**Renin-Angiotensin System Genes Polymorphisms and Long-Term Prognosis in Taiwanese Patients with Hypertension and Coronary Artery Disease**


**Objectives:** The objective of this study was to evaluate the renin-angiotensin system genetic effects and pharmacogenetic interactions for angiotensin-converting enzyme (ACE) inhibitors in hypertensive coronary artery disease (CAD) patients.

**Methods:** Subjects with hypertension and angiographic CAD were recruited from 1995 to 2003. Baseline characteristics and genetic polymorphisms [ACE gene insertion/deletion (I/D) polymorphism, six polymorphisms of the angiotensinogen (AGT) gene, and A1166C polymorphisms of the angiotensin II type I receptor gene (AGT1R)] were collected. Patients were assigned to 2 groups (ACE inhibitor or No-ACE inhibitor) and followed-up for up to 12 years. Kaplan-Meier curves and Cox regression models were used to demonstrate the survival and major cardiovascular events (MACE) event-free survival trends. Pharmacogenetic effects were determined by several Cox regression models.

**Results:** Of the 518 patients in our study, 290 were treated with ACE inhibitors and 228 were not. Prescription of ACE inhibitors was associated with a lower rate of MACE at 4000 days. In addition, ACE I/D gene D was associated with a higher rate of MACE in a multivariate regression analysis [hazard ration (HR): 1.64, 95% confidence interval (CI): 1.27-1.98, p < 0.001]. This effect could be attenuated by the pharmacogenetic interaction of ACE inhibitors and the ACE gene (ACE inhibitors*ACE D gene, HR: 0.68, 95% CI: 0.52-0.84, p = 0.014).

**Conclusions:** The use of ACE inhibitors was associated with a significant decrease in MACE in hypertensive patients diagnosed with CAD. Genetic variants were also associated with event-free survival, but their effects were modified by the use of ACE inhibitors.

**Key Words:** Angiotensin-converting enzyme inhibitors • Coronary artery disease • Hypertension • Pharmacogenetic

**INTRODUCTION**

Hypertension is prevalent in disorders of the vascular system, and has become one of the leading health problems worldwide. On the other hand, coronary artery disease (CAD) is the major cause of death and may lead to angina, heart failure, and myocardial infarction. The formation of atheromatous plaques and coronary thrombosis is a multi-factorial process. Health professionals are dedicated to reducing hypertension-related comorbidity either by medical treatment or through interventional procedures. Angiotensin-converting enzyme (ACE) inhibitors are among the most frequently
used drugs to treat hypertension and stable CAD in the current health care system; however, the role of and evidence showing the effect of ACE inhibitors is not apparent in hypertensive patients with CAD. In some previous studies involving hypertensive CAD patients treated with ACE inhibitors, only modest or no clinical efficacy in stable CAD patients compared to control groups was observed. It is important to optimize the use of ACE inhibitors in selected patients with CAD who may benefit the most, especially among those at high risk. However, it is not easy to identify high risk patients based on clinical parameters.

The vascular system is modulated by ACE mediated vasoconstriction resulting from hydrolysis of angiotensin-I to angiotensin-II, and vasodilation by angiotensin II-mediated bradykinin degradation. Ju et al. investigated the effect of angiotensin on the expression of cardiac Ca\(^{2+}\) transporter proteins and showed that angiotensin II significantly decreased the expression of Na\(^+/\)Ca\(^{2+}\) exchanger and calcium pumps, which were important targets for the development of hypertension and CAD. Accordingly, Flesch et al. showed that ACE treatment can improve cardiac function in rats with hypertensive cardiomyopathy. ACE also stimulates smooth muscle cell proliferation and is associated with the increase of vascular resistance which in turns leads to the development of hypertension. Genetic polymorphisms in the ACE gene have been found to be a major determinant of ACE serum level, which may influence the extent of vasoconstriction. This polymorphism on chromosome 17 also predicts clinical outcome in cardiovascular disease, including CAD, myocardial infarction, left ventricular hypertrophy, atrial fibrillation, diastolic heart failure, and hypertension. It is unclear whether the genetic variation modifies the clinical efficacy of ACE inhibitors. In order to address these issues, a cohort of hypertensive patients hospitalized for coronary angiography or for a health examination was followed. It was hypothesized that genetic variation in the renin-angiotensin system (RAS) pathways is associated with the treatment benefit of ACE inhibitors. A total of 8 polymorphisms were genotyped among RAS genes. The aim was to examine the genetic- and pharmacogenetic-effects of these polymorphisms on major adverse cardiac events in hypertensive patients with CAD.

**MATERIAL AND METHODS**

**Study subjects**

A total of 1254 consecutive subjects with angiographic documented CAD were enrolled from the National Taiwan University Hospital Cardiac Catheterization Laboratory between July 1995 and March 2003. The case patients were unrelated, from Taiwan, and had angiographically documented (≥ 50%) stenosis in more than one of the epicardial coronary arteries. Angiograms were assessed by 2 cardiologists blinded to patient inclusion in the study. CAD was defined in patients with significant coronary arterial stenosis (≥ 50%) affecting at least one vessel by means of coronary angiography. Among the patients, we selected those with hypertension to evaluate the effect of ACE inhibitors and genetic contributions. Hypertension was defined as systolic blood pressure of ≥ 140 mm Hg, diastolic blood pressure of ≥ 90 mm Hg, or the use of at least one class of antihypertensive agent. Patients who had renal failure, significant hepatic disease, pericardial disease, severe valvular heart disease, cancer, chronic obstructive pulmonary disease, chronic atrial fibrillation or acute coronary syndrome history were excluded. Patients who died or experienced cardiovascular events < 60 days after enrollment were also excluded from the study. Consequently, a total of 518 patients fulfilled the above criteria and were enrolled. The decision to prescribe ACE inhibitors or an angiotensin receptor blocker (ARB) was based upon the discretion and preference of the attending cardiologists. Demographic data and risk factors of CAD including smoking history, blood pressure, serum lipid profile, and glucose levels were collected from patient medical records. Type 2 diabetes mellitus was defined as a fasting blood glucose concentration > 126 mg/dL and/or the use of at least one oral hypoglycemic agent. Medication information, such as the use of ACE inhibitors and/or ARBs, calcium channel blockers, diuretics, nitrates, statins, aspirin or β-blockers, was also recorded. The study was approved by the local institutional committee, and the subjects gave their informed consent.

**Identification of diallelic polymorphisms**

Eight diallelic polymorphisms, including the ACE gene insertion/deletion (I/D) polymorphism (rs1799752),
G-217A (rs5049), G-152A (rs11568020), A-20C (rs5050), G-6A (rs5051), T4072C (rs699; T4072C), and C3889T (rs4762; C3889T) polymorphisms of the angiotensinogen (AGT) gene, and the A1166C polymorphism (rs5186) of the angiotensin II type 1 receptor (AGT1R) gene within the RAS were analyzed in each of the patients with CAD. Genomic deoxyribonucleic acid was extracted using a nonenzymatic method. Deoxyribonucleic acid fragments were amplified by polymerase chain reaction (PCR). ACE gene I/D polymorphisms were genotyped as previously reported.\(^{20,21}\) AGT1R gene A1166C polymorphisms were genotyped using the PCR-restriction fragment length polymorphism method. To genotype AGT gene polymorphisms, we used mini-PCR direct sequencing as previously described.\(^{22}\)

**End points**

The outcomes were defined as death from any cause and major cardiovascular events (MACE), including hospitalization due to myocardial infarction, recurrent coronary artery disease, stroke, peripheral artery occlusion disease, heart failure, and arrhythmia.

**Follow-up**

The follow-up period ended on June 30, 2007. All patients visited their outpatient clinic at least every 3 months in addition to annual telephone interviews, and all patients were carefully followed. The longest follow-up time was 4593 days. Outcome information was documented in each patient’s medical records and as communicated by telephone interviews.

**Statistics**

Baseline characteristics and genetic data were compared between patients in the ACE inhibitor and No-ACE inhibitor groups respectively, and were analyzed by the student’s t-test (continuous variables) and chi-square test (categorical variables). Hardy-Weinberg equilibrium of the polymorphism distribution was tested by chi-square test. Survival time was defined as the duration from the day of enrollment to the occurrence of an event. If an event did not occur, the case was regarded as censorship at the end of the study (July 30, 2007). Kaplan-Meier curves were plotted to show the survival trend; hazard ratios, 95% confidence intervals, and p-values were reported for comparison between the two groups. A multiple Cox regression model in which the eight polymorphisms were added on top of ACE inhibitor status was applied to demonstrate the genetic effect on survival and MACE. To determine the adjusted effects of RAS genes and ACE inhibitors, we used 2 Cox regression models. Confounders were selected with clinical apparent factors for CAD and hypertension (such as age, gender, BMI, DM) or the genetic polymorphisms associated with endpoints. In model 1, we evaluated the effects of ACE gene I/D polymorphism and ACE inhibitor for MACE. To examine the pharmacogenetic effect between ACE inhibitor and genes, we developed interaction terms of ACE D allele*ACE inhibitors. For patients who receive ACE inhibitor, the value of ACE D allele*ACE inhibitors would be ACE D allele*1. Therefore, in model 2, we incorporated ACE D allele*ACE inhibitors, ACE D allele, and use of ACE inhibitor as independent variables. All models were adjusted by age, gender, BMI, and DM. For plotting survival curves, we separated the patients into four groups according to genetic differences and use of ACE inhibitors. Between these groups, differences were determined by log-rank tests in the survival plots.

For all tests, a p value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) 16.0 (SPSS Inc. Chicago, IL, USA; www.spss.com). The study was approved by the Institutional Review Board at National Taiwan University Hospital, and informed consent was obtained from all patients. The authors had full access to the data and take responsibility for its integrity. All authors have read and concur with the contents of the manuscript as written.

**RESULTS**

**Baseline characteristics**

ACE inhibitors were prescribed initially to 290 of the 518 hypertensive CAD patients (56%). Baseline characteristics, echocardiographic data, and genetic polymorphisms are shown in Table 1. The baseline characteristics were comparable in both groups. The use of additional medications and polymorphism distribution were not associated with the prescription of ACE inhibitors.
End point

The outcome of all-cause mortality occurred in 63 (22%) patients in the ACE inhibitor group and 59 (26%) patients in the No-ACE inhibitor group. The Kaplan-Meier curve showed no statistical difference between the two groups at 4000 days. On the other hand, at the end of 4000 days, there was a significant statistical difference in MACE between the two groups that favored the use of ACE inhibitors [hazard ratio (HR) = 0.51, 95% confidence interval (CI): 0.41-0.86, p = 0.032] (Figure 1).

Genotypes and survival

The genotype distribution of the ACE gene I/D polymorphism, G-217A, G-152A, A-20C, G-6A, T4072C, and C3889T polymorphisms of the AGT gene, and the A1166C polymorphism of the AGT1R gene in the two groups are listed in Table 1. The genotype proportions were in Hardy-Weinberg equilibrium. In the multiple Cox regression model for all-cause death, there was no significant difference for all genotypes between those

Table 1. Baseline demographics by treatment group

<table>
<thead>
<tr>
<th></th>
<th>ACE inhibitor (n = 290)</th>
<th>No-ACE inhibitor (n = 228)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ± SD, years</td>
<td>52.1 ± 7.2</td>
<td>54.7 ± 6.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Sex (Male/Female), n</td>
<td>137/153</td>
<td>105/123</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.1 ± 5.1</td>
<td>23.2 ± 6.2</td>
<td>0.70</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>110</td>
<td>87</td>
<td>0.3</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>134</td>
<td>92</td>
<td>0.1</td>
</tr>
<tr>
<td>WBC ± SD, mm³</td>
<td>7154 ± 2170</td>
<td>6214 ± 2336</td>
<td>0.53</td>
</tr>
<tr>
<td>Cholesterol ± SD, mg/dl</td>
<td>187.1 ± 26.4</td>
<td>183.2 ± 34.2</td>
<td>0.65</td>
</tr>
<tr>
<td>Triglyceride ± SD, mg/dl</td>
<td>151.2 ± 56.1</td>
<td>160.2 ± 59.1</td>
<td>0.36</td>
</tr>
<tr>
<td>Low density cholesterol ± SD, mg/dl</td>
<td>132.3 ± 22.8</td>
<td>131.3 ± 32.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138 ± 24</td>
<td>137 ± 22</td>
<td>0.85</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 ± 14</td>
<td>75 ± 11</td>
<td>0.76</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-blocker, n</td>
<td>83</td>
<td>72</td>
<td>0.14</td>
</tr>
<tr>
<td>Calcium channel blocker, n</td>
<td>131</td>
<td>113</td>
<td>0.42</td>
</tr>
<tr>
<td>Statins, n</td>
<td>60</td>
<td>45</td>
<td>0.88</td>
</tr>
<tr>
<td>Aspirin</td>
<td>250</td>
<td>208</td>
<td>0.73</td>
</tr>
<tr>
<td>Genetic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGT C3889T (TT:TM:MM)</td>
<td>229:52:9</td>
<td>178:44:6</td>
<td>0.75</td>
</tr>
<tr>
<td>AGT T4072C (TT:TM:MM)</td>
<td>209:74:7</td>
<td>162:61:5</td>
<td>0.77</td>
</tr>
<tr>
<td>AGT A-20C (AA:AC:CC)</td>
<td>259:22:9</td>
<td>208:16:4</td>
<td>0.86</td>
</tr>
<tr>
<td>AGT G-152A (GG:GA:AA)</td>
<td>266:20:4</td>
<td>210:17:1</td>
<td>0.74</td>
</tr>
<tr>
<td>AGT G-217A (GG:GA:AA)</td>
<td>208:69:13</td>
<td>158:60:10</td>
<td>0.68</td>
</tr>
<tr>
<td>ACE I/D (II:ID:DD)</td>
<td>73:134:83</td>
<td>61:104:63</td>
<td>0.86</td>
</tr>
<tr>
<td>AGT1R A1166C (AA:AC:CC)</td>
<td>268:18:4</td>
<td>207:19:2</td>
<td>0.54</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; AGT, angiotensinogen; AGT1R, angiotensin II type 1 receptor; BMI, body mass index; I/D, insertion/deletion; SD, standard deviation; WBC, white blood cell.

Figure 1. Kaplan-Meier plot of major cardiovascular event-free survival in the patients with coronary artery disease according to the use of angiotensin-converting enzyme (ACE) inhibitors.
patients in the ACE inhibitor and No-ACE inhibitor group. However, regarding MACE, the ACE I/D gene D allele induced a 1.64-fold hazard compared to the I-allele (HR: 1.64, 95% CI: 1.27-1.98, p < 0.001) (Table 2). To adjust for confounding effects of other clinical factors, we performed Cox regression models analysis and found that different genotypes were still associated with MACE after adjusting for age, gender, body mass index, diabetes, use of ACE inhibitors, and ACE gene I/D polymorphism (ACE D allele: HR: 1.52, 95% CI: 1.37-1.97, p < 0.005; Table 3, model 1). The use of ACE inhibitors was associated with better prognosis in both model 1 and model 2 (Table 3). We further evaluated the pharmacogenetic interaction of ACE, AGT1R genes, and ACE inhibitors for MACE by Cox regression analysis. After adjusting the confounding factors and incorporating the interaction terms of ACE gene D allele*ACE inhibitors into the analysis, the effect of ACE gene D allele was still significant (ACE D allele: HR: 1.44, 95% CI: 1.21-1.85, p = 0.004; Table 3, model 2). Moreover, the interaction between ACE gene I/D polymorphism and ACE inhibitors offered a protective effect for the development of MACE (ACE D allele*ACE inhibitors: HR: 0.68, 95% CI: 0.52-0.84, p = 0.014; Table 3, model 2). The pharmacogenetic interaction may add an additional 32% preventive effect for MACE in hypertensive CAD patients. To further explore whether the ACE I/D status could really “modify” the therapeutic effects of ACE inhibitors, we examined the HR of ACE inhibitor in subjects with the ACE I allele and those with D allele separately (ACE inhibitors for MACE in I allele patients: HR: 0.86, 95% CI: 0.65-1.08, p = 0.12; ACE inhibitors for MACE in D allele patients: HR: 0.64, 95% CI: 0.45-0.81, p = 0.03). ACE inhibitors protected hypertensive CAD patients from MACE, especially in those subjects with the ACE gene D allele.

The effect of the ACE I/D gene by plotting Kaplan-Meier curves separately in hypertensive CAD patients considering their genotypes and use of ACE inhibitors was further examined. Patients with the ACE gene I allele along with the use of ACE inhibitors had the least chance of experiencing MACE, while those with the ACE gene D allele and no ACE inhibitors had the highest risk (log rank p < 0.001; Figure 2). This result suggests that ACE inhibitors modulate the association between the ACE gene I/D polymorphism and MACE in hypertensive CAD patients.

### Table 3. Cox regression models for MACE event-free survival

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>ACE D allele</td>
<td>1.52</td>
<td>1.34-1.97</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor</td>
<td>0.51</td>
<td>0.41-0.86</td>
</tr>
<tr>
<td>Model 2</td>
<td>ACE D allele</td>
<td>1.44</td>
<td>1.21-1.85</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor</td>
<td>0.62</td>
<td>0.51-0.94</td>
</tr>
<tr>
<td></td>
<td>D allele* ACE inhibitor</td>
<td>0.68</td>
<td>0.52-0.84</td>
</tr>
</tbody>
</table>

All models adjusted for age, gender, diabetes, hypertension, and body mass index.

ACE, angiotensin-converting enzyme; AGT1R, angiotensin II type 1 receptor.

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### Table 2. HR in relation to the genotypes obtained from Cox regression analysis of survival time in hypertensive coronary artery disease patients or time to MACE

<table>
<thead>
<tr>
<th>Gene locus (alleles)</th>
<th>MACE HR (95% CI)</th>
<th>p-value</th>
<th>All-cause death HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGT C3889T (T:M)</td>
<td>0.84 (0.67-1.32)</td>
<td>0.52</td>
<td>0.82 (0.48-1.38)</td>
<td>0.55</td>
</tr>
<tr>
<td>AGT M2345T (T:M)</td>
<td>0.92 (0.75-1.49)</td>
<td>0.79</td>
<td>0.75 (0.40-1.35)</td>
<td>0.43</td>
</tr>
<tr>
<td>AGT A-6G (A:G)</td>
<td>1.25 (0.88-1.61)</td>
<td>0.42</td>
<td>1.09 (0.72-1.49)</td>
<td>0.79</td>
</tr>
<tr>
<td>AGT A-20C (A:C)</td>
<td>0.62 (0.36-1.09)</td>
<td>0.09</td>
<td>0.72 (0.43-1.30)</td>
<td>0.30</td>
</tr>
<tr>
<td>AGT G-152A (G:A)</td>
<td>0.86 (0.43-1.36)</td>
<td>0.54</td>
<td>0.91 (0.57-1.73)</td>
<td>0.74</td>
</tr>
<tr>
<td>AGT G-217A (G:A)</td>
<td>0.93 (0.70-1.63)</td>
<td>0.88</td>
<td>0.92 (0.72-1.47)</td>
<td>0.73</td>
</tr>
<tr>
<td>ACE I/D (D:I)</td>
<td>1.64 (1.27-1.98)</td>
<td>&lt;0.001</td>
<td>1.13 (0.64-1.98)</td>
<td>0.48</td>
</tr>
<tr>
<td>AGT1R A1166C (C:A)</td>
<td>1.28 (0.94-2.21)</td>
<td>0.12</td>
<td>1.08 (0.84-1.46)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; AGT, angiotensinogen; AGT1R, angiotensin II type 1 receptor; CI, confidence interval; HR, hazard ratio; MACE, major cardiovascular events.
RAS Genes and Prognosis in Hypertensive CAD Patients

Figure 2. Kaplan-Meier plot of major cardiovascular event-free survival in the patients with coronary artery disease according to the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin converting enzyme gene I/D polymorphism genotypes. (The case numbers of the 4 subgroups are listed as follows: I allele with ACE inhibitors: 280, D allele with ACE inhibitors: 300, I allele without ACE inhibitors: 226, and D allele without ACE inhibitors: 230)

DISCUSSION

In the current study, we demonstrated a substantial benefit of using ACE inhibitors for MACE in a population of hypertensive patients with angiographic coronary artery disease. Furthermore, the study demonstrated a clear pharmacogenetic interaction between ACE inhibitors and the ACE gene after long-term follow up. These findings may help to select the best treatment options for ongoing patient care, including the use of ACE inhibitors to optimize therapy.

To our best knowledge, this is the first study to address pharmacogenetics effects between RAS gene polymorphisms and ACE inhibitor use in hypertensive CAD patients in Han populations. Although there have been studies investigating the use of ACE inhibitors, they were performed in Caucasian populations, different from the current study in genetics and ethnicity. The frequency of deletion and insertion alleles among the Chinese are 0.3 and 0.7 respectively, indicating a much higher prevalence of the insertion allele than had been reported among Caucasians.23 The concept of pharmacogenetics to help optimize individual medicine is emerging rapidly and is of increasing importance since it has the potential to revolutionize clinical practice. The current study confirmed ACE inhibitors interact with ACE gene polymorphisms in Han populations, but not with AGT and ATR gene polymorphisms. Brugts et al. came to similar conclusions — use of ACE inhibitors in a group of ACE I polymorphisms was favored. Identifying pharmacogenomics will help optimize therapy with ACE inhibitors for use in hypertensive CAD patients. This may decrease healthcare costs.

Rather than focusing on one single polymorphism, we genotyped several candidate genes, ACE I/D, AGT1R, and AGT gene polymorphisms, all of which are involved in the RAS, in order to clarify the role of genetic variation with ACE inhibitors therapy. While ACE inhibitors work with multiple pathways in RAS, single gene polymorphism analysis may diminish in importance and fail to clarify clinical significance of RAS genes variation with ACE inhibitors use. In the current study, the selected eight genes were known to play an important role in the pharmacodynamic pathway of ACE inhibitors and RAS.24

Genetic influence of RAS gene polymorphisms on cardiovascular disease, especially the susceptibility and progression of hypertension, CAD or heart failure, has been widely studied.19,24 In the general population, the ACE I/D D allele has been related to cardiovascular mortality in several meta-analyses, although this association has not been duplicated by others.25,26 Recent studies have found that patients with the ACE I/D gene D allele and AGT1R gene A1166C C allele in RAS genes were more likely to develop CAD.27-29 In the current study, we demonstrated that the ACE I/D gene D allele and AGT1R gene A1166C C allele were associated not only with the development of CAD but also with long-term cardiovascular events. Furthermore, the genetic association of the ACE I/D polymorphism with MACE was attenuated in those patient who took ACE inhibitors. This pharmacogenetic interaction suggests that the adverse effects associated with genetic polymorphisms could be counteracted, or even reversed, by appropriate medical treatment. Recently, the PERindopril GENetic (PERGENE) association study investigated the genetic determinants of treatment benefits of ACE inhibitor therapy, and concluded that genetic variants modifying the treatment effect of perindopril are particularly located in the AGT1R and bradykinin 1-receptor genes.24 However, that study was limited due to its relatively short follow-up period (mean 4.2 years). The current study followed a modest number of hypertensive, CAD patients for a longer duration and replicated the PERGENE study to some extent. We also demonstrated that the genetic variants associated with long-term outcomes of hypertensive CAD patients are located in the AGT1R and ACE genes.
According to our unpublished data, the effects of ACE inhibitors over the ACE gene in hypertensive CAD patients seemed to have similar effects for whole CAD patients. The pharmacogenetic effects for ACE inhibitors and ACE gene are consistent whether or not the patients have hypertension. However, in our recent observations, AGT1R gene C alleles were associated with a higher MACE rate based on a multivariate regression analysis in whole CAD patients but not in the subgroup of patients with hypertension. Hypertension modified the genetic effect of AGT1R gene to some extent.

The effect of the single-nucleotide polymorphism on the functional nature of ACE is not known and we can only speculate on the underlying mechanisms. Previous studies have revealed that subjects with ACE DD genotypes were associated with a higher level of plasma angiotensin II concentrations. It has been shown that angiotensin II impaired endothelial function in both normal and resistance arteries, which subsequently increased the susceptibility for CAD or congestive heart failure. Cytokines were also recently found to regulate adrenal vascular tone and thus concurrently increase adrenal blood flow and steroidogenesis. All of the above mechanisms provide a framework for the hypothesis that increased serum angiotensin II levels may further lead to the development of left ventricular systolic function, lung congestion, increased risk of CAD, and may also increase morbidity or MACE rates. On the other hand, AGT1R is the major receptor that mediates most of the physiologic action of angiotensin II, which is known to increase collagen synthesis in the myocardium. Sanderson et al. showed that a variant of the AGT1R gene C allele was associated with an increased frequency of hospital admissions in patients with congestive heart failure. The current results imply that increased myocardial collagen synthesis and stiffness associated with the AGT1R C allele may lead to the development of heart failure, or CAD, and result in increased MACE rates, which may not be resolved by the use of ACE inhibitors.

**LIMITATIONS**

Several limitations were present in the current study. First, the decision to prescribe ACE inhibitors was made by attending cardiologists, a process that was not randomized. In addition, the sample size was relatively small. Consequently, a large-scale randomized trial with a time span of up to 10 years is still warranted. However, the current cases were followed carefully for an extended period of time. All of the underlying variables were documented and adjusted by regression models, thereby improving the validity of the results. The case number, in spite of being moderate, is sufficient to provide enough power to demonstrate the benefit of ACE inhibitors in reducing cardiovascular events.

**CONCLUSION**

In conclusion, the current study has demonstrated that use of ACE inhibitors is associated with a significant decrease in MACE in hypertensive patients with CAD. In addition, genetic variation or polymorphisms in the RAS is also associated with long-term MACE-free survival in this group of patients; however, the effects can be modified by the use of ACE inhibitors.

**ACKNOWLEDGEMENTS**

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**DISCLOSURE OF INTEREST**

The authors declare that they have no competing interests.

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