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AGTR1 A1166C gene polymorphism is associated with the effectiveness of valsartan monotherapy in Chinese patients with essential hypertension: A retrospective analysis

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ABSTRACT

Objective: To investigate whether angiotensin Ⅱ type 1 receptor (*AGTR1* A1166C) gene polymorphism was associated with the effectiveness of valsartan monotherapy in Chinese patients with essential hypertension.

Methods: This retrospective analysis included 198 patients (≥18 years of age) who received valsartan monotherapy (80 mg/day) for newly developed essential hypertension at the authors' center between January 1, 2020 and December 31, 2023. Genotyping for *AGTR1* A1166C gene polymorphism was done by polymerase chain reaction (PCR)-melting curve analysis of genomic DNA from peripheral blood samples. A dominant genetic model for *AGTR1* A1166C (AA genotype *versus* AC+CC genotype) was used. Multivariate regression analysis of baseline variables and *AGTR1* polymorphism was conducted to identify predictors of target blood pressure attainment (<140/90 mmHg) at the 4-week follow-up.

Results: The median age of the 198 patients was (53.7±13.5) years, and 58% were men. Genotyping assays showed that 164 patients had the AA genotype, and 34 patients were of the AC/CC genotype, including 30 with the AC genotype and 4 with the CC genotype. Allele distribution was consistent with Hardy Weinberg equilibrium. 109 Patients (55.1%) attained the blood pressure target. Multivariate analysis showed that smoking (*versus* no smoking, *HR* 0.314, 95% *CI* 0.159-0.619, *P*=0.001) and *AGTR1* A1166C AA genotype (*versus* AC/CC, *HR* 2.927, 95% *CI* 1.296-6.611, *P*=0.023) were significant and independent predictors of target attainment. 25 Patients (73.5%) with *AGTR1* A1166C AC/CC genotype attained the target *versus* 51.2% (51/164) of patients with *AGTR1* A1166C AA genotype (*P*=0.017). Patients with *AGTR1* A1166C AC/CC genotype had a significantly greater reduction in systolic blood pressure [(33.1±10.8) mmHg *versus* (29.2±11.7) mmHg in AA carriers; *P*=0.029)].

Conclusions: Hypertensive patients carrying one or two C alleles of the *AGTR1* A1166C gene were more responsive to valsartan treatment.

KEYWORDS: Essential hypertension; Angiotensin Ⅱ type 1 receptor antagonist; Valsartan; *AGTR1* A1166C; Gene polymorphism

Significance

AGTR1 A1166C polymorphism has been associated with treatment response to angiotensin receptor antagonists, but results in previous studies are inconsistent. A variety of factors, including ethnic background and disease stage, may have contributed to such a discrepancy. Results from the current study showed hypertensive patients carrying C allele(s) of the *AGTR1* A1166C gene were more responsive to first-line valsartan treatment. These findings could guide clinical practice in the real-world setting.

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1. Introduction

Hypertension is a leading cause of cardiovascular disease and premature death globally and it is a significant risk factor of stroke, vascular dementia and chronic kidney disease in the world[1–3]. Despite a decline in mortality rate, the prevalence of hypertensive cardiovascular disease has increased over the past decades[4]. Essential hypertension accounts for approximately 90% of all cases of hypertensive diseases in clinical practices[5]. Despite the 2017 American College of Cardiology/American Heart Association Blood Pressure Treatment Guidelines recommending more intensive blood pressure treatment, there was a striking decline in blood pressure control among the US adults with hypertension from 2013-2014 to 2017-2018[6]. In China, there is a large burden of hypertension with one third of the adult population being hypertensive, and the overall control rate of hypertension is less than 5% for the hypertensive population while only 29.6% for those receiving hypertension treatment[7,8].

Essential hypertension is considered to be the result of the interaction between environmental and genetic factors, with approximately 30% of interindividual blood pressure variability determined by genetics[9]. There are reports indicating that polymorphisms in drug metabolism enzymes, drug targeting receptors, and regulatory genes may lead to differences in individual drug responses[10]. This may also lead to different responses of essential hypertension patients to antihypertensive drugs.

The renin angiotensin aldosterone system plays an important role in blood pressure regulation and is closely related to the pathogenesis of essential hypertension. Angiotensin Ⅱ receptors are one of the important members of the renin angiotensin aldosterone system, and mainly divided into two types: type 1 (*AGTR1*) receptors and type 2 (AGTR2) receptors[11]. The *AGTR1* gene is composed of 5 exons located on chromosome 3q, with the first 4 exons encoding the 5'-untranslated region (5'-UTR), and the last exon encoding the 3'-UTR[12]. Polymorphisms in the 3'-UTR result in the conversion of A at position 1166 to C[13], which may affect individual differences in response to antihypertensive treatment. Angiotensin receptor antagonists (ARBs), represented by valsartan and irbesartan, are currently among the first-line antihypertensive drugs in clinical practices. Significant individual differences were noted in antihypertensive response to the same dose of ARBs. However, scant research has been conducted on the relationship between *AGTR1* (A1166C) gene polymorphism and the efficacy of ARBs, which requires further investigation.

The purpose of this study was to explore the impact of *AGTR1* (A1166C) gene polymorphism on the effectiveness of valsartan monotherapy for essential hypertension in order to guide personalized and precise treatment of essential hypertension patients.

2. Subjects and methods

2.1. Ethics approval

The study protocol was approved by the Medical Ethics Committee of the First People's Hospital of Xuzhou City (No. xyyll-2021-098). The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was not required due to the retrospective nature of the study; however, consent was obtained from all patients prior to genotyping. Patient data were anonymized in the report.

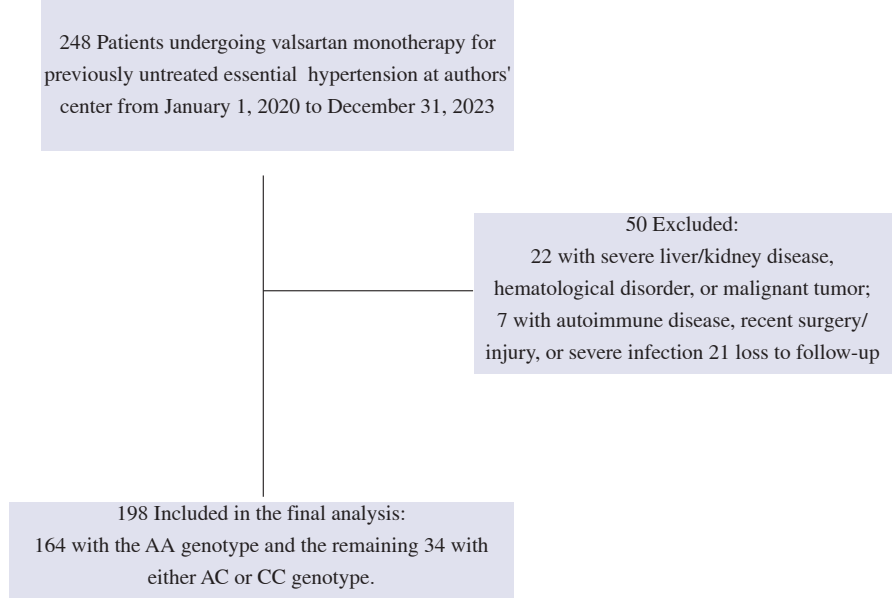

Figure 1. Flow chart of the selection process.

2.2. Patients

This retrospective cohort study included 198 adult patients (≥18 years) who received valsartan monotherapy for previously untreated essential hypertension at the Affiliated Xuzhou Municipal Hospital of Xuzhou Medical University from January 1, 2020 and December 31, 2023 (Figure 1). The median age was 53.7 years (ranged 27-91) and 58.1% of the patients were men. Essential hypertension was diagnosed according to the 2018 European Society of Cardiology/ European Society of Hypertension Blood Pressure Guidelines[14]. Patients should have received antihypertensive treatment with valsartan 80 mg/day for at least 4 continuous weeks. Patients were excluded if their baseline systolic blood pressure was ≥180 mmHg and/or diastolic blood pressure was ≥110 mmHg. We also excluded patients with secondary hypertension, severe liver or kidney disease, malignant tumor, or autoimmune disease.

2.3. Genotyping and laboratory testing

Genomic DNA was extracted from peripheral blood samples using a commercially available kit from Qiagen (Hilden, Germany). Polymerase chain reaction (PCR) melting curve analysis was conducted for genotyping for *AGTR1* A1166C gene polymorphism using the following primers: forward, 5'-CATTCCTCTGCAGCACTTCAC-3' and backward, 5'-AGAAAAGTCGGTTCAGTCAAC-3' (GenBank accession code: NG_008468.2). PCR products (519 bp) were digested overnight with the restriction enzyme DdeI. Visualization of two fragments (385 and 134 bp, respectively) on agarose gel containing 2% ethidium bromide indicated the A1166C allele. All laboratory tests were conducted using routine methods at the author's center.

2.4. Variables and definitions

Target attainment was defined as systolic blood pressure ≤139 mmHg and diastolic blood pressure ≤89 mmHg at 4 weeks after treatment initiation. Variables collected at the baseline include sex, age, body mass index, smoking status, alcohol consumption, blood pressure, co-morbid diseases, and blood lipid profile.

2.5. Statistical analysis

Categorical variables were presented as number (%), and analyzed using χ^2 test. Continuous variables were presented as mean±standard deviation (SD) or median and interquartile range (IQR), and analyzed using Student's t test or Mann Whitney U test as appropriate. A goodness of fit χ^2 test was used to evaluate whether the genotype distributions of *AGTR1* A1166C polymorphisms were in accordance with Hardy-Weinberg equilibrium. Univariate logistic regression analysis was used to evaluate the association between baseline variables and *AGTR1* A1166C polymorphisms and the response to valsartan treatment. Variables with P<0.05 were entered into multivariate logistic regression to determine the factors associated with the antihypertensive activities of valsartan. The data were presented as hazards ratios (*HRs*) with 95% confidence intervals (*CIs*). All statistical analyses were conducted using the SPSS 21.0 software. P<0.05 (2-sided) was considered statistically significant.

3. Results

3.1. Demographic and baseline characteristics

The analysis included 198 patients. The mean systolic blood pressure was (166.1±17.1) mmHg and diastolic blood pressure was (104.2±12.3) mmHg. Patient demographic and baseline characteristics of the overall cohort are described in Table 1.

Table 1. Demographic and baseline characteristics of the entire cohort (n=198).

Variable	N=198
Male sex, n (%)	115 (58.1)
Age, years	53.7±13.5
BMI, kg/m^2	26.0±2.7
Overweight, n (%)[#]	20 (10.1)
Obese, n (%)[$]	1 (0.5)
Smoking status, n (%)[^]	
Current	122 (61.6)
Past	17 (8.6)
Never	59 (29.8)
Drinking, n (%)[&]	60 (30.3)
Co-morbid diseases, n (%)	
Diabetes	36 (18.2)
Hyperlipidemia	13 (6.6)
CHD	1 (0.5)
SBP, mmHg	166.1±17.1
DBP, mmHg	104.2±12.3
TC, mmol/L	4.79±1.18
TG, mmol/L	2.43±1.64
HDL, mmol/L	1.16 (0.97, 1.46)
LDL, mmol/L	2.96±0.74
APO-A1, g/L	1.26±0.23
APO-B, g/L	0.87±0.22

Data are expressed as mean±standard deviation or median (IQR) unless otherwise specified. Definitions: #Overweight is defined as BMI >24 but <28 kg/m^2. [$]Obesity is defined as BMI≥28 kg/m^2. [^]Current smokers: Individuals who have smoked continuously or cumulatively for 6 months or more in their lifetime and have smoked within the 30 days prior to the survey. Past smokers: individuals who smoked continuously for at least 6 months every day but no longer smoke at the time of investigation. & Drinking alcohol at least once a week for a duration ≥1 year. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; APO-A1, apolipoprotein A1; APO-B, apolipoprotein B; CHD, coronary heart disease.

Table 2. Demographic and baseline characteristics of the patients stratified by *AGTR1* A1166C genotype.

Variable	AA (*N*=164)	AC/CC (*N*=34)	*P* value
Male sex, *n* (%)	95 (57.9)	20 (58.8)	0.932
Age, years	53.2±13.4	53.2±8.9	0.863
BMI, kg/m^2	25.9±2.8	26.0±2.6	0.882
Overweight, *n* (%)[#]	18 (11.0)	2 (5.9)	0.537
Obese, *n* (%)[$]	1 (0.6)	0 (0)	/
Smoking status, *n* (%)[^]			0.803
Current	101 (61.6)	21 (61.8)	
Past	15 (9.2)	2 (5.9)	
Never	48 (29.3)	11 (32.4)	
Drinking, *n* (%)[&]	50 (30.5)	10 (29.4)	0.901
Co-morbid diseases, *n* (%)			
Diabetes	31 (18.9)	5 (14.7)	0.807
Hyperlipidemia	11 (6.7)	2 (5.9)	0.860
CHD	0 (0)	1 (2.9)	/
SBP, mmHg	166±16	166±17	0.492
DBP, mmHg	104±12	103±12	0.209
TC, mmol/L	4.63±1.09	4.95±1.27	0.184
TG, mmol/L	2.13±1.39	2.72±1.89	0.150
HDL, mmol/L	1.11 (0.97, 1.32)	1.21 (1.00, 1.46)	0.591
LDL, mmol/L	2.82±0.66	3.09±0.82	0.163
APO-A1, g/L	1.28±0.25	1.24±0.20	0.528
APO-B, g/L	0.85±0.20	0.88±0.25	0.547

Data are expressed as mean±standard deviation or median (IQR) unless otherwise specified. Definitions: [#]Overweight is defined as BMI >24 but <28 kg/m^2. [$]Obesity is defined as BMI ⩾28 kg/m^2. [^]Current smokers: Individuals who have smoked continuously or cumulatively for 6 months or more in their lifetime and have smoked within the 30 days prior to the survey. Past smokers: individuals who smoked continuously for at least 6 months every day but no longer smoke at the time of investigation. [&]Drinking alcohol at least once a week for a duration ⩾1 year. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; APO-A1, apolipoprotein A1; APO-B, apolipoprotein B; CHD, coronary heart disease.

Table 3. Univariate and multivariate analysis of predictors of blood pressure target attainment in essential hypertension patients.

Variables	Univariate			Multivariate		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
Sex (male *vs*. female)	1.060	0.601-1.869	0.841			
Age, years	1.004	0.983-1.025	0.740			
Smoking (yes *vs*. no)	0.303	0.164-0.562	<0.001	0.314	0.159-0.619	0.001
Drinking (yes *vs*. no)	0.822	0.448-1.510	0.528			
Diabetes (yes *vs*. no)	0.551	0.311-0.978	0.042	0.772	0.401-1.486	0.439
Hyperlipidemia (yes *vs*. no)	0.898	0.348-2.316	0.824			
Obesity/Overweight (yes *vs*. no)	0.798	0.316-2.013	0.633			
SBP, mmHg	0.992	0.962-1.024	0.627			
DBP, mmHg	0.998	0.966-1.032	0.925			
Genotypes (AA *vs*. AC/CC)	2.927	1.296-6.611	0.010	2.891	1.156-7.226	0.023

Abbreviation: SBP: systolic blood pressure; DBP: diastolic blood pressure; Overweight was defined as BMI >24 but <28 kg/m^2; obesity was defined as BMP ⩾28 kg/m^2. Definition of drinking: Drinking alcohol at least once a week for a duration of ⩾1 year; Smoking: Individuals who have smoked continuously or cumulatively for 6 months or more in their lifetime and have smoked within the 30 days prior to the survey; *HR*: hazards ratio; 95% *CI*: 95% confidence interval.

3.2. Genotype distribution

Genotyping assays showed that 164 patients had the AA genotype, and 34 patients were of the AC/CC genotype, including 30 patients with the AC genotype and 4 with the CC genotype. The distribution of allele frequencies of *AGTR1* A1166C was in accordance with the Hardy-Weinberg equilibrium. A dominant genetic model for *AGTR1* A1166C (AA genotype *versus* AC+CC genotype) was used in the subsequent analysis. The two groups were comparable in the demographics and baseline characteristics including systolic blood pressure [(166±16) mmHg *versus* (166±17) mmHg, *P*=0.492] and diastolic blood pressure [(104±12) mmHg *versus* (103±12) mmHg, *P*=0.209] (Table 2).

3.3. Genotype versus blood pressure control

Twenty-five of 34 patients (73.5%) with *AGTR1* A1166C AC/CC genotype attained the blood pressure control target *versus* 51.2% (51/164) of patients with *AGTR1* A1166C AA genotype (χ^2=5.665, *P*=0.017). Patients with *AGTR1* A1166C AC/CC genotype had a significantly greater reduction in systolic blood pressure [(33.1±10.8) *versus* (29.2±11.7) mmHg in AA carriers; *t*=2.194, *P*=0.029]. Meanwhile, no statistical difference was observed in the amplitude of reduction in diastolic blood pressure (*P*=0.576).

A total of 109 patients (55.1%) attained the blood pressure target after 4 weeks, with a mean reduction of (31.2±11.3) mmHg in systolic blood pressure and (23.7±11.8) mmHg in diastolic blood pressure. Univariate analysis showed that smokers (*HR* 0.303 *versus* non-smokers, 95% *CI* 0.164-0.562, *P*<0.001), diabetes patients (*HR* 0.551 *versus* no diabetes, 95% *CI* 0.311-0.978, *P*=0.042) and patients with *AGTR1* A1166C AA genotype (*HR* 2.927 *versus* AC/CC carriers, 95% *CI* 1.296-6.611, *P*=0.010) were significantly more likely to attain the blood pressure control target. Multivariate analysis further demonstrated that smoking (*HR* 0.314 *versus* no smoking, 95% 0.159-0.619, *P*=0.001) and *AGTR1* A1166C AA genotype (*HR* 2.891 *versus* AC/CC carriers, 95% *CI* 1.156-7.226, *P*=0.023) were independent and significant predictors of blood pressure control target attainment (Table 3).

3.4. Subgroup analysis in smokers and diabetic patients

In a subgroup analysis that included smokers only (either past or current), the blood pressure control rate was 73.9% (17/23) in patients with *AGTR1* A1166C AC/CC genotype *versus* 48.3% (56/116) in patients with *AGTR1* A1166C AA genotype (χ^2=5.059, *P*=0.024). In a subgroup analysis that included diabetic patients only, the blood pressure control rate was 80.0% (4/5) in patients with *AGTR1* A1166C AC/CC genotype *versus* 54.8% (17/31) in patients with *AGTR1* A1166C AA genotype (χ^2=0.325, *P*=0.569).

4. Discussion

In this study, after a 4-week valsartan monotherapy, the overall blood pressure control target attainment rate of essential hypertension patients was 55.1%. 73.5% Patients with the AC/CC genotype attained the blood pressure control target while 51.2% of the patients with the AA genotype attained the blood pressure control target after 4 weeks treatment. The better response of our patients with the AC/CC genotype to valsartan monotherapy was largely driven by a significantly greater reduction in systolic blood pressure in patients with the AC/CC genotype than that in the AA group. No significant difference in reduction in diastolic blood pressure was found between patients with the AC/CC genotype and those with the AA genotype. Higher response rate in patients with the AC/CC genotype is also evident in subgroup analysis that included smokers only and diabetic patients only.

Essential hypertension remains a significant risk of cardiovascular disease, chronic renal disease, and other chronic diseases globally including China, posing a public health challenge and incurring a heavy financial burden to the society. However, the control rate of hypertension is not optimistic, accounting for only 16.8% of the hypertensive population[15-17]. Despite public health initiatives, 750 000 cardiovascular disease deaths could be attributed to uncontrolled hypertension alone in China in 2010[8]. Apart from other factors that could impact on blood pressure control in essential hypertension patients[18-20], gene polymorphisms could be a contributory factor. In the present retrospective study, we analyzed the association of *AGTR1* A1166C polymorphisms with response to valsartan monotherapy. We found that *AGTR1* A1166C AC/CC genotype was present in 17.2% of the patients and patients with this phenotype were approximately 3.4 times more likely to attain the blood pressure control target with valsartan monotherapy than those with *AGTR1* A1166C AA genotype. The findings suggested that the C allele of *AGTR1* A1166C is an independent predictor of treatment response to valsartan.

Several studies have explored the impact of *AGTR1* gene polymorphism on the onset of essential hypertension. Deepak *et al*.[21] reported that *AGTR1* C gene mutation confers a 1.74-fold risk of primary hypertension, which may serve as a predictive marker for susceptibility to familiar hypertension. Similarly, we have previously shown that individuals with the AC/CC genotype are more susceptible to essential hypertension[22]. Meanwhile, Chen *et al*. found no significant correlation between *AGTR1* A1166C gene polymorphism between hypertensive patients and normotensive subjects[23]. Previous studies have shown that *AGTR1* gene polymorphisms affect the antihypertensive efficacy of ARBs, but the conclusion is still conflicting. An early study in patients with

heart failure showed higher sensitivity to candesartan in subjects carrying A allele than C allele[24]. However, a subsequent study in hypertensive patients with anti-AT1-receptor autoantibodies reported an association between the C allele of *AGTR1* with increased efficacy of candesartan in reducing systolic blood pressure[25]. A recent study in patients with essential hypertension also reported higher response to valsartan in AC/CC genotype carriers than in AA genotype carriers[26]. Results from the current study added support to the association between AC/CC genotype and higher response to ARBs.

Blood lipid metabolism plays a very important role in the occurrence and development of hypertension[27–30]. Our univariate and multivariate analysis showed no significant difference in the plasma levels of triglycerides, cholesterol, high and low-density lipoprotein, APO-A1 and APO-B between patients with the *AGTR1* AC/CC genotype and those with the AA genotype.

The current study has several limitations. The study is retrospective thus cannot establish a causal relationship. In addition, only *AGTR1* A1166 C polymorphism was examined in the study patients. *AGTR1* CYP2C9*3 polymorphism, which was not examined in the current study, has been shown not to be associated with response to valsartan monotherapy in hypertensive patients in previous studies[25].

In conclusion, *AGTR1* A1166C gene polymorphism can affect the effectiveness of valsartan monotherapy for essential hypertension, and patients with essential hypertension carrying the C allele have a more sensitive systolic blood pressure to valsartan monotherapy.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Conceptualization: HZY and LW; methodology: LL; software: SYW; validation: HZY, YWZ and LL; formal analysis: LW; investigation: QQK; resources: LW; data curation: SYW; writing-original draft preparation: HZY; writing-review and editing: LL; visualization: WN; supervision: BD; project administration: HZY; funding acquisition: LW. All authors have read and agreed to the published version of the manuscript. The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work, if that information is not provided in another form.

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