Title	Renin-angiotensin-aldosterone system polymorphisms and 5-year mortality in survivors of acute myocardial infarction a report from the osaka acute coronary insuffi ciency study
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Citation	International Heart Journal. 2014, 55(3), p. 190-196
Version Type	VoR
URL	https://hdl.handle.net/11094/78723
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Renin-Angiotensin-Aldosterone System Polymorphisms and 5-Year Mortality in Survivors of Acute Myocardial Infarction

A Report From the Osaka Acute Coronary Insufficiency Study

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Summary

This study sought to evaluate whether genetic variants in the renin-angiotensin-aldosterone system (RAAS) have an impact on long-term mortality after acute myocardial infarction (AMI) in the percutaneous coronary intervention (PCI) era. We investigated the impacts of individual and combinations of 4 major RAAS genetic variants, angiotensinogen (AGT) T1311C, angiotensin-converting enzyme (ACE) insertion/deletion (I/D), angiotensin 2 type 1 receptor A1166C, and aldosterone synthase T4660C on 5-year mortality in 3149 post-AMI patients using multivariate Cox regression analysis. The predictive accuracy of all possible RAAS genetic combinations was evaluated using Cox regression analysis, and the best combination that affected prognosis was determined based on the minimal Akaike Information Criterion. There were 220 deaths during a median follow-up of 4.9 years. Independent analyses of any single RAAS variant did not show significant impacts on 5-year mortality. However, analyses in combination revealed that absence of both AGT CC genotype and ACE D allele was associated with lower 5-year mortality (log-rank $P = 0.005$). Patients with at least either of the AGT CC or ACE D allele had increased mortality with adjusted hazard ratios of 2.07 (95% confidence interval 1.18-3.65, $P = 0.012$), compared with those with neither the AGT CC nor ACE D allele. Among the 4 RAAS genetic variants examined, a combination of AGT and ACE polymorphisms was associated with 5-year mortality after AMI. (Int Heart J 2014; 55: 190-196)

Key words: Genetics, Secondary prevention

The renin-angiotensin-aldosterone system (RAAS) plays important roles in the pathogenesis of cardiovascular disease, including hypertension which results in the progression of atherosclerosis and acute myocardial infarction (AMI). For this reason, the clinical impacts of genetic variants in RAAS have been intensively investigated. In particular, the angiotensinogen (AGT) T1311C, angiotensin-converting enzyme (ACE) insertion/deletion (I/D), angiotensin 2 type 1 receptor (AGTR1) A1166C, and aldosterone synthase (CYP11B2) T4660C polymorphisms are the most studied RAAS genetic variants in this regard.[1-13] These polymorphisms are associated with the onset or development of hypertension, left ventricular hypertrophy, and AMI, although some conflicting evidence exists.[1-13]

Despite the abundant evidence in primary prevention settings of cardiovascular diseases, whether these variants influence mortality in post-AMI patients, namely, in the secondary prevention setting[14-16] has not been well studied and remains controversial. For example, the ISIS trial concluded that ACE I/D polymorphism is not associated with the 5-year survival rate after AMI.[15] Meanwhile, Palmer, *et al* reported that the ACE D allele was associated with higher mortality after AMI.[16] One possible reason for this inconsistency is that these studies did not evaluate gene-gene interactions among variants of the RAAS cascade, which may provide a different conclusion.[11,17] Thus, systematic investigations of the impacts of

RAAS variants considering gene-gene interactions using large-scale post-AMI cohorts have been warranted to examine the prognostic impacts of RAAS genetic variants in combination.

The aim of the study was to evaluate whether 4 RAAS genetic variants, AGT T1311C, ACE I/D, AGTR1 A1166C, and CYP11B2 T4660C, either alone or in combination, impact 5-year mortality after AMI.

METHODS

Study patients: Among 8,957 AMI patients registered in the Osaka Acute Coronary Insufficiency Study (OACIS) between April 1998 and December 2008, 3,256 patients who agreed to deoxyribonucleic acid (DNA) genotyping were enrolled in the present study (Figure 1). Of the enrolled patients, 3,149 patients were successfully genotyped and analyzed. OACIS is a multicenter, prospective, observational registry for AMI patients in Japan that was initiated in April 1998, and as of 2013, contained data for more than 11,000 patients who had been hospitalized in 1 of the 25 collaborating hospitals. The details of OACIS are described elsewhere.[18-21]

The diagnosis of AMI was based on the World Health Organization criteria, which uses a combination of patient symptoms, electrocardiographic findings, and serum cardiac enzyme elevations. All study candidates were informed about data collection, blood sampling, and genotyping, and provided written informed consent. The study protocol complied with the Helsinki Declaration and the guidelines for genome/genetic research issued by the Japanese government. The study was approved by the institutional ethical committee of each participating institution.

Study endpoint: The primary endpoint of the study was all-cause mortality after survival discharge for AMI. Follow-up clinical data were obtained at 3, 6, and 12 months after the onset of AMI and annually thereafter for 5 years.

Genotyping: Deoxyribonucleic acid (DNA) isolation and genotyping were performed using peripheral blood samples. Genomic DNA was extracted from blood samples using a commercially available kit (Qiagen, Hilden, Germany), and all patients were genotyped for the following 4 genetic polymorphisms of RAAS: AGT T1311C (rs699), ACE I/D (rs1799752), AGTR1 A1166C (rs5186), and CYP11B2 T4660C (rs1799998). All 4 variant genotypes were determined using an intercalator-mediated fluorescence resonance energy transfer probe method, and/or a polymerase chain reaction-based method, as previously described.[21-23]

Statistical analysis: Categorical data are presented as the percentage and were compared using chi-square statistics. Continuous data are expressed as the median (25-75 percentiles) and were compared using the Wilcoxon rank sum test. The Kaplan-Meier method was employed to estimate survival rates, and differences were compared by the log-rank test. Candidate combinations of RAAS polymorphisms for best predicting 5-year mortality using Cox regression analysis were searched based on Akaike information criterion (AIC) where AIC is commonly used as a goodness-of-fit statistic and a smaller value suggests a better-fitted model.[24] Specifically, the predictive accuracy of all possible RAAS genetic variant combinations was evaluated using Cox regression analysis, and the best combination that affected prognosis was determined based on
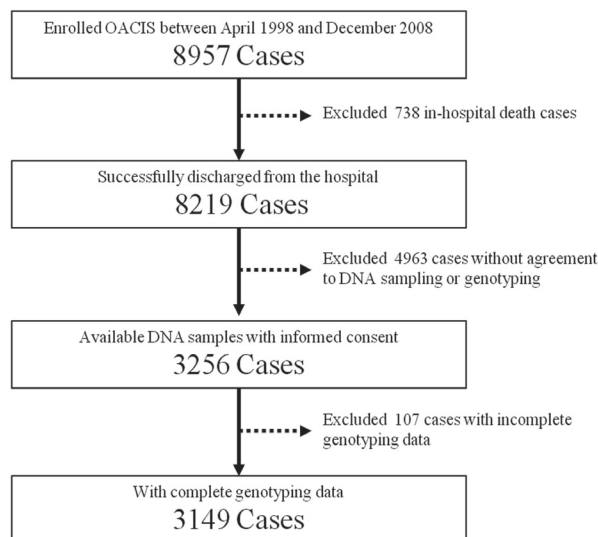

Figure 1. Flow chart of study population selection.

the minimal AIC. The purpose of evaluating the predictive accuracy of all possible RAAS genetic variant combinations based on minimal AIC was to avoid problems concerning multiple testing. The impact of the above determined RAAS genetic combination on 5-year mortality was compared using Cox regression analysis that estimates the hazard ratio (HR) and its 95% confidence interval (CI). To reduce the bias of possible confounding factors related to patient background in the comparisons, we used multivariate Cox regression analysis with the following variables as covariates: age, gender, body mass index, ST-elevation myocardial infarction, diabetes, hypertension, dyslipidemia, smoking, previous myocardial infarction, Killip classification, reperfusion therapy, peak creatine phosphokinase, and beta-blocker, statin, antiplatelet agent, aldosterone antagonist, and calcium channel blocker therapy. In addition, as there were missing values in the Killip classification (data missing for 129 patients) and peak creatine phosphokinase values (data missing for 328 patients), we imputed Killip classification and peak creatine phosphokinase values by the mean of the Markov Chain Monte Carlo imputation method and then the same analyses were performed to evaluate the robustness of the conclusions. Because multivariate Cox regression analysis was performed only once with the best predictive RAAS genetic combination during gene-gene interaction evaluation, statistical significance was set as $P < 0.05$. All statistical analyses were performed using SAS version 9.3 for Windows (SAS Inc., Cary, NC) and R software packages version 2.15.1 (R Development Core Team).

RESULTS

Patient characteristics are shown in Table I (a comparison of patient characteristics among genotypes in each genetic variant is shown in Supplementary Table). Median age was 65 years, 77.6% were male, 86.2% had ST-elevation myocardial infarction, and 88.8% had undergone percutaneous coronary intervention (PCI). A total of 220 deaths occurred during the median follow-up period of 1772 (1093-1801) days. The call

Table I. Patient Characteristics

	Total	Reference group	Risk group	P
n	3149	432	2717	–
Age, years	65 (57-72)	64 (57-72)	65 (57-72)	0.484
Male, %	77.6	83.1	76.7	0.003
BMI, kg/m^2	23.6 (21.6-25.8)	23.7 (22.0-25.5)	23.6 (21.6-25.8)	0.653
STEMI, %	86.2	86.4	86.2	0.892
Coronary risk factor				
Diabetes, %	35.9	36.1	35.8	0.904
Hypertension, %	58.8	59.0	58.7	0.921
Dyslipidemia, %	48.0	51.1	47.5	0.172
Smoking, %	65.4	67.6	65.0	0.292
Previous MI, %	11.7	11.3	11.8	0.760
KILLIP $\geqq$ 2, %	12.9	14.4	12.7	0.341
Reperfusion therapy, %	91.2	91.4	91.2	0.855
PCI, %	88.8	87.5	89.0	0.373
CABG, %	1.6	2.5	1.4	0.073
Laboratory data				
eGFR, mL/min/1.73m^2	67.6 (53.3-82.6)	66.9 (51.6-84.7)	67.9 (53.6-82.3)	0.984
HbA1c, %	6.0 (5.5-7.0)	6.0 (5.5-7.0)	6.0 (5.5-7.0)	0.714
T-Chol, mg/dL	192 (165-223)	194 (162-222)	192 (165-223)	0.811
LDL-Chol, mg/dL	124 (100-150)	121 (100-148)	124 (101-150)	0.165
HDL-Chol, mg/dL	45 (38-53)	45 (37-53)	44 (38-53)	0.688
TG, mg/dL	97 (60-146)	95 (60-149)	97 (60-145)	0.982
Peak CPK, IU/L	2100 (1029-3832)	2016 (1040-3831)	2092 (1029-3786)	0.654
Medication at discharge				
ACEI or ARB, %	74.1	74.6	74.0	0.771
Beta-blocker, %	44.3	45.3	44.2	0.644
Statin, %	38.7	40.2	38.5	0.484
Aldosterone antagonist, %	14.9	12.6	15.2	0.150
Antiplatelet, %	98.3	99.3	98.2	0.093
Calcium channel blocker, %	21.5	18.8	22.0	0.143

We defined patients without the AGT CC genotype and ACE D allele as the Reference group and others as the Risk group. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CPK, creatine phosphoki-nase; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-Chol, high density lipoprotein cholesterol; LDL-Chol, low density lipo-protein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; T-Chol, total cholesterol; and TG, triglycerides.

rate of the AGT genotype was 99.0% (32 of 3256 genotyping attempts failed), ACE genotype 99.0% (32 of 3256 failed), AGTR1 genotype 99.1% (28 of 3256 failed), and the CYP11B2 genotype was 98.7% (41 of 3256 failed). Among all tested samples, all 4 variants were successfully genotyped in 3149 patients, who were analyzed in the present study (Figure 1).

First, we demonstrated that the individual genotype classification of each RAAS variant could not statistically stratify mortality risk in post-AMI patients although there were no events in patients with AGTR1 CC genotype (Figure 2 and Table II). Candidate RAAS polymorphisms for prognostic analysis considering gene-gene interaction were then selected based on the minimal AIC determined from the Cox regression analysis for 5-year mortality (Table III). The best estimated model for predicting 5-year mortality included both the AGT CC genotype and ACE D allele. Kaplan-Meier survival estimates were clearly discerned between patients without the AGT CC genotype and ACE D allele and others with log-rank $P = 0.005$ (Figure 3). According to this result, we defined patients without the AGT CC genotype and ACE D allele as the Reference group and others as the Risk group (Figure 3). This result from Figure 3 indicates the absence of additive effects on mortality between the ACE D allele and AGT CC genotype. For example, adverse impacts of ACE D allele or AGT CC can be detectable only when the patients do not have the other risk vari-

ant.

There are slight differences in patient backgrounds between the Reference and Risk groups (Table I). Thus, we employed multivariate Cox regression analysis to evaluate the impact of risk genetic variant combination on 5-year mortality. It revealed that the Risk group had statistically significant increased mortality when compared to the Reference group with an adjusted HR of 2.07 (95% CI 1.18-3.65, $P = 0.012$).

DISCUSSION

The present study, which included a total of 3,149 post-AMI patients, represents one of the largest scale RAAS genetic analyses conducted to date in post-AMI patients. Using an AIC-based analysis, we revealed that the presence of either the AGT CC genotype or ACE D allele negatively impacts 5-year mortality in the secondary prevention setting after AMI. Interestingly, this association was not found when the impact of each RAAS polymorphism was assessed individually even though the impact of AGTR1 CC genotype could not be assessed in detail due to the small sample size ($n = 19$). The present data may provide novel insights into the relationship between RAAS genetic variants and long-term prognosis in post-AMI patients, and help us to understand the inconsistency among the studies investigating the prognostic impacts of ACE
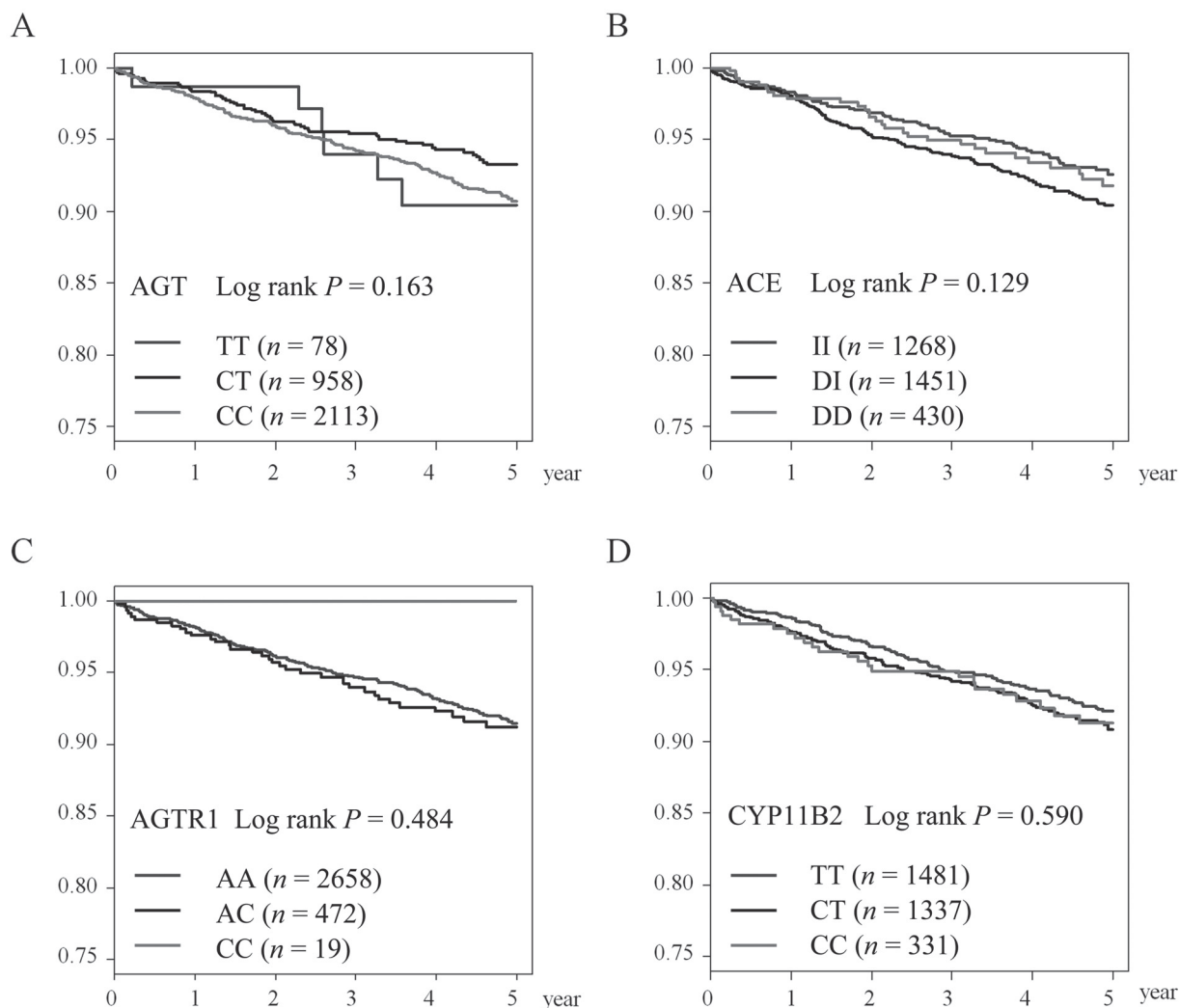
A

B

C

D

Figure 2. Difference in Kaplan-Meier survival estimates due to genotypes for each RAAS genetic variant. ACE indicates angiotensin-converting enzyme; AGT, angiotensinogen; AGTR1, angiotensin 2 type 1 receptor; CYP11B2, aldosterone synthase; and RAAS, renin-angiotensin-aldosterone system.

I/D polymorphism on mortality after AMI.[14-16]

The RAAS polymorphisms, AGT T1311C, ACE I/D, AGTR1 A1166C, and CYP11B2 T4660C have been shown to confer susceptibility to several cardiovascular diseases although conflicting evidence has been reported.[1-13] The ACE D and AGTR1 C allele are associated with hypertension, left ventricular hypertrophy, and myocardial infarction, which are thought to result from increased ACE activity and sensitivity to angiotensin II, respectively.[2-6,9-12] Similar associations have been suggested for the AGT C allele which may be related to higher concentrations of plasma angiotensinogen,[7,8] while the CYP11B2 C allele is associated with left ventricular dilatation in hypertensive patients possibly by influencing renal sodium handling.[13] Thus, the 4 RAAS genetic variants examined in this study were assumed to have unfavorable impacts on prognosis after AMI. However, we failed to detect a higher mortality risk for any RAAS variant when the impact of each variant was examined individually (Figure 2 and Table II), which is consistent with the previously reported data from the ISIS and other studies.[14,15] By contrast, it was clearly demonstrated that

the presence of either or both of two RAAS variants, the AGT CC genotype and ACE D allele, increases the risk of 5-year mortality in post-AMI patients (Figure 3). Interestingly, there was no additive impact on mortality between the two polymorphisms. Considering our results, we speculated that this phenomenon could be explained by a mechanism that both AGT CC and ACE D allele activate RAAS but only one of these two variants is efficient to make this activation (there are no additive or synergistic impacts).

This finding was of clinical significance, because this could be a reason why ACE D allele was not seemingly associated with increased mortality by individual variant assessment in the previous studies, including the ISIS study.[14,15] In the present study, the prognostic impact of ACE D allele was not significant without considering the AGT CC genotype (like in the previous studies), but was significant after considering the AGT CC genotype. Thus, our findings underline the importance of considering gene-gene interactions when evaluating the genetic impacts on diseases.[11,17]

Another possible explanation for the lack of prognostic

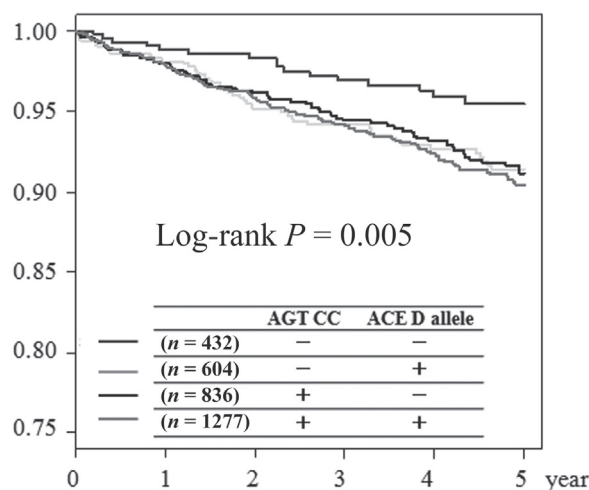**Table II.** Impact of Genotype on 5-year Mortality for Each RAAS Polymorphism

Multivariate Cox regression analysis ($n = 2800$, event = 190)			
	adjusted HR	95% CI	P
AGT			
AGT CT versus TT	0.68	0.27-1.72	0.412
AGT CC versus TT	0.84	0.34-2.07	0.700
AGT TC/CC versus TT	0.79	0.32-1.95	0.609
AGT CC versus TC/TT	1.20	0.87-1.66	0.273
ACE			
ACE DI versus II	1.36	0.99-1.86	0.057
ACE DD versus II	1.06	0.66-1.70	0.803
ACE ID/DD versus II	1.29	0.95-1.74	0.101
ACE DD versus ID/II	0.89	0.58-1.37	0.604
AGTR1			
AGTR1 AC versus AA	1.08	0.73-1.60	0.692
AGTR1 CC versus AA	< 0.01	< 0.01- > 10	0.992
AGTR1 AC/CC versus AA	1.01	0.69-1.49	0.950
AGTR1 CC versus AC/AA	< 0.01	< 0.01- > 10	0.992
CYP11B2			
CYP11B2 CT versus TT	0.98	0.72-1.34	0.921
CYP11B2 CC versus TT	1.35	0.85-2.14	0.211
CYP11B2 TC/CC versus TT	1.05	0.79-1.40	0.751
CYP11B2 CC versus TC/TT	1.36	0.87-2.11	0.177

Impact of each variant was calculated in additive (above 2 rows), dominant (3rd row), and recessive (4th row) models. ACE indicates angiotensin-converting enzyme; AGT, angiotensinogen; AGTR1, angiotensin 2 type 1 receptor; CI, confidence interval; CYP11B2, aldosterone synthase; HR, hazard ratio; and RAAS, renin-angiotensin-aldosterone system.

Table III. Best 20 Combinations of 4 Renin-Angiotensin-Aldosterone System Polymorphisms for Predicting 5-year Mortality Based on Akaike Information Criterion of Cox Regression Analysis

	AIC	AGT	ACE	AGTR1	CYP11B2
1	3445.229	recessive	dominant		
2	3446.307		dominant		
3	3446.343	recessive	dominant		dominant
4	3446.461	recessive			
5	3446.526	recessive	additive		
6	3446.619	additive	dominant		
7	3447.023			recessive	
8	3447.150	recessive	dominant		recessive
9	3447.218	recessive	dominant	dominant	
10	3447.325		dominant		dominant
11	3447.494	recessive			dominant
12	3447.533		additive		
13	3447.634	recessive	additive		dominant
14	3447.724	additive	dominant		dominant
15	3447.876	additive			
16	3447.944	additive	additive		
17	3448.188	dominant	dominant		
18	3448.204		dominant		recessive
19	3448.296		dominant	dominant	
20	3448.329	recessive	dominant	dominant	dominant

Each variant has 4 options; no consideration, additive model, recessive model, and dominant model. Additive models of AGT, ACE, AGTR1 and CYP11B2 are defined as TT versus TC versus CC, II versus ID versus DD, AA versus AC versus CC, and TT versus TC versus CC, respectively. Recessive models of AGT, ACE, AGTR1 and CYP11B2 are defined as TT/TC versus CC, II/ID versus DD, AA/AC versus CC, and TT/TC versus CC, respectively. Dominant models of AGT, ACE, AGTR1 and CYP11B2 are defined as TT versus TC/CC, II versus ID/DD, AA versus AC/CC, and TT versus TC/CC, respectively. Predictive accuracy of all possible 255 combinations was evaluated using Cox regression analysis, and the best combination that affected prognosis was determined based on the minimal Akaike Information Criterion.

Figure 3. Kaplan-Meier survival estimates for each genetic combination. ACE indicates angiotensin-converting enzyme; and AGT, angiotensinogen.

impacts of each individual RAAS genetic variant in this study was the implementation of evidence-based medical treatment in the secondary prevention setting after AMI. First of all, the high treatment rate of PCI in this study likely contributed to lowering mortality, and made it difficult to detect the prognostic impact of RAAS variants due to the low event rate. Indeed, 5-year mortality in the present study was estimated to be only 8.5% (95% CI 7.4-9.6) which was significantly lower than those reported in the previous studies performed in the no PCI eras.[25] Furthermore, the use of secondary preventive medications that were recommended for improving long-term prognosis after AMI, such as RAAS inhibitors, beta-blockers, statins, and antiplatelet agents were also believed to contribute to the low event rate in the present study.[26] Consequently, even though RAAS variants might have a moderate prognostic impact, it is possible that optimal treatments for AMI likely reduced the mortality events and thus might have masked the adverse effects of RAAS polymorphism. Accordingly, the number of events during the 5-year follow-up of post-AMI patients receiving optimal medication was expected to be insufficient to detect the small genetic effects of an individual RAAS variant. In general, we often encounter the problem of detecting statistical significance after correction for multiple testing in gene-gene interaction analysis, particularly when the event rates are low despite a large sample size like in the present study. Therefore, we employed the AIC method to avoid problems concerning multiple testing and successfully examined all possible genetic combinations for risk stratification in the present study. Thus, estimation of the best predictive RAAS genetic combination for 5-year mortality using AIC of Cox regression analysis would be the one of the strengths of the present study.

The results of two relatively large case-control studies of RAAS variants (613 cases versus 723 controls and 205 cases versus 209 controls, respectively) suggest a gene-gene interaction between ACE and AGTR1 polymorphisms in the primary prevention setting of AMI.[11,17] Therefore, we also investigated the impact of the combination of ACE and AGTR1 variants, but the data suggested that the combination of AGT and ACE

variants was superior to that of ACE and AGTR1 variants for prediction of 5-year mortality in the present study according to the AIC-based analysis (Table III). The major difference between these case-control studies and the present study is the clinical setting; the former studies focused on the primary prevention setting, whereas we focused on the secondary prevention setting. In addition, these two case-control studies only analyzed the additive impact of gene-gene interaction on the development of coronary artery disease by selecting statistically positive variants, whereas we examined all the impacts of possible RAAS variant combinations in additive, dominant and recessive models using the AIC of Cox regression analysis. As a consequence, we found that both the AGT CC genotype and ACE D allele should be considered for mortality risk stratification in post-AMI patients, namely, in the secondary prevention setting of AMI. Accordingly, even though more comprehensive coverage of genetic variations of RAAS might be ideal, our approach to identify the best predictive combination of RAAS polymorphisms using 4 variants at the same time may be a strength of this study because many prior studies only focused on one or two polymorphisms of RAAS.[27]

The present study has several limitations that warrant mention. First, since the study population only consisted of patients who provided written informed consent, there may have been selection bias with possible unmeasured confounding factors influencing the study outcomes due to the inherent nature of an observational registry. However, a strength of our study is that OACIS is one of the largest scale trials with thousands of DNA samples available and long-term (5 years) follow-up clinical data in the real world secondary prevention setting of AMI. Second, the primary endpoint was all-cause mortality, which may have been due to causes other than cardiovascular disorders. Third, our study lacked a replication cohort. However, validation cohorts are more difficult to select in a prospective study design than in case-control studies that enroll patients cross-sectionally. In fact, all prospective studies referenced in this manuscript did not include a replication cohort.[14-16] The data should be interpreted within the context of these potential limitations.

In conclusion, RAAS genetic variant is associated with 5-year mortality in survivors of AMI. In particular, AGT and ACE polymorphisms should be considered in combination to more accurately stratify mortality risk.

Disclosure

Acknowledgments

Appendix

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