Cardiovascular Risk in Relation to α-Adducin Gly460Trp Polymorphism and Systolic Pressure
A Prospective Population Study

Yan Li, Lutgarde Thijss, Tatiana Kuznetsova, Laura Zagato, Harry Struijker-Boudier, Giuseppe Bianchi, Jan A. Staessen

Abstract—Preliminary evidence from 1 case-control study suggested that in hypertensive patients, the α-adducin 460Trp allele might be associated with a 2-fold higher risk of coronary heart disease. In a prospective population study, we investigated whether the α-adducin Gly460Trp polymorphism predicted mortality and morbidity. From August 1985 until July 2003, we randomly recruited 2235 Belgian residents. We obtained information on vital status (until July 1, 2004) and the incidence of events via registries and repeat examinations (median 3). In Cox regression, before and after adjustment for other risk factors, we found strong interaction between systolic blood pressure at baseline, analyzed as a continuous variable, and the α-adducin polymorphism in relation to total (P=0.01) and cardiovascular mortality (P=0.007) and all cardiovascular (P=0.003), cardiac (P=0.001), and coronary events (P=0.03). The hazard ratio for total mortality associated with the Trp allele relative to GlyGly homozygosity was 2.30 (95% confidence interval, 1.12 to 4.72; P=0.02) in patients with stage-2 systolic hypertension (≥160 mm Hg) and 0.88 (0.61 to 1.26; P=0.48) in the other participants. For all cardiovascular complications, these estimates were 2.94 (1.28 to 6.74; P=0.01) and 0.83 (0.58 to 1.20; P=0.32), respectively. For all cardiovascular events, the positive predictive value and the attributable risk associated with the Trp allele in patients with stage-2 systolic hypertension were 76.9% and 44.3%, respectively. In conclusion, the α-adducin Gly460Trp polymorphism, in combination with systolic blood pressure, is a strong predictor of cardiovascular mortality and morbidity. (Hypertension. 2005;46:527-532.)

Key Words: genes ■ epidemiology ■ morbidity

Adducin is a heterodimeric cytoskeleton protein.1 Investigations in rats2,3 and in vitro transfection studies4 revealed that a Gly to Trp point mutation at position 460 in the adducin α-subunit gene leads to higher activity of the sodium pump, hence increased tubular sodium reabsorption in the kidney and ultimately hypertension. Subsequent studies5 of the blood pressure responses of never-treated hypertensive patients to diuretics and epidemiologic observations6–12 provided indirect evidence for the higher salt sensitivity of Trp allele carriers. Although some cross-sectional studies suggested that the α-adducin Trp allele might be associated with a higher risk of cardiovascular disease13 or renal disorders,14,15 by and large, the evidence remains inconsistent.16,17 On the other hand, in a retrospective population-based case-control study,18 carriers of the mutated α-adducin had a lower risk of combined myocardial infarction or stroke when treated with diuretics rather than other antihypertensive drugs.

In a prospective case-control study, nested within the Atherosclerosis Risk in Communities Survey (ARIC), Morrison et al19 found that the α-adducin Trp allele was associated with a 2-fold higher risk of coronary heart disease but only in hypertensive patients. These researchers suggested that the α-adducin Gly460Trp polymorphism might interact with blood pressure as predictor of adverse health outcomes. In line with this a priori hypothesis19 and our previous research,2–4,7,9,12 we investigated in a prospective study whether the α-adducin polymorphism predicts cardiovascular health outcomes and to what extent it interacts with established risk factors, in particular, systolic blood pressure.19

Methods

Study Population

The ethics committee of the University of Leuven approved the Flemish Study on Environment, Genes, and Health Outcomes...
(FLEMENGHO). From August 1985 until November 1990, a random sample of the households living in a geographically defined area in northern Belgium was investigated with the goal to recruit an equal number of participants in each of 6 subgroups by sex and age (20 to 39, 40 to 59, and ≥60 years). All household members ≥20 years of age were invited to take part until the quota of their sex–age group had been fulfilled. To further study the role of genetic factors, from June 1996 until July 2003, nuclear families including children who were ≥10 years of age were recruited using the former participants (1985 to 1990) as index persons. The participants, and in case of underaged offspring, their parents or custodians, gave informed consent.

The study population included 2740 subjects. The participation rate among the subjects contacted averaged 64.3%. Blood for DNA extraction could not be obtained from 505 participants because they did not consent (n=171) or because they had died (n=100), were terminally ill (n=30), or had moved out of the area (n=204). The 2235 subjects included in the present analysis, compared with those not genotyped, were an average of 2.7 years younger (P=0.01) but otherwise had similar (0.11<P<0.99) baseline characteristics, including sex distribution and cardiovascular risk factors.

Data Collection

At the enrollment home visit, trained nurses measured anthropometric characteristics and blood pressure. They also administered a questionnaire to collect information about each subject’s medical history, smoking and drinking habits, and intake of medications. Blood pressure was the average of 5 consecutive readings. Hypertension was defined as a blood pressure of ≥140 mm Hg systolic or 90 mm Hg diastolic or as the use of antihypertensive drugs. Stage-2 hypertension was a systolic blood pressure of ≥160 mm Hg irrespective of treatment status. Body mass index was weight in kilograms divided by the square of height in meters. Venous blood samples were drawn for DNA extraction and measurement of serum total cholesterol.

Via the National Population Registry (Rijksregister) in Brussels, Belgium, we ascertained the vital status of all participants until July 1, 2004. We obtained the International Classification of Disease codes for the immediate and underlying causes of death from the Flemish Registry of Death Certificates. We collected information on the incidence of nonfatal events in 2203 subjects via follow-up visits with repeat administration of the same standardized questionnaire as that used at baseline. The number of follow-up visits was 1, 2, 3, or >3 in 180, 749, 511, and 583 subjects, respectively. Physicians blinded with regard to the genetic results ascertained the diseases reported via the death certificates or via the questionnaires against the records held by general practitioners or hospitals.

Coronary events included fatal and nonfatal myocardial infarction and procedures for myocardial revascularization. Cardiac events consisted of fatal and nonfatal left ventricular heart failure and coronary events. Fatal and nonfatal cardiovascular events comprised cardiac end points, stroke not including transient ischemic attacks, aortic aneurysm, cor pulmonale, and pulmonary embolism. For all end points, we censored subjects from further analysis after occurrence of the first event.

Genotypes

Genomic DNA from white blood cells was amplified and genotyped for the α-adducin Gly460Trp and the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphisms as described previously.9

Statistical Analysis

We used the SAS software package (SAS Institute), version 8.2, for database management and statistical analysis. We compared means and proportions by the standard normal z test and the χ² statistic, respectively, and survival curves by Kaplan–Meier survival function estimates and the log-rank test. We used Cox proportional hazard regression as implemented in the PROC SURVIVAL procedure of the Sudaan software (Research Triangle Institute) version 9.01 to calculate relative hazard ratios (RHRs) while allowing for covariables, confounders, and family clusters. The baseline characteristics evaluated as potential covariables in Cox regression were sex, age, systolic blood pressure, body mass index, smoking, intake of alcohol, use of antihypertensive drugs, serum total cholesterol, and previous cardiovascular complications. For all cardiovascular events, we computed the positive predictive value and the attributable risk associated with the α-adducin Trp allele in patients with stage-2 systolic hypertension20 using published formulas21 and the observed risk of 47.1%.

Results

Baseline Characteristics of the Participants

The 2235 participants included 1099 (49.2%) men and 594 (26.6%) hypertensive patients, of whom 244 (10.9%) were on antihypertensive drug treatment. Age at entry ranged from 10 to 91 years. Women compared with men (P<0.01) had lower systolic (122.4 versus 128.1 mm Hg) and diastolic (74.2 versus 77.0 mm Hg) blood pressures and less frequently reported smoking (27.1% versus 35.1%), intake of alcohol (12.5% versus 35.7%), and previous cardiovascular complications (2.3% versus 4.6%). The frequencies of the α-adducin (GlyGly 59.2%; GlyTrp 35.3%; and TrpTrp 5.5%; P=0.64) and ACE (DD 24.8%; DI 51.2%; and II 24.0%; P=0.27) genotypes did not deviate from Hardy–Weinberg equilibrium. The baseline characteristics of the study participants were similar across the α-adducin genotypes (Table 1).

α-Adducin Genotype as Risk Factor

Median follow-up time was 10.0 years (5th to 95th percentile interval; 1.8 to 18.7 years) for fatal end points and 7.2 years (1.5 to 15.5 years) for all fatal and nonfatal cardiovascular events combined. Before and after cumulative adjustment for sex, age, systolic blood pressure, body mass index, serum total cholesterol, smoking, alcohol intake, use of antihypertensive drugs, and previous cardiovascular complications, the α-adducin polymorphism per se was not significantly related to any outcome, with the exception of heart failure (Table 2). During follow-up, 24 and 17 cases of new-onset heart failure occurred in Trp allele carriers and GlyGly homozygotes, respectively (RHR, 2.04; 95% confidence interval [CI], 1.11 to 3.74; P=0.02). Among the incident cases of heart failure, the prevalence of hypertension at baseline tended to be higher in Trp allele carriers than GlyGly homozygotes (83.3% [20 of 24] versus 58.8% [10 of 17]; P=0.08).

Interaction Between α-Adducin Genotype and Systolic Blood Pressure

Before and after adjustment, we found strong interaction between systolic blood pressure at baseline, analyzed as a continuous trait, and the α-adducin polymorphism in relation to total and cardiovascular mortality and all cardiovascular, cardiac, and coronary events (Table 3). Figure 1 shows the continuous risk function for total mortality and all cardiovascular events adjusted for covariables by Cox regression. For all cardiovascular events (Figure 1B), the risk function and its upper and lower 95% confidence boundaries crossed unity at ≈140, 120, and 160 mm Hg, respectively.

To further illustrate the continuous blood pressure by genotype interaction, we dichotomized the distribution of systolic
blood pressure at entry, contrasting patients with stage-2 systolic hypertension with the rest of the study population. Figure 2 shows the Kaplan–Meier survival function estimates for total mortality and all cardiovascular events along with the unadjusted \( P \) values obtained by the log-rank test. The adjusted RHRs for cardiovascular mortality and for cardiac and coronary events associated with the Trp/Thr adducin polymorphism in the 2 blood pressure strata appear in Table 3. In patients with stage-2 systolic hypertension, the positive predictive value and the attributable risk for all cardiovascular events associated with the risk-carrying Trp allele were 76.9% and 44.3%, respectively.

In a sensitivity analysis in which we used a systolic threshold of 140 mm Hg and all fatal and nonfatal cardiovascular events as outcome, the findings were consistent. Indeed, among 1653 subjects with a normal systolic pressure, 82 experienced a cardiovascular event (RHR associated with the Trp allele, 0.62; 95% CI, 0.39 to 0.98; \( P=0.04 \)), whereas in 370 subjects with a systolic pressure of \( \geq 140 \) mm Hg, 80 such events occurred (RHR, 1.58; 95% CI, 1.03 to 2.41; \( P=0.04 \)). Additional adjustment for cohort effects (recruitment before 1996 or later) or exclusion of 164 teenagers from the study sample also did not change our findings (data not shown). Finally, when we substituted systolic blood pressure by pulse pressure and additionally adjusted for mean arterial pressure, we also found a strong interaction between pulse pressure at baseline and the Trp/Thr adducin polymorphism in relation to total and cardiovascular mortality.

### TABLE 1. Baseline Characteristics of Study Participants by α-Adducin Genotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GlyGly Homozygotes (n=1323)</th>
<th>Trp Allele Carriers (n=912)</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42.0±16.8</td>
<td>43.2±17.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125.4±17.3</td>
<td>124.9±17.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75.8±19.3</td>
<td>75.2±19.3</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypertensive patients, n (%)</td>
<td>343 (25.9)</td>
<td>251 (27.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>On antihypertensive medication, n (%)</td>
<td>137 (10.4)</td>
<td>107 (11.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cardiovascular history, n (%)‡</td>
<td>47 (3.6)</td>
<td>29 (3.21)</td>
<td>0.63</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.2±4.6</td>
<td>25.2±4.4</td>
<td>0.97</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.48±1.24</td>
<td>5.48±1.25</td>
<td>0.90</td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>410 (31.0)</td>
<td>284 (31.1)</td>
<td>0.94</td>
</tr>
<tr>
<td>Consuming alcohol, n (%)</td>
<td>317 (24.0)</td>
<td>217 (23.8)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

†Plus–minus values are mean±SD.
‡Previous cardiovascular complications consisted of myocardial infarction, coronary revascularization, heart failure, stroke, aortic aneurysm, cor pulmonale, and pulmonary embolism.

### TABLE 2. Hazard Ratios for Adverse Health Outcomes in α-Adducin Trp Allele Carriers Relative to GlyGly Homozygotes

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>No. at Risk</th>
<th>No. of Cases (per 1000 person-years)</th>
<th>Hazard Ratios (95% CI)</th>
<th>Hazard Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality*</td>
<td>2235</td>
<td>173 (7.7)</td>
<td>1.08 (0.80–1.47)</td>
<td>1.05 (0.76–1.44)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2235</td>
<td>68 (3.0)</td>
<td>1.22 (0.76–1.96)</td>
<td>1.27 (0.77–2.10)</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>2235</td>
<td>83 (3.7)</td>
<td>1.31 (0.84–2.03)</td>
<td>1.25 (0.78–1.99)</td>
</tr>
<tr>
<td>All cardiovascular events‡</td>
<td>2023</td>
<td>162 (11.2)</td>
<td>1.07 (0.79–1.45)</td>
<td>1.01 (0.74–1.40)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2023</td>
<td>38 (2.5)</td>
<td>0.70 (0.35–1.37)</td>
<td>0.64 (0.31–1.32)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>2023</td>
<td>111 (7.6)</td>
<td>1.11 (0.78–1.59)</td>
<td>1.04 (0.71–1.53)</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>2023</td>
<td>41 (2.7)</td>
<td>2.15 (1.17–3.96)§</td>
<td>2.04 (1.11–3.74)§</td>
</tr>
<tr>
<td>Coronary events</td>
<td>2023</td>
<td>82 (5.6)</td>
<td>0.78 (0.51–1.21)</td>
<td>0.73 (0.45–1.17)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2023</td>
<td>51 (3.4)</td>
<td>0.75 (0.43–1.31)</td>
<td>0.74 (0.41–1.35)</td>
</tr>
<tr>
<td>New-onset hypertension</td>
<td>1455</td>
<td>398 (42.4)</td>
<td>1.07 (0.88–1.30)</td>
<td>1.06 (0.88–1.29)</td>
</tr>
</tbody>
</table>

*The cause of death was unknown in 22 subjects.
†Hazard ratios account for family clusters and are adjusted for baseline characteristics, including sex, age, systolic blood pressure, body mass index, serum total cholesterol, smoking, alcohol intake, use of antihypertensive drugs, and previous cardiovascular complications; §212 participants who were alive on July 1, 2004, did not have a follow-up visit; §§P values of the RHRs for left ventricular failure were 0.01 and 0.02 in the unadjusted and adjusted analysis, respectively; ¶new-onset hypertension was defined as a blood pressure (average of 5 consecutive readings at a follow-up home visit) of \( \geq 140 \) mm Hg systolic or \( \geq 90 \) mm Hg diastolic or use of antihypertensive drugs.

For new-onset hypertension, adjustments did not include systolic blood pressure and use of antihypertensive drugs at baseline.
and all cardiovascular, cardiac, and coronary events. These pulse pressure results are presented in detail in a supplemental Figure (continuous analysis) and a supplemental Table (pulse pressure ≥60 mm Hg versus <60 mm Hg) available online at http://www.hypertensionaha.org.

**Interaction Between α-Adducin Genotype and Other Risk Predictors**

With regard to other cardiovascular risk factors, we found for cardiac events a weak interaction between the α-adducin genotype and age at entry analyzed as a continuous variable. For each 10-year increment in age, the RHR associated with the Trp allele increased by 39.7% (95% CI, 3.0 to 87.7%; P=0.03). For cardiac events (P=0.004), we noticed interaction between the α-adducin genotype and smoking. The RHR associated with the Trp allele revealed different trends in nonsmokers (1.62; 95% CI, 1.00 to 2.62; P=0.05) and smokers (0.46; 95% CI, 0.22 to 0.96; P=0.04). Furthermore, our analysis showed significant interaction between the α-adducin Trp allele and ACE DD homozygosity in relation to all cardiovascular events. ACE DD homozygous carriers of the α-adducin Trp allele, compared with the remainder of the study population, had an RHR of 2.63 (95% CI, 1.20 to 5.76; P=0.016). For new-onset hypertension, the latter interaction

### Table 3. Hazard Ratios for Adverse Health Outcomes in α-Adducin Trp Allele Carriers Relative to GlyGly Homozygotes by Stratum of Systolic Pressure at Baseline

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Systolic Pressure ≥160 mm Hg</th>
<th>Systolic Pressure &lt;160 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/No. at Risk*</td>
<td>Hazard Ratio (95% CI)†</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>38/95</td>
<td>2.30 (1.12–4.72)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>22/95</td>
<td>5.27 (2.10–13.2)</td>
</tr>
<tr>
<td><strong>Fatal and nonfatal events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>29/93</td>
<td>2.94 (1.28–6.74)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>20/93</td>
<td>8.14 (1.66–28.0)</td>
</tr>
<tr>
<td>Coronary</td>
<td>11/93</td>
<td>3.06 (0.56–16.6)</td>
</tr>
</tbody>
</table>

*No. of subjects with event during follow-up/No. of subjects in stratum of systolic blood pressure at baseline.
†For the covariables used for adjustments, see Table 2; ‡P indicates the significance of the RHRs; §Pint indicates the significance of the interaction between systolic blood pressure at baseline analyzed as a continuous trait and the α-adducin genotype.

![Figure 1](image1.png)

**Figure 1.** Hazard ratios for total mortality (A) and all cardiovascular complications (B) in α-adducin Trp allele carriers relative to GlyGly homozygotes in function of systolic blood pressure at baseline. The continuous risk function with 95% confidence limits and the P values for interaction (Pint) were computed by multiple Cox regression. For the covariables used for adjustment, see Table 2.

![Figure 2](image2.png)

**Figure 2.** Kaplan–Meier survival function estimates for total mortality (A) and all cardiovascular events (B) by α-adducin genotype and blood pressure stratum. SBP indicates systolic blood pressure. nTrp and nGlyGly are the number of Trp allele carriers and GlyGly homozygotes, respectively. Unadjusted P values were computed by the log-rank test.
was borderline significant, with an RHR of 1.56 (95% CI, 0.96 to 2.54; \( P = 0.08 \)). Finally, although the risk of cardiovascular events increased with serum cholesterol (RHR for 1 mmol/L increment, 1.21; 95% CI, 1.07 to 1.36; \( P = 0.003 \)), the interactions with the \( \alpha \)-adducin genotype in relation to mortality or morbidity were not significant (0.16 < \( P < 0.89 \)).

**Discussion**

To our knowledge, our study provides the first prospective evidence that in the population at large, the \( \alpha \)-adducin Gly460Trp polymorphism in association with systolic blood pressure is a strong predictor of total and cardiovascular mortality as well as cardiovascular and cardiac events. We also found interactions of the \( \alpha \)-adducin genotype with age, smoking, and the ACE \( \text{I/D} \) polymorphism but not with other cardiovascular risk factors, such as serum total cholesterol.

Over the past decade, several studies addressed the question whether mutation of the \( \alpha \)-adducin gene possibly contributes to the pathogenesis of essential hypertension.2,6–12 On balance, the overall evidence from these experimental and clinical studies demonstrated that carriers of the \( Trp \)-allele have an increased risk of hypertension attributable to an innate stimulation of the sodium pump and enhanced renal tubular sodium reabsorption.3,4,6,22–24 However, most studies in humans suggest that mutation of the \( \alpha \)-adducin gene on its own is insufficient to cause hypertension.22 Indeed, the pathogenesis of high blood pressure is complex, involves multiple genes, and depends on ecogenetic context, which itself consists of lifestyle and environmental factors, and population-specific frequencies of other risk-carrying alleles.23 For instance, several studies showed strong interaction between adducin variants and salt intake in relation to blood pressure.22,26 Age is another important determinant of the penetrance of genetic variants. Older age increases sodium sensitivity, makes the relationship between blood pressure and exchangeable body sodium steeper, decreases the gain of the baroreceptor reflex, reduces renal perfusion, and compromises the buffering effects of the large arteries on systolic and diastolic pressure.24 At younger age, compensatory feedback loops have a greater potential to maintain the homeostasis of the sodium balance. These age-related mechanisms might explain why in our study population, with an average age of 42.5 years at baseline, systolic blood pressure and the prevalence of hypertension were similar in \( Trp \)-homozygotes and \( Trp \) allele carriers and, why, in a single gene analysis, the relative risk of new-onset hypertension associated with the \( Trp \) allele was nonsignificant. However, our present findings and previous studies in the same population9 showed that the presence of the \( \alpha \)-adducin \( Trp \) allele increased the risk of hypertension associated with ACE DD homozygosity from \( \approx 31\% \) to \( 60\% \).

In genetic analyses, which did not account for interaction with other risk factors, the \( \alpha \)-adducin \( Trp \) allele was associated with a significant 2-fold increase in the risk of heart failure. Among cases, the prevalence of hypertension at baseline tended to be higher in \( Trp \) allele carriers than \( GlyGly \) homozygotes. Therefore, sodium retention, volume overload, and hypertension might have contributed to the higher risk of heart failure. On the other hand, mutation of the \( \alpha \)-adducin gene was not directly related to other cardiovascular outcomes or mortality, but it modulated the role of other risk factors, in particular systolic blood pressure. In line with our findings, the ARIC investigators recently observed in a prospective case-control study19 that while adjusting for multiple risk factors, the \( \alpha \)-adducin \( Trp \) allele was associated with a higher risk of coronary heart disease and peripheral arterial disease but only in hypertensive patients. The RHRs were 2.30 (95% CI, 1.20 to 4.42) and 2.61 (95% CI, 1.27 to 5.37), respectively.

In our prospective population study, we analyzed systolic pressure as a continuous variable. These analyses revealed that for all cardiovascular events, the continuous risk function and its lower and upper 95% confidence boundaries crossed unity at \( \approx 140 \), 120, and 160 mm Hg, respectively. According to recent guidelines,20 these thresholds correspond with an optimal systolic pressure and stages 1 and 2 of systolic hypertension. In patients with the latter condition, the risk of total and cardiovascular mortality and cardiovascular events increased 2- to 8-fold in \( Trp \) allele carriers compared with \( GlyGly \) homozygotes. We hypothesize that sodium retention in salt-sensitive \( Trp \) allele carriers3,4,6,22–24 might strengthen the age-related increase in systolic blood pressure and hence amplify the cardiovascular risk conferred by systolic hypertension. On the other hand, if, in the presence of the \( Trp \) allele, the age-related increase in systolic blood pressure is less pronounced, compensatory mechanisms or other genetic factors counteracting sodium retention might exert a protective effect and lead to a better prognosis. In keeping with a large case-control study,16 we found a lower risk of myocardial infarction in \( Trp \) allele carriers, for which systolic blood pressure was <160 mm Hg. If further studies confirm that the \( Trp \) allele might protect against myocardial infarction, then this is likely to be through a cellular mechanism different from its effect leading to hypertension, or \( \alpha \)-adducin might be in linkage disequilibrium to a protective gene variant.16

The present study must be interpreted within the context of its limitations. First, compared with other prospective studies, our sample size and the number of deaths and incident cardiovascular complications was relatively small. Second, we did not prove causality. We also cannot exclude that genetic polymorphisms in linkage disequilibrium with the \( \alpha \)-adducin gene contributed to our findings. Third, in long-term surveys, the definition of events is likely to be less precise than in short-term studies or trials, in which end points are collected via a single channel of information. On the other hand, our results were consistent across all events considered in the analyses, including total mortality, which is a binary outcome not requiring any medical diagnosis. We did not detect cohort effects. Use of a prospective design in a closed cohort protects against confounding by population stratification. Furthermore, our prospective analyses confirmed a hypothesis independently raised by the ARIC researchers.19

**Perspectives**

Our present observations built on evidence from in vitro studies,5 rodent models,2,3 and intervention studies with diuretics in hypertensive patients.5,18 If confirmed, they might have important implications for the management of hypertension and public health. Carriers of the \( Trp \) allele with uncontrolled or untreated systolic hypertension over a follow-up of \( \approx 10 \) years might have a probability of experiencing a major cardiovascular event of \( >70\% \). Of these incident cases, 40% might be directly attributable to the
risk-carrying Trp allele. In keeping with the hypothesis of increased renal sodium reabsorption, Psaty et al demonstrated in a case-control study with a retrospective design that antihypertensive treatment with diuretics was associated with a lower risk of combined myocardial infarction or stroke than therapies with other antihypertensive agents in Trp allele carriers but not in GlyGly homozygotes. In light of the present findings and current guidelines for antihypertensive treatment, Psaty’s suggestion that a large subgroup of the hypertensive population might especially benefit from diuretic treatment now needs to be tested in actively controlled randomized pharmacogenetic trials. In conclusion, the common 460Trp point mutation in the α-adducin gene substantially magnifies the risk of total and cardiovascular mortality and major cardiovascular complications associated with systolic blood pressure. These findings need replication in other populations, in particular in ethnic groups with a higher prevalence of the Trp allele, such as Asians.

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References

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