Angiotensinogen M235T and T174M Gene Polymorphisms in Combination Doubles the Risk of Mortality in Heart Failure


Abstract—Angiotensinogen M235T and T174M polymorphisms have individually been associated with elevated levels of plasma angiotensinogen, hypertension, and left ventricular hypertrophy. In this study, heart failure patients (n=451) were genotyped for the angiotensinogen M235T and T174M polymorphisms to investigate association with survival (recorded over 4 years of follow-up) and prognostic hormone markers. Patients carrying the 235 TT genotype (n = 86) were 3 years younger at admission (P = 0.011), and, in those with hypertension, diagnosis was made approximately 10 years earlier than other patients. Patients carrying ≥ 1 174M allele (n = 94) were more likely to have a previous history of heart failure (P = 0.044) and increased mortality during follow-up (risk ratio: 1.69, 95% CI: 1.03 to 2.79; P = 0.038) compared with 174TT homozygotes (n = 355), despite having a higher left ventricular ejection fraction (P = 0.009). “High-risk” genotype combinations (defined as 235TT and/or ≥ 1 174M allele; n = 144; 32%) were independently predictive of mortality, conferring a 2-fold greater risk of dying during the follow-up period (odds ratio: 2.0; 95% CI: 1.3 to 3.0; P = 0.001). This study suggested that angiotensinogen gene variants M235T and T174M may provide prognostic information for long-term survival in heart failure patients. (Hypertension. 2007;49:1-6.)

Key Words: angiotensinogen ■ polymorphism ■ single nucleotide ■ mortality ■ heart failure ■ association

The renin–angiotensin system (RAS) is a key element in pressure/volume homeostasis and exerts a wide range of systemic and local effects through endocrine, paracrine, and autocrine signaling.1 In patients with cardiovascular disease, activity of the RAS is often increased and contributes to a poor prognosis.2 Detrimental effects include promotion of inappropriate sodium and water retention, increased peripheral vascular resistance, and promotion of adverse vascular and cardiac remodeling in response to cardiac injury.3 Gene polymorphisms that increase baseline RAS activity are, therefore, candidates for increasing risk of, and adverse outcomes in, heart disease.

The gene encoding angiotensinogen (AGT) has been implicated in hypertension both through genetic linkage studies4,5 and by allelic association. A missense mutation in exon 2 of the gene (AGT M235T) has been associated with elevated levels of AGT, with 235TT homozygotes having between 10% and 20% more plasma AGT than 235MM individuals.4,6,7 These individuals also have increased blood pressure,4,8–11 although a large-scale study of 9100 men and women from the Danish general population found that this was only true in women.7 The frequency of the 235T allele has been shown to be significantly greater in hypertensive patients than in normotensive control subjects4,12–14 and has also been linked with pre-eclampsia,15 left ventricular hypertrophy,16 increased risk of coronary heart disease,17,18 and atrial fibrillation.19 A second variant within the AGT gene, T174M, has also been associated with hypertension, with the M allele associated with an increased risk.4,14 The M235T and T174M variants are in linkage disequilibrium.4,14 However, a large-scale meta-analysis found no consistent association between either AGT polymorphism and increased risk for ischemic heart disease, myocardial infarction, or ischemic cerebrovascular disease in the Danish population.20

To date, no studies have examined the combined influence of AGT M235T and T174M variants in heart failure (HF). Neither has the influence of these variants on long-term patients survival been explored. We hypothesized that these gene variants might adversely influence the level of activation of the RAS in HF patients, rendering the heart and kidney more vulnerable to adverse cardiac remodeling and renal impairment. We investigated whether the AGT M235T and T174M variants, individually or in combination, provide useful prognostic information in HF, independent of established hormone and echocardiography markers.

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Methods

Patients
From December 1, 1997, to August 31, 2000, patients admitted to Christchurch Hospital, New Zealand, considered by the admitting physician to have HF and meeting the Framingham Society of Cardiology criteria for HF, were included in the Christchurch Heart Failure Registry (n=2700). More than 90% of all the patients had frank pulmonary interstitial or alveolar edema at admission with resolution on anti-HF treatment. All of the patients were New York Heart Association class IV at time of hospital admission, and those who survived were New York Heart Association class II to III at time of discharge. A subgroup of patients who were considered fit for discharge and who consented to DNA sampling were subsequently followed-up for clinical end points (n=451). There were no significant differences in demographics, clinical history, neurohormone levels, echocardiography, or renal function between those sampled and the larger HF group.

The mean age of HF patients on admission was 74.2 years, and 51% of patients were men. Nearly 60% of patients had hypertension documented before admission, 23% had type 2 diabetes, approximately one third had a previous history of myocardial infarction (MI), and >30% had a previous history of HF.

Previous history of MI or HF was defined as a previous hospital admission for which HF or MI was the primary cause. Treatment with diuretics, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, spironolactone, digoxin, and statins prescribed to the patient on discharge was recorded. No patients were treated with device therapies or received a heart transplant during the study.

Systolic and diastolic blood pressures were recorded by a registered nurse with an automatic sphygmomanometer (PRO 300 monitor; Dinamap, Critikon) 30 minutes after admission to the emergency department according to standard operating procedures. Mortality was recorded over 4 years. Date of death was confirmed by searching the National Health Index linked to the National Register of Deaths.

Echocardiography was performed according to clinical history, neurohormone levels, echocardiography, or renal function between those sampled and the larger HF group.

The investigation was approved by the Canterbury Human Ethics Committee (Ethics Approval Reference No. CTY/99/02/014), and all of the participants provided written informed consent. The study adhered to the principles outlined in the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 14, 2001. All of the procedures followed were in accordance with institutional guidelines.

Neurohormone Assays, DNA Extraction, and Echocardiography
Plasma N-terminal brain natriuretic peptide (N-BNP) and angiotensin II (Ang II) were measured by radioimmunoassay as described previously. DNA was extracted from whole blood and stored at 4°C. Echocardiography was performed according to clinical criteria for 316 patients (70%). These patients did not differ significantly from patients for whom echocardiography was not performed in terms of age, gender, N-BNP levels, or survival. Left ventricular internal diastolic and systolic dimensions and their derived volumes, mass index, and ejection fraction (LVEF) were assessed by standard methods.

AGT M235T and T174M Genotyping
Amplification-refractory mutation system PCR assays were developed for detecting AGT M235T (National Center for Biotechnology Information single nucleotide polymorphism cluster ID rs699) and T174M (National Center for Biotechnology Information single nucleotide polymorphism cluster ID rs4762) polymorphisms. Primers and detailed reaction conditions are provided as supplementary information available online at http://hyper.ahajournals.org. After each amplification-refractory mutation system assay, amplimers were separated on a 1% agarose/0.5× 90 mM Tris/90 mM boric acid/2 mM EDTA (pH 8) gel and visualized with ethidium bromide staining with a Bio-Rad Fluor-S imaging system. Genotypes were verified by regenotyping 100 randomly selected samples and were 100% concordant with the original genotype.

Statistical Analysis
For all of the analyses, patients with AGT M235T genotypes were combined in 3 separate groups. Because of the very low frequency of the AGT 174MM genotype (1%), patients with a 174TM or 174MM genotype were combined for comparison with the AGT 174TT group. Patients with predicted high-risk combinations of M235T and T174M genotypes (235TT and/or a 174M allele) were combined into a single high-risk group (n=144) and compared with the remaining “low-risk” genotype combinations (AGT 235MM or MT combined with 174TT, n=304).

Univariate analyses were performed using χ², Mann–Whitney U and ANOVA tests to relate AGT risk groups and M235T and T174M genotypes to demographic data and echocardiographic and neurohormone measurements. Hormone data displayed consistently skewed distributions and were log-transformed before analysis, and geometric means with 95% CIs have been reported here. Survival in patients from each genotype and risk group was compared using Kaplan–Meier survival curves and log-rank tests. Multivariate analysis was performed using a Cox proportional hazards model to test for independent associations between genotype and survival independent of established risk factors including age, gender, ethnicity, previous history of MI, previous history of HF, type 2 diabetes, LVEF, renal function (plasma creatinine), plasma N-BNP and Ang II levels, and treatment with ACE inhibitors, β-blockers, spironolactone, digoxin, statins, and diuretics. An estimate of the proportion of deaths in the cohort that could be attributed to the presence of high-risk genotypes (proportional attributable risk) was calculated using the risk ratio (obtained from Cox proportional hazards analysis) as an approximation of the relative risk and the frequency of the high-risk genotype combinations (0.32) for this HF cohort. All of the statistical analyses were performed using SPSS version 11 (SPSS Inc). A P value <0.05 was taken to indicate statistical significance.

Results
AGT M235T Polymorphism
Genotype frequencies for the AGT M235T polymorphism were 34% MM, 47% MT, and 19% TT and were in Hardy–Weinberg equilibrium (P=0.896). Patients with a 235TT genotype were, on average, 3.3 years younger than other patients at their index admission for HF (mean age ± SD: MM, 76.0±9.5 years; MT, 74.1±11.4 years; TT, 71.6±11.8 years; P=0.011). In those with documented hypertension, this diagnosis had been made at 10 years earlier in 235TT homozygotes (mean age at diagnosis ±SD: MM, 54.2±10.0 years; MT, 55.1±13.5 years; TT, 46.0±15.1 years; P=0.038). There was no association between M235T genotype and diastolic, systolic, or mean arterial blood pressure (P=0.967, P=0.323, and P=0.726 respectively; data not shown) and no association between M235T genotype and prevalence of previously diagnosed hypertension (MM, 51%; MT, 61%; TT, 60%; P=0.203). Only 30% of 235TT patients were treated with β-blockers compared with 38% of 235MM and 50% of 235MT patients (P=0.003). There were no differences between AGT M235T genotypes with regard to smoking status, previous history of HF, MI, type 2 diabetes, treatment with ACE inhibitors, spironolactone, digoxin, statins or diuretics, dose of diuretics, plasma creatinine, cholesterol, or echocardiographic and neurohormone measurements, including LVEF (P=0.132), plasma N-BNP...
(P=0.589), and plasma Ang II levels (P=0.488). There were no differences in mortality between genotypes (MM, 56%; MT, 50%; TT, 56%; P=0.385).

**AGT T174M Polymorphism**

Genotype frequencies for the T174M polymorphism were 79% TT, 20% TM and 1% MM, and were in Hardy–Weinberg equilibrium (P=0.953). Patients with ≥1 174M allele were more likely to have a previous history of HF (TT, 29%; TM/MM, 40%; P=0.043), and Cox proportional hazards analysis indicated that the 174M allele was associated with increased mortality (risk ratio: 1.69; 95% CI: 1.03 to 2.79; P=0.038), independent of established prognostic indicators. Despite this, these patients had better cardiac function, as indicated by a lower average left ventricular internal systolic volume (TT, 95±4 mL; TM/MM, 79±6 mL; P=0.036) and higher LVEF (TT, 42.8±1.0%; TM/MM, 48.6±1.8%; P=0.009). Only 3% of TM/MM patients were treated with spironolactone compared with 12% of TT patients (P=0.013). There were no differences between AGT T174M genotype groups with regard to smoking status; diastolic, systolic, or mean arterial blood pressure; documented hypertension; type 2 diabetes; previous history of MI; treatment with ACE inhibitors, β-blockers, digoxin, statins, or diuretics; dose of diuretics; plasma N-BNP (P=0.954); plasma Ang II levels (P=0.397); plasma creatinine; or cholesterol.

**AGT Genotype Combinations: High- Versus Low-Risk Groups**

In light of previously reported associations between AGT M235T and T174M polymorphisms and hypertension, predicted high-risk AGT genotype combinations (235TT and/or 174M alleles; n=144; 32%; Table 1) were combined into a putatively high-risk group and compared with the remaining low-risk genotypes (235MM or MT in combination with 174TT; n=304; 68%; Table 1).

Patients with a high-risk genotype combination were more likely to have a previous history of HF (Table 2; P=0.043) and a higher left ventricular mass index (Table 3; P=0.028).
These patients were, on average, >2 years younger (Table 2; \( P = 0.029 \)), and only 34% were treated with \( \beta \)-blockers compared with 46% of patients in the low-risk group (\( P = 0.019 \), Table 2). Smoking status; previous history of hypertension; type 2 diabetes; previous MI; treatment with ACE inhibitors, spironolactone, digoxin, statins, or diuretics; dose of diuretics (Table 2); plasma N-BNP (\( P = 0.881 \)); Ang II (\( P = 0.936 \)); plasma creatinine; and cholesterol (Table 3) did not differ significantly between AGT risk groups.

Mortality among the high-risk patients was significantly greater (high-risk group: 58%; low-risk group: 46%; \( P = 0.004 \); Figure). In combination, AGT M235T and T174M genotypes were independently predictive of mortality (\( P = 0.001 \); risk ratio: 2.00; 95% CI: 1.32 to 3.03; Table 4) and conferred a markedly greater risk than the either genotype alone. This was demonstrated by Cox proportional hazards analysis, which showed that the combined AGT high-risk genotypes remained significantly prognostic of survival (\( P = 0.011 \); risk ratio: 4.72; 95% CI: 1.42 to 15.63), even when the individual AGT M235T and T174M genotypes were included as main effects in the model (\( P = 0.197 \) and \( P = 0.172 \), respectively).

Because LVEF was not a significant predictor of mortality in this model and LVEF data were available for only 70% of patients, the analysis was repeated excluding LVEF. The Cox proportional hazards analysis excluding LVEF (and, therefore, including the entire cohort) confirmed that AGT high-risk genotypes were significantly prognostic of mortality (\( P = 0.006 \)). The total number of deaths in the HF cohort over the follow-up period was 224 (49.7%). The proportion of deaths in the cohort that could be attributed to the presence of high-risk genotypes (proportional attributable risk) was estimated as 24%.

### Ethnicity

Overall, genotype frequencies for the AGT M235T and T174M polymorphisms were consistent with those reported previously in patients of European ancestry.\(^4,5,18\) The fre-

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Predicted Low-Risk Group (n=304)</th>
<th>Predicted High-Risk Group (n=144)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-BNP, pmol/L</td>
<td>367</td>
<td>190 (168 to 215)</td>
<td>193 (161 to 232)</td>
<td>0.881</td>
</tr>
<tr>
<td>Ang II, pmol/L *</td>
<td>362</td>
<td>13.8 (12.6 to 15.1)</td>
<td>13.9 (12.2 to 15.8)</td>
<td>0.936</td>
</tr>
<tr>
<td>LVEF, %†</td>
<td>316</td>
<td>43.5 (41.4 to 45.5)</td>
<td>44.9 (41.8 to 47.9)</td>
<td>0.445</td>
</tr>
<tr>
<td>LVEDV, mL†</td>
<td>303</td>
<td>155 (146 to 163)</td>
<td>157 (145 to 169)</td>
<td>0.777</td>
</tr>
<tr>
<td>LVESV, mL†</td>
<td>303</td>
<td>91.9 (84.3 to 99.4)</td>
<td>92.7 (81.7 to 104)</td>
<td>0.899</td>
</tr>
<tr>
<td>LVMI, g/m²†</td>
<td>191</td>
<td>308 (290 to 325)</td>
<td>341 (317 to 366)</td>
<td>0.028</td>
</tr>
<tr>
<td>Creatinine, mmol/L *</td>
<td>431</td>
<td>0.104 (0.099 to 0.108)</td>
<td>0.106 (0.099 to 0.113)</td>
<td>0.628</td>
</tr>
<tr>
<td>Cholesterol, mmol/L ‡</td>
<td>177</td>
<td>5.0 (4.8 to 5.2)</td>
<td>5.0 (4.7 to 5.4)</td>
<td>0.724</td>
</tr>
</tbody>
</table>

LVEDV indicates left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVMI, left ventricular mass index.

*Geometric mean and 95% CI reported.
†Arithmetic mean and 95% CI reported.
‡Statistical significance \( P < 0.05 \).
TABLE 4. Cox Proportional Hazards Analysis of Factors Predictive of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.01 to 1.06</td>
<td>0.006*</td>
</tr>
<tr>
<td>Gender</td>
<td>1.03</td>
<td>0.68–1.57</td>
<td>0.879</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>...</td>
<td>...</td>
<td>0.416</td>
</tr>
<tr>
<td>Previous history of MI</td>
<td>1.65</td>
<td>1.10 to 2.48</td>
<td>0.016*</td>
</tr>
<tr>
<td>Previous history of HF</td>
<td>1.43</td>
<td>0.94 to 2.20</td>
<td>0.096</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1.49</td>
<td>0.96 to 2.32</td>
<td>0.076</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.99</td>
<td>0.98 to 1.01</td>
<td>0.301</td>
</tr>
<tr>
<td>Plasma creatinine, mmol/L</td>
<td>4.27</td>
<td>1.26 to 14.48</td>
<td>0.020*</td>
</tr>
<tr>
<td>Plasma N-BNP, pmol/L</td>
<td>2.24</td>
<td>1.24 to 4.03</td>
<td>0.007*</td>
</tr>
<tr>
<td>Plasma Ang II, pmol/L</td>
<td>3.13</td>
<td>1.56 to 6.26</td>
<td>0.001*</td>
</tr>
<tr>
<td>ACE inhibitor treatment</td>
<td>0.92</td>
<td>0.55 to 1.55</td>
<td>0.753</td>
</tr>
<tr>
<td>β-blocker treatment</td>
<td>0.79</td>
<td>0.50 to 1.25</td>
<td>0.315</td>
</tr>
<tr>
<td>Spirolactone treatment</td>
<td>0.54</td>
<td>0.32 to 0.93</td>
<td>0.026*</td>
</tr>
<tr>
<td>Digoxin treatment</td>
<td>0.91</td>
<td>0.57 to 1.43</td>
<td>0.673</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>0.89</td>
<td>0.51 to 1.55</td>
<td>0.680</td>
</tr>
<tr>
<td>Diuretic treatment</td>
<td>0.97</td>
<td>0.45 to 2.12</td>
<td>0.945</td>
</tr>
<tr>
<td>AGT high vs low risk groups</td>
<td>2.00</td>
<td>1.32 to 3.02</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Results of a Cox proportional hazards model analysis of factors predictive of death as an end point for the HF cohort. Hormone data and plasma creatinine levels were log transformed before analysis, and the risk ratios reported for these variables indicate the risk associated with a 10-fold increase in plasma levels. The risk ratio reported for LVEF indicates the risk associated with a decrease in ejection fraction of 1%.

*Statistical significance P<0.05.

Discussion

We report associations between increased mortality and AGT gene variants M235T and T174M in HF. By combining these high-risk genotypes (the 235TT allele and ≥1 174M alleles), we identified a set of patients with a 2-fold increased risk of dying during follow-up after admission with HF.

These high-risk combinations predicted mortality independent of established risk factors, including age, gender, ethnicity, previous history of HF or MI, LVEF, renal dysfunction, β-blocker and spironolactone treatment, and plasma N-BNP or Ang II levels and conferred a markedly greater risk than the either genotype alone. It was estimated that nearly one quarter of deaths in this HF cohort could be attributed to the AGT M235T and T174M polymorphisms, indicating the significant impact of AGT genotypes on mortality in HF. Furthermore, in patients with an AGT 235TT genotype who had recognized pre-existing hypertension, the age of diagnosis of hypertension was ∼10 years earlier. These patients were significantly younger when admitted to hospital with HF, suggesting that the AGT 235TT genotype might accelerate the development of hypertension and that treatment for hypertension should be targeted to these individuals to delay or prevent the onset of HF.

A large meta-analysis performed by Sethi et al20 investigating risk of ischemic heart disease, MI, or ischemic cerebrovascular disease found no consistent associations between either M235T and T174M variants and increased risk. Our study, exploring the influence of these variants on long-term survival in HF, demonstrated a significant association between these variants and mortality. This suggests that these AGT variants may be associated with disease progression rather than increased susceptibility to heart disease.

AGT and Mortality in HF

Plasma levels of AGT have been shown to be 10% to 20% greater in those with the M235T variant,46 although these studies found no change in plasma AGT in association with the T174M variant. To date, tissue AGT levels have not been investigated in association with M235T or T174M genotypes, individually or in combination. It remains possible that AGT M235T and T174M variants may increase the level of activation of the RAS within the heart and kidney, rendering these organs more vulnerable to adverse cardiac remodeling and renal impairment and, hence, influencing outcome in HF.2 It is possible that patients carrying high-risk combinations of these variants may exhibit better responses to ACE inhibitor treatment or AT1R blockade. Future directions arising from this work include prospective studies to determine the clinical use of AGT variants as prognostic markers and identification of the cardiac signaling pathways altered in association with these variants in HF patients. This may indicate the mechanism underlying the association between the “high-risk” AGT genotype combinations and increased mortality in HF.

Although plasma Ang II and blood pressure levels did not differ between AGT genotypes in the present study, this does not exclude the possibility that these factors may mediate the association between AGT variants M235T and T174M and all-cause mortality. Plasma Ang II levels at admission do not reflect the true level of activation of the RAS in the heart and kidney and are confounded by drug treatments. This may also be the case for blood pressure, which may be associated with long-term structural and functional effects preceding the onset of disease and drug treatment.

Limitations

The degree to which associations between genotype and mortality were independent of left ventricular function was limited by the availability of echocardiography data in only 70% of patients. Nearly 40% of these patients had previously suffered an MI. Post-MI remodeling may cause focal regional wall motion abnormality, making the commonly used M-mode assessment of left ventricular volumes unreliable. In addition, the association between AGT genotype and cardiovascular (as opposed to all-cause) mortality could not be determined, because detailed information on the exact cause of death of patients within this cohort was incomplete. Finally, the scope of the present study could have been...
widened to include tag single nucleotide polymorphisms, which represent independent haplotype blocks, to explore associations between the entire store of genetic variation at the AGT locus and survival in HF. This is a key area for future study and may refine the definition of the high- and low-risk genotype groups.

Perspectives
This study provides strong evidence for an independent association between a certain combination of 2 AGT gene variants and mortality in HF. Because of their high prevalence (~33% in European populations), these variants may have clinical relevance in the setting of HF. Our findings, in combination with previous studies that showed both association and linkage of the AGT gene locus with increased risk of hypertension and heart disease, emphasize the potential importance the renin–angiotensin hormone system, and of this genomic region in particular, in the development and progression of cardiovascular disease.

Conclusions
AGT variants M235T and T174M were independently predictive of morality in HF patients and may provide additional prognostic information in the clinical setting.

Acknowledgments
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Disclosures
None.

References
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