Genetics

Polymorphism in the Angiotensinogen Gene, Hypertension, and Ethnic Differences in the Risk of Recurrent Coronary Events

Ilan Goldenberg, Arthur J. Moss, Daniel Ryan, Scott McNitt, Shirley W. Eberly, Wojciech Zareba

Abstract—The M235T mutation of the human angiotensinogen gene has been shown to be associated with elevated circulating angiotensinogen concentrations and essential hypertension. The frequencies of the 235T allele are significantly different in black and white subjects. We analyzed the independent contribution of the angiotensinogen M235T mutation to the development of recurrent coronary events (coronary-related death, nonfatal myocardial infarction, or unstable angina) in a cohort of 916 black (n=145) and white (n=771) postmyocardial infarction patients who were prospectively studied during an average follow-up of 28 months. The frequency of the 235T allele was significantly higher among black (82%) than among white (44%) patients (P<0.001). There was no evidence for Hardy–Weinberg disequilibrium. During follow-up, 41 cardiac events (28%) occurred in blacks and 197 (26%) in whites (P=0.49). Multivariate Cox proportional hazards regression analysis demonstrated that 235T homozygosity was independently associated with increased risk of coronary events among black (hazard ratio: 2.37; P=0.04) but not white (hazard ratio: 0.93; P=0.68) patients, with a significant ethnic-related interaction effect (P for the difference=0.04). Among hypertensive black patients, the TT genotype was associated with a 3.3-fold (P=0.02) increase in the risk of coronary events. Our findings suggest that homozygosity for the 235T mutation in the angiotensinogen gene is an independent risk factor for coronary events in black postmyocardial infarction patients. The presence of hypertension significantly augments the risk associated with this genetic mutation. (Hypertension. 2006;48:693-699.)

Key Words: angiotensinogen blacks coronary disease

Coronary heart disease (CHD) is a multifactorial condition influenced by environmental and genetic factors. The renin–angiotensin system plays an important role in cardiovascular physiology. Angiotensin II may have direct toxic effects on myocardial cells, activates the sympathetic nervous system, stimulates fibroblast proliferation, and vasoconstricts coronary vessels.1,2 Angiotensinogen (AGT) is major precursor of this system, and its plasma levels have been shown to correlate with blood pressure.3,4 The human AGT gene has been identified.5,6 The T allele of a polymorphism, which encodes threonine instead of methionine at position 235 (M235T), has been shown to be associated with increased circulating AGT concentrations7 and an increased risk of essential hypertension.7–10 Apart from hypertension, which is an established risk factor for CHD, several studies have reported a significant association with the risk of CHD or myocardial infarction (MI) among individuals with the TT genotype.11–13 However, a recent meta-analysis failed to detect such an association.14 Notably, published data are limited mostly to white and Asian subjects, whereas the association between the AGT polymorphism and CHD among black subjects, in whom the average allele frequencies of 235T are significantly higher,14 has not been studied.

Available evidence suggests that the outcome of black patients after an acute coronary event is different than whites, with a higher case fatality rate among the former population reported in several studies.15,16 It is possible that variations in risk factors, including genotype and hypertension or its treatment, may also contribute to the different outcome of black and white patients.

We hypothesized that AGT 235T homozygosity may confer a different risk of recurrent coronary events in post-MI black and white subjects enrolled in the prospective Thrombogenic Factors and Coronary Events (THROMBO) Study. We also studied the independent contribution of the TT genotype to the risk of recurrent coronary events among hypertensive and nonhypertensive patients and the relationship between the benefit of therapy with angiotensin-converting enzyme (ACE) inhibitors and the AGT M235T mutation.

Methods

Study Population

The THROMBO Study was a prospective, multicenter investigation that enrolled patients with acute MI from 13 participating hospitals...
in the United States between October 1, 1994, and June 30, 1997. A total of 1161 patients were enrolled at the time of hospital discharge. Blood samples for genetic analysis were collected at study enrollment on 1012 of the enrolled patients. The average follow-up was 28 months. The details of this study have been reported in the primary publication, and the clinical parameters that defined this study population included a full spectrum of traditional postinfarction risk factors. The study was composed mainly of 3 self-reported ethnic populations: blacks (n=145), Latinos (n=81), and whites (n=771) living in the United States; other populations including Asian or Pacific Islanders, American Indians, native Alaskans, and Indians composed a relatively small proportion of study patients (n=15). In the current study, we compared the clinical course of black and white patients (n=916).

Demographic information and medical history were obtained on enrollment in the trial, and medication usage was recorded during the baseline visit 2 months after the index MI. Ejection fraction was determined by an echocardiogram, a nuclear study, or angiography during the initial hospitalization after the MI. Patients were categorized as having a history of hypertension if they were ever treated with antihypertensive medications before their index MI. A single blood pressure measurement was taken before discharge; however, blood pressure was not monitored throughout the study, because hypertension was not the primary scope of the original THROMBO Study.

### End Points

The prespecified coronary event end points were first occurrence of death from CHD, enzyme-documented nonfatal MI, and hospitalization for unstable angina. A 2-member committee categorized the coronary events from appropriate medical records according to prespecified written criteria. The risk of the end point was assessed by ethnicity and stratified by the presence of the AGT M235T mutation (categorized in the primary analysis as TT genotype carriers versus MM or MT genotype carriers), hypertension, and treatment with ACE inhibitors.

### Laboratory Methods

#### Biochemical Measurements

Blood (55 mL) was drawn in the fasting state at the baseline clinic visit 2 months after the index MI. Plasma and serum samples were each separated, frozen, and sent to Rochester, NY, for central storage in a −70°C freezer. Colorimetric assays were used to measure total cholesterol, high-density lipoprotein cholesterol, and triglycerides (all by Vitros Chemistry Products); apolipoprotein A-I and B were measured by Beckman Immunocombo Systems; lipoprotein (a) was measured by immunoassay (Macra, Strategic Diagnostics); and insulin was measured by radioimmunoassay (Coat-A-Count Diagnostic Products). The concentration of low-density lipoprotein cholesterol was calculated by the Friedewald formula. Analyses were run according to the manufacturers’ specifications, and quality control was within the recommended precision for each test.

#### Genotyping

Buffy coats were isolated and stored at −70°C until extracted for DNA analysis. Genotyping was performed through a contractual agreement with Millennium Pharmaceuticals. The AGT (M235T) polymorphism was typed using the TaqMan method. Primers used were: AGT1, 59 GAT GCC CAC AAG GTC CTG TC39 and AGT2, 59 CAG GGT GCT GTC CAC ACT GGC TCG C. TaqMan assays were validated by retesting 5% to 10% of samples using independent methods, including melting curve analysis (Light Cycler, Roche Diagnostics) or PCR/restriction digest. If >1% disagreement was present between assays, PCR/restriction digest was used as a definitive standard to determine the correct assignment of the discrepant samples, and all 1012 of the samples were reassayed using the validated methods.

### Statistical Analysis

The clinical characteristics and genotype frequencies of black and white patients were compared using the χ² test and the Fisher’s exact test, as appropriate. The Hardy–Weinberg equilibrium (which predicts genotype frequencies in populations) was tested in both ethnic groups. The Kaplan–Meier life table method was used to assess the time to first coronary end point and the cumulative event rates for each group and within each group by genotype and hypertension. The results were compared using the log-rank test.

The outcome analysis used the Cox proportional hazards survivorship model. The outcome measure was time from enrollment to a first recurrent coronary event. In the analysis of the effect of medical therapy on outcome, follow-up was assessed from the baseline 2-month visit. A stepwise forward selection procedure was used to identify important clinical risk predictors for the time to end point. Ethnicity, hypertension, and the additional contribution of the AGT M235T mutation to the basic clinical model were forced into the model. Analyses were performed with the use of SAS software (version 9.13). A 2-sided P<0.05 was used for declaring statistical significance.

### Study Population

The clinical characteristics, medical therapy, and laboratory of study patients by ethnic group are presented in Table 1A. Compared with black patients, white patients were older, had a higher proportion of males, and a lower body mass index; the proportion of patients with hypertension and diabetes mellitus was significantly higher among black patients. Pre-discharge systolic and diastolic blood pressures were significantly higher among black than white patients. In patients with a history of hypertension, mean systolic blood pressure was 10 mm Hg higher than those without a history of hypertension (124 versus 114 mm Hg; P<0.001), whereas diastolic blood pressure was 3 mm Hg higher among hypertensive patients (72 versus 69 mm Hg; P=0.01). During follow-up, medical therapy with ACE inhibitors, calcium-channel blockers, and nitrates was administered more frequently to black as compared with white patients. Thrombolytic therapy during the index MI and revascularization procedures during follow-up were administered to a similar proportion of black and white patients. The 2 ethnic groups displayed similar serum levels of total cholesterol and low-density lipoprotein cholesterol but significantly different levels of high-density lipoprotein cholesterol and triglycerides.

The distribution of AGT genotypes in black and white patients and within each group by the presence of hypertension are shown in Table 2. Genotype frequencies in our population were consistent with the results in published reports and showed a significantly higher frequency of the 235T allele among black (82%) as compared with white patients (44%). The AGT gene was found to be in Hardy–Weinberg proportion for both blacks and whites. The allele frequency within each ethnic group was similar among hypertensive and nonhypertensive patients.

Blood pressure levels were higher in black as compared with white patients in both TT (mean systolic blood pressure: 123 versus 118 mm Hg, respectively; mean diastolic blood pressure: 73 versus 70 mm Hg, respectively) and non-TT (mean systolic blood pressure: 122 versus 118 mm Hg, respectively; mean diastolic blood pressure: 73 versus 69 mm Hg, respectively) genotype carriers.
Effect of AGT M235T Polymorphism on the Risk of Recurrent Coronary Events in Black and White Patients

During an average follow-up of 28 months, 238 patients experienced a first recurrent coronary event, including 41 black patients (28%) and 197 white patients (26%; P=0.49). The presence of 235T homozygosity was independently associated with a significant increase in the risk of recurrent coronary events among black patients but not among white patients (P value for TT genotype×ethnic interaction=0.04; Table 3). Among the former ethnic group, there was a significant 2.4-fold increase in the risk of coronary events in patients carrying the genotype, which was attributed mainly to the presence of the TT genotype in hypertensive patients (3.3-fold increase; P=0.02).

At 2 years, the probability of a first recurrent coronary event was 32% among black patients with the TT genotype as compared with 16% among patients with either the MM or MT genotypes (Figure 1A), whereas the probability of recurrent coronary events was similar among white patients with and without the TT genotype (Figure 1B). The significant increase in the rate of recurrent coronary events among blacks with the TT genotype was observed mainly in hypertensive patients (2-year rates for TT genotype versus MM or MT carriers: 40% and 14%, respectively; P=0.015; data not shown), whereas among nonhypertensive blacks, event rates were identical (16%) in TT and non-TT genotype carriers (data not shown).

Relation of the AGT M235T Mutation to Ethnic Differences in the Risk of Recurrent Coronary Events

The adjusted risk of recurrent coronary events was similar among black patients and white patients (hazard ratio [HR]: 1.09; 95% CI: 0.75 to 1.60; P=0.49). However, when stratified by the presence of hypertension or the TT genotype, the risk of events was higher in black than white patients with either risk factor (Table 4). Furthermore, among patients with a combination of the 2 risk factors, there was a >2-fold increase in the risk of recurrent coronary events among blacks as compared with white patients. By contrast, no significant

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Black (N=145)</th>
<th>White (N=771)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>57±11</td>
<td>60±12*</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>67</td>
<td>77*</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>64</td>
<td>40*</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>28</td>
<td>16*</td>
</tr>
<tr>
<td>Smoking at anytime, %</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29±6</td>
<td>28±5*</td>
</tr>
</tbody>
</table>

**Laboratory values (mean±SD)**

| Total cholesterol, mmol/L† | 196±46 | 196±43 |
| HDL, mmol/L†               | 123±41 | 118±36 |
| Triglycerides, mmol/L†     | 42±12  | 39±12* |
| Apo A, g/L                 | 118±0.26 | 119±25 |
| Apo B, g/L                 | 124±0.32 | 122±27 |
| Glucose, mmol/L†           | 6.0±2.5 | 5.6±2.4* |
| Insulin, IU/mL             | 23±41  | 18±24* |

Values are percentages or mean±SD. BMI indicates body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein. *P<0.05.
†To convert cholesterol (total, HDL, LDL) to mg/dL, multiply by 38.61; to convert triglycerides to mg/dL, multiply by 88.5; to convert glucose to mg/dL, multiply by 18.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Black (N=145)</th>
<th>White (N=771)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>68</td>
<td>19*</td>
<td></td>
</tr>
<tr>
<td>MT</td>
<td>28</td>
<td>49*</td>
<td></td>
</tr>
<tr>
<td>Nonhypertensive</td>
<td>25</td>
<td>49*</td>
<td></td>
</tr>
<tr>
<td>hypertensive</td>
<td>67</td>
<td>19*</td>
<td></td>
</tr>
<tr>
<td>Nonhypertensive</td>
<td>4</td>
<td>32*</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2</td>
<td>32*</td>
<td></td>
</tr>
<tr>
<td>Nonhypertensive</td>
<td>8</td>
<td>31*</td>
<td></td>
</tr>
</tbody>
</table>

All characteristics are given as percentages. *P<0.05.

Table 3. Among the former ethnic group, there was a significant 2.4-fold increase in the risk of coronary events in patients carrying the genotype, which was attributed mainly to the presence of the TT genotype in hypertensive patients (3.3-fold increase; P=0.02).

At 2 years, the probability of a first recurrent coronary event was 32% among black patients with the TT genotype as compared with 16% among patients with either the MM or MT genotypes (Figure 1A), whereas the probability of recurrent coronary events was similar among white patients with and without the TT genotype (Figure 1B). The significant increase in the rate of recurrent coronary events among blacks with the TT genotype was observed mainly in hypertensive patients (2-year rates for TT genotype versus MM or MT carriers: 40% and 14%, respectively; P=0.015; data not shown), whereas among nonhypertensive blacks, event rates were identical (16%) in TT and non-TT genotype carriers (data not shown).

**Relation of the AGT M235T Mutation to Ethnic Differences in the Risk of Recurrent Coronary Events**

The adjusted risk of recurrent coronary events was similar among black patients and white patients (hazard ratio [HR]: 1.09; 95% CI: 0.75 to 1.60; P=0.49). However, when stratified by the presence of hypertension or the TT genotype, the risk of events was higher in black than white patients with either risk factor (Table 4). Furthermore, among patients with a combination of the 2 risk factors, there was a >2-fold increase in the risk of recurrent coronary events among blacks as compared with white patients. By contrast, no significant
differences in the risk between the 2 groups were detected among nonhypertensive patients and non-TT genotype carriers ($P$ for interaction between high-risk and low-risk groups=0.02). Accordingly, Kaplan–Meier curves, describing the probability of a first coronary event, demonstrated similar rates among black and white patients (Figure 2, a marginally significant difference between the 2 ethnic groups among hypertensive patients (Figure 2B), and a significantly higher rate of events among hypertensive blacks with the TT genotype (Figure 2C).

### Relation of AGT M235T Mutation to Benefit of Therapy With ACE Inhibitors

Baseline medical therapy with ACE inhibitors was associated with a marginally significant 23% reduction in the risk of recurrent coronary events in study patients ($P=0.11$). Risk reduction with ACE inhibitor therapy was nonsignificantly higher in blacks as compared with white patients (41% versus 19%, respectively; $P$ for ACE inhibitor×ethnic interaction=0.45).

When stratified by the presence of the M235T mutation, the benefit of ACE inhibitor therapy was more pronounced

### TABLE 4. Black Versus White Adjusted HR for Coronary Events in Risk Groups Including Hypertension and the TT Genotype

<table>
<thead>
<tr>
<th>High Risk</th>
<th>HR (95% CI)</th>
<th>Low Risk</th>
<th>HR (95% CI)</th>
<th>$P$ for Interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive (n=401)</td>
<td>1.33 (0.84 to 2.09)</td>
<td>Nonhypertensive (n=504)</td>
<td>0.79 (0.42 to 1.49)</td>
<td>0.17</td>
</tr>
<tr>
<td>TT genotype (n=245)</td>
<td>1.52 (0.94 to 2.45)</td>
<td>MM or MT genotypes (n=671)</td>
<td>0.59 (0.28 to 1.27)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertensive with TT genotype (n=121)</td>
<td>2.13 (1.09 to 4.17)</td>
<td>Hypertensive with MM or MT (n=280)</td>
<td>0.53 (0.19 to 1.47)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Adjusted for age, history of diabetes mellitus, and MI type (Q wave vs non-Q wave).

*Denotes the interaction value for the difference in the risk between the corresponding high- and low-risk variables in each row.
among patients identified as homozygous carriers of the 235T allele (adjusted HR: 0.53; 95% CI: 0.27 to 1.04; P=0.06) than among MM or MT genotype carriers (adjusted HR: 0.89; 95% CI: 0.60 to 1.32; P=0.56).

Discussion
In this prospective study of post-MI patients, we have shown that the AGT M235T mutation confers a different risk of recurrent coronary events in black and white patients. Blacks, identified as homozygous carriers of the AGT 235T allele, had a significantly higher risk of coronary events during follow-up as compared with non-TT carriers. The positive correlation between genotype and coronary risk in this population was observed mainly among hypertensive patients. By contrast, no significant association between the AGT M235T mutation and outcome was shown in hypertensive and nonhypertensive whites.
A higher rate of adverse events after MI among black patients compared with white patients was reported previously and was ascribed to differences in blood pressure control, access to health care, socioeconomic status, and risk factor management.\textsuperscript{15,16,20--22} In addition, a higher prevalence of hypertension in black than white patients has been suggested to contribute to the different risk for CHD and outcome.\textsuperscript{16,21} In the current study, we have shown that the higher risk of recurrent coronary events among hypertensive blacks as compared with whites was attributed mainly to subjects identified as TT-genotype carriers. Notably, the increase in the risk in the former ethnic group occurred despite similar rates of early intervention during the index MI and revascularization procedures during follow-up.

In a recent meta-analysis of 45,267 subjects, the TT genotype was shown to be associated with a 19% and 60% increase in risk of hypertension in white and Asian individuals, respectively, whereas no association with the risk of CHD or MI was detected in these 2 populations.\textsuperscript{14} These data are in agreement with a previous report on white and Asian subjects.\textsuperscript{23} The present study is the first to analyze the association between the AGT M235T mutation and the risk of recurrent coronary events in post-MI patients. Consistent with these reports, we did not show a significant association between 235T homozygosity and the risk of coronary events in white patients. However, among black patients, in whom the relation between the M235T mutation and CHD risk was not studied previously, we have shown that the TT genotype is an independent risk factor, mainly in hypertensive patients.

Possible Explanation of the Association
Plasma renin activity (PRA) has been suggested as a mechanism relating the AGT M235T mutation to adverse outcome in hypertensive patients.\textsuperscript{24} High PRA levels were shown to be significantly associated with increased risk of coronary events among hypertensive subjects,\textsuperscript{25} whereas a similar association was not demonstrated for normotensive subjects.\textsuperscript{26} The TT genotype was shown to be associated with a significant 11% increase in plasma AGT levels,\textsuperscript{14} and, under basal condition, carriers of this genotype were demonstrated to have lower PRA than MM or MT carriers.\textsuperscript{24} Therefore, it seems that higher AGT levels, associated with the TT genotype, lead to lower PRA levels in nonhypertensive patients. This is consistent with the known low-renin profiles in women and blacks.\textsuperscript{27} The frequency of the T allele was reported to be 81% in blacks,\textsuperscript{28} and women have also higher AGT levels because of the estrogen effect.\textsuperscript{29} However, patients carrying the TT genotype also have a higher potential to produce angiotensin II than non-TT carriers because of a higher availability of the renin substrate. Hypertension has been shown to increase PRA levels.\textsuperscript{25,26} Therefore, a possible explanation for the significant association between the TT genotype and the risk of coronary events in hypertensive black patients may be that a concurrent existence of high AGT concentration, associated with the TT genotype, and a stimulated PRA, associated with hypertension, can induce a sustained vascular response, leading to a potentially long-term adverse outcome. By contrast, the association between high AGT levels with lower PRA levels in nonhypertensive black TT carriers may result in a neutral effect of this genotype on outcome in this population.

The lack of a significant association between the AGT M235T mutation and the risk of recurrent coronary events in both hypertensive and nonhypertensive white patients suggests that the mutation plays a less dominant role in this population and that other observed or unobserved background risk factors may be more closely associated with outcome in white post-MI patients. It is also possible that the long-term effects of the AGT M235T mutation on the level of hypertension are more pronounced in black than in white patients, leading to a more adverse outcome among hypertensive patients with the genetic mutation in the former ethnic group.

ACE Inhibitor Therapy and the AGT M235T Mutation
Previous studies have suggested that treatment with ACE inhibitors has reduced efficacy in blacks for the end point of heart failure and that vasodilator therapy may be more effective in this population.\textsuperscript{30,31} However, the results of vasodilator trials were inconsistent and did not show a statistically significant interaction between treatment and ethnicity. Furthermore, the drug was shown to be equally efficacious in blacks and in whites in reducing the incidence of the combined end point of death or development of a new onset of heart failure.\textsuperscript{30} Similarly, no interaction with ethnicity was observed for the relative benefit of ACE inhibitors in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.\textsuperscript{32} We have consistently shown similar trends suggesting that ACE inhibitor therapy is effective in black patients. Furthermore, treatment with the drug in both ethnic groups was associated with a trend toward greater risk reduction among TT-genotype carriers than among MM or MT carriers. Thus, our preliminary findings suggest that this form of medical therapy may be important in the treatment of post-MI black patients in whom the frequency of the TT genotype is \(\approx 70\%\). These data need to be validated in future studies.

Study Limitations
Several limitations of this study should be considered. The present results provide evidence of the association between the M235T mutation and the risk of recurrent coronary events in post-MI black patients at the gene level but do not demonstrate the direct mechanism by which the mutation affects outcome. In addition, further evaluation is required to determine whether AGT M235T polymorphism mediates coronary risk directly or acts as a marker of other gene polymorphisms.

We cannot rule out a "survival-of-the-fittest" bias in our post-MI cohort. High-risk white patients with the TT genotype may have died during the index event, leading to a reduced effect of the genotype on the risk of recurrent events among survivors. Approximately 15% of patients die during their first MI.\textsuperscript{33} Thus, considering the relatively low frequency of the TT genotype among white patients (\(\approx 20\%\)), the potential contribution of such selection effects to outcome in this population is relatively small.

Treatment with ACE inhibitors was not randomly assigned in study patients. In addition, the lack of a significant interaction among the effect of this mode of therapy, ethnic-
ity, and genotype may be because of sample size limitations. Therefore, the interpretation of the results regarding the efficacy of ACE inhibitor therapy should be reserved, despite adjustments for important clinical covariates.

Perspectives
Our data provide evidence that the TT genotype is an important factor affecting outcome after MI in hypertensive black patients and seems to play a less dominant role in nonhypertensive black and white patients. These findings suggest that the risk associated with renin–angiotensin system genetic polymorphisms may be different among ethnic groups and stress the importance of identifying specific genetic risk factors within individual ethnic populations. The data regarding ACE inhibitor efficacy in black post-MI patients and the relationship to polymorphism in the AGT gene suggest important therapeutic implications and need to be further evaluated in prospective randomized trials.

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Disclosures
A.J.M. and W.Z. are employed by the University of Rochester. The remaining authors report no conflicts.

References
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