Original Article

Increased Cardiovascular Risks in Prehypertensives Expressing Angiotensin-Converting Enzyme Gene Polymorphism

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Abstract

Background and Aim: Although angiotensin-converting enzyme (*ACE*) gene polymorphism has been documented to play an important role in the genesis of hypertension, its role in the development of prehypertension has not been investigated. To study the association of ACE genotypes and their link to SVI and CV risks in young prehypertensives in Indian population. **Methods:** This cross-sectional study was conducted in 172 individuals divided into prehypertensives ($n = 57$) and normotensives ($n = 115$) based on their level of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Body mass index, cardiovascular (CV) parameters such as heart rate (HR), SBP, DBP, mean arterial pressure (MAP), rate pressure product, stroke volume, left ventricular ejection time, cardiac output, total peripheral resistance, and baroreflex sensitivity (BRS) were recorded by continuous BP variability (BPV) monitoring using finapres, and sympathovagal imbalance (SVI) was assessed by spectral analysis of HR variability (HRV). Biochemical parameters such as homeostatic model assessment of insulin resistance (HOMA-IR), lipid risk factors, inflammatory markers, renin and oxidative stress (OS) parameters were measured. Genotyping for *ACE* gene polymorphism (insertion [I]/deletion [D] or ID polymorphism) was done by polymerase chain reaction-restriction fragment length polymorphism methods. Multiple regression analysis was done to assess the association between SVI and metabolic markers, and logistic regression was done to determine the BRS prediction of prehypertension status and CV risks in *ACE* genotypes. The BPV, HRV, and biochemical parameters were significantly altered in prehypertensives. **Results:** The ID genotype of ACE was most commonly distributed among the population (33.3% prehypertensives and 50.4% in normotensives). LH-HF ratio, the marker of SVI, was significantly associated with MAP, HOMA-IR, interleukin-6, tumor necrosis factor-alpha, renin, and BRS in ID genotype of prehypertensive population. BRS, the marker of CV risk, had significant prediction of prehypertension status in ID genotypes population. **Conclusion:** The *ACE* ID gene polymorphism appears to be the candidate gene for prehypertension. ID contributes to SVI in young prehypertensives attributed by insulin resistance and inflammation. The CV risks are strongly associated with prehypertension status in ID genotypes in prehypertensives.

Keywords: Angiotensin-converting enzyme gene polymorphism, autonomic imbalance, baroreflex sensitivity, blood pressure variability, cardiovascular risks, heart rate variability, prehypertension

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Introduction

Prehypertension range has been reported to be associated with all-cause mortality.[1] Furthermore, there is report of increased cardiovascular (CV) risks in prehypertension.[2] We have reported sympathovagal imbalance (SVI) attributed by increased sympathetic and decreased vagal drives as the major physiological basis in the causation of prehypertension.[3-5] Recent reports from our laboratory have documented the association of SVI with CV risks in prehypertensives, which is linked to insulin resistance, dyslipidemia, inflammation, and oxidative stress (OS).[6,7] Since long, many genome-wide association studies have demonstrated genetic basis of pathophysiology and management of hypertension.[8,9] A recent study has demonstrated the role of angiotensin II receptor type-1 gene in the genesis of prehypertension.[10] However, there is a paucity of data on the genomics of prehypertension.

Angiotensin-converting enzyme (ACE) converts angiotensinogen to angiotensin-I, which is further converted to

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angiotensin-II (A-II), and A-II is the most potent physiological vasoconstrictor that plays major role in the regulation of blood pressure (BP) in conditions of hypovolemia and hypotension.[11] However, excess production of A-II plays a major role in the pathophysiology of hypertension.[12] Inhibitors of ACE are known to reduce BP and CV risks by decreasing synthesis of ACE, and thereby decreasing BP and CV stress.[13] As *ACE* has been reported to be candidate gene in hypertension,[14] we suggest *ACE* gene as a potential candidate gene for prehypertension. ACE has been reported to control sympathetic output and CV autonomic functions.[15] Further, *ACE* gene (I or D) has been suggested to be involved in increase in BP in prehypertension range in normal and obese population.[16,17] Furthermore, there is a report of *ACE* genotype predicting CV risks in high-risk population.[18] Therefore, in the present study, we have assessed the association of *ACE* genotypes and their link to SVI and CV risks in young prehypertensives in Indian population.

Materials and Methods

Subjects

After obtaining the approval of Research Advisory Council and Institutional Ethics Committee of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, 172 volunteers were recruited from undergraduate medical course of JIPMER, Pondicherry. All the individuals were clinically examined to rule out the presence of any acute or chronic illness. Informed written consent was obtained from all of them before the recordings. After 10 min of supine rest, basal heart rate (HR), systolic BP (SBP), and diastolic BP (DBP) were recorded by oscillometric method using automated BP monitor Omron MX3 (Omron Healthcare Co. Ltd, Kyoto, Japan). The individuals were then classified into two groups based on their level of SBP and DBP as per seventh report of the Joint National Committee-7 classification.[19]

1. Normotensives (n = 115): Healthy controls having SBP 100–119 mm Hg and DBP 60–79 mmHg
2. Prehypertensives (n = 57): Healthy controls having SBP 120–139 mm Hg and DBP 80–89 mmHg.

Individuals with history of smoking and/or alcoholism, acute or chronic ailments, and known cases of diabetes, hypertension, cardiac and renal disease or any endocrinal disorder were excluded from the present study. As physical training contributes to vagosympathetic tone,[20] individuals practicing athletic activities were excluded from the study.

Recording of cardiovascular parameters

Individuals were asked to report to autonomic function testing laboratory of physiology department at about 8 AM following overnight fast. The temperature of the laboratory was maintained at 25°C for all the recordings. Their age, height, body weight, and body mass index (BMI) were recorded.

The CV parameters were measured by continuous BP variability method using Finapres (Finometer version 1.22a, Finapres Medical Systems BV, Amsterdam, the Netherlands), a noninvasive continuous hemodynamic CV monitor based on the principle of measurement of finger arterial pressure with the volume clamp technique of Penaz and the physiocal criteria of Wesseling.[21] In this method, the brachial artery pressure measured was the reconstructed pressure from the finger pressure, estimated through generalized waveform inverse modeling and generalized level correction. The individuals were asked to lie down, and the brachial cuff of finapres was tied around the midarm about 2 cm above the cubital fossa and the finger cuff of small, medium, or large size were tied around the middle phalanx of the middle finger depending on the finger width. For the height correction, two sensors were placed, one at the heart level and another at the finger level. The recordings were obtained following connection of cables of the cuffs to the Finometer, after 10 min of supine rest. The "return to flow calibration and the Physiocal" was done for the level correction between the brachial and finger pressure during the initial 5 min of the recordings. Following this, the continuous BP recording was done for a period of 10 min.

The reconstructed brachial pressure was acquired through a PC-based data acquisition system (Finapres Medical Systems BV, Amsterdam, the Netherlands). The following parameters were recorded from the reconstructed brachial pressure tachogram: HR; SBP; DBP; mean arterial pressure (MAP); rate pressure product (RPP); interbeat interval; left ventricular ejection time; stroke volume; cardiac output; total peripheral resistance (TPR); and baroreflex sensitivity (BRS).

Recording of heart rate variability

After 15 min of supine rest, electrocardiogram (ECG) was recorded for short-term HR variability (HRV) analysis following the procedures recommended by Task Force,[22] using BIOPAC MP-100 data acquisition system (BIOPAC Inc., Goleta, CA, USA). For the purpose, ECG electrodes were connected and lead II ECG was acquired at a rate of 1000 samples/second during supine rest using BIOPAC MP-100, continuously for 10 min. The data were transferred from BIOPAC to a windows-based PC with AcqKnowledge software version 3.8.2 (BIOPAC Inc., Goleta, CA, USA). Ectopics and artifacts were removed from the recorded ECG. The RR tachogram was extracted from the edited ECG using the R-wave detector in the AcqKnowledge software. HRV analysis was done using the HRV analysis software version 1.1 (Bio-signal Analysis group, Kuopio, Finland). Frequency domain indices of HRV such as total power (TP), low-frequency power (LF), high-frequency power (HF), ratio of low-frequency to high-frequency power (LF-HF ratio), and square root of the mean of the sum of the squares of the differences between adjacent NN intervals (RMSSD), and the main time domain parameter were recorded.

Measurement of biochemical parameters

Five milliliters of fasting blood sample was collected. The serum was separated from blood samples of all the individuals for estimation of biochemical parameters. Fasting blood

glucose (FBG) was estimated by glucose oxidase method using glucometer (LifeScan Inc., Milpitas, CA, USA). For determination of insulin resistance, homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the formula, HOMA-IR = FBS (mMol) × Insulin (μIU/L)/22.5. Lipid profile parameters (total cholesterol [TC], triglycerides [TGs], high-, low-, and very low-density lipoproteins [HDL, LDL, VLDL]) were assessed using fully automated chemistry analyzer (AU400, Olympus, Orlando, FL, USA). Atherogenic index (AI) was calculated using the formula, $\log_{10}$(TG/HDL). The high-sensitive C-reactive protein (hsCRP) was estimated by enzyme immunoassay method using ELISA kit (dbc Diagnostics Biochem Canada Inc., Ontario, Canada). OS was assessed by estimating thiobarbituric acid reactive substance (TBARS) using ELISA kit (Cayman Chemical Co., Ann Arbor, MI, USA). Renin was estimated by enzyme immunoassay method using the ELISA kit of DRG Diagnostics (DRG Instruments GmbH, Frauenbergstr, Marburg, Germany).

DNA extraction and genotyping

Five ml of venous blood was collected in tubes containing 100 μL of 10% ethylenediaminetetraacetic acid and centrifuged for 5 min at 2500 g. Plasma was discarded, and the pellets containing red blood corpuscles with the buffy coat were stored at −20°C until DNA extraction. Genomic DNA was extracted from peripheral leucocytes using standard phenol–chloroform method. The extracted DNS was analyzed qualitatively and quantitatively using TECAN infinite M200 multianalyzer. Each DNA sample was diluted to an optimal concentration of 50 ng/μl suitable for further downstream analysis and stored in aliquots at 4°C. The *ACE* ID polymorphism was determined by allele-specific polymerase chain reaction (PCR). The primers for PCR amplification of *ACE* ID were 5'-CTGGAGAG CCACTCCCATCCTTTCT-3' (Forward) and 5'-GACGTGGCCATCACATTCGTCAGAT-3' (Reverse). The PCR products were run on 2% agarose gel electrophoresis. The different fragments obtained were 490 bp corresponds to homozygous for II, 190 bp corresponds to homozygous for DD, and 490 bp and 190 bp correspond to heterozygous for ID. The samples with homozygous deletion DD by this assay were retyped using a third insertion specific primer 5'-TTTGAGACGGAGTCTCGCTC-3'. This was done to rule out the possibility of mistyping individuals due to preferential amplification of the deletion fragment over the longer insertion fragment.

Statistical analysis

SPSS version 19 (SPSS Software Inc., Chicago, IL, USA) was used for statistical analysis. All the data were expressed as mean ± standard deviation. Normality of data was tested by Kolmogorov–Smirnov test. For parametric data, the level of significance between the groups was tested by Student's unpaired *t*-test, and for nonparametric data, Welch's corrected *t*-test was used. Differences in allele and genotype distributions were compared using Chi-square square/Fisher's exact test. There was no difference in age and smoking status between the two groups. The observed genotype frequencies of prehypertensives and normotensives were tested for the Hardy–Weinberg equilibrium (HWE), following the basic principles of genetic association studies.[23] Multiple regression analysis was done to analyze the association of LF-HF with metabolic biomarkers in prehypertensive individuals expressing ACE (ID) genotypes, and multivariate logistic regression was done to assess the prediction of prehypertension status by BRS in individuals expressing ACE genotype adjusted for BMI and gender. $P < 0.05$ was considered statistically significant.

Results

Cardiovascular parameters

There was no significant difference in age between prehypertensives and normotensives [Table 1]. The HR, MAP, RPP, stroke volume, cardiac output, and TPR were significantly increased and BRS was significantly decreased in prehypertensives. Among the HRV indices, TP, HF, and RMSSD were significantly decreased and LF-HF ratio was significantly increased in prehypertensive individuals compared to normotensives [Table 1].

Biochemical parameters

FBG, insulin, HOMA-IR, TC, LDL, VLDL, AI, TBARS, hsCRP, and renin were significantly high in prehypertensives compared to normotensives [Table 1].

Genotype distribution and allele frequencies

The percentages of I and D alleles of the *ACE* polymorphism in prehypertensives were 53 and 61, respectively, in the study population. The percentages of ACE variant genotypes were as follows: II = 29.8%, ID = 33.3%, DD = 36.9%, and these were concordant with HWE [Table 2].

Regression analysis

Multiple regression analysis revealed significant association of LF-HF ratio with BMI, MAP, BRS, HOMA-IR, interleukin-6, tumor necrosis factor-alpha (TNF-α), and renin in prehypertensive individuals expressing *ACE* polymorphism [Table 3]. Bivariate logistic regression demonstrated significant prediction of prehypertension status by BRS in all individuals expressing *ACE* polymorphism [Table 4].

Discussion

Although there are many reports of *ACE* gene polymorphism in the causation of hypertension,[23-27] to the best of our knowledge, there is no report of this gene involvement in prehypertension, except that one report has indicated association of *ACE* insertion (I)/deletion (D) or ID polymorphism with adiposity and increase in BP.[17] In the present study, the expression of ID (A-OR 2.725, confidence interval [CI] 1.247–7.162, $P = 0.009$) and ID + DD (A-OR 2.908, CI 1.352–7.862, $P = 0.003$) were statistically significant [Table 2] although the expression of DD and individual alleles (I or D) were not significant. Therefore, only the prehypertensive individuals expressing ID genotype were considered for further analysis.

Table 1: Demographic and cardiovascular profiles, heart rate variability parameters, metabolic profile, and inflammatory markers of normotensive (*n*=115) and prehypertensive (*n*=57) population

Parameters	Normotensives	Prehypertensives	*P*
Age (years)	20.78±2.82	21.57±3.42	0.109
Gender (males/females)	40/74	27/30	-
Smoker/nonsmoker	Nil/all	Nil/all	-
BMI (kg/m^2)	21.80±3.56	27.25±3.78	<0.0001
Cardiovascular parameters			
Heart rate (beats/min)	73.18±9.97	78.52±9.86	0.001
Mean arterial pressure (mmHg)	79.02±5.96	99.70±3.90	<0.0001
Rate-pressure product (mmHg/min)	76.32±8.48	102.70±9.22	<0.0001
Stroke volume (ml)	65.12±7.95	72.92±11.38	<0.0001
Cardiac output (l/min)	4.77±1.14	5.72±1.25	<0.0001
TPR (mmHg/min/l)	0.894±0.22	1.125±0.24	<0.0001
Baroreflex sensitivity (ms/mmHg)	28.72±9.96	17.22±8.60	<0.0001
HRV parameters			
Total power of HRV (ms^2)	915.20±245.24	525.32±180.10	<0.0001
LF	325.50±122.58	290.48±110.62	0.071
HF	537.20±180.40	165.65±70.6	<0.0001
LF:HF ratio	0.63±0.35	1.78±0.73	<0.0001
RMSSD (ms)	65.28±23.15	36.98±13.42	<0.0001
Metabolic and inflammatory markers			
FBG (mg/dl)	79.10±8.65	89.96±12.17	<0.0001
Insulin (μIU/ml)	7.15±2.88	17.10±5.45	<0.0001
HOMA-IR	1.38±0.77	4.00±1.78	<0.0001
Total cholesterol (mg/dl)	155.40±22.40	181.06±23.86	<0.0001
TG (mg/dl)	97.56±22.75	136.28±27.62	
LDLs (mg/dl)	99.85±22.80	123.95±24.10	<0.0001
VLDLs (mg/dl)	19.15±8.62	27.33±7.50	<0.0001
HDL (mg/dL)	43.78±9.32	35.98±9.15	<0.0001
AI	0.36±0.15	0.58±0.17	<0.0001
TBARS (μM/L)	1.98±0.62	3.80±1.07	<0.0001
hsCRP (ng/dL)	580.24±164.80	951.94±155.28	<0.0001
IL-6	36.78±11.56	83.52±23.15	<0.0001
TNF-α	117.50±33.92	250.88±59.24	<0.0001
Renin (pg/ml)	30.78±8.33	105.65±17.48	<0.0001

Data expressed as mean±SD. $P<0.05$ was considered significant. AI=Log10 (TG/HDL), HOMA-IR=FBG (mMol) × insulin (μIU/l)/22.5. FBG: Fasting blood glucose, HOMA-IR: Homeostatic model for assessment of insulin resistance, TPR: Total peripheral resistance, hsCRP: High-sensitive C-reactive protein, TBARS: Thiobarbituric acid reactive substance, SD: Standard deviation, AI: Atherogenic index, LF: Low-frequency power, HF: High-frequency power, HRV: Heart rate variability, RMSSD: Square root of the mean of the sum of the squares of the differences between adjacent NN intervals, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha, HDL: High-density lipoprotein, TG: Triglyceride, BMI: Body mass index, LDLs: Low-density lipoproteins, VLDLs: Very low-density lipoproteins

There was a significant increase in LF-HF ratio in prehypertensives compared to normotensives [Table 1] indicating the presence of considerable SVI in prehypertension, as increase in LF-HF ratio indicates increased sympathetic and decreased vagal drive.[22,28] Furthermore, significant decrease in TP power, HF power, and RMSSD of HRV in prehypertensives [Table 1] indicate a substantial decrease in vagal modulation of cardiac activities, as these parameters represent vagal drive to the heart.[22,28] In prehypertensives, there was a significant increase in resting HR, which is an index of decreased vagal tone, and resting tachycardia has recently been reported to be associated with CV morbidity and mortality.[29] Further, there was substantial increase in RPP in prehypertensives [Table 1]. Increase in RPP indicates increased oxygen demand by myocardium and increased myocardial work stress, which has been documented as an important CV risk.[30] Increased cardiac output and TPR in these individuals predispose them to further myocardial stress.

The MAP was directly associated with LF-HF ratio in prehypertensives expressing ACE gene ($\beta = 0.362$, $P = 0.027$) [Table 3]. This finding indicates the direct link of *ACE* gene polymorphism with SVI in prehypertension in the Indian population. Moreover, there was significant decrease in BRS in prehypertensives [Table 1]. Decreased BRS is a marker of SVI and is reported to be associated with CV dysfunctions.[31] Although independent contribution of LF-HF ratio to RPP was not quite significant ($\beta = 0.247$, $P = 0.078$), there was significant contribution to BRS ($\beta = 0.402$, $P = 0.008$) [Table 3], indicating the close association of SVI and CV risks in individuals expressing *ACE* ID gene polymorphism. Further, the prediction of prehypertension status by BRS was significant (OR 2.36, $P = 0.015$) in these individuals [Table 3]. Therefore, the findings of the present study suggest SVI is closely associated with prehypertension and SVI could predict CV risks in individuals expressing ID genotype of *ACE*. To the best of our knowledge, this is the first report on link of CV risk to *ACE* gene polymorphism in prehypertension.

The findings of the present study demonstrate that prehypertensive individuals have the early signs of inflammatory and altered metabolic markers in the form of insulin resistance, atherogenic lipid profile, and OS compared to their normotensive controls [Table 1]. HOMA-IR was significantly associated with *ACE* (ID) gene polymorphism [Table 3], indicating that *ACE* (ID) genotype is linked to insulin resistance. The results of the present study indicate that the *ACE* polymorphism is not associated with altered lipid profile and OS. However, there was a strong association of LF-HF ratio with TNFa ($\beta = 0.496$, $P = 0.003$) [Table 3], indicating that *ACE* (ID) gene contributes to SVI attributed by retrograde inflammation. Early features of inflammation have been reported in prehypertension, and low-grade inflammation has been reported to be linked to SVI.[32] Recently, TNFa has been reported to be a better marker of inflammation in metabolic disorders.[33] Therefore, it is likely that TNFa is the key factor in inflammation-mediated SVI involved in the genesis of prehypertension in individuals expressing *ACE* (ID) gene polymorphism.

Obesity and gender are the major confounders of SVI in prehypertension. In the present study, we found a strong

Table 2: Genotype and allele distribution of angiotensin-converting enzyme (insertion/deletion) gene polymorphisms among prehypertensives and normotensives

Genotypes and alleles	PHT (*n*=57), *n* (%)	NT (*n*=115), *n* (%)	OR (95% CI)	*P*	AOR (95% CI)	*P*
ACE (D > I)						
Genotypes						
II	17 (29.8)	21 (18.3)	1 (reference)			
ID	19 (33.3)	58 (50.4)	2.471 (1.08–5.62)	0.034	2.725 (1.247–7.162)	0.009
DD	21 (36.9)	36 (31.3)	0.522 (0.401–3.202)	0.522	0.726 (0.541–2.705)	0.437
ID + DD	40 (70.2)	94 (81.7)	2.537 (1.186–5.426)	0.023	2.908 (1.352–7.862)	0.003
Alleles						
I	53 (46.5)	100 (43.5)	1			
D	61 (53.5)	130 (56.5)	1.130 (0.719–1.773)	0.645	1.652 (0.805–3.117)	0.356

ACE: Angiotensin-converting enzyme, I: Insertion, D: Deletion, OR: Odds ratio, AOR: Adjusted odds ratio; the reference OR of 1 was set for the wild-type genotype, PHT: Prehypertensives, NT: Normotensives, CI: Confidence interval

Table 3: Multiple regression analysis for assessment of association of ratio of low-frequency power to high-frequency power of heart rate variability (dependent variable) with mean arterial pressure, metabolic and inflammatory biomarkers, renin, rate pressure product, and baroreflex sensitivity (as independent variable) in individuals expressing angiotensin-converting enzyme (insertion/deletion) gene polymorphism among prehypertensive population

Parameters	Standardized coefficient (β)	95% CI		*P*
		LB	UB	
BMI	0.325	−0.015	0.007	0.038
MAP	0.362	0.002	0.058	0.027
HOMA-IR	0.396	0.001	0.033	0.008
AI	0.132	0.112	0.246	0.309
TBARS	0.205	0.224	0.566	0.097
hsCRP	0.116	0.107	0.204	0.205
IL-6	0.330	−0.03	0.147	0.035
TNF-α	0.496	0.002	0.077	0.003
Renin	0.356	−0.07	0.008	0.030
RPP	0.247	0.002	0.077	0.078
BRS	0.402	0.001	0.048	0.008

CI: Confidence interval of unstandardized β, LB: Lower bound, UB: Upper bound, MAP: Mean arterial pressure, HOMA-IR: Homeostatic model for assessment of insulin resistance, AI: Atherogenic index, TBARS: Thiobarbituric acid reactive substance, hsCRP: High-sensitive C-reactive protein, RPP: Rate pressure product, BRS: Baroreflex sensitivity, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha, BMI: Body mass index

Table 4: Bivariate logistic regression analysis for prediction of prehypertension status (as dependent variable) by baroreflex sensitivity (as independent variables) in all individuals expressing angiotensin-converting enzyme gene (insertion/deletion) polymorphisms (*n*=77), after adjusting for body mass index and gender

OR (CI)	*P*
2.36 (1.162-7.560)	0.015

CI: Confidence interval; OR was calculated after adjusting for BMI and gender, waist-hip ratio, BMI, and body fat mass index, OR: Odds ratio, BMI: Body mass index

prediction of prehypertension status by BRS in population expressing *ACE* gene polymorphism after adjusting for BMI and gender [Table 4]. Thus, it is likely that prehypertension is associated with SVI and CV risks (decreased BRS, increased RPP, insulin resistance, and inflammation) in young prehypertensives expressing *ACE* gene polymorphism.

Limitations of the study

Although from the present study, it could be suggested that the *ACE* (ID) gene polymorphism is associated with increased CV risk in prehypertensives, attributed by SVI and metabolic derangements, moderate sample size is the limitation of the present study. Therefore, the future large-scale studies should be conducted to validate the heritability of autonomic imbalance, metabolic, and inflammatory traits in prehypertensive individuals.

Conclusion

From the findings of the present study it appears that in Indian population the prehypertension is associated with SVI and CV risks (decreased BRS, increased RPP, insulin resistance, and inflammation) in young prehypertensives expressing ACE gene polymorphism.

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Conflicts of interest

There are no conflicts of interest.

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