Atrial natriuretic peptide T2238C gene polymorphism and the risk of cardiovascular diseases: A meta-analysis

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Abstract. The present study aimed to investigate the association between atrial natriuretic peptide (ANP) T2238C (rs5065) gene polymorphism and the risk of cardiovascular disease. Relevant literature was obtained by searching databases. The odds ratios (ORs) of the ANP T2238C locus genotype distribution in the case group of cardiovascular diseases and the control group of a non-cardiovascular population were pooled using R software. Sensitivity analysis was used to verify the stability of the results. Egger's linear regression test was used to assess the publication bias of the included literature. Studies were classified according to quality assessment score of the Newcastle-Ottawa scale, year, region, sample size and underlying disease for subgroup analysis, and meta-regression analysis was performed. A total of 12 studies comprising 45,619 patients were included. ANP rs5065 mutant gene C allele was a significant risk factor for myocardial infarction relative to T allele (OR=2.55, 95% CI=1.47-4.43, P=0.0008), CC+CT genotype was a significant risk factor for cerebrovascular events relative to TT (OR=1.14, 95% CI=1.04-1.26, P=0.0048) and the mutant CC genotype was a potential risk factor for the composite cardio-cerebral vascular events (CVE) relative to CT+TT (OR=1.40, 95% CI=0.96-2.04, P=0.081). In studies fulfilling the Hardy-Weinberg equilibrium, the CC genotype was a significant risk factor for the composite CVE relative to TT (OR=2.39, 95% CI=1.40-4.10, P=0.0018) and the CC genotype was a significant risk factor for composite CVE relative to CT+TT (OR=2.41, 95% CI=1.41-4.13, P=0.0015). The P-value of the Egger's test for publication bias was 0.436, which was not statistically significant. The results of the sensitivity analysis were relatively stable. Subgroup analysis indicated that the publication year was a potential source of heterogeneity. Regression analysis was performed for the recessive model in the composite CVE and the results showed that the study region (Europe) was one of the sources of heterogeneity (P=0.016). In conclusion, ANP 2238T/C mutation may increase the risk of myocardial infarction, cerebrovascular events and composite CVE.

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Introduction

Atrial natriuretic peptide (ANP) has a pivotal role in maintaining cardiac and renal homeostasis (1). Despite the highly conserved structure of the peptide across species, some genetic variants of ANP have been identified in humans, such as rs5065 (T2238C). This variant, occurring in 13-23% of the general population, results in a T to C transition at position 2,238 of the gene, leading to the production of a long α-carboxy-terminal peptide of 30 amino acids instead of 28 amino acids. *In vitro* studies suggest that this transition may increase levels of reactive oxygen species, contributing to endothelial damage, vascular smooth muscle cell contraction and increased platelet aggregation (1-4). Several population-based studies have shown an increased risk of stroke and myocardial infarction in those carrying such ANP variants (5-7).

The existing literature on the T2238C gene polymorphism of ANP and its relation to cardiovascular diseases reveals a noticeable gap in understanding, necessitating focused investigation. Numerous studies have hinted at the correlation between ANP polymorphisms, particularly the T2238C single nucleotide polymorphism, and various cardiovascular conditions, including microalbuminuria, hypertension, cardiac hypertrophy and stroke (8,9). However, a comprehensive assessment of the research landscape indicated several critical evidence gaps. While some studies suggested a potential association between the T2238C polymorphism and diabetic complications, myocardial infarction and stroke, conflicting results and limited ethnic diversity in participant cohorts raise questions about the generalizability of these findings. The need for more inclusive studies that encompass diverse populations to validate and extend these associations is evident. Furthermore, the intricate interplay between ANP and cardiovascular function remains incompletely understood. While studies have explored the role of ANPs in natriuresis, blood pressure regulation and vascular remodeling (10), there is a

dearth of research on the broader impact of ANP gene polymorphisms on endothelial protection, coagulation, fibrinolysis and platelet activation (11). The limited understanding of these multifaceted interactions also hinders us from unraveling the true extent of the influence of ANPs on cardiovascular health.

Despite that there is much evidence that ANP T2238C is associated with cardiovascular disease risk (5,12,13), a comprehensive synthesis and analysis of the existing data are lacking. Therefore, the present study aimed to fill this gap by systematically collecting and summarizing available data on the association between ANP T2238C and cardiovascular disease risk. By undertaking this meta-analysis, the present study not only consolidates the current evidence but also provides a novel perspective on the implications of ANP T2238C in cardiovascular disease risk factors. This contribution is particularly relevant to daily clinical practice, where a deeper understanding of genetic factors influencing cardiovascular health is crucial. In essence, our research bridges the existing gap by offering a comprehensive analysis of the association between ANP T2238C and cardiovascular diseases, thereby enhancing the current understanding of the genetic underpinnings of these conditions.

Materials and methods

Literature search. The terms 'rs5065', 'T2238C', 'ANP', 'atrial natriuretic peptide', 'heart', 'cardiovascular', 'cardiac' and 'coronary' were used as keywords to conduct a search in the Embase (https://www.embase.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/), Google Scholar (https://scholar.google.com/) and ISI web of science (http://www. webofknowledge.com/) databases, and the reference lists of all included studies were also searched manually. The present study was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (14).

Literature inclusion and exclusion. The following inclusion criteria were applied: i) Studies investigating the association of ANP-rs5065 polymorphism with cardiovascular events. Patients from the case group had cardiovascular diseases and the control group included non-cardiovascular controls. ii) Available data of the frequency of each genotype in the case and control groups. iii) For repeatedly reported studies, those that were recently published or provided larger sample sizes were included. The exclusion criteria were as follows: i) Duplicate publications; and ii) studies without complete loci polymorphism frequencies.

Data extraction and quality evaluation. Literature screening, data extraction and quality evaluation were performed independently by 2 evaluators (JW and YY), and the consistency of results was checked after completion. Studies with contradictory inclusion were double-checked and discussed. Extracted data included the following: Author, year of publication, study region, sample size in the case and control groups, genotyping method, frequency of genotypes and various events including atrial fibrillation, cerebrovascular events, coronary artery disease, death, myocardial infarction and the composite outcome, all cardiovascular events, which includes a variety of all cardio-cerebral vascular events (CVE); if the composite CVEs were not counted, it was selected as the most prevalent CVE. The quality of the study was assessed according to the Newcastle-Ottawa scale (NOS) (15) evaluation criteria in three aspects: Selection of study population, comparability between groups and exposure information.

Statistical analysis. The Hardy-Weinberg equilibrium (HWE) test was performed for gene polymorphisms using the *genhwcci* function in Stata software (version 15; StataCorp LP). The HWE was calculated for the control group and $P>0.05$ was considered to indicate that the equilibrium was reached. Meta-analysis was performed by the 'meta' package of R software (version 4.3.0). The 'metabin' function was employed for computing the pooled effect sizes. The χ^2 test was used to evaluate the heterogeneity among the included literature and if there was no significant heterogeneity ($I^2<50\%$ and $P>0.05$), a fixed-effects model was selected for analysis; conversely, a random-effects model was selected. Forest plots were generated using the 'forest' function in R. The combined odds ratio (OR) and 95% CI were used as the effect size to evaluate the relationship between the ANP-T2238C polymorphism and susceptibility to cardiovascular and cerebrovascular diseases. Sensitivity analysis was performed using the 'metainf' function. Egger's linear regression test was applied to assess the publication bias of the included literature. Funnel plots related to publication bias were created using the 'funnel' function. In the subgroup analysis, studies were categorized according to quality assessment score by NOS, year, region, sample size and underlying disease. Subgroup analysis was performed by specifying the parameter of 'subgroup' within the 'metabin' function. Meta-regression analysis was used to explore potential heterogeneity in variables using the 'metareg' function in R software.

Results

Characteristics of the included studies. Initially, 436 and 15 documents were retrieved from the databases and citation lists, respectively. Subsequently, 254 duplicate records were excluded. After reviewing the titles and abstracts of the documents, and further reading of the full text, 12 documents (8,11,13,16-24) including 45,619 patients were finally included in the present meta-analysis (Fig. S1). The quality evaluation results showed that all 12 included studies had a relatively good quality with an NOS score ≥6. Two studies did not report available data to calculate the HWE, and five studies (13,17,19,21,23) met the HWE. Details of the studies are provided in Table I.

Meta-analysis results for all studies. The allele model results (C vs. T) showed that minor allele C was a significant risk factor for myocardial infarction (OR=2.55, 95% CI=1.47-4.43, $P<0.001$; Fig. S2), while other pooled outcomes were not statistically significant. The homozygote model and heterozygote model results (CC vs. TT; Fig. S3; CT vs. TT; Fig. S4) showed no statistically significant results for any of the pooled outcomes. The dominant model results (CC+CT vs. TT) showed that CC+CT was a significant risk factor for cerebrovascular events (OR=1.14, 95% CI=1.04-1.25, P=0.005; Fig. S5). The

Table I. Characteristics of included studies.

First author	Year	Study location	Sample size	Basic disease	HWE test P-value	NOS score	Study outcome	(Refs.)
Gruchala	2003	Poland	847	Coronary heart disease	<0.001	8	Composite CVE	(16)
Rubattu	2004	Italy	442	Ischemic stroke	0.922	7	Composite CVE, cerebrovascular event	(17)
Zhang	2006	China	323	Coronary heart disease	<0.001	6	Composite CVE, coronary heart disease	(18)
Lynch	2008	US and Canada	38,428	Hypertension	<0.001	7	Composite CVE, cerebrovascular event, coronary heart disease, death	(11)
Larifla	2012	France	218	Coronary heart disease	NA	6	Composite CVE, coronary heart disease	(8)
Barbato	2012	Belgium	1,397	Coronary heart disease	0.33	8	Composite CVE, coronary heart disease, death, myocardial infarction	(19)
Cannone	2013	US	1,623	None	NA	8	Composite CVE, atrial fibrillation, cerebrovascular event, coronary heart disease, death, myocardial infarction	(20)
Francia	2013	Italy	336	Atrial fibrillation	0.409	6	Composite CVE, atrial fibrillation	(21)
Ziaee	2014	Iran	866	Coronary heart disease	0.004	7	Composite CVE, coronary heart disease	(22)
Rubattu	2016	Italy	379	None	0.16	6	Composite CVE, myocardial infarction	(23)
Siebert	2017	Poland	203	Coronary heart disease	<0.001	6	Composite CVE, atrial fibrillation	(24)
Pastori	2021	Italy	557	Atrial fibrillation	0.1	7	Composite CVE	(13)

HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; CVE, cardio-cerebrovascular events.

recessive model results of CC vs. CT+TT showed that genotype CC tended to be a risk factor for composite CVE but with a non-significant P-value (OR=1.40, 95% CI=0.96-2.04, P=0.081; Fig. S6). The over-dominant model results of CT vs. TT+CC showed no statistically significant results for any of the pooled outcomes, as presented in Fig. S7. Table SI summarizes the specific data for the above results.

Meta-analysis results for studies fulfilling the HWE. As presented in Table I, five studies met the HWE. Given that most studies did not fulfill the HWE, it was suitable to analyze these 5 papers that met the HWE. The specific results were as follows. The allele model results for C vs. T showed no statistically significant results for pooled OR with more than one available study (Fig. S8). The homozygote model showed that CC was a significant risk factor for the composite CVE (OR=2.39, 95% CI=1.40-4.10, P=0.002), with no heterogeneity (I^2=0) (Fig. S9). The heterozygote model and dominant model (Figs. S10 and S11) showed no statistically significant pooled results. The recessive model showed that CC was a significant risk factor for composite CVE (OR=2.41, 95% CI=1.41-4.13, P=0.002) and without heterogeneity (I^2=0) (Fig. S12). The over-dominant model showed no statistically significant results regarding composite CVE, as presented in Fig. S13. Table SII summarizes the specific data for the above results.

Publication bias analysis. The dominant model of CC+CT vs. TT was selected for publication bias analysis. The choice of suitable variables for publication bias analysis was guided by the pragmatic consideration of having a sufficient number of studies for a robust analysis. The outcome of composite CVE had the highest number of reported studies compared to other outcomes, such as cerebrovascular events, coronary heart disease and mortality. Therefore, it was chosen to perform this analysis on the outcome of CVE, given the necessity for a substantial number of studies to effectively assess publication bias. As depicted in the funnel plot (Fig. S14), a slight asymmetry was observed among individual studies, suggesting a potential for publication bias. However, the P-value of Egger's test for publication bias was 0.436. This non-significant result indicates a lack of statistically significant publication bias. Therefore, these results suggest that there was no substantial publication bias that would significantly impact the validity of the results within this particular subset of outcomes.

Sensitivity analysis. Given the relatively limited number of studies included in the present meta-analysis, the potential fragility of these results should not be ignored. Therefore, the sensitivity analysis was conducted to further validate the findings. For the recessive model of the composite CVE outcome, the analysis was more stable, with two studies (11,16) excluded resulting in P<0.05. This suggests a potential association between the C allele vs. the T allele in the recessive model and the risk of cardiovascular events. However, it is important to note that the evidence presented in Fig. S15 remains inconclusive and further investigations are warranted.

In the 4 studies fulfilling the HWE, only the homozygote model and the recessive model exhibited statistical significance. Consequently, sensitivity analysis was performed for these models in 4 studies fulfilling the HWE. The results of the sensitivity analysis for the homozygote model (Fig. S16) and the recessive model (Fig. S17) demonstrated overall stability, with the majority of the outcomes maintaining statistical significance.

Subgroup analysis. Subgroup analysis in the recessive model was performed for the composite CVE outcome. The subgroup analysis included the following categories: NOS score (Fig. S18), year (Fig. S19), study region (Fig. S20), sample size (Fig. S21) and underlying disease (Fig. S22). The results of the pooled subgroup analysis suggest that publication year appears to be a source of heterogeneity.

Meta-regression. Meta-regression in the recessive model was performed for the composite CVE outcome. After adjusting the factors in Table II, the heterogeneity of the study (I^2) could be reduced to 31.61% (P=0.2266), and the P-value for the study location of Europe was 0.016, indicating that study location could be one of the sources of heterogeneity.

Discussion

The level of ANP is closely related to vasodilation and the development of heart failure; it is an important indicator for the diagnosis of cardiovascular diseases (1,2,7). Human ANP consists of 28 amino acids, mainly in α, β and γ forms, of which α-ANP is the main form and the most active (1,2,7). ANP is mainly generated in atrial muscle cells and stored in the secretory granules near the Golgi apparatus in the form of pro-ANP (4,25,26). When stimulated, it is released and processed through proteolysis, becoming a peptide hormone with 24 to 28 amino acids in the blood circulation (4,25,26). ANP is involved in a variety of physiological activities in the human body and has multiple biological effects, including natriuresis and cardiovascular diastole- and blood pressure-lowering properties, thus having an important role in maintaining cardiovascular homeostasis (26). There is increasing evidence that ANP can modulate the process of myocardiogenesis and development (27,28). Genetic variants of ANP genes or elevated serum ANP levels can inhibit vascular endothelial cell growth and promote endothelial cell apoptosis *in vivo* (29-31). Therefore, variation in ANP genotype shows altered biological function and thus affects the development of cardiovascular diseases, such as ischemic stroke, heart failure and chronic pulmonary heart disease (19,32-34).

In the present meta-analysis, the relationship of ANP gene polymorphisms with the occurrence of cardiovascular diseases was evaluated, and 12 studies were included (8,11,13,16-24). The results of the analysis showed that the ANP 2238T/C polymorphism was significantly associated with the occurrence of myocardial infarction, cerebrovascular events and the composite CVE outcomes, while the ANP 2238T/C polymorphism was not associated with the risk of other cardiovascular events (e.g., atrial fibrillation or coronary artery disease). Given the number of studies included in the present meta-analysis, the potential fragility of these results should be considered. The composite outcome of all CVE was associated with a relatively robust number of studies, thus the publication bias and sensitivity

Table II. Meta-regression results of all cardiovascular events analysis based on different characteristics.

Study characteristic	Estimate	SE	P-value
NOS score			
6 (Ref.)			
7	0.489	1.113	0.660
8	-0.58	1.213	0.630
Publication year			
2012 and earlier (Ref.)			
2013 and after	-0.586	0.811	0.470
Study region			
North America (Ref.)			
Asia	1.463	1.568	0.350
Europe	1.513	0.63	0.016
Basic disease			
Ischemic stroke (Ref.)			
Coronary heart disease	-0.392	1.278	0.759

SE, standard error; NOS, Newcastle-Ottawa scale.

analyses were performed for the outcome of composite CVE outcome. The publication bias and sensitivity analysis results overall demonstrated robustness in the present findings. In the sensitivity analysis, the exclusion of two studies in the recessive model for CVE revealed statistically significant differences, underscoring the substantial impact of the ANP T2238C gene polymorphism on CVE risk. Furthermore, sensitivity analyses performed on studies meeting the HWE for both recessive and homozygote models of CVE consistently showed robust results with odds ratios well above 1, further supporting the significant influence of the ANP T2238C gene polymorphism on CVE. These results highlight the importance of future research to delve deeper into the relationship between ANP T2238C gene polymorphism and cardiovascular diseases, and to elucidate the underlying mechanisms and potential clinical implications.

Although the exact functions and mechanisms of ANP genes in the development and progression of cardiovascular diseases are not fully understood, the most likely explanation at present is that alterations in ANP genotypes may alter their functions in regulating water and electrolyte homeostasis, stabilizing the cardiovascular and cerebrovascular internal environment and regulating endothelial cell proliferation. Previous studies have shown that mutant ANP is involved in vascular endothelial cell injury and dysfunction, and can increase individual susceptibility to ischemia, particularly in relation to the occurrence of cerebrovascular events, suggesting that changes in serum ANP may be an aspect of the complex pathophysiological changes in ischemic diseases.

Atrial fibrillation remains a clinical challenge, with its pathogenic mechanisms not fully elucidated. The genetic susceptibility of atrial fibrillation has been confirmed in previous studies (35). Compelling evidence suggests that the continuous low-dose infusion of ANP during cardiac surgery may reduce central venous pressure, the systemic vascular resistance index and the pulmonary vascular resistance index. Furthermore, compared to patients not receiving ANP infusion, lower levels of renin, angiotensin II, aldosterone and pleural effusion were observed in those who did receive ANP infusion (36). Since pleural effusion and atrial fluid overload are considered contributing factors to postoperative atrial fibrillation, these observations may indicate a potential role of ANP in the pathogenesis of arrhythmias. On the other hand, a previous report has demonstrated a relationship between ANP gene polymorphism and a history of supraventricular tachycardia in patients with dilated cardiomyopathy (37). However, inconsistent results have been reported by studies (21,24) investigating the significant association between ANP gene polymorphism and atrial fibrillation. It is important to note that the impact of ANP on atrial fibrillation may not be direct but rather exerted through indirect pathways, as demonstrated by the aforementioned observations. This indirect influence on arrhythmia occurrence may contribute to the difficulty in observing significant differences, necessitating validation through long-term cohort studies.

The rs5065 variant has been identified to lead to the translation of modified ANP peptides. The latter has been proven to diminish the vitality, proliferation and tube formation of endothelial cells *in vitro*, while also regulating common mechanisms associated with the transition from stable to unstable plaques. Elevated levels of myeloperoxidase, a biomarker linked to plaque vulnerability, were observed in carriers of the rs5065 minor allele, corroborating previous *in vitro* evidence of dysfunctional peptides. A few studies have reported an increased risk of coronary artery disease in carriers of the rs5065 minor allele. In the present meta-analysis, while a significantly substantial impact of ANP gene polymorphism on coronary artery disease was not discerned, it is imperative to highlight the pivotal influence of the study by Lynch *et al* (11) on the overall outcomes. Their study, encompassing a vast cohort of 38,462 individuals, significantly outweighs other studies included in the present meta-analysis regarding coronary artery disease outcome. This substantial weightage may have contributed to the lack of statistical significance in the synthesized results. Furthermore, the variability in antihypertensive medications administered to different patients in the study by Lynch *et al* (11) raises uncertainty about its potential influence on the occurrence of coronary artery disease, warranting further investigation. It is also noteworthy that other studies have reported, to varying extents, the role of ANP gene polymorphism in affecting the risk of CAD. The inconsistent findings across studies underscore the complexity of the relationship between ANP gene variants and coronary artery disease susceptibility. Future research should aim to elucidate the underlying mechanisms and consider factors such as medication heterogeneity to provide a more nuanced understanding of the impact of ANP gene polymorphism on CAD risk.

The current study on the genetic polymorphism of ANP T2283C has preliminarily indicated that the minor allele of ANP rs5065 is associated with varying degrees of risk for certain cardiovascular and cerebrovascular diseases. However, the understanding of this gene polymorphism remains relatively limited, and thus, the definitive biological significance

of which genotype is more crucial for the phenotype of the diseases has yet to be clarified. In addition, it is imperative to consider that the same genotype may have different roles in different diseases. For instance, the CT genotype may tend to be a risk factor in cerebrovascular events, while in studies meeting the HWE, it may act as a protective factor on composite CVE outcome. This raises intriguing questions that warrant investigation in the future.

The present study has certain limitations. First, the included primary literature only involved European, Asian and North American populations, but no other populations (e.g., African). Furthermore, the present study has flaws, such as heterogeneity and unbalanced HWE in several studies. Lastly, for some comparisons, only one study presented suitable data; thus, data synthesis was not available. Yet we still include these comparisons in the forest plot in the figures to fully provide the current evidence.

In conclusion, the results of the current meta-analysis suggest that the ANP 2238T/C mutation increases the risk of myocardial infarction, cerebrovascular events and composite CVE outcomes. Further large-scale studies are needed to further confirm the findings of this study.

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Availability of data and materials

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

Authors' contributions

Conception and design: JW, YY and MZ. Literature search and selection: JW, YY, LZ, MZ and MW. Collection and assembly of data: JW, YY and MZ. Data analysis and interpretation: JW, YY and MZ. Checking and confirmation of the authenticity of the raw data: JW and YY. Manuscript writing: All authors. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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