4G/4G Genotype of PAI-1 Gene Is Associated With Reduced Risk of Stroke in Elderly

Tiny Hoekstra, PhD; Johanna M. Geleijnse, PhD; Cornelis Kluft, PhD; Erik J. Giltay, PhD; Frans J. Kok, PhD; Evert G. Schouten, PhD

Background and Purpose—Plasminogen activator inhibitor type 1 (PAI-1) is the main inhibitor of fibrinolysis, and high levels may increase the risk of cardiovascular disease. The 4G/5G polymorphism affects PAI-1 gene transcription with lower levels of plasma PAI-1 in the presence of the 5G allele. We investigated whether plasma PAI-1 and 4G/5G genotype would predict the occurrence of cardiovascular events at old age.

Methods—Relative risks for cardiovascular events and all-cause mortality were obtained in strata of PAI-1 activity and 4G/5G genotype in a population-based study of 637 Dutch elderly with 7.8 years of follow-up.

Results—The 4G/4G genotype was associated with a decreased risk of stroke (relative risk [RR] = 0.4; 95% CI, 0.2 to 0.9), transient ischemic attack (RR = 0.3; 95% CI, 0.1 to 0.8), and cardiovascular mortality (RR = 0.5; 95% CI, 0.3 to 1.0) after adjustment for age, sex, and time of blood sampling. 4G carriers had an increased risk of myocardial infarction, but this was not statistically significant. Subjects with high plasma PAI-1 activity were at increased risk of stroke (RR = 3.3 in highest versus lowest tertile; 95% CI, 1.5 to 7.1), cardiovascular mortality (RR = 2.3; 95% CI, 1.2 to 4.4), and all-cause mortality (RR = 1.5; 95% CI, 1.1 to 2.1).

Conclusions—Our results provide support for a protective effect of the 4G allele against stroke, which is notable given the direct relationship between stroke and PAI-1 activity. We hypothesize that a local increase in tissue PAI-1 may stabilize plaques, thereby reducing the risk of cerebrovascular disease. (Stroke. 2003;34:2822-2829.)

Key Words: cerebral ischemia, transient ■ cerebrovascular accident ■ fibrinolysis ■ polymorphism

Plasminogen activator inhibitor type 1 (PAI-1), which forms a complex with tissue-type plasminogen activator (tPA), is a strong inhibitor of fibrinolysis. High PAI-1 activity has been associated with an increased risk of coronary events in populations with angina pectoris and in post–myocardial infarction (MI) patients. However, PAI-1 is probably not an independent risk factor for coronary heart disease in general (healthy) populations.

The 4G/5G polymorphism is a common polymorphism in the promoter region of the PAI-1 gene. Both the 4G and 5G alleles have a binding site for an activator of transcription. The 5G allele, however, has an additional binding site for a repressor, resulting in lower transcription rates and less PAI-1 activity. An association between the 4G/5G polymorphism and cardiovascular disease (CVD) would provide support for a causal role of PAI-1 since the genetically determined level is unlikely to be influenced by the inflammatory disease process and cardiovascular risk factors. A recent meta-analysis of 9 studies showed a 20% increased risk of MI for the 4G/4G genotype.

The associations of PAI-1 and the 4G/5G polymorphism with stroke received little attention compared with the relation with coronary heart disease. In the Northern Sweden Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study, the risk of first stroke was predicted by the tPA*PAI-1 complex but not by PAI-1 activity. Epidemiological data suggest a protective effect of the 4G allele against cerebrovascular events. In the present population-based study in 637 Dutch elderly, we examined the separate and combined effects of PAI-1 activity and the 4G/5G polymorphism on incidence of cardiovascular events.

Subjects and Methods

Study Population
The Arnhem Elderly Study is a population-based cohort study that started in 1991/1992. We invited a random sample (stratified for age and sex) of 1793 independently living men and women aged 65 to 84 years in the city of Arnhem, Netherlands. A total of 1012 subjects agreed to be interviewed, and 685 agreed to have a physical examination and venipuncture. Study design and population characteristics have been described in detail elsewhere.

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A single nonfasting blood sample was obtained in 641 subjects. Data on both PAI-1 activity and the 4G/5G polymorphism were missing for 4 subjects, leaving 637 subjects for the present analysis. PAI-1 activity could not be assessed for 31 subjects, and genotyping was unsuccessful for 8 subjects. The population for the present study included more men than the population that did not participate or only had an interview (52% versus 44%; P=0.01) and was significantly younger (73.6 versus 76.1 years; P<0.001). Other characteristics, including lifestyle factors and self-perceived health, did not significantly differ between these groups. All subjects provided written informed consent, and the study was approved by the ethical committee of Wageningen University.

Data Collection
Trained interviewers collected data on lifestyle, current and past health, and medication. Smoking status was coded as current, former, or never. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). CVD was considered present if subjects reported a history of heart disease or stroke. Subjects were considered to be on cardiovascular medication if they had used angiotensin-converting enzyme inhibitors, β-blockers, thrombolytic agents, lipid-reducing agents, and/or salicylates during the 3 months before the interview. Hypertension was defined as blood pressure ≥160/95 mm Hg or use of antihypertensive medication.

Laboratory Determinations
Venipuncture was performed between 8 AM and 5:30 PM with the use of citrate collection tubes, and time of blood sampling was recorded. Samples were stored at –80°C. Plasma PAI-1 activity was determined with the Chromolize kit (Biopool). The variable for PAI-1 that was used in this study is the portion of total PAI-1 that remains after formation of the tPA*PAI-1 complex. tPA antigen was measured with the Imulyse kit (Biopool). The variable for PAI-1 that could not be assessed for 31 subjects, and genotyping was unsuccessful for 8 subjects. The population for the present study included more men than the population that did not participate or only had an interview (52% versus 44%; P=0.01) and was significantly younger (73.6 versus 76.1 years; P<0.001). Other characteristics, including lifestyle factors and self-perceived health, did not significantly differ between these groups. All subjects provided written informed consent, and the study was approved by the ethical committee of Wageningen University.

Follow-Up
Municipal registries provided data on mortality and migration until February 2001. One person was lost to follow-up because of emigration. Data on morbidity and cause-specific mortality were obtained from general practitioners by means of a standard form. In the Netherlands, the general practitioner forms the central link to all specialized medical care, and clinical events are unlikely to be missed by our follow-up procedure. Thirty-nine subjects gave no permission for collection of follow-up data. For a number of subjects, the general practitioner could not be traced (n=31), did not cooperate (n=39), or did not provide proper data (n=10). Follow-up on morbidity and cause-specific mortality was complete for 518 subjects (268 men and 250 women; 81% of subjects with data on PAI-1 and/or 4G/5G genotype). Characteristics of subjects who were followed were similar to those who were not followed, except for a lower serum cholesterol level (6.0 versus 6.3 mmol/L; P=0.02).

Cardiovascular events and causes of death were coded by a physician (E.J.G.) on the basis of information obtained by the general practitioner, according to the International Statistical Classification of Diseases, 10th Revision (ICD-10). End points comprised all-cause mortality, cardiovascular mortality (ICD codes I00 to I96), incidence of MI (I21 to I22, fatal and nonfatal), incidence of stroke (I60 to I69, fatal and nonfatal), and incidence of transient ischemic attack (TIA) (G45). In case of recurrent events, only the first event was considered in the analysis.

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the Dutch Elderly Men and Women by 4G/5G Polymorphism</th>
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<tr>
<td>Genotype distribution, %</td>
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<tr>
<td>4G/4G (n=193)</td>
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<td>Genotype distribution, %</td>
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<td>31</td>
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<td>History of CVD, †%</td>
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<td>Use of cardiovascular medications, †%</td>
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<td>PAI-1 activity, I.U./mL</td>
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<td>T-PA antigen, ng/mL</td>
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Continuous variables are presented as mean±SD or as median (Q1–Q3) for skewed data. *P<0.01; †P<0.05 for difference among genotypes. Skewed variables were log-transformed.

Based on self-report.
Subject characteristics by 4G/5G genotype are presented in Table 1. The genotype distribution was not in Hardy-Weinberg equilibrium ($\chi^2=4.3; 1 \text{ df}; P<0.05$). Median plasma PAI-1 activity was lower for 5G/5G than for other genotypes (1.4 versus 2.2 IU/mL; $P=0.02$). Only 1% of the variance in PAI-1 was explained by the 4G/5G polymorphism. Plasma PAI-1 was positively associated with BMI, LDL cholesterol, CRP, and insulin ($r$, from 0.13 to 0.34; $P<0.05$) and inversely with age ($r$, $=-0.11; P=0.005$) and HDL cholesterol ($r$, $=-0.31; P<0.001$). During 7.8 years of follow-up, 49% of the male and 35% of the female subjects died in our study population ($n=637$). In the subgroup with complete follow-up data ($n=518$), these figures were 46% and 34%, respectively. Mortality was significantly related to sex, smoking, hypertension, total cholesterol, LDL cholesterol, insulin, and CRP.

### Results

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### Statistical Analysis

Differences in subject characteristics among the 4G/5G genotypes were tested with ANOVA (continuous variables) or $\chi^2$ testing (categorical variables). The presence of Hardy-Weinberg equilibrium for 4G/5G polymorphism was examined by $\chi^2$ test. Spearman correlation coefficients ($r$) were calculated for the association of PAI-1 with other cardiovascular risk factors. Hazard rate ratios (categorical variables). The presence of Hardy-Weinberg equilibrium ($P>0.05$) but not to serum lipids. CVD was the main cause of death in men (38%) and women (45%).

The risk of cardiovascular events and all-cause mortality in tertiles of PAI-1 activity (<0.9, 0.9 to 3.9, and >3.9 IU/mL) is shown in Table 2. A 3-fold increased risk of stroke was observed in the middle and highest tertiles of PAI-1, which became stronger (RR $>5$) after adjustment for cardiovascular risk factors (mainly BMI and serum lipids). Exclusion of 129 subjects with a history of CVD did not change the relationships (data not shown). Additional adjustment for tPA attenuated somewhat the association of PAI-1 with cardiovascular mortality (RR=2.0; 95% CI, 1.0 to 3.9 in middle tertile, and RR=2.5; 95% CI, 1.1 to 5.7 in highest tertile) and overall mortality (RR=1.1; 95% CI, 0.8 to 1.6, and RR=1.4; 95% CI, 0.9 to 2.1, respectively). PAI-1 activity was positively
associated with incidence of MI and TIA, but the trend across tertiles did not reach statistical significance (Table 2).

The association of 4G/5G genotype with cardiovascular events and all-cause mortality is presented in Table 3. After adjustment for age and sex, the risk of stroke, TIA, and cardiovascular mortality was reduced by 50% in subjects with the 4G/4G genotype. Adjustment for cardiovascular risk factors (model 2) did not materially change these associations. Restricting the analysis to ischemic stroke yielded a more strongly decreased risk for the 4G/4G genotype (RR = 0.2; 95% CI, 0.04 to 1.0). The 4G/5G polymorphism did not significantly predict incident MI and all-cause mortality (Table 3).

Figure 1 shows an overview of epidemiological studies on 4G/5G polymorphism and stroke. Figure 2 presents risk of stroke in categories of plasma PAI-1, 4G/5G genotype, and these factors combined. Predicted 10-year stroke-free survival was strongly reduced to 72.2% in 5G carriers with elevated PAI-1 (>0.9 IU/mL) compared with 97.6% for 4G homozygotes with low PAI-1 (<0.9 IU/mL). Cox proportional hazard analysis adjusted for age, sex, and time of blood sampling showed similar results.

Analysis of plasma tPA antigen in tertiles (<8.5, 8.5 to 11.7, and >11.7 ng/mL; data not shown in tables) using the fully adjusted model showed an increased risk of MI in the middle but not in the highest tertile (RR = 4.2; 95% CI, 1.4 to 12.8, and RR = 1.1; 95% CI, 0.3 to 4.0, respectively). The associations of tPA with incident stroke (RR = 0.8 and 1.4, respectively) and incident TIA (RR = 0.7 and 0.8, respectively) were not statistically significant (P trend > 0.2). tPA, however, was predictive of cardiovascular mortality (RR = 0.8; 95% CI, 0.4 to 1.5 in middle tertile, and RR = 1.8; 95% CI, 1.0 to 3.4 in highest tertile; P trend = 0.037) and all-cause mortality (RR = 1.2; 95% CI, 0.8 to 1.7, and RR = 1.7; 95% CI, 1.2 to 2.4, respectively; P trend = 0.003).

**Discussion**

In a general population of Dutch elderly, we found a strongly reduced risk of stroke, TIA, and cardiovascular mortality for the 4G/4G genotype of the PAI-1 gene. In contrast to this finding, high PAI-1 activity in plasma was associated with an increased risk of cerebrovascular events. The risk of stroke was notably high in 5G carriers with elevated plasma PAI-1.
Our study population was not in Hardy-Weinberg equilibrium for the 4G/5G polymorphism (4G/4G, 31%; 4G/5G, 46%; and 5G/5G, 24%). The 5G/5G genotype seems overrepresented in our population compared with another Dutch study in >12,000 women (distribution of 31%, 51%, and 18%, respectively). Discrepancy in our study may result from selection related to genotype, possibly due to exclusion of institutionalized elderly or differential survival. However, the 4G/5G genotype distribution in our study was not very deviant from that of other white populations. In the Insulin Resistance Atherosclerosis Study, the distribution in whites was 29% for 4G/4G, 47% for 4G/5G, and 25% for 5G/5G, which was reported to be in Hardy-Weinberg equilibrium. In 205 subjects aged ≥80 years, the corresponding distributions were 30%, 47%, and 23%. Because of the prospective nature of our analyses, we do not think that the absence of a Hardy-Weinberg equilibrium for the 4G/5G polymorphism has resulted in a major distortion of our findings.

We report a protective effect of the 4G allele against stroke, which is in agreement with previous epidemiological studies. A Korean study yielded contrasting data, possibly as a result of racial differences. With regard to other outcomes, we observed a modest risk elevation for incident MI in 4G/4G subjects. This finding, although not statistically significant, is in agreement with the meta-analysis by Boekholdt et al., who reported an overall odds ratio of 1.2 (95% CI, 1.0 to 1.4). We found a strongly reduced risk of cardiovascular mortality for 4G/4G, probably as a result of cerebrovascular diseases that constituted 43% of the fatal cases.

Plasma PAI-1 appeared not to be a very strong risk factor for MI in our study (RR ~1.5). Adjustment for the inflammatory marker CRP or exclusion of prevalent CVD cases did not affect this relationship. Our data are in accord with the Cardiovascular Health Study among elderly subjects, in which PAI-1 was not a strong predictor of coronary events. A relationship between PAI-1 and incident MI has mainly been found in patients with coronary disorders, which may explain the relatively weak association in a general population of elderly. We are among the first to demonstrate that elevated plasma PAI-1 (mainly independent of 4G/5G) is a strong risk indicator for stroke at old age. The underlying mechanism of PAI-1 elevation can be of genetic origin, but the genetic regulation of plasma PAI-1 is largely unknown. Alternatively, PAI-1 elevation could be caused by an underlying mechanism of insulin resistance and systemic inflammation, as part of the CVD process.

Our data suggest that the genotype-phenotype association for 4G/5G polymorphism and PAI-1 is weak. Differential regulation or function of PAI-1 in plasma and tissue may explain the contrasting findings for the 4G/5G polymorphism and PAI-1 activity that we found in relation to stroke. In animals, local cellular production of PAI-1 and tPA and a definite role of this protease system in tissues have been demonstrated. Localized inflammatory processes play a major role in the process of atherosclerosis and plaque rupture. On the basis of our data, we suggest that there are local mechanisms in brain tissue that account for the protective effect of 4G/5G against stroke. We hypothesize that at inflammatory sites, the putative increase of PAI-1 is stronger for the 4G allele and that this inhibits proteolysis. This may, for instance, result in plaque stabilization and increased neutralization of tPA, which is potentially neurotoxic.

In conclusion, our data suggest a protective role for the 4G allele in the development of stroke at old age, whereas PAI-1 activity in plasma appears to be detrimental. This apparently paradoxical relationship needs to be confirmed in large.

Figure 1. Overview of epidemiological studies on 4G/4G polymorphism and stroke.

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**Case-control**
- Hindorf (2002) - Ischaemic
- Endler (2000) - Ischaemic (+ TIA)
- Elbaz (2001) - Ischaemic
- Catto (1997) - Total
- Hindorf (2002) - Hemorrhagic
- Bang (2001) - Ischaemic

**Prospective**
- Roest (2000) - Total (fatal)
- Heijmans (1999) - Total (fatal)
- Hoekstra (present) - Total (fatal + non-fatal)

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In conclusion, our data suggest a protective role for the 4G allele in the development of stroke at old age, whereas PAI-1 activity in plasma appears to be detrimental. This apparently paradoxical relationship needs to be confirmed in large.


Genetic Make-Up for Increased PAI-1 Expression Protects Against Stroke

This issue of *Stroke* reports findings that the 4G variant of the PAI-1 4G/5G polymorphism is associated with a reduced incidence of stroke. Those findings are in agreement with 7 other studies that observed a similar relationship between the 4G variant of PAI-1 and a reduced stroke risk. This consistency in 8 independent studies minimizes the possibility that the relationship between the PAI-1 4G variant of PAI-1 and reduced stroke risk is a chance finding.

PAI-1 4G/5G is an interesting “functional” polymorphism because the alleles are the real cause of variation in PAI-1 expression. The 4G allele of the PAI-1 4G/5G polymorphism lacks a binding site for a transcription repressor protein, which is present on the 5G allele. Therefore, the 4G is the high PAI-1 expresser allele and the 5G the low expresser allele. Subjects who are homozygous for the 4G allele have 25% higher plasma concentrations than subjects homozygous for the 5G allele. Those findings indicate that homozygosity for the 4G allele stands for lifelong exposure to increased PAI-1 expression. The PAI-1 4G/5G polymorphism is an important tool in investigating the etiological involvement of PAI-1 in stroke because genetic make-up is fixed at conception; therefore, an association between genetic make-up for increased PAI-1 expression (PAI-1 4G allele) and a reduced risk of stroke is not confounded by other risk factors of stroke. For the same reason, genetic make-up for high PAI-1 expression is not a consequence of stroke. A relationship between the PAI-1 4G allele and a reduced risk of stroke is therefore causal evidence for a protective role of PAI-1 against stroke.

The notion that PAI-1 protects against stroke is further supported by findings in large cohort studies that tPA levels predict an increased incidence of stroke, while plasma PAI-1 concentrations seem not associated with stroke risk. Still, careful consideration is required to draw definite conclusions from observational studies on the relationship between tPA or PAI-1 levels and stroke incidence because plasma variations of tPA and PAI-1 depend on APOE genotype, the renin-angiotensin system, VLDL levels, unsaturated fatty acids content, insulin-like molecules, and pro-inflammatory cytokines (reviewed in Kohler and Grant).

Therefore, a relationship between tPA or PAI-1 levels and stroke is subject to confounding by such factors. Until recently, PAI-1 was considered as a potentially harmful factor in stroke etiology because PAI-1 was best known for its antifibrinolytic properties. New insights from transgenic mouse models show that the involvement of PAI-1 in stroke is more complicated because PAI-1 is involved in both harmful and protective steps in arterial disease etiology. An important protective function of PAI-1 is the inhibition of the activation of matrix-degrading enzymes in the atherosclerotic plaque, thereby preventing cardiac rupture followed by an ischemic infarction. Furthermore, PAI-1 is necessary to protect against tPA, which may cause local damage in the neurological tissue after an ischemic stroke.

In conclusion, 8 independent studies observed that genetic make-up for increased PAI-1 expression protects against stroke. Those reproducible genetic associations can be considered as causal evidence that genetic make-up for increased PAI-1 expression protects against stroke because genotype is not subject to confounding and is not a consequence of stroke. The protective involvement of PAI-1 in stroke needs to be investigated further, but the properties of PAI-1 to prevent plaque rupture and protect against neurological damage after an ischemic infarction are both plausible pathways.

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Editorial Comment— Genetic Make-Up for Increased PAI-1 Expression Protects Against Stroke
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