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Review Article

The Gene Polymorphism of Angiotensin-Converting Enzyme Intron Deletion and Angiotensin-Converting Enzyme G2350A in Patients With Left Ventricular Hypertrophy: A Meta-analysis

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ABSTRACT

Objectives: The aim of the study was to evaluate the correlation between left ventricular hypertrophy and the gene polymorphism of angiotensin-converting enzyme (ACE) intron deletion (I/D) and ACE G2350A.

Methods: Information related to the sample size and genotype frequencies was extracted from each study.

Results: Our results found that the D allele ($p = 0.0180$) and DD genotype ($p = 0.0110$) of ACE I/D had a significant association with increasing the risk of left ventricular hypertrophy, whereas the I allele ($p = 0.0180$), but not II ($p = 0.1660$) and ID genotypes ($p = 0.1430$), was associated with decreasing the risk of left ventricular hypertrophy. On other hand, we found that the A allele ($p = 0.0020$) and GA genotype of ACE G2350A ($p = 0.0070$) had the correlation with increasing the risk of left ventricular hypertrophy.

Conclusions: Our meta-analysis reveals that the D allele of ACE I/D and the A allele of ACE G2350A are associated with increasing the risk of left ventricular hypertrophy.

1. Introduction

Left ventricular hypertrophy, described as pathological changes in the cardiac structure,[1] has been widely reported to cause several fatal complications such as heart failure,[2] coronary artery disease,[3] peripheral arterial disease,[4] mitral regurgitation,[5] and stroke.[6] Therefore, because of the associated widely fatal complication, this pathological state may contribute to the increasing health cost expenditure. To anticipate the worsening of this condition, a comprehensive understanding regarding left ventricular hypertrophy pathogenesis including genetic levels is crucial for the development of an advanced concept especially in the genetic model. In the pathogenesis of left ventricular hypertrophy, it has been globally known that the renin-angiotensin-aldosterone system (RAAS) has a pivotal role in the development of the disease. Moreover, in the RAAS, angiotensin-converting enzyme (ACE) is known to have a central role in influencing several RAAS-associated conditions including left ventricular hypertrophy.[7]

In the development of left ventricular hypertrophy, cardiac remodeling is triggered by several pathways including increasing oxidative stress and rapid pressure, recapitulation of myosin gene expression, and sodium retention. These pathways are governed by ACE through angiotensin II and aldosterone.[7] Moreover, regulation of ACE has been shown to affect several cardiovascular diseases such as hypertension, vascular hypertrophy, and ventricle hypertrophy.[1] On the other hand, previous studies have revealed that the ACE serum level and ACE activity are governed by gene polymorphism of ACE intron deletion (I/D) and ACE

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G2350A.[8–15] Until now, several studies have been conducted to evaluate the correlation between the gene polymorphism (ACE I/D and ACE G2350A) and left ventricular hypertrophy.[16–33] However, conflicting results were found in those previous studies. Therefore, our present study aimed to perform a meta-analysis concerning the association between left ventricular hypertrophy and the polymorphism of ACE I/D and ACE G2350A.

2. Methods

2.1. Study designs

A meta-analysis was conducted from December 2018 to January 2019 to assess the correlation between left ventricular hypertrophy and both ACE I/D and ACE G2350A gene polymorphism. To achieve this purpose, several studies retrieved from PubMed and Embase were included for our analysis, and the pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using the fixed- or random-effect model. We adapted the meta-analysis design from our previous studies.[33–37]

2.2. Eligibility criteria

Published articles with the following criteria were included in our meta-analysis: (1) retrospective studies; (2) prospective studies; (3) cross-sectional studies; (4) randomized-controlled trials; (5) controlled before-and-after studies; (6) crossover studies; (7) evaluating the association between left ventricular hypertrophy and both ACE I/D and G2350A gene polymorphism; and (8) having sufficient data for calculation of the OR and 95% CI or data presented in the Hardy–Weinberg equilibrium as described by Rodriguez et al[38] ($\underline{X} < 3.84$ was considered in the Hardy–Weinberg equilibrium). But articles with the following criteria were excluded for the study: (1) an obvious irrelevant title and or abstract, (2) a review and or commentary, and (3) incomplete and/or ungeneralized data. All articles included in the study were evaluated for the quality in accordance with the Newcastle–Ottawa scale.[39]

2.3. Search strategy

We, with no language restrictions, systematically searched the published articles in PubMed and Embase using specified search terms to identify studies published up to January 10, 2019. For searching the articles, we used the combination of the following key words (left ventricular hypertrophy or LVH) and (angiotensin-converting enzyme intron deletion or ACE I/D) and (angiotensin-converting enzyme G2350A or ACE G2350A). We restricted the publication language to English.

2.4. Data extraction

To perform a comprehensive analysis, the following information was extracted from each study: (1) the name of first author; (2) the year of publication; (3) study design, (4) the sample size of patients with left ventricular hypertrophy and controls, (5) frequencies and the percent of genotypes and alleles of patients with left ventricular hypertrophy and controls, and (6) the country of origin. The genotype and allele frequencies were analyzed in both left ventricular hypertrophy and control groups.

2.5. Statistical analysis

We evaluated the correlation between left ventricular hypertrophy and the polymorphism of both ACE I/D and ACE G2350A genes by calculating pooled ORs and 95% CIs. We used a Z-test to determine the significance of pooled ORs ($p < 0.05$ was considered statistically significant); whereas to assess the heterogeneity, a Q-test was performed. If heterogeneity existed ($p < 0.10$), a random-effect model was used; otherwise, a fixed-effect model was used. Moreover, Egger's test was used to assess the publication bias ($p < 0.05$ was considered statistically significant). All analyses in our study were performed using Comprehensive Meta-Analysis (CMA, New Jersey, USA) version 2.1 and Review Manager (RevMan; Cochrane, London, UK) version 5.3.

3. Results

3.1. Eligible studies

Based on the searching strategy, a total of 680 and 889 articles regarding ACE I/D and ACE G2350A, respectively, were identified from PubMed and Embase. Of these, 1527 articles (654 articles concerning ACE I/D and 871 articles concerning ACE G2350A) were excluded because of irrelevant titles and/or abstracts. After reading the full texts, eight articles were excluded because of review; 14 articles were excluded because data were not presented in the Hardy–Weinberg equilibrium; and five articles were excluded because of unavailable full texts. Fig. 1 displays a flowchart demonstrating the inclusion or exclusion of studies. Finally, a total of 17 articles (ACE I/D = 13 articles and ACE G2350A = four articles) were included in the meta-analysis.

3.2. Quantitative data synthesis

For the association between ACE I/D gene polymorphism and left ventricular hypertrophy, a total of 13 articles consisting of 1219 cases and 3202 controls were included for the study. Overall, our result found that the D allele (D *vs*. I: OR = 1.26, 95% CI = 1.04–1.52, p = 0.0180) and DD genotype (DD *vs*. II+ID: OR = 1.43, 95% CI = 1.08–1.88, p = 0.0110) of ACE I/D had a significant association with increasing the risk of left ventricular hypertrophy, whereas the I allele (I *vs*. D: OR = 0.80, 95% CI = 0.66–0.96, p = 0.0180) was associated with decreasing the risk of left ventricular hypertrophy. For II (II *vs*. ID+DD: OR = 0.82, 95% CI = 0.61–1.09, p = 0.1660) and ID genotypes (ID *vs*. II+DD: OR = 0.84, 95% CI = 0.67–1.06, p = 0.1430), we did not find any association with left ventricular hypertrophy. The summary of ACE I/D polymorphism in left ventricular hypertrophy and control groups is described in Table 1 and Fig. 2.

For the association between ACE G2350A gene polymorphism and left ventricular hypertrophy, we collected four articles consisting of 546 cases and 538 controls. Of those, the A allele (A *vs*. G: OR = 1.67, 95% CI = 1.21–2.31, p = 0.0020) and GA genotype (GA *vs*. GG+AA: OR = 2.12, 95% CI = 1.22–3.67, p = 0.0070) had the correlation with increasing the risk of left ventricular hypertrophy, whereas the G allele (G *vs*. A: OR = 0.60, 95% CI = 0.43–0.82, p = 0.0020) and GG genotype (GG *vs*. GA+AA: OR = 0.36, 95% CI = 0.21–0.61, p < 0.0001) were associated with decreasing the risk of left ventricular hypertrophy. For the AA genotype (AA *vs*. GG+GA: OR = 1.23, 95% CI = 0.92–1.64, p = 0.1720), we failed to show the correlation. Table 2 and Fig. 3 describe the polymorphism of ACE G2350A in left ventricular hypertrophy and control groups.

In subgroup analysis, we also evaluated the correlation between these genes (ACE I/D and ACE G2350A) and left ventricular hypertrophy in the essential hypertension end point subgroup. For ACE I/D, we failed to confirm the association in all allele and genotype models, whereas for ACE G2350A, the association was observed in GG (GG *vs*. GA+AA: OR = 0.27, 95% CI = 0.20–0.36, p < 0.0001) and GA genotypes (GA *vs*. GG+AA: OR = 2.41, 95% CI = 1.36–4.28, p = 0.0030). The summary of the association of left

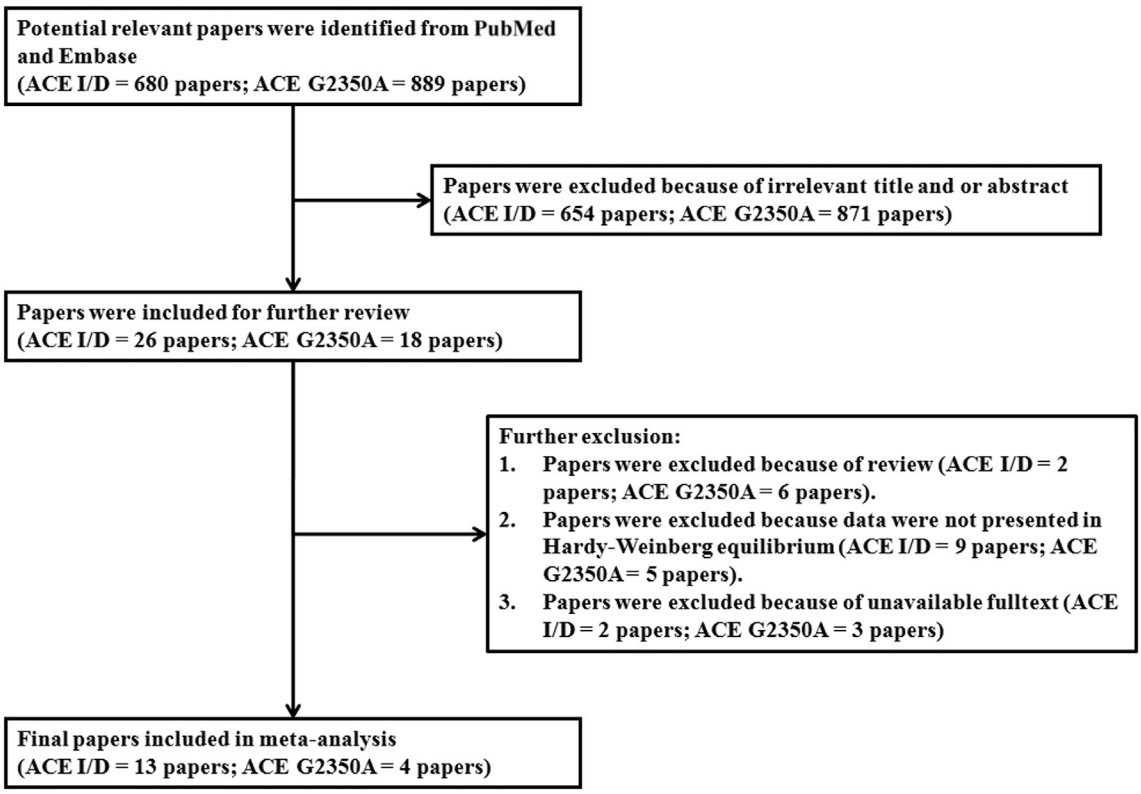

Fig. 1. A flowchart of inclusion and exclusion process in our study. ACE, angiotensin-converting enzyme; I/D, intron deletion.

Table 1
The frequency of the ACE I/D genotype in left ventricular hypertrophy and control groups.

Author and year	LVH				Control				Country	Genotyping	χ^2 for HWE	End point
	II	ID	DD	N	II	ID	DD	N				
Bahramali et al 2016	9	50	29	88	25	43	20	88	Iran	PCR	3.46	LVH with HF
Gharavi et al 1996	4	11	10	25	8	11	20	39	USA	PCR	0.11	LVH with EHT
Hernández et al 2003	0	13	19	32	3	18	8	29	Spain	PCR	2.08	LVH in athletes
Iwai et al 1994	20	23	13	56	34	31	7	72	Japan	PCR	1.53	LVH with HCM
Karaali et al 2004	3	9	15	27	12	29	26	67	Turkey	PCR	0.77	LVH with MI
Lindpaintner et al 1996	74	169	110	353	399	1074	613	2086	USA	PCR	0.37	LVH with EHT
Liu et al 2018	9	15	19	43	44	71	74	189	China	PCR	2.96	LVH with SCA
Lo'pez-Contreras et al 2000	7	28	25	60	3	5	14	22	Spain	PCR	0.04	LVH with EHT
Ortlep et al 2002	6	14	6	26	28	43	29	100	UK	PCR	0.15	LVH with HCM
Perticone et al 1999	5	39	52	96	13	56	35	104	Italy	PCR	0.45	LVH with EHT
Schunkert et al 1994	48	136	106	290	48	170	72	290	Germany	PCR	0.15	LVH with EHT
Ueno et al 1999	18	16	9	43	19	21	4	44	Japan	PCR	2.11	LVH with EHT
Wong et al 1995	22	36	22	80	11	43	18	72	Australia	PCR	0.80	LVH with EHT

ACE, angiotensin-converting enzyme; LVH, left ventricular hypertrophy; PCR, polymerase chain reaction; χ^2, chi-square; HWE, Hardy–Weinberg equilibrium; HF, heart failure; EHT, essential hypertension; HCM, hypertrophic cardiomyopathy; MI, myocardial infarction; SCA, sudden cardiac arrest; I/D, intron deletion.

ventricular hypertrophy with the essential hypertension end point subgroup is presented in Table 4 and Fig. 3C.

3.3. Source of heterogeneity and potential publication bias

In overall analysis, evidence for heterogeneity among studies was found in all multiplications (pH < 0.10), except for the AA genotype of ACE G2350A. Therefore, data in our study were assessed using the random-effect model, whereas for the AA genotype of ACE G2350A, the correlation was assessed using the fixed-effect model. Moreover, for evaluating publication bias, we used Egger's test, and we found publication bias in only the AA genotype of ACE G2350A. The summary of heterogeneity evidence and publication bias is shown in Table 3.

For subgroup analysis in left ventricular hypertrophy with essential hypertension, the random-effect model was used to assess the association in I and D alleles of ACE I/D, ID and DD genotypes of ACE I/D, and the GA genotype of ACE G2350A because evidence for heterogeneity was found, whereas because no heterogeneity existed, the fixed-effect model was used to evaluate the correlation in the II genotype of ACE I/D, G and A alleles of ACE G2350A, and GG and AA genotypes of ACE G2350A. Moreover, in this subgroup analysis, publication bias was found in the AA genotype of ACE G2350A and G and A alleles of ACE G2350A. We

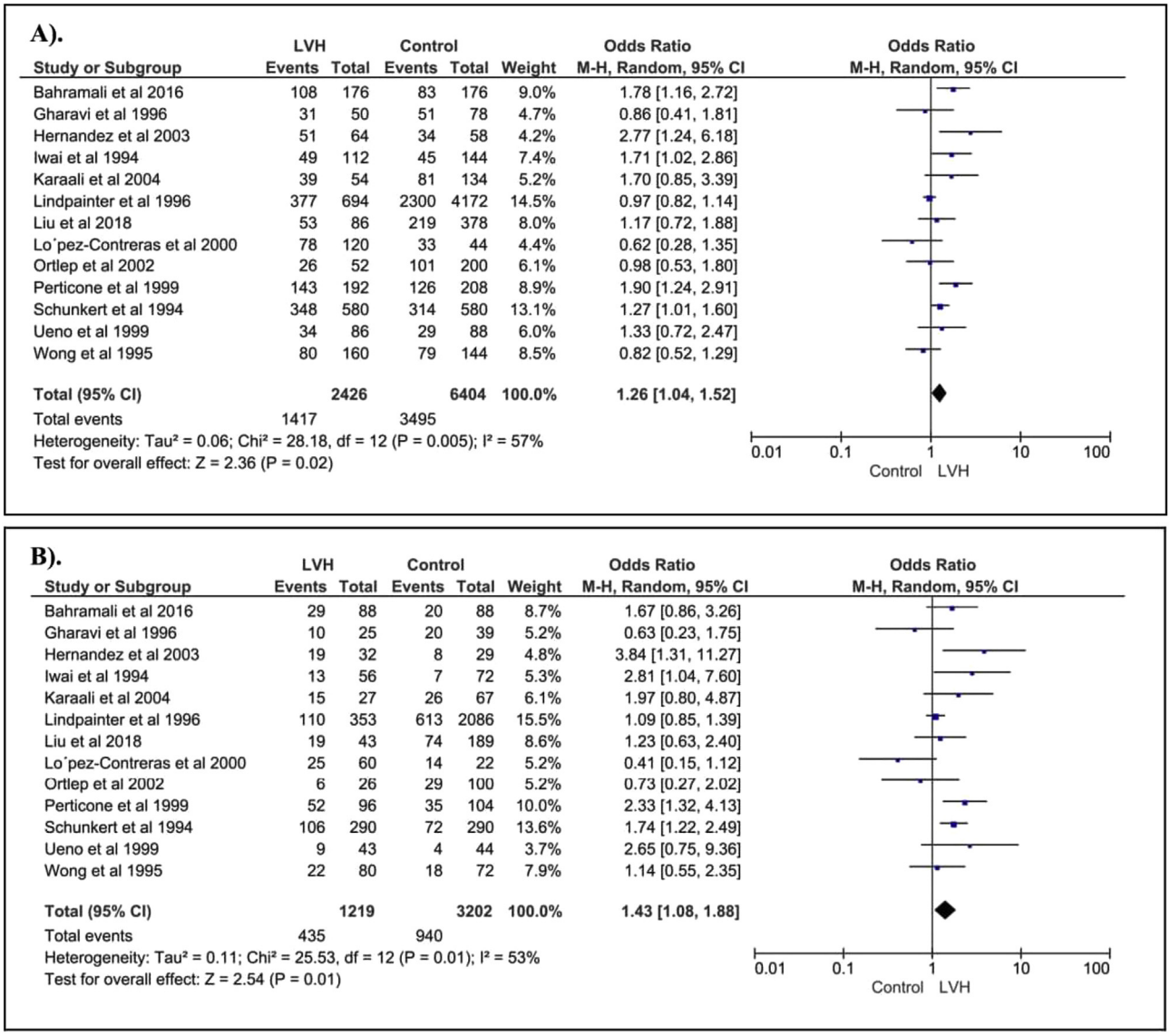

Fig. 2. Forest plot of the association between left ventricular hypertrophy and ACE I/D gene polymorphism. (A) D *vs.* I. (B) DD *vs.* II+ID. ACE, angiotensin-converting enzyme; CI, confidence interval; LVH, left ventricular hypertrophy; I/D, intron deletion.

Table 2
The frequency of the ACE G2350A genotype in left ventricular hypertrophy and control groups.

Author and year	LVH				Control				Country	Genotyping	χ^2 for HWE	End point
	GG	GA	AA	N	GG	GA	AA	N				
Jang and Kim 2012	4	12	7	23	9	29	22	60	Korea	PCR	0.09	LVH in athletes
Pan et al 2007	10	37	21	68	40	47	23	110	China	PCR-RFLP	0.94	LVH with EHT
Ruan et al 2016	93	208	104	405	133	52	53	238	China	PCR	0.32	LVH with EHT
Saeed et al 2005	13	25	12	50	59	43	28	130	Pakistan	PCR-RFLP	0.00	LVH with EHT

ACE, angiotensin-converting enzyme; LVH, left ventricular hypertrophy; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; χ^2, chi-square; HWE, Hardy–Weinberg equilibrium; EHT, essential hypertension.

summarize evidence for heterogeneity and publication bias of this subgroup analysis in Table 4.

4. Discussion

Left ventricular hypertrophy is a pathological state characterized by an abnormal increase in left ventricular mass[40] and has been associated with several fatal complication such as coronary artery disease,[3] stroke,[6] heart failure,[2] and peripheral arterial disease.[4] The pathogenesis of left ventricular hypertrophy is a complex involving many aspects and has a close correlation with the RAAS.[41] In the RAAS, ACE has a pivotal role in regulating the pathological condition, and its inhibition has a tremendous benefit in disease treatment.[42] Our present study reported the

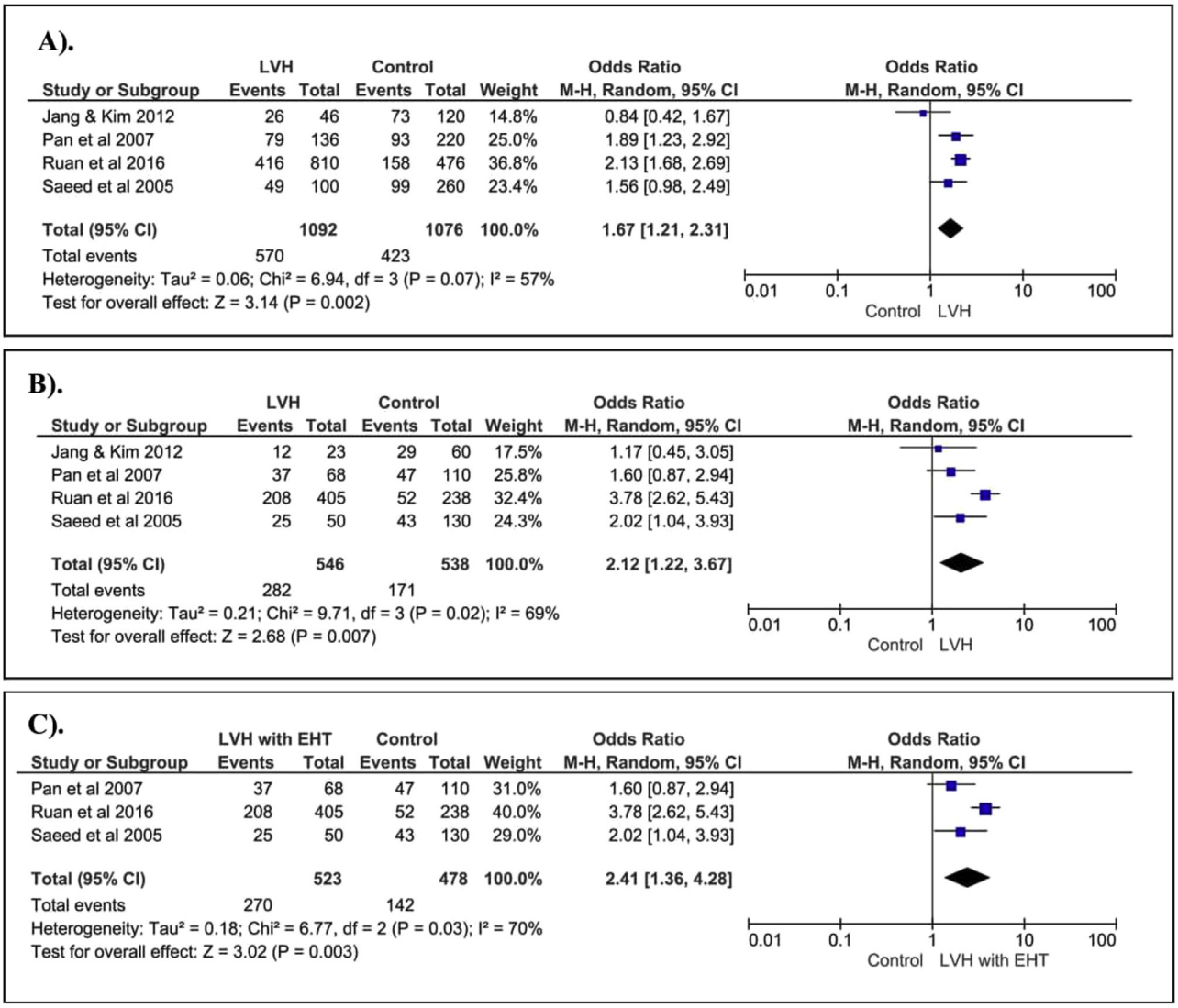

Fig. 3. Forest plot of ACE G2350A gene polymorphism in patients with left ventricular hypertrophy: (A) A *vs.* G; (B) GA *vs.* GG+AA. Forest plot of ACE G2350A gene polymorphism in patients with left ventricular hypertrophy and essential hypertension: (C) GA *vs.* GG+AA. ACE, angiotensin-converting enzyme; CI, confidence interval; LVH, left ventricular hypertrophy; EHT, essential hypertension.

Table 3
Summary of ORs and 95% CIs of the association between left ventricular hypertrophy and the polymorphism of both ACE I/D and ACE G2350A genes.

ACE genes	Allele and genotype	Model	OR	95% CI	pH	pE	P
ACE I/D	I vs. D	Random	0.80	0.66–0.96	0.0050	0.2410	0.0180
	D vs. I	Random	1.26	1.04–1.52	0.0050	0.2410	0.0180
	II vs. ID+DD	Random	0.82	0.61–1.09	0.0690	0.3030	0.1660
	ID vs. II+DD	Random	0.84	0.67–1.06	0.0520	0.2490	0.1430
	DD vs. II+ID	Random	1.43	1.08–1.88	0.0130	0.3340	0.0110
ACE G2350A	G vs. A	Random	0.60	0.43–0.82	0.0740	0.2420	0.0020
	A vs. G	Random	1.67	1.21–2.31	0.0740	0.2420	0.0020
	GG vs. GA+AA	Random	0.36	0.21–0.61	0.0690	0.4060	<0.0001
	GA vs. GG+AA	Random	2.12	1.22–3.67	0.0210	0.4560	0.0070
	AA vs. GG+GA	Fixed	1.23	0.92–1.64	0.635	<0.0001	0.1720

ACE, angiotensin-converting enzyme; CI, confidence interval; OR, odds ratio; pH, p heterogeneity; pE, p Egger; I/D, intron deletion.

polymorphism of ACE I/D and ACE G2350A in patients with left ventricular hypertrophy.

ACE genes are complex, and the most common ACE genes widely studied are ACE I/D and ACE G2350A. Our results found 13 articles evaluating the correlation between ACE I/D and left ventricular hypertrophy. Of those, five articles[16–19,21] showed that ACE I/D had a significant association with left ventricular hypertrophy, and eight others[22–29] showed otherwise. Our pooled calculation found that the D allele of ACE I/D was associated with a 1.26-fold increase in the risk of left ventricular hypertrophy. During

Table 4
Summary of ORs and 95% CIs of the association between the gene polymorphism of ACE I/D and ACE G2350A and the risk of left ventricular hypertrophy in hypertensive patients.

ACE genes	Allele and genotype	Model	OR	95% CI	pH	pE	p
ACE I/D	I vs. D	Random	0.91	0.72–1.14	0.0250	0.2150	0.4100
	D vs. I	Random	1.10	0.88–1.39	0.0250	0.2150	0.4100
	II vs. ID+DD	Fixed	1.07	0.87–1.31	0.3320	0.1270	0.5530
	ID vs. II+DD	Random	0.79	0.58–1.08	0.0360	0.2810	0.1370
	DD vs. II+ID	Random	1.27	0.87–1.84	0.0100	0.3680	0.2110
ACE G2350A	G vs. A	Fixed	0.51	0.42–0.61	0.5010	<0.0001	<0.0001
	A vs. G	Fixed	1.98	1.64–2.39	0.5010	<0.0001	<0.0001
	GG vs. GA+AA	Fixed	0.27	0.20–0.36	0.3370	0.0900	<0.0001
	GA vs. GG+AA	Random	2.41	1.36–4.28	0.0340	0.4220	0.0030
	AA vs. GG+GA	Fixed	1.28	0.94–1.73	0.6730	<0.0001	0.1140

ACE, angiotensin-converting enzyme; OR, odds ratio; pH, p heterogeneity; pE, p Egger; CI, confidence interval; I/D, intron deletion.

this time, a meta-analysis had been performed to evaluate the correlation between ACE I/D gene polymorphism and the risk of left ventricular hypertrophy.[43] Their results were consistent with our result. They also found that the D allele of ACE I/D was associated with increasing the risk of left ventricular hypertrophy. However, data discrepancy was found in the previous meta-analysis. Totally, we found six studies having irrelevant data. Therefore, although our meta-analysis was considered more up to date, our meta-analysis also had more relevant and accurate data. Theoretically, it is difficult to explain the exact mechanism between ACE I/D polymorphism and the risk of left ventricular hypertrophy. However, previous studies have shown that the D allele of ACE I/D was associated with an elevated level of ACE in the circulation[8–11] and increased ACE mRNA expressions[12] and activity.[13] Moreover, ACE has been globally known to have a crucial role in the development of cardiac remodeling through either angiotensin II or aldosterone.[7] This explication may be a benchmark for the result of our study showing that the D allele of ACE I/D had a significant association with increasing the risk of left ventricular hypertrophy.

For the association between ACE G2350A gene polymorphism and the risk of left ventricular hypertrophy, we collected four articles. Of those, two articles[30,31] showed that ACE G2350A gene polymorphism was correlated with left ventricular hypertrophy, and two others[20,32] showed no correlation. Our combination data found that the A allele was correlated with a 1.67-fold increase in the odds of having left ventricular hypertrophy. Compared with the D allele of ACE I/D, the A allele of ACE G2350A had greater risk of left ventricular hypertrophy. Our study was the first meta-analysis concerning the correlation between ACE G2350A gene polymorphism and the risk of left ventricular hypertrophy. Although ACE G2350A was proven to influence the ACE activity and ACE level in the circulation compared with ACE I/D,[14,15] the A allele of ACE G2350A is difficult to explain. Our results were contrary to previous studies. They found that the G allele of ACE G2350A was associated with the elevated ACE level in the circulation.[44,45] For these results, we had no answer. We tried to correlate with other pathways of left ventricular hypertrophy. However, we did not find any trend. Further meta-analysis involving a larger sample size may be required to confirm our findings.

The mechanism bridging between left ventricular hypertrophy and the polymorphism of ACE I/D and ACE G2350A genes may occur through the RAAS. The role of the RAAS in the pathogenesis of left ventricular hypertrophy has been well described. The pathogenesis may involve angiotensin II and aldosterone.[46] Angiotensin II stimulates transforming growth factor β and causes the downstream of nicotinamide adenine dinucleotide phosphate oxidase activation and reactive oxygen species generation. This mechanism leads to increase oxidative stress and rapid pressure, and as a result, it has a crucial role in cardiac hypertrophy.[47] Moreover, angiotensin II has been shown to trigger the expression of atrial natriuretic peptide and brain natriuretic peptide, therefore leading to the downregulation of α-myosin heavy chain (MHC) and upregulation of β-MHC. Recapitulation of these gene expressions is the basic mechanism of hypertrophic cardiac remodeling.[48] Besides, left ventricular hypertrophy is also triggered by aldosterone. Aldosterone causes sodium retention and reduces myocardial norepinephrine uptake and sensitivity of baroreceptors. As a result, this process leads to cardiac remodeling cascades including myocardial fibrosis, fibroblast proliferation, and changes in sodium channel expression.[49] In the RAAS, angiotensin I is cleaved by ACE to angiotensin II and stimulates the production of aldosterone.[7,38] Therefore, ACE has a fundamental role in the development of left ventricular hypertrophy through either angiotensin II or aldosterone. Moreover, ACE inhibition was shown to have a protective effect against left ventricular hypertrophy.[50,51] Our results found that ACE I/D and ACE G2350A gene polymorphism had a significant correlation with left ventricular hypertrophy and were supported by previous studies showing that the elevated ACE level was closely influenced by ACE I/D and ACE G2350A;[8–15] it clarifies better understanding that ACE has a pivotal role in the development of left ventricular hypertrophy. However, further investigations are required to elucidate the exact mechanism how ACE I/D and ACE G2350A gene polymorphism affects left ventricular hypertrophy.

Moreover, in subgroup analysis, we evaluated the role of these genes (ACE I/D and ACE G2350A) in left ventricular hypertrophy with essential hypertension. Our combination data revealed that all genetic models of ACE I/D had no significant correlation with the risk of left ventricular hypertrophy with essential hypertension. However, the correlation was found in GG and GA genotypes of ACE G2350A. Because essential hypertension and ACE have been globally known to play an important role in the development of left ventricular hypertrophy,[7,38] our results might confirm that ACE G2350A had a more dominant role governing the ACE level and activity in circulation than ACE I/D. However, further investigations are required to clarify the precise mechanism comparing the role of ACE I/D and ACE G2350A to the ACE level and activity, essential hypertension, and left ventricular hypertrophy. Furthermore, because ACE G2350A was widely genotyped using polymerase chain reaction (PCR) and PCR-restriction fragment length polymorphism, it might govern the overall analysis. However, subgroup analysis for this genotyping method was not possible because of the small sample size.

Our results showed the potent correlation between left ventricular hypertrophy and both ACE I/D and ACE G2350A polymorphism, and therefore, our results might clarify the controversy during this time and confirm better understanding concerning the role of these genes in patients with left ventricular hypertrophy. However, for this time, it was not possible to recommend these

genes as the biomarkers and/or a predictive value in patients with left ventricular hypertrophy. Because the reported studies used nonrandomized design, it might result in a low level of evidence. Therefore, further studies with a higher design may be required.

Our meta-analysis had several limitations. First, our meta-analysis was based on gross effect estimation. Therefore, the precipitating factors including age, gender, valve disease, exercise, and family history of heart disease, which might affect left ventricular hypertrophy, were not managed. Second, because of the small sample size, the possibility of a false negative finding should be considered even when combined. Third, the proportion of ethnicity in our study was unequal. Therefore, the potency for bias might not be ruled out.

5. Conclusions

Our findings reveal that the D allele of ACE I/D and the A allele of ACE G2350A are associated with increasing the risk of left ventricular hypertrophy. Moreover, our results show that the A allele of ACE G2350A has a greater odds of having left ventricular hypertrophy than the D allele of ACE I/D. Our results may provide better understanding concerning the ACE gene polymorphism in patients with left ventricular hypertrophy.

Conflict of interest

There is no conflict of interest.

Financial disclosure

There is no financial disclosure.

Author contributions

B.S.P. and J.K.F. contributed to the idea/concept and design of the study. B.S.P. and T.H. were involved in the control/supervision of the study. B.S.P., J.K.F., E.P.S., P.N.B.S., and R.R.A. were involved in data collection/processing. J.K.F. was involved in analysis/interpretation. E.P.S., P.N.B.S., and R.R.A. were involved in literature review. J.K.F. was involved in writing the article. B.S.P. and T.H. were involved in critical review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2019.07.002.

References

1. Gosse P. Left ventricular hypertrophy–the problem and possible solutions. *J Int Med Res*. 2005;33(Suppl 1):3A–11A.
2. Gradman AH, Alfayoumi F. From left ventricular hypertrophy to congestive heart failure: management of hypertensive heart disease. *Prog Cardiovasc Dis*. 2006;48(5):326–341.
3. Brown DW, Giles WH, Croft JB. Left ventricular hypertrophy as a predictor of coronary heart disease mortality and the effect of hypertension. *Am Heart J*. 2000;140(6):848–856.
4. Albuquerque PF, Albuquerque PH, Albuquerque GO, Servantes DM, Carvalho SM, Oliveira Filho JA. Ankle-brachial index and ventricular hypertrophy in arterial hypertension. *Arq Bras Cardiol*. 2012;98(1):84–86.
5. Ghanem-Wisam MA, Murin J, Sleiman O, et al. Relation of left ventricular hypertrophy to cardiovascular complications in diabetic hypertensives. *Bratisl Lek Listy*. 2001;102(12):564–569.
6. Bruno A, Brooks DD, Abrams TA, et al. Left ventricular hypertrophy in acute stroke patients with known hypertension. *Clin Exp Hypertens*. 2017;39(6):502–504.
7. Masuyer G, Schwager SL, Sturrock ED, Isaac RE, Acharya KR. Molecular recognition and regulation of human angiotensin-I converting enzyme (ACE) activity by natural inhibitory peptides. *Sci Rep*. 2012;2:717.
8. Foy CA, McCormack LJ, Knowler WC, Barrett JH, Catto A, Grant PJ. The angiotensin-I converting enzyme (ACE) gene I/D polymorphism and ACE levels in Pima Indians. *J Med Genet*. 1996;33(4):336–337.
9. Montgomery HE, Clarkson P, Dollery CM, et al. Association of angiotensin-converting enzyme gene I/D polymorphism with change in left ventricular mass in response to physical training. *Circulation*. 1997;96(3):741–747.
10. Das S, Roy S, Sharma V, Kaul S, Jyothy A, Munshi A. Association of ACE gene I/D polymorphism and ACE levels with hemorrhagic stroke: comparison with ischemic stroke. *Neurol Sci*. 2015;36(1):137–142.
11. Kostadinova ES, Miteva LD, Stanilova SA. ACE serum level and I/D gene polymorphism in children with obstructive uropathies and other congenital anomalies of the kidney and urinary tract. *Nephrology (Carlton)*. 2017;22(8):609–616.
12. Mizuiri S, Hemmi H, Kumanomidou H, et al. Angiotensin-converting enzyme (ACE) I/D genotype and renal ACE gene expression. *Kidney Int*. 2001;60(3):1124–1130.
13. Ajala AR, Almeida SS, Rangel M, et al. Association of ACE gene insertion/deletion polymorphism with birth weight, blood pressure levels, and ACE activity in healthy children. *Am J Hypertens*. 2012;25(7):827–832.
14. Zhu X, Bouzekri N, Southam L, et al. Linkage and association analysis of angiotensin I-converting enzyme (ACE)-gene polymorphisms with ACE concentration and blood pressure. *Am J Hum Genet*. 2001;68(5):1139–1148.
15. Niu W, Qi Y, Gao P, Zhu D. Association between angiotensin converting enzyme G2350A polymorphism and hypertension risk: a meta-analysis. *J Renin-Angiotensin-Aldosterone Syst JRAAS*. 2011;12(1):8–14.
16. Iwai N, Ohmichi N, Nakamura Y, Kinoshita M. DD genotype of the angiotensin-converting enzyme gene is a risk factor for left ventricular hypertrophy. *Circulation*. 1994;90(6):2622–2628.
17. Schunkert H, Hense HW, Holmer SR, et al. Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. *N Engl J Med*. 1994;330(23):1634–1638.
18. Perticone F, Maio R, Cosco C, et al. Hypertensive left ventricular remodeling and ACE-gene polymorphism. *Cardiovasc Res*. 1999;43(1):192–199.
19. Hernández D, de la Rosa A, Barragán A, et al. The ACE/DD genotype is associated with the extent of exercise-induced left ventricular growth in endurance athletes. *J Am Coll Cardiol*. 2003;42(3):527–532.
20. Saeed M, Saleheen D, Siddiqui S, Khan A, Butt ZA, Frossard PM. Association of angiotensin converting enzyme gene polymorphisms with left ventricular hypertrophy. *Hypertens Res*. 2005;28(4):345–349.
21. Bahramali E, Rajabi M, Jamshidi J, et al. Association of ACE gene D polymorphism with left ventricular hypertrophy in patients with diastolic heart failure: a case-control study. *BMJ Open*. 2016;6(2). e010282.
22. Wong KK, Summers KM, Burstow DJ, West MJ. Angiotensin-converting enzyme and angiotensinogen genes in patterns of left ventricular hypertrophy and in diastolic dysfunction. *Clin Exp Pharmacol Physiol*. 1995;22(6–7):438–440.
23. Gharavi AG, Lipkowitz MS, Diamond JA, Jhang JS, Phillips RA. Deletion polymorphism of the angiotensin-converting enzyme gene is independently associated with left ventricular mass and geometric remodeling in systemic hypertension. *Am J Cardiol*. 1996;77(15):1315–1319.
24. Lindpaintner K, Lee M, Larson MG, et al. Absence of association or genetic linkage between the angiotensin-converting-enzyme gene and left ventricular mass. *N Engl J Med*. 1996;334(16):1023–1028.
25. Ueno H, Takata M, Yasumoto K, Tomita S, Inoue H. Angiotensin-converting enzyme gene polymorphism and geometric patterns of hypertensive left ventricular hypertrophy. *Jpn Heart J*. 1999;40(5):589–598.
26. López-Contreras J, Blanco-Vaca F, Borrás X, et al. Usefulness of the I/D angiotensin-converting enzyme genotype for detecting the risk of left ventricular hypertrophy in pharmacologically treated hypertensive men. *J Hum Hypertens*. 2000;14(5):327–331.
27. Ortlepp JR, Vosberg HP, Reith S, et al. Genetic polymorphisms in the renin-angiotensin-aldosterone system associated with expression of left ventricular hypertrophy in hypertrophic cardiomyopathy: a study of five polymorphic genes in a family with a disease causing mutation in the myosin binding protein C gene. *Heart*. 2002;87(3):270–275.
28. Karaali ZE, Agachan B, Yilmaz H, Isbir T. Angiotensin-converting enzyme I/D gene polymorphisms and effects of left ventricular hypertrophy in Turkish myocardial infarction patients. *Acta Cardiol*. 2004;59(5):493–497.
29. Liu A, Wang S, Zhang C, Sun D, Song X. Role of angiotensin-converting enzyme insertion/deletion polymorphism in sudden cardiac arrest. *J Cell Biochem*. 2018. https://doi.org/10.1002/jcb.27622.
30. Pan M, Zhu JH, Liu ZH, et al. Angiotensin-converting enzyme gene 2350 G/A polymorphism is associated with left ventricular hypertrophy but not essential hypertension. *Hypertens Res*. 2007;30(1):31–37.
31. Ruan ZB, Li JM, Zhu L. Relationship of ACE2350 G/A and chymase genetic polymorphisms with left ventricular hypertrophy in Chinese essential hypertension patients. *Int J Clin Exp Pathol*. 2016;9(1):237–243.
32. Jang Y, Kim SM. Influences of the G2350A polymorphism in the ACE gene on cardiac structure and function of ball game players. *J Negat Results Biomed*. 2012;11:6.
33. Fajar JK. The β fibrinogen gene G-455A polymorphism in Asian subjects with coronary heart disease: a meta analysis. *Egypt J Med Hum Genet*. 2017;18(1):19–28.
34. Fajar JK. The association of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) K121Q gene polymorphism with the risk of type 2 diabetes mellitus

in European, American, and African populations: a meta-analysis. *J Health Sci*. 2016;6(2):76–86.
35. Fajar JK, Mahendra AI, Tamara F, Mahdi BA, Heriansyah T, Rohman MS. The association between complete blood count and the risk of coronary heart disease. *Turkiye Klinikleri J Med Sci*. 2018. https://doi.org/10.5336/medsci.2018-61970.
36. Rohman MS, Fajar JK, Kuncahyo BH, et al. Angiotensin-converting enzyme (ACE) I/D and bradykinin B2 receptor T/C genes polymorphism in patients with ACE inhibitors-related cough. *Egypt J Med Hum Genet*. 2018;19(4):307–313.
37. Fajar JK, Heriansyah T, Rohman MS. The predictors of no reflow phenomenon after percutaneous coronary intervention in patients with ST elevation myocardial infarction: a meta-analysis. *Indian Heart J*. 2018;70(Suppl 3):S406–S418.
38. Rodriguez S, Gaunt TR, Day IN. Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. *Am J Epidemiol*. 2009;169(4):505–514.
39. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603–605.
40. Aronow WS. Hypertension and left ventricular hypertrophy. *Ann Transl Med*. 2017;5(15):310.
41. Cowan BR, Young AA. Left ventricular hypertrophy and renin-angiotensin system blockade. *Curr Hypertens Rep*. 2009;11(3):167–172.
42. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm*. 2007;13(8 Suppl B):9–20.
43. Kuznetsova T, Staessen JA, Wang JG, et al. Antihypertensive treatment modulates the association between the D/I ACE gene polymorphism and left ventricular hypertrophy: a meta-analysis. *J Hum Hypertens*. 2000;14(7):447–454.
44. Saeed-Mahmood M, Saboohi K, Osman Ali S, Bokhari AM, Frossard PM. Association of the angiotensin-converting enzyme (ACE) gene G2350A dimorphism with essential hypertension. *J Hum Hypertens*. 2003;17(10):719–723.
45. Zawilla N, Shaker D, Abdelaal A, Aref W. Angiotensin-converting enzyme gene polymorphisms and hypertension in occupational noise exposure in Egypt. *Int J Occup Environ Health*. 2014;20(3):194–206.
46. Schlaich MP, Schmieder RE. Left ventricular hypertrophy and its regression: pathophysiology and therapeutic approach: focus on treatment by antihypertensive agents. *Am J Hypertens*. 1998;11(11 Pt 1):1394–1404.
47. Kurdi M, Booz GW. New take on the role of angiotensin II in cardiac hypertrophy and fibrosis. *Hypertension*. 2011;57(6):1034–1038.
48. Crowley SD, Gurley SB, Herrera MJ, et al. Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney. *Proc Natl Acad Sci U S A*. 2006;103(47):17985–17990.
49. Feniman De Stefano GM, Zanati-Basan SG, De Stefano LM, et al. Aldosterone is associated with left ventricular hypertrophy in hemodialysis patients. *Ther Adv Cardiovasc Dis*. 2016;10(5):304–313.
50. Suzuki H, Kanno Y, Ikeda N, Nakamoto H, Okada H, Sugahara S. Selection of the dose of angiotensin converting enzyme inhibitor for patients with diabetic nephropathy depends on the presence or absence of left ventricular hypertrophy. *Hypertens Res*. 2002;25(6):865–873.
51. Ruggenenti P, Iliev I, Costa GM, et al, Bergamo Nephrologic Diabetes Complications Trial Study Group. Preventing left ventricular hypertrophy by ACE inhibition in hypertensive patients with type 2 diabetes: a prespecified analysis of the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT). *Diabetes Care*. 2008;31(8):1629–1634.