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PHYSIOLOGICAL REGULATION OF ANGIOTENSIN CONVERTING ENZYME GENE POLYMORPHISM IN CARDIOVASCULAR DISEASE

Midhun T M¹, P Punita², Jeyapal V³, N Muninathan⁴, Sinha Mathew¹, Sony Peter¹,
Reshma Gopan M¹, Swathi T¹, Harisree P H¹, Jisha A M¹, Bonny Benny¹, Dinesh Roy D⁵

¹Research Scholar, Meenakshi Academy of Higher Education and Research (MAHER- Deemed to be University), West K.K Nagar, Chennai, Tamil Nadu, India.

²Professor, Department of Physiology, Meenakshi Medical College Hospital and Research Institute, Kanchipuram, Tamil Nadu, India.

³Chairman and Senior Cardiologist, Hridayala Heart and Robotic Research Centre pvt-Ltd., Thiruvananthapuram, Kerala, India.

⁴Scientist, Central Research Laboratory, Meenakshi Medical College Hospital & Research Institute, Kanchipuram, Tamil Nadu, India.

⁵CEO & Senior Cytogeneticist, Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala, India.

***Corresponding Authors:** Dr. P Punita & Dr. Dinesh Roy D

E-mail: punithap@mmchri.ac.in & drdineshroyd@gmail.com

Phone No: 9884054169 & 9447074202

Orcid ID: 0000-0002-5692-5403 & 0009-0005-7124-148X

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Abstract

Cardiovascular disease (CVD) is a significant global health concern shaped by genetic, environmental, and lifestyle factors. The ACE gene, particularly its I/D polymorphism, impacts ACE activity and the RAAS system. This gene influences blood pressure, fluid balance, and vascular function by modulating angiotensin II levels, a crucial peptide in cardiovascular regulation and disease. This review explores the physiological implications of ACE gene polymorphisms, focusing on how they influence cardiovascular risk through modulation of RAAS activity. By examining the genetic basis and functional outcomes of these polymorphisms, this review aims to shed light on their contribution to CVD development and progression, highlighting potential avenues for targeted therapies and risk management strategies.

Keywords: Angiotensin converting enzyme, Cardiovascular disease, ACE inhibitors, Coronary Artery Disease.

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity worldwide, posing a significant public health challenge [1]. CVD encompasses a broad spectrum of conditions, including coronary artery disease, heart failure, stroke, and hypertension, which affect the heart and blood vessels. Extensive research over the years has identified several key risk factors contributing to the development of CVD. These risk factors include elevated low-density lipoprotein (LDL) cholesterol, smoking, high blood pressure, diabetes, abdominal obesity, psychosocial stress, inadequate consumption of fruits and vegetables, excessive alcohol intake, and physical inactivity [2]. While these traditional risk factors are well-established, the etiology of CVDs is complex, involving the interplay of genetic predispositions, environmental influences, and lifestyle choices [3]. ACE gene polymorphisms have been widely researched for their impact on cardiovascular risk.

The ACE gene is crucial to the RAAS, which regulates blood pressure, fluid balance, and vascular tone [4]. In this system, renin converts angiotensinogen to angiotensin I, which ACE then converts to angiotensin II. Angiotensin II regulates cardiovascular function through vasoconstriction, sodium retention, and cell growth promotion [5,6]. Altered ACE activity and RAAS dysregulation have been associated with various cardiovascular conditions, highlighting ACE's role in cardiovascular health.

The ACE gene has a notable I/D polymorphism that influences circulating ACE levels and RAAS activity. The D allele is linked to higher ACE levels, increasing cardiovascular risk through vasoconstriction and inflammation, while the I allele is associated with lower ACE activity, potentially improving endothelial function and reducing vascular resistance [7,8]. This genetic variation has a significant impact on the physiological regulation of blood pressure and the risk of developing CVD, making it a critical area of research in understanding the genetic basis of cardiovascular health.

Studying ACE gene polymorphisms is vital for understanding their role in cardiovascular disease risk and progression. Recent research highlights the need to explore molecular mechanisms regulating ACE expression to develop targeted CVD prevention and management strategies. This review examines ACE gene polymorphic role in cardiovascular disease, focusing on their physiological regulation and impact on disease development. It explores genetic mechanisms to suggest new strategies for managing cardiovascular risk and improving outcomes.

METHODS

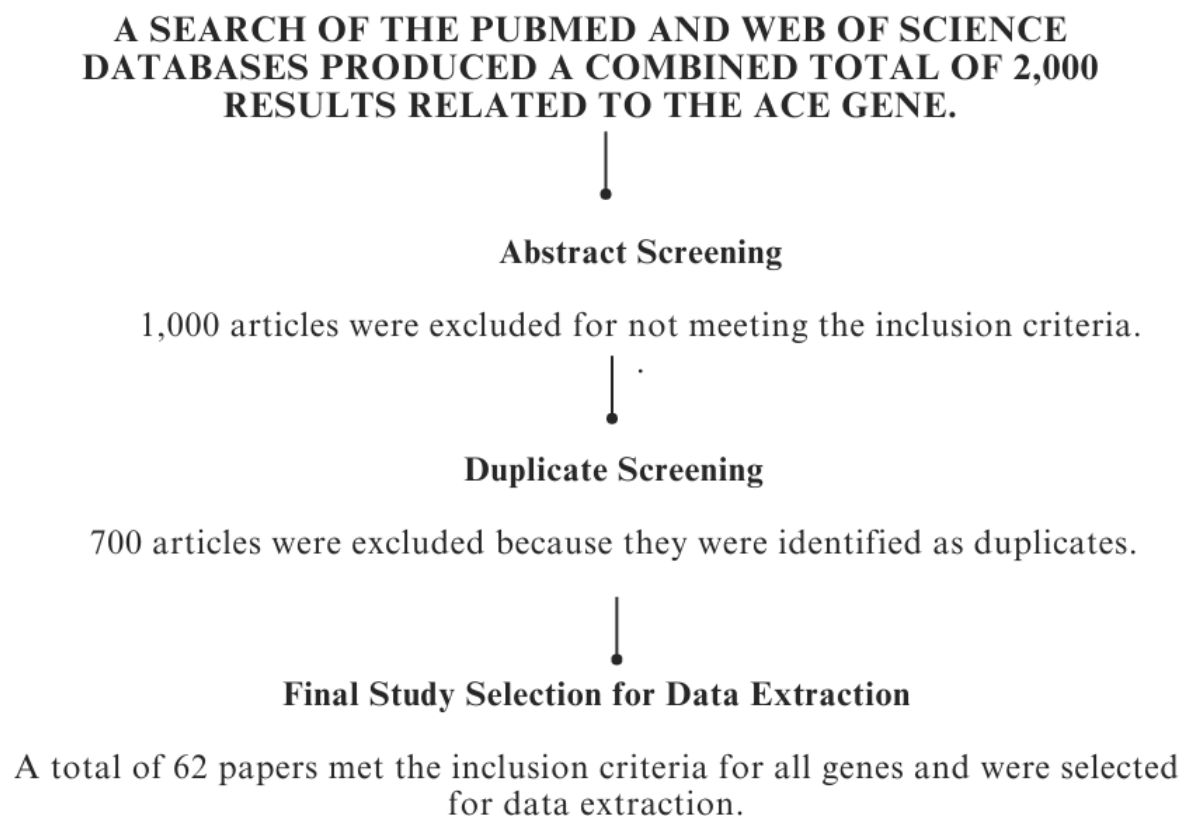


Figure 1: Methodology for Study Selection on ACE Gene

Angiotensin Converting Enzyme (ACE)

Angiotensin-Converting Enzyme (ACE) is crucial in the renin-angiotensin system, converting angiotensin I to II and degrading bradykinin, and works with renin to regulate blood pressure and electrolyte balance [9]. ACE activity in mammals is typically evaluated by measuring substrate cleavage reduction in the presence of specific inhibitors like captopril and lisinopril [10].

Structure

The human ACE gene, located on chromosome 17q23, spans 21 kilo bases and comprises 26 exons. It produces two isoforms: somatic ACE (sACE) and germinal ACE (gACE) [10]. sACE, found in somatic tissues, consists of 1,306 amino acids and has two active sites due to a tandem duplication. gACE, present in male testes, is shorter

(732 residues) with a single active site. These isoforms are produced from different promoters: sACE is transcribed from an upstream promoter, while gACE is transcribed from a promoter within intron 12 [11].

Both isoforms share a common C-terminal transmembrane domain and an N-terminal signal peptide. Differences in chloride ion dependence and inhibitor affinities distinguish the domains of sACE [12]. ACE homologues with similar activities are found across species, though the double-domain form is unique to vertebrates. In humans, ACE2, a homologue of ACE, acts as a carboxypeptidase with a distinct substrate spectrum, unaffected by typical ACE inhibitors [13,14]. Non-vertebrate ACE-like proteins are extracellular, soluble, and lack the transmembrane anchor, suggesting diverse functions beyond peptidase activity.

Function

ACE (Angiotensin-Converting Enzyme) converts angiotensin I to II by cleaving a dipeptide from the C-terminus and degrades bradykinin, functioning as an endopeptidase in the mammalian renin-angiotensin system (RAS). However, its function is more complex in other species. Some species, such as *Drosophila melanogaster*, lack a recognizable RAS but still exhibit similar enzyme activity, highlighting ACE's diverse roles beyond the mammalian context [15]. In *Drosophila melanogaster*, for instance, ACE efficiently processes bioactive peptides like tachykinins [16,17].

Knockout studies further reveal the diverse roles of ACE. Complete knockouts result in reduced male fertility, spontaneous hypotension, and kidney malformations, with the severity of these effects varying across studies [18,19]. The testicular isozyme (gACE), which is expressed exclusively in sperm, is specifically associated with fertility, emphasizing its distinct role [20]. Moreover, experiments that disrupted the ACE gene to express only the N-domain form prevented the severe kidney abnormalities seen in full knockouts, underscoring the functional specificity of ACE's domains [18].

In another study, replacing the ACE gene promoter with an albumin promoter shifted ACE expression from the endothelium to the liver. Despite this change, genetically modified mice maintained normal blood pressure and kidney function, suggesting that the extracellular localization of ACE is not essential for maintaining basal physiological control [21]. Corvol P et al. proposed that variations in phenotypes observed in such studies could result from the C-domain's specific affinity for hydrolyzing angiotensin I and bradykinin. Additionally, the N-domain of ACE may have roles beyond the RAS, particularly in processing bioactive peptides like Ac-SDKP, which is crucial for regulating hematopoietic stem cell recruitment. These findings highlight the importance of ACE in peptide hormone regulation [22]. Coates D et al. showed that *Drosophila melanogaster* gene products (Acer and Ance), corresponding to the N- and C-domains of mammalian sACE, likely have distinct functions in vivo [23].

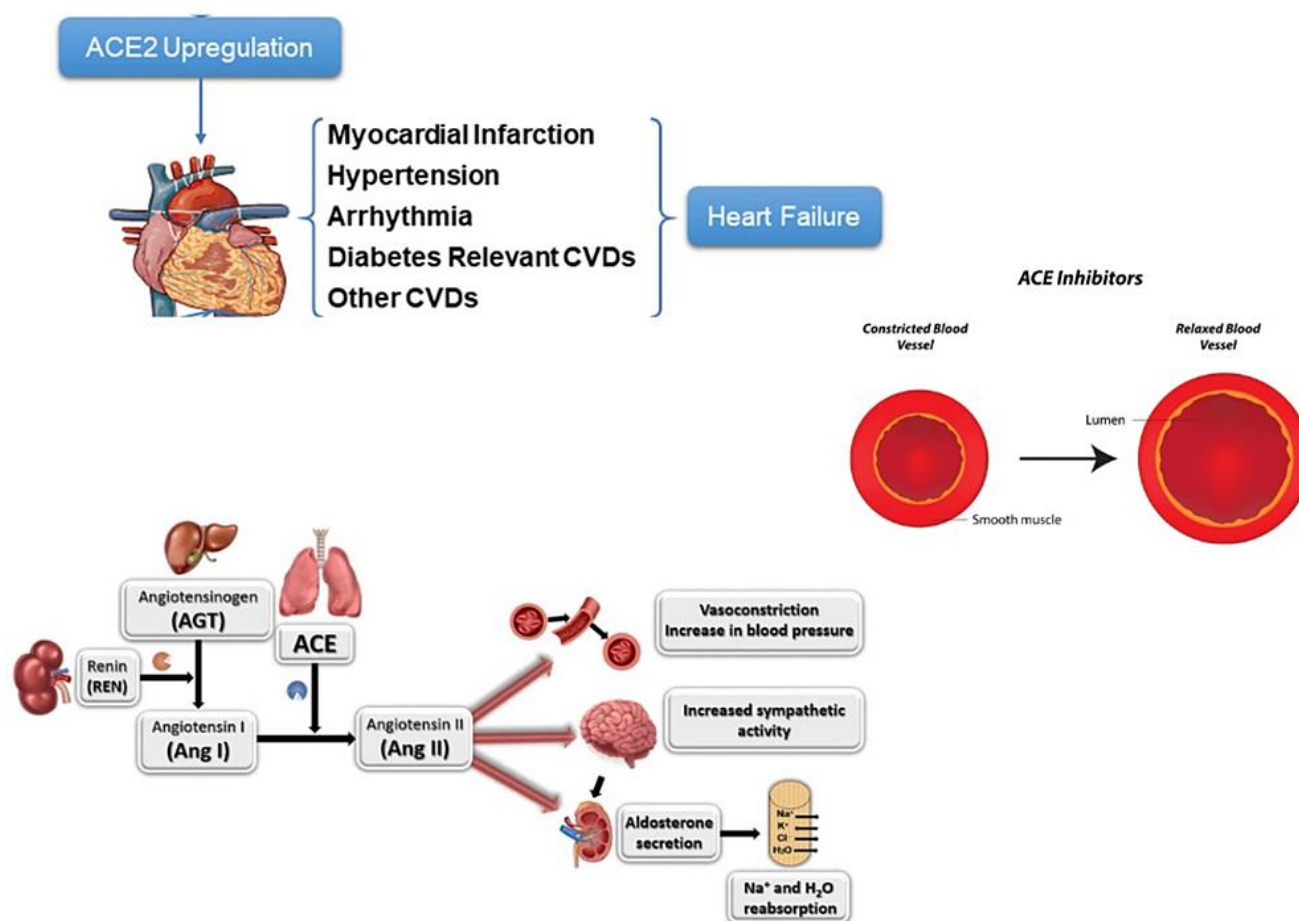


Figure 2: Angiotensin Converting Enzyme and Cardiovascular Disease

Physiological Role of the ACE Gene

Somatic Angiotensin-Converting Enzyme (sACE) is crucial for blood pressure and fluid balance regulation [24]. The systemic RAS controls blood pressure and salt balance, while the local RAS affects tissue growth, remodeling, and inflammation [25]. Angiotensin II (Ang II), by binding to the AT1 receptor, activates a range of signaling pathways in various organs, including the heart, blood vessels, kidneys, and brain, which leads to both normal and abnormal effects associated with the RAS [26]. Due to its broad substrate specificity and extensive presence in tissues, ACE influences many biological processes [27]. Lambert et al. highlighted that ACE2, highly expressed in the heart and involved in hydrolyzing angiotensin peptides, is crucial for cardiovascular health [28]. Le et al. noted that ACE inhibitors, as dipeptidyl carboxylases (EC 3.4.15.1), lower blood pressure by affecting the renin-angiotensin system [29].

ACE Gene Polymorphisms and their Variants

Niu et al. and Al-Harbi et al. studied the 287-base pair I/D polymorphism in intron 16 of the ACE gene, which results in DD, II, and ID genotypes and is associated with serum ACE activity and cardiovascular conditions

[30,31]. It has been linked to factors such as overweight, obesity, and blood pressure regulation [32]. Differences in ACE activity associated with this polymorphism are related to susceptibility to cardiovascular diseases like hypertension, heart failure, and myocardial infarction. Rigat et al. showed that the I/D polymorphism accounts for about 47% of the variability in serum ACE levels, underscoring its importance in ACE concentration [33].

Mechanisms of ACE Gene Regulation

ACE gene expression is shaped by genetic, epigenetic, and environmental factors. The key genetic factor is the 287 bp I/D polymorphism in intron 16, resulting in II, DD, and ID genotypes [34]. Epigenetic mechanisms also play a key role in regulating ACE expression. Somatic ACE levels are affected by CpG methylation and histone deacetylation. The methylation pattern of the ACE-1 gene promoter is specific to cell type and correlates with the transcription of sACE [35]. For ACE2, epigenetic regulation includes DNA methylation, histone modifications, and micro-RNAs (miRNAs) that influence gene expression [36]. For example, miRNAs like hsa-miR-125a-5p and the miR-200 family regulate ACE2 by targeting its 3' untranslated region. Additionally, histone demethylation, particularly H3K4me3 demethylation controlled by KDM5B, affects ACE2 transcript levels and miR-125a expression [37].

Environmental factors also impact ACE2 regulation. Exposure to toxicants, certain drugs, and hypoxia can alter ACE2 expression [38]. Reducing dietary salt intake modestly has been shown to lower cardiovascular event rates significantly [39]. Local RAS activation, especially in aldosterone-induced hypertension, can increase oxidative stress in the vasculature through the induction of p47phox, a crucial component of NAD(P)H oxidase [40]. Regular physical activity positively affects ACE levels, which may reduce cardiovascular disease risk. Together, these factors regulate ACE gene expression and activity, impacting cardiovascular health and susceptibility to disease.

ACE Gene Polymorphism and Cardiovascular Diseases (CVDs)

Polymorphisms in the ACE gene, especially the 287 bp insertion/deletion (I/D) polymorphism, have been widely studied for their associations with various cardiovascular conditions. This polymorphism produces three genotypes: insertion homozygote (II), deletion homozygote (DD), and heterozygote (ID). These genotypes correlate with different levels of ACE activity, which can affect cardiovascular disease susceptibility.

Hypertension: He et al. and Eisenmann et al. link the DD genotype of the ACE gene to higher hypertension and cardiovascular risks due to elevated plasma ACE activity, with DD associated with more hypertension than II [41,42].

Myocardial Infarction: Tran Cong et al. found that the ACE I/D polymorphism influences coronary artery disease severity in AMI patients, with the DD genotype linked to more severe disease. The ACE I/D polymorphism influences ACE activity, with individuals carrying the D/D genotype showing increased levels of

both plasma and myocardial ACE activity [43]. Elevated ACE activity contributes to greater plaque vulnerability, ulceration, and thrombosis, which are linked to myocardial infarction [44,45]. Clinical evidence indicates that individuals with the DD genotype have a higher likelihood of experiencing myocardial infarction compared to those with the II genotype.

Heart Failure: ACE gene polymorphisms are also associated with heart failure (HF). Several studies have demonstrated a link between ACE gene variations and a heightened risk of HF, even among those with otherwise low risk factors [46]. The DD genotype leads to worse heart failure outcomes due to higher ACE activity and angiotensin II, but isn't significantly linked to ischemic heart failure or dilated cardiomyopathy [47]. Overall, DD genotype individuals have more severe heart failure compared to those with the II genotype [48].

Evidence from Studies: Da Agostini et al. link the ACE I/D polymorphism to cardiovascular risk factors like high blood pressure, coronary heart disease, and myocardial infarction, highlighting its role in disease susceptibility [49].

Table No 1: Association of ACE Gene Polymorphisms with Cardiovascular Diseases

Condition	ACE I/D Polymorphism Association	Key Findings
Hypertension	DD genotype linked to increased risk	Higher ACE activity and prevalence in DD genotype [41,42].
Myocardial Infarction	DD genotype associated with severe coronary artery disease	Higher ACE activity in DD linked to greater plaque vulnerability [43,44,45].
Heart Failure	DD genotype linked to worse outcomes	Associated with cardiac hypertrophy and poorer survival rates; no significant link with ischemic heart failure [46,47,48].

Pathophysiological Mechanisms Involving ACE Gene Polymorphisms

ACE Gene Variants and Atherosclerosis

The ACE gene, which exhibits insertion (I) and deletion (D) polymorphisms, plays a significant role in regulating ACE enzyme activity and thus influences cardiovascular health. Notably, the D allele is associated with a higher risk of cardiovascular diseases due to its link with increased ACE levels and enhanced angiotensin II production, which contribute to vasoconstriction and endothelial dysfunction. Individuals carrying the D allele are more prone

to increased plaque formation and instability within arterial walls, elevating their risk for atherosclerotic cardiovascular diseases [50]. In contrast, the I allele correlates with lower ACE levels in the plasma, which may reduce vasoconstriction in skeletal muscles [10].

ACE Gene Variants and Endothelial Dysfunction

Polymorphisms in the ACE gene are closely linked to endothelial dysfunction, a critical factor in cardiovascular disease development. Tanriverdi et al. and Kuzubova et al. indicate that patients with the DI or II genotypes have a lower incidence of endothelial dysfunction compared to those with the DD genotype [52,53]. The DD genotype is characterized by elevated ACE activity and higher angiotensin II levels, which can impair the function of endothelial nitric oxide synthase (eNOS), reducing the availability of nitric oxide and weakening vasodilation [7]. Moreover, angiotensin II acts through the AT1 receptor to activate protein phosphatase 2A (PP2A), which further decreases eNOS phosphorylation and nitric oxide production, contributing to endothelial dysfunction [55]. Increased ACE activity also heightens oxidative stress and inflammation, leading to further endothelial injury and dysfunction.

ACE and Inflammation Related to Cardiovascular Disease (CVD)

The ACE gene plays a key role in inflammation and oxidative stress, which are critical to cardiovascular disease progression. Angiotensin II (AngII), through its AT1 and AT2 receptors, regulates inflammatory and fibrotic processes, with the AT1 receptor mediating most of AngII's pro-inflammatory effects [56]. For example, AT1 receptor activation promotes the expression of profibrotic factors like connective tissue growth factor (CTGF) and aids in the recruitment of inflammatory cells [7]. AngII binding to the AT1 receptor boosts NADPH oxidase activity, raising ROS levels and worsening endothelial dysfunction [57]. Angiotensin receptor blockers (ARBs) reduce ROS and C-reactive protein levels, increase inhibitory I κ B expression, and may benefit acute coronary syndromes and type II diabetes by improving insulin sensitivity [58].

Clinical Implications and Potential Biomarker Use

Potential Use of ACE Gene Polymorphisms as Biomarkers for CVD Risk Assessment and Prognosis

The ACE gene deletion polymorphism (I/D) has been identified as a significant factor in cardiovascular disease risk [59]. This polymorphism influences plasma ACE activity and could serve as a genetic marker to identify individuals at higher risk for CVD, allowing for early intervention and tailored management strategies [60].

Implications for Personalized Treatment Strategies Based on ACE Genotype

Understanding ACE genotype can guide personalized treatment strategies for CVD. While ACE inhibitors are typically the first-line treatment, and ARBs are also used, combining these therapies has not shown significant

benefits in clinical trials. However, novel RAAS modulation strategies offer potential advancements [61]. The response to ACE inhibitors and ARBs may vary based on ACE genotype, with II or DI genotypes potentially requiring alternative approaches. ACE inhibitor exposure can increase angiotensin II responsiveness, while ARB exposure can decrease it, influencing patient selection and dosing [62]. Personalized treatment based on ACE genotype could enhance clinical outcomes and reduce adverse effects.

Potential for New Therapeutic Targets or Interventions

Identifying ACE gene polymorphisms in CVD highlights opportunities for targeted risk assessment and treatment. Modulating ACE activity and targeting related inflammation and oxidative stress could effectively reduce cardiovascular disease risk.

Conclusion

ACE gene polymorphisms, especially the I/D variant, are crucial in cardiovascular disease susceptibility and progression. The D allele is associated with increased ACE activity, elevated angiotensin II levels, and heightened cardiovascular risk, while the I allele is linked to reduced ACE activity and potentially protective effects. Understanding these genetic variations offers significant potential for personalized medicine, allowing for targeted risk assessment and tailored therapeutic strategies. By identifying individuals at higher risk through ACE genotyping and exploring novel RAAS modulation approaches, clinicians can improve treatment outcomes and mitigate adverse effects. Further research into the molecular mechanisms of ACE regulation and its impact on cardiovascular health will enhance our ability to develop effective interventions and advance personalized care for CVD.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interests.

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