C*-R1 AngII genotype showed no better control of BP values when treated with ACEIs (Taverne et al 2010). Also, there was no relationship between the AA or AC genotype and the reduction of BP values in hypertensive patients on ACEIs treatment (Yan et al 2011, Gluszek et al 2008).

ARBs and M235T AGT and T174M AGT genetic polymorphism

Studies conducted so far have shown that the *M235T*-AGT genetic polymorphism was not associated with the control of increased BP values under ARBs treatment (Taverne et al 2010, Gong et al 2019).

ARBs and ACE- I/D genetic polymorphism

Most of the studies found no statistical correlation between the response to antihypertensive ARBs treatment and the ACE-I/D genetic variation.

Few studies have reported that homozygous carriers of the D/D genotype had a better therapeutic control of essential HTN compared to carriers of the I/I and I/D genotypes (Emdin et al 2014). High diastolic BP values improved after ARBs treatment in patients carrying the D allele; this can be explained by the fact that the D allele is associated with increased ACE and Ang I concentrations (Taverne et al 2010).

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Conclusion

ACEIs and ARBs treatment is effective in the prevention and regression of HTN-mediated target organ involvement. Regression of complications under treatment indicates an improvement of the disease prognosis. The response to treatment is influenced by genetic factors, such as RAAS genetic polymorphism. In the future, antihypertensive treatment should be individualized depending on patient's genetic profile.

The genetic profile of hypertensive patients can provide information about the disease staging, the adaptive response to HTN, as well as the personalized drug therapy used to prevent the cardiovascular and cerebral complications of essential HTN. An approach focusing on the individual genetic profile would prevent the occurrence of adverse effects to treatment, would reduce the costs by preventing HTN complications, and would improve adherence to treatment.

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