AT1R gene polymorphism contributes to MACCEs in Hypertension patients

Jun-Yi Luo
First Affiliated Hospital of Xinjiang Medical University
Guo-Li Du
First Affiliated Hospital of Xinjiang Medical University
Yang-Min Hao
First Affiliated Hospital of Xinjiang Medical University
Fen Liu
First Affiliated Hospital of Xinjiang Medical University
Tong Zhang
First Affiliated Hospital of Xinjiang Medical University
Bin-Bin Fang
Clinical Medical Research Institute of First Affiliated Hospital of Xinjiang Medical University
Xiao-Mei Li
First Affiliated Hospital of Xinjiang Medical University
Xiao-Ming Gao
First Affiliated Hospital of Xinjiang Medical University
Yi-Ning Yang (yangyn5126@163.com)
People's Hospital of Xinjiang Uygur Autonomous Region

Research Article

Keywords: Angiotensin II type 1 receptor (AT1R), Coronary heart disease (CHD), Hypertension, Major adverse cardiovascular events (MACCEs)

Posted Date: September 21st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2062190/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Cardiovascular Disorders on June 3rd, 2023. See the published version at https://doi.org/10.1186/s12872-023-03223-w.

Abstract

OBJECTIVE:

To investigate the possible association between AT1R gene polymorphisms and major adverse cardiovascular and cerebrovascular events (MACCEs) in hypertension patients combined with or without coronary heart disease (CHD) in Xinjiang.

METHODS:

374 CHD patients and 341 non-CHD individuals were enrolled as study participants and all of them have a hypertension diagnosis. AT1R gene polymorphisms were genotyped by SNPscan™ typing assays. During the follow-up in the clinic or by telephone interview, MACCEs were recorded. Kaplan–Meier curves and Cox survival analyses were used to explore the association between AT1R gene polymorphisms and the occurrence of MACCEs.

RESULTS:

AT1R gene rs389566 was associated with MACCEs. The TT genotype of the AT1R gene rs389566 had a significantly higher probability of MACCEs than the AA+AT genotype (75.2% vs 24.8%, P=0.033). Older age (OR=1.028, 95% CI: 1.009-1.0047, P=0.003) and TT genotype of rs389566 (OR=1.770, 95% CI: 1.148-2.729, P=0.01) were risk factors of MACCEs. AT1R gene rs389566 TT genotype may be a predisposing factor for the occurrence of MACCEs in hypertensive patients.

CONDLUSION:

AT1R SNP rs389566 may be a common genetic loci and optimal genetic susceptibility marker for MACCEs in hypertension patients.

Introduction

Coronary heart disease (CHD) and hypertensive are common diseases that endanger human health. As blood pressure regulatory system in the body, the renin-angiotensin system (RAS) is an important risk factors for CHD [1–3]. The angiotensin II (Ang II) type 1 receptor (AT1R) is involved in the classical physiological actions of Ang II, and plays a pivotal role in the pathogenesis of atherosclerosis in human [4].

Hypertension is a major risk factor for CHD and 25% of patients with CHD have hypertension [5]. CHD is the first cause of morbidity and mortality in hypertension [6]. As referred above, AT1R is very important for the CHD, but its roles in pathogenesis of hypertension patients combined with CHD remains to be understood, although the associations between the AT1R polymorphisms, CHD and hypertension had been proved in French and English Caucasians population respectively [7, 8].

In this study, two single nucleotide polymorphisms (SNPs) of the AT1R gene were sequenced [9], and the differences in the distribution frequencies of these SNPs were compared between CHD patients and non-CHD patients combined with hypertension, and the association between AT1R gene polymorphisms and major adverse cardiovascular and cerebrovascular events (MACCEs) were analyzed.

Materials And Methods

Study Population

In this case-control study, we recruited adult hypertension patients combined with CHD or non-CHD who were long-term residents of the Xinjiang region, China, and they were admitted to the Heart Center of the First Affiliated Hospital of the Xinjiang Medical University with symptoms of chest tightness or precordial discomfort during 2010–2018. Each subject signed an informed consent before participating in this study. Additionally, we excluded those patients with incomplete data and complicated with one or more than one disease, such as secondary hypertension, rheumatic heart disease, congenital heart disease, heart failure, systemic immune system diseases, and multiple organ failure.

General data collection

The medical record system of our hospital was consulted according to the name and hospitalization certificate number, and the required data were collected according to the inclusion criteria, and data entry was performed using an Excel sheet. General data were collected including gender, age, body mass index (BMI), hypertension, type 2 diabetes mellitus (T2DM), smoking, alcohol intake, family history of CHD, etc. Laboratory tests for blood glucose, lipids including cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c) were also collected.

Diagnostic of MACCEs, CHD and Hypertension

MACCEs is defined as the occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, ischemia-driven revascularization, and stroke [10]. Typical symptom of CHD is exertional angina, with pressure pain in the precordial region during activity or emotional stress. It can radiate to the left shoulder or/and left upper arm for 5–10 minutes and can be relieved by rest or medications such as nitroglycerin. Diagnosis CHD is based on symptoms, signs and ancillary tests such as electrocardiography and coronary angiography (CAG). CAG is the gold standard for diagnosing CHD. Diagnosis of CHD should be at least one coronary arterial stenosis of 50% or its major branches in the CAG [11]. According to the Chinese Guidelines for the Prevention and Treatment of Hypertension 2010 [12], hypertension is diagnosed under the following conditions: systolic blood pressure (SBP) ≥ 140mmHg and / or diastolic blood pressure (DBP) ≥ 90mmHg on three different days in the absence of antihypertensive drugs; patients with a history of hypertension and currently taking antihypertensive drugs although their blood pressures were lower than 140 / 90mmHg.

Genotyping assay

A total of 5 mL of fasting peripheral venous blood was drawn from the subjects into ethylenediaminetetraacetic acid (EDTA)-containing blood collection tubes, and plasma and blood cells were separated through centrifugation and stored in a − 80°C refrigerator until further use. Plasma was were measured by biochemical indicator and blood cells were subjected to genomic DNA extraction using a whole blood genome extraction kit (Tiangen Biotech, China). AT1R gene polymorphism was detected by TaqMan® SNP genotyping qRT PCR. Genotyping accuracy was determined by genotypic concordance between replicate samples, and the accuracy of each SNP was 100%. The reaction system of qPCR amplification was composed of following reagents: 3 μL of TaqMan Universal Master Mix, 0.12 μL probes and 1.88 μL ddH_2O in a 6 μL final reaction volume containing 50 ng DNA. Amplification cycling conditions were as follows: 95°C for 5 min; 35 cycles of 95°C for 15 s and 60°C for 1 min.

Statistical methods

SPSS 26.0 statistical software was used for statistical analysis. T-test was used for comparison between groups; χ chi-square test was used for comparison of count data. Cox regression was used for multi-factor analysis. The associations between patients' survival rate and the AT1R gene polymorphism were evaluated using Kaplan–Meier analysis. A difference was considered statistically significant as $P < 0.05$ (two-sided).

Ethic declaration

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University and conducted according to the standards of the Declaration of Helsinki and written informed consents were obtained from participants.

Results

General clinical characteristics

In this study, we compared the general characteristics of patients between non-CHD and CHD patients combined with hypertension. We found that CHD patients tended to be older (55.7±9.7 vs 59.6 ±10.7 years, P<0.001), higher glucose levels of BMI (26.93±3.85 vs 26.07±3.10 kg/m^2, P=0.030), SBP (132±17 vs 129±18 mmHg, P=0.023), DBP (80±11 vs 78±12 mmHg, P=0.043) compared with non-CHD patients. Patients with CHD also have higher levels of TC (4.17±1.01 vs 4.45±1.18 mmol/L, P=0.001), LDL-c (2.60±0.83 vs 2.76±0.96 mmol/L, P=0.010) and lower HDL-c (1.04±0.29 vs 0.99±0.28 mmol/L, P=0.020, Table 1).

General characteristics and biochemical parameters between control (non-MACCEs) and MACCEs groups had been compared, as shown in Table 2. There was no significant difference regarding gender, smoking, alcohol intake, T2DM between these groups (P > 0.05). The prevalence of MACCEs in CHD patients was significantly higher than non-CHD patients (79.5% vs 20.5%), P<0.001. Patients with MACCEs showed

higher blood glucose compared with those non-MACCEs patients (8.15±3.42 vs 6.93±3.22 mmol/L), P<0.001.

Patients with MACCEs showed higher age (Table 2) compared with those non-MACCEs patients (57.1±10.3 vs 59.1±9.7 years), P<0.001. We then compared characteristics among different age groups in Table 3. In 51-60 years old and over 60 years old groups, MACCEs occurrence increased significantly (31.6% and 54.7%, respectively, P=0.001). The BMI, blood pressure, glucose, TG, HDL-c showed significantly difference among different age groups (P<0.05). There was no difference regarding rs16860760, rs389566 TT genotype among different age groups (P=0.932, P=0.446 respectively).

Occurrence of MACCEs in patients with different genotypes of rs16860760 in AT1R gene

There was no significant difference regarding the frequency of MACCEs in different AT1R rs16860760 SNPs (P>0.05), but the AT1R gene rs389566 polymorphism showed significant association with the probability of MACCEs in patients with hypertension (Table 4). And the patients carrying TT genotype at rs389566 locus had a higher risk of MACCEs than those carrying the AA+AT gene type (24.8% vs 75.2%, P=0.033).

Risk factors of MACCEs

In the present study, the mean follow-up duration was 65.6 (38.3, 91.8) months. The Kaplan–Meier analysis revealed that the MACCEs-free cumulative survival rate in the TT genotype group was obviously lower than that in the AA+AT genotype group (P=0.009, Fig. 1).

Through univariate Cox survival analysis, we found that elderly, glucose, coronary heart disease, and rs389566 TT gene types may be risk factors for MACCEs in patients with hypertension. As shown in Table 5, age, AT1R gene rs389566 TT genotype, CHD and glucose variables were included to construct a multifactorial COX proportion-al risk model. The results showed old age may be a predisposing factor on the occurrence of MACCEs (OR=1.028, 95% CI: 1.009-1.047, P=0.003), and rs389566 TT genotype may be a predisposing factor on the occurrence of MACCEs (OR=1.770, 95%CI 1.148-2.729, P=0.010). Patients with CHD were prone to MACCEs (OR=4.118, 95%CI 2.542-6.672, P<0.001). However, the glucose showed no significant different effect on occurrence of MACCEs in the final model (P>0.05).

Discussion

Many factors influence the occurrence of MACCEs, such as family history of CHD, smoking, obesity, hypertension, diabetes, abnormal lipid metabolism, insulin resistance, and homocysteine mia [13]. In the present study, AT1R gene rs389566 TT genotype was found to be associated with the occurrence of MACCEs in hypertension patients.

Cardiovascular disease is the leading cause of death worldwide [14], and hypertension is the most common chronic disease and the most important risk factor for cardiovascular disease [15]. Although CHD mortality rates have gradually declined in Western countries over the past few decades, the condition still causes about one-third of deaths in people over 35 years of age [16]. MACCEs remain the major cause of mortality and morbidity in patients both in hypertension or CHD patients [17, 18].

However, it has been reported in the literature that the incidence of MACCEs is significantly higher in CHD combined with hypertension patients compared with non-CHD or non-hypertension patients [10, 19], but the reasons remain to be unknown. The traditional risk factors of MACCEs include fasting glucose, heart rate variability, blood pressure [20-23] and dyslipidemia [24]. As previous reported, AT1R gene polymorphism was found to be associated with the development of CHD in Chinese population [25, 26]. Here we found AT1R rs389566 TT genotype may be an independent risk factor for the development of MACCEs in patients with hypertension especially those combined with CHD. The main effects of Renin-Angiotensin-Aldosterone System (RAAS) on cardiovascular system are atherosclerosis and hypertension, leading to congestive heart failure and MACCEs [27]. And Ang II also promotes the development of atherosclerosis through AT1 receptors, stimulating the secretion of inflammatory mediators, and converting stable plaques into vulnerable plaques [28]. Overexpression of the AT1R gene leads to myocardial hypertrophy and ventricular remodeling [29]. The previously study demonstrates that the AT1R polymorphism is associated with abnormal coronary vasoconstriction which causes rupture of plaque and thrombus formation [30].

Our study found that AT1R gene mutation was associated with the occurrence of MACCEs in hypertension patients in the Xinjiang. The patients with hypertension carrying TT genotype of the AT1R gene rs389566 were prone to MACCEs. Previous studies have been conducted on AT1R gene polymorphisms in the Chinese population, but mainly on hypertension, atherosclerosis, cardiovascular disease risk factors, and intravascular restenosis. The association of AT1R gene polymorphisms with the occurrence of MACCEs events has not been reported before. Most previous studies have focused on the association of the AT1R rs5186 (A1166C) locus polymorphism and acute myocardial infarction in Caucasian, Asian, African, Brazilian, and Durban populations, and the C allele was proved to be a risk factor for occurrence of myocardial infarction [31]. In Asia, previous studies [31-33] reported that AT1R A1166C polymorphism may influence the occurrence of myocardial infarction susceptibility in Chinese. However, the sample size of these studies is relatively small, and fewer studies have focused on the relationship between AT1R rs16860760 and MACCEs. In the present study, we found the significant association between AT1R rs389566 polymorphism and MACCEs in Chinese hypertensive population which could help provide a clinical basis for future targeted interventions.

Besides AT1R gene polymorphism, the age is also a factor affecting the occurrence of MACCEs. Our study found that the occurrence of MACCEs is higher in older age population, Patients with hypertension over 60 years are more likely to occur MACCEs and the prevalence is about 54.7% and it was consistent with previous study [34]. For aged population, MACCEs prevention should be emphasized in future.

Our study confirmed that AT1R rs389566 TT genotype increased the occurrence of MACCEs in hypertension patients.

Conclusion

In summary, this study provides the current status of risk factors for the occurrence of MACCEs in hypertensive patients combined with CHD in Xinjiang, China. Especially those aged hypertensive patients carrying A1TR rs389566 TT genotype requires avoidance of unhealthy lifestyles, raising awareness about the prevention and better management of MACCEs. The present findings provide potential intervention targets for the prognosis of patients who are at high risk of MACCEs, and this will help clinician do genomics-based personalized therapy in future.

Limitation

This study also has some limitations. First, the sample size was not large enough. Second, participants in the current study were recruited only at the First Affiliated Hospital of Xinjiang Medical University, which may not necessarily reflect the true prevalence of hypertension combined with CHD and the occurrence of MACCEs at the provincial or national level. Finally, we focused our interest on the AT1R gene polymorphism: as discussed, many other factors are involved in MACCEs and may cause increase in occurrence. Broader analyses are therefore encouraged to better understand the complexity of the MACCEs occurrence process.

Declarations

Ethics approval and consent to participate

The study conducted according to the standards of the Declaration of Helsinki and its experimental protocols was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University. Written informed consent was obtained from all subjects and/or their legal guardian(s). All participants consented for drawing their blood samples and collection of their relevant clinical data.

Consent for publication

Not applicable.

Data availability

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Competing Interests

All of these authors declared that they had no competing interests.

Funding

The survey was funded by the National Natural Science Foundation of China (82160054, 81960078), State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia, Xinjiang Medical University (SKL-HIDCA-2021-XXG4), and Xinjiang Young Scientific and Technical Talents Training Project (2019Q040).

Author contributions

X-ML, X-MG and Y-NY were involved in the study design of the experiments. J-YL, G-LD, Y-MH, FL, TZ and B-BF performed the experiments, evaluated the data and wrote the manuscript. J-YL, G-LD and Y-MH were involved in data analysis and manuscript editing. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Alderman M, Madhavan S, Ooi W, Cohen H, Sealey J, Laragh J. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. N Engl J Med. 1991;324:1098–104.
2. Yusuf S, Pepine C, Garces C, Pouleur H, Rousseau M, Salem D, Kostis J, Benedict C, Bourassa M, Pitt B. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. Lancet. 1992;340:1173–8.
3. Xiang KS, Zheng TS, Sun DQ, Li J. The relationship between angiotensin type 1receptor gene and coronary heart disease, hypertension and diabetes mellitus in Chinese. Chin J Med Genet. 1998;15:12–5.
4. Smith RD, Timmermans PB. Human angiotensin receptor subtypes. Curr Opin Nephrol Hypertens. 1994;3:112–22.
5. Collins R, McMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. Br Med Bull 994, 50:278–298.
6. Escobar E. Hypertension and coronary heart disease. J Hum Hypertens. 2002;16:61–3.
7. Tiret L, Bonnardeaux A, Poirier O, Ricard S, Marques-Vidal P, Evans A, Arveiler D, Luc G, Kee F, Ducimetiere P, et al. Synergistic effects of angiotensin-converting enzyme and angiotensin-II type 1 receptor gene polymorphisms on risk of myocardial infarction. Lancet. 1994;344:910–3.
8. Bonnardeaux A, Davies E, Jeunemaitre X, Fery I, Charru A, Clauser E, Tiret L, Cambien F, Corvol P, Soubrier F. Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension. Hypertension. 1994;24:63–9.

9. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science. 1996;273:1516–7.
10. Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK, Jørgensen E, Kelbæk H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2011;33:734–44.
11. Li B, Liu ZM, Li YQ. Comparison of coronary angiography and three kinds of noninvasive methods in the diagnosis of coronary artery disease. Chin J Cardiovasc Med. 1999;27:105–6.
12. Writing group. of 2010 Chinese guidelines for the management of hypertension: 2010 Chinese guidelines for the management of hypertension. Chinese Journal of Hypertension 2010, 19.
13. Ran JJ, Jiang Y, Liu QL. Meta-analysis on the risks factors of coronary heart diease. Med J West China. 2014;26:1629–32.
14. Lino CA, Barreto-Chaves ML. Beta-arrestins in the context of cardiovascular diseases: Focusing on angiotensin II type 1 receptor (AT1R). Cell Signal. 2022;92:110253.
15. Writing Group of 2018 Chinese Guidelines for the Management of Hypertension, Chinese Hypertension League. Chinese Society of Cardiology, Chinese Medical Doctor Association Hypertension Committee, Hypertension Branch of China International Exchange and Promotive Association for Medical and Health Care, Hypertension Branch of Chinese Geriatric Medical Association: 2018 Chinese guidelines for the management of hypertension. Chin J Cardiovasc Med. 2019;24:24–56.
16. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Trans Med 2016, 4.
17. Miao B, Hernandez AV, Alberts MJ, Mangiafico N, Roman YM, Coleman CI. Incidence and predictors of major adverse cardiovascular events in patients with established atherosclerotic disease or multiple risk factors. J Am Heart Assoc. 2020;9:e014402.
18. Wong YK, Cheung CY, Tang CS, Au KW, Hai JS, Lee CH, Lau KK, Cheung BM, Sham PC, Xu A. Age-biomarkers-clinical risk factors for prediction of cardiovascular events in patients with coronary artery disease. Arterioscler Thromb V asc Biol. 2018;38:2519–27.
19. Zhang JL. The Characteristics of Blood Pressure and Its Relationship with the Incidence of Cardiovascular Event in Patients with Essential Hypertension Combining Coronary Heart Disease. Chin J Integr Med cardiovscular disease. 2009;7:141–3.
20. Cao X, Kang YT, Tian YX, Wang X, Chen Z, Zhang L, Zheng CF, Chen LY, Zhou HQ, Wang ZW. Attributable risk of cardiovascular mortality associated with different glycometabolic status among different regions in China. Chin J Cardiovasc Med. 2022;27:60–5.
21. Jiao XH, Guo LX, Zhang BY, Tian YJ. The influence of heart rate variability on the prognosis of elderly patients with heart failure. Chin J Cardiovasc Med 2022, 27.
22. Keith MD, Tanner RM, Falzon L, Levitan EB, Reynolds K, Shimbo D, Muntner P. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. Hypertension. 2014;64:965–82.

23. Gosmanova EO, Mikkelsen MK, Molnar MZ, Lu JL, Yessayan LT, Kalantar-Zadeh K, Kovesdy CP. Association of Systolic Blood Pressure Variability With Mortality,Coronary Heart Disease, Stroke,and Renal Disease. J Am Coll Cardiol. 2016;68:1375–86.
24. Boey E, Gay GMW, Poh K-K, Yeo T-C, Tan H-C, Lee C-H. Visit-to-visit variability in LDL- and HDL-cholesterol is associated with adverse events after ST-segment elevation myocardial infarction: A 5-year follow-up study. Atherosclerosis. 2016;244:86–92.
25. Liu C, Li Y, Guan T, Lai Y, Shen Y, Zeyaweiding A, Zhao H, Li F, Maimaiti T. ACE2 polymorphisms associated with cardiovascular risk in Uygurs with type 2 diabetes mellitus. Cardiovasc. 2018;17:127.
26. Li Y, Li X, Jia N, Guo S, Chu S, Niu W. Meta-analysis of the association between angiotensin II receptor, type 1 gene A1166C polymorphism and coronary artery disease in Chinese populations. J RENIN-ANGIO-ALDO S. 2013;14:82–90.
27. Kumar R, Singh VP, Baker KM. The intracellular renin–angiotensin system: implications in cardiovascular remodeling. Curr Opin Nephrol Hypertens. 2008;17:168–73.
28. Paradis P, Dali-Youcef N, Paradis FW. Overexpression of angiotensin I type I receptor in cardiomyocytes induces cardiachypertrophy and remodeling. Proc Natl Acad Sei U S A 2000:931–936.
29. Paradis P, Dali-Youcef N, Paradis FW, Thibault Gt, Nemer M. Overexpression of angiotensin II type I receptor in cardiomyocytes induces cardiac hypertrophy and remodeling. Proc Natl Acad Sci. 2000;97:931–6.
30. Amant C, Hamon M, Bauters C, Richard F, Helbecque N, McFadden EP, Escudero X, Lablanche JM. The Angiotensin II Type 1 Receptor Gene Polymorphism Is AssociatedWith Coronary Artery Vasoconstriction. J Am Coll Cardiol. 1997;29:486–90.
31. Feng X, Zheng BS, Shi JJ, Qian J, He W, Zhou HF. A systematic review and meta-analysis of the association between angiotensin II type 1 receptor A1166C gene polymorphism and myocardial infarction susceptibility. J RENIN-ANGIO-ALDO S. 2014;15:307–15.
32. Su SY, Chen JH, Zhao JG, Huang JF, Wang XL, Chen RS, Gu DF. Angiotensin II type I receptor gene and myocardial infarction: tagging SNPs and haplotype based association study. The Beijing atherosclerosis study. Pharmacogenet. 2004;14:673–81.
33. Zhang H, Sun ML, Peng J, Sun T, Zhang Y, Yang JM. Association of the angiotensin type 1 receptor gene A1166C polymorphisms with myocardial infarction: a meta-analysis. J THROMB HAEMOST. 2011;9:1258–60.
34. Shuyao W, Yan L, Qian S. Multivariate Analysis of Risk and Prognostic Factors in Patients with Coronary Heart Disease. Chin Gen Pract. 2018;21:3562–70.

Tables

Table 1. General characteristics in hypertension patients stratified with CHD

Characteristics	non-CHD（n=341）	CHD（n=374）	*P* Value
Age (years)	55.7±9.67	59.6±10.73	<0.001
Gender, n (%)			
Male	173 (50.7%)	234 (62.6%)	0.001
Female	168 (49.3%)	140 (37.4%)	
Smoking, n (%)			
No	242 (71.0%)	229 (61.2%)	0.006
Yes	99 (29.0%)	145 (38.8%)	
Alcohol intake, n (%)			
No	251 (73.6%)	282 (79.5%)	0.582
Yes	90 (26.4%)	92 (20.5%)	
T2DM			
No	289 (84.8%)	261 (69.8%)	<0.001
Yes	52 (15.2%)	113 (30.2%)	
SBP (mmHg)	132±17	129±19	0.023
DBP (mmHg)	80±12	79±13	0.043
BMI (kg/m^2)	26.93±3.85	26.07±3.10	0.030
Glucose (mmol/L)	5.67±1.96	8.44±3.66	<0.001
TG (mmol/L)	1.96±1.48	2.13±1.76	0.181
TC (mmol/L)	4.17±1.01	4.45±1.18	0.001
HDL−c (mmol/L)	1.04±0.29	0.99±0.28	0.020
LDL−c (mmol/L)	2.60±0.83	2.76±0.96	0.010

CHD: Coronary heart disease, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TG: Triglycerides, TC: Total Cholesterol, HDL-c: High Density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol, T2DM: Type 2 Diabetes Mellitus, P< 0.05 was considered significant difference.

Table 2. Biochemical parameters in hypertension patients stratified with MACCEs

Biochemical parameters	non-MACCEs (n=598)	MACCEs (n=117)	*P* Value
Age (years)	57.1±10.39	59.1±9.79	<0.001
Gender, n (%)			
Male	337 (56.4%)	70 (59.8%)	0.488
Female	261 (43.6%)	47 (40.2%)	
Smoking, n (%)			
No	391 65.4%	80 68.4%	0.533
Yes	207 34.6%	37 31.6%	
Alcohol intake, n (%)			
No	440 (73.6%)	93 (79.5%)	0.180
Yes	158 (26.4%)	24 (20.5%)	
T2DM			
No	461 77.1%	89 76.1%	0.810
Yes	137 22.9%	28 23.9%	
CHD			
No	317 (53.0%)	24 (20.5%)	<0.001
Yes	281 (47.0%)	93 (79.5%)	
SBP (mmHg)	131±18	129±19	0.227
DBP (mmHg)	80±12	79±13	0.412
BMI (kg/m^2)	26.55±3.50	25.83±3.06	0.097
Glucose (mmol/L)	6.93±3.22	8.15±3.42	<0.001
TG (mmol/L)	2.04±1.57	2.09±1.94	0.810
TC (mmol/L)	4.30±1.10	4.40±1.16	0.389
HDL–c (mmol/L)	1.04±0.29	0.99±0.28	0.093
LDL–c (mmol/L)	2.68±0.89	2.73±0.96	0.542

MACCEs: Major adverse cardiovascular and cerebrovascular events, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TG: Triglycerides, TC: Total cholesterol, HDL-c: High

density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol, T2DM: Type 2 Diabetes Mellitus, CHD: Coronary heart disease, P< 0.05 was considered significant difference.

Table 3. Comparison of general characteristics in patients with hypertension according to different ages

Characteristics	<40 years old (n=20)	41-50 years old (n=178)	51-60 years old (n=218)	>60 years old (n=293)	*P* Value
Gender, n (%)					
Male	18 90.0%	139 77.7%	123 56.2%	127 42.8%	<0.001
Female	2 10.0%	40 22.3%	96 43.8%	170 57.2%	
Smoking, n (%)					
No	7 35.0%	83 46.4%	146 66.7%	235 79.1%	<0.001
Yes	13 65.0%	96 53.6%	73 33.3%	62 20.9%	
Alcohol intake, n (%)					
No	9 1.7%	104 19.5%	164 30.8%	256 48.0%	<0.001
Yes	11 55.0%	75 41.9%	55 25.1%	41 13.8%	
T2DM					
No	17 85.0%	155 86.6%	171 78.1%	207 69.7%	<0.001
Yes	3 15.0%	24 13.4%	48 21.9%	90 30.3%	
CHD					
No	15 75.0%	101 56.4%	107 48.9%	118 39.7%	<0.001
Yes	5 25.0%	78 43.6%	112 51.1%	179 60.3%	
SBP (mmHg)	137±16	129±17	129±16	132±20	0.039
DBP (mmHg)	87±14	82±12	80±11	77±13	<0.001
BMI (kg/m^2)	29.34±3.52	27.03±2.91	26.60±3.61	25.63±3.34	<0.001
Glucose(mmol/L)	6.16±2.06	7.06±3.27	6.30±2.63	7.76±3.58	<0.001
TG (mmol/L)	2.68±3.04	2.36±1.84	2.00±1.73	1.84±1.20	0.004
TC (mmol/L)	4.72±1.17	4.37±1.07	4.31±1.15	4.26±1.11	0.311
HDL−c (mmol/L)	1.02±0.25	0.96±0.23	1.04±0.31	1.08±0.30	0.001
LDL−c (mmol/L)	3.12±0.79	2.74±0.90	2.68±0.87	2.62±0.93	0.096
MACCEs, n (%)	1 (0.9%)	15 (12.8%)	37 (31.6%)	64 (54.7%)	0.001
RS389566 TT, n (%)	13 (2.8%)	116 (25.1%)	133 (28.7%)	201 (43.4%)	0.446
RS16860760,	20 (2.8%)	179 (25%)	219 (30.6%)	297 (41.5%)	0.932

n (%)

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TG: Triglycerides, TC: Total Cholesterol, HDL-c: High density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol, MACCEs: major adverse cardiovascular events. P< 0.05 was considered significant difference.

Table 4. AT1R gene polymorphisms in patients with MACCEs and control group.

Polymorphisms	non-MACCEs (n=598)	MACCEs (n=117)	*P* Value
Rs16860760			
AA+AG	62 (10.3%)	9 (7.7%)	0.599
GG	536 (89.6%)	108 (92.3%)	
Rs389566			
AA+AT	223 (37.3%)	29 (24.8%)	0.033
TT	375 (62.7%)	88 (75.2%)	

MACCEs: Major adverse cardiovascular and cerebrovascular events, P < 0.05 was considered significant difference

Table 5 Univariate and multivariate Cox analyses among the hypertension patients

Risk factors	Univariate cox regress		Multivariate cox regress	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
rs389566 AA+AT/TT	1.731 (1.138-2.635)	0.010	1.770(1.148-2.729)	0.010
CHD	4.912 (3.128-7.714)	<0.001	4.118(2.542-6.672)	<0.001
Age	1.041(1.023-1.060)	<0.001	1.028(1.009-1.047)	0.003
Gender	0.789 (0.545-1.142)	0.208	-	-
BMI	0.951(0.890-1.016)	0.136	-	-
SBP	0.992 (0.982-1.002)	0.135	-	-
DBP	0.992(0.977-1.007)	0.278	-	-
Glucose	1.107(1.060-1.156)	<0.001	1.036(0.985-1.089)	0.167
TG	1.008(0.897-1.132)	0.895	-	-
TC	1.101(0.930-1.303)	0.264	-	-
HDL-c	0.578(0.297-1.127)	0.108	-	-
LDL-c	1.108(0.900-1.363)	0.334	-	-

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TG: Triglycerides, TC: Total Cholesterol,

HDL-c: High density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol, MACCEs: major adverse cardiovascular

events. CHD: Coronary heart disease, OR: Odds ratio, CI: Confidence Interval, P< 0.05 was considered significant difference.

Figures

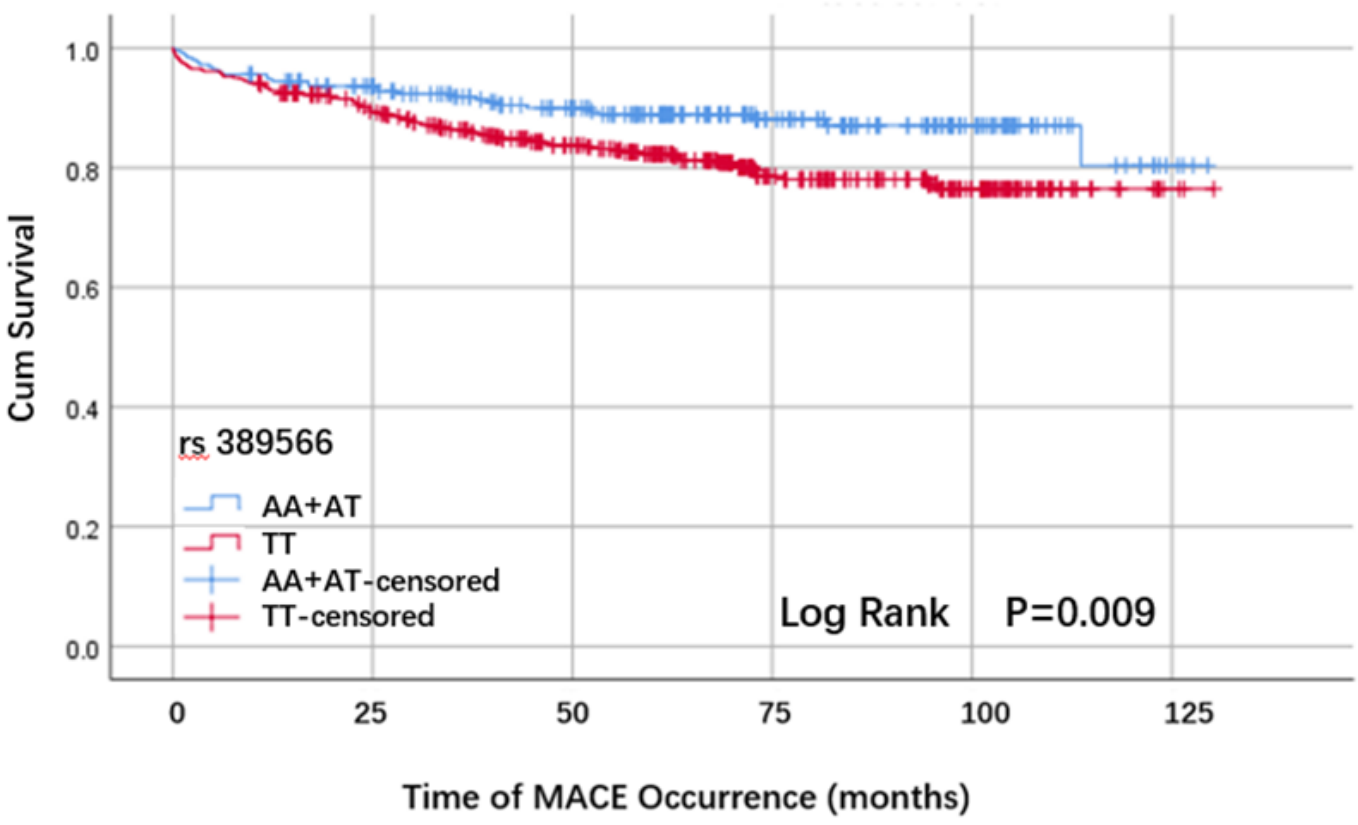

Figure 1

Kaplan-Meier curves of MACE survival analysis according to the rs389566 genotype.