The ACE Gene I/D Polymorphism Is Not Associated With the Blood Pressure and Cardiovascular Benefits of ACE Inhibition

Stephen B. Harrap, Christophe Tzourio, François Cambien, Odette Poirier, Segolene Raoux, John Chalmers, Neil Chapman, Samuel Colman, Solenn Leguennec, Stephen MacMahon, Bruce Neal, Takayoshi Ohkubo, Mark Woodward for the PROGRESS Collaborative Group*

Abstract—The insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme (ACE) gene might have consequences for the risks of vascular diseases. We examined the ACE genotype and the effects of a perindopril-based blood pressure–lowering regimen on macrovascular events, dementia, and cognitive decline among hypertensive and nonhypertensive patients with a history of cerebrovascular disease. ACE I/D genotypes were measured in 5688 of 6105 individuals with previous stroke or transient ischemic attack who participated in the PROGRESS trial. The DD genotype was significantly (P<0.0001) less frequent in Asian subjects (Chinese and Japanese, 14.7%) than in non-Asian subjects (32.0%). Controlling for racial background, there were no associations between ACE genotypes and cerebrovascular disease history or cardiovascular risk factors, including baseline blood pressure. The ACE genotype was not associated with the long-term risks of stroke, cardiac events, mortality, dementia, or cognitive decline; neither did the ACE genotype predict the blood pressure reduction associated with the use of the ACE inhibitor perindopril. Similarly, there was no evidence that the ACE genotype modified the relative benefits of ACE inhibitor–based therapy over placebo. This study provides no evidence that in patients with cerebrovascular disease, knowledge of ACE genotype is useful for predicting either the risk of disease or the benefits of perindopril-based blood pressure–lowering treatment.

(Hypertension. 2003;42:297-303.)

Key Words: genes ■ blood pressure ■ stroke ■ coronary disease ■ clinical trials

Ischemic and hemorrhagic stroke and their associated risk factors show familial aggregation, such that the relative risk of stroke is approximately doubled in the presence of stroke in a first-degree relative.1 Genetic causes have been found for rare, specific cerebrovascular abnormalities.1 More generally, a recent genome scan identified a susceptibility locus for stroke on chromosome 5q12,2 and other studies have suggested candidate genes, including that encoding the angiotensin-converting enzyme (ACE).

Common variation in the ACE gene structure is defined by the insertion (I) or deletion (D) of 287 bp of nonsense DNA in intron 16, resulting in 3 genotypes (DD, ID, II). The ACE I/D polymorphism is presumed to be in linkage disequilibrium with functional variants that determine enzyme activity,3 such that the D allele is associated with increased ACE activity in white4 and Asian5,6 subjects. However, the I/D polymorphism does not appear to be associated with ACE activity in black subjects.7 Although the polymorphism is not associated with differences in plasma angiotensin II or aldosterone even in white subjects,8 changes in tissue ACE activity9 might be relevant to blood vessels and stroke.

Most studies of the ACE gene, blood pressure, and stroke have been neither large nor prospective, and the findings have been either inconclusive or conflicting. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a large-scale, randomized trial designed to determine the effects of an ACE inhibitor–based blood pressure–lowering regimen on the risks of major vascular events among individuals with a history of stroke or transient ischemic attack (TIA).10 There were substantial benefits of this regimen for the risk of stroke,10 and we report here the associations between the ACE gene I/D polymorphisms and blood pressure, the risk of vascular events, and the effects of study treatment on vascular events.

Methods

Study Design

The design of the PROGRESS study has been described in detail elsewhere.10 In brief, 6105 participants were recruited from 172 collaborating centers in 10 countries from Australasia, Europe, and Asia between 1995 and 1997. The institutional ethics committee of each collaborating center approved the trial and the genetic substudy,
and all participants provided written, informed consent. Individuals were potentially eligible if they had a history of cerebrovascular disease (stroke or TIA, but not subarachnoid hemorrhage) within the previous 5 years and no clear indication for or contraindication to treatment with an ACE inhibitor. There were no blood pressure criteria for entry.

Potentially eligible individuals entered a 4-week, prerandomization run-in period, during which they received open-labeled perindopril (2 mg daily for 2 weeks, followed by 4 mg daily for another 2 weeks). Participants who tolerated and adhered to the run-in therapy with perindopril were randomly assigned, in a double-blind manner, to continued active treatment or matching placebo(s). Active treatment comprised a flexible treatment regimen based on perindopril (4 mg daily) in all participants, with the addition of indapamide (2.5 mg daily, or 2 mg daily in Japan) in those for whom the responsible study physician judged that there was no specific indication for nor contraindication to the use of a diuretic. Those participants assigned to placebo received 1 or 2 tablets identical in appearance to the active agent(s). All other aspects of medical care were left to the discretion of the responsible physician.

Data Collection and Follow-Up

Before randomization, information was collected about the history of vascular disease, vascular risk factors, and current medications. After randomization, participants were scheduled to be seen on 5 occasions in the first year and every 6 months thereafter until the end of the scheduled follow-up period or death. At each visit, blood pressure was measured in duplicate, to the nearest 2 mm Hg, by using a standard mercury sphygmomanometer.

Outcomes

In addition to blood pressure, outcomes for these analyses included major vascular events and cognitive decline, which were defined as follows: (1) fatal and nonfatal stroke, with separate classification of ischemic and hemorrhagic stroke subtypes; (2) major coronary heart disease, defined as nonfatal myocardial infarction or death due to coronary heart disease,11 with separate analyses of nonfatal myocardial infarction; (3) major vascular events, defined as a composite of nonfatal stroke, nonfatal myocardial infarction, or death due to any vascular cause (including sudden unexplained death); (4) mortality from any cause; (5) dementia, diagnosed according to DSM-IV criteria;12 and (6) cognitive decline, defined as a fall of at least 3 points in the Mini-Mental State Examination between baseline and final available assessment.12 An independent end-point adjudication committee, blinded to study treatment allocation, reviewed source documentation for all suspected strokes, myocardial infarctions, and all deaths during follow-up; a separate dementia adjudication committee reviewed all dementia assessments.12

DNA Analyses

Samples of venous blood were collected in EDTA for extraction of DNA from buffy coats by using a salting-out procedure. Genotyping of the ACE I/D polymorphism was performed after polymerase chain reaction amplification of the region encompassing the polymorphism with 3 primers, ACE3U (TCTGATCCTCTGGACCTCGTATCC), ACE2L (CCCTTAGAATCCTGTCTGTTAAG), and ACE1U (CTTGAAGAACCTTCCACTTTTCT), by hybridization with allele-specific oligonucleotides. The sequence of allele-specific oligonucleotide and assay conditions are available at the Internet address http://www.genecanvas.org/polymorphism.asp-pol=ACE_ID.htm.

Statistical Analysis

Baseline characteristics were compared between the 3 genotypes by \( \chi^2 \) tests and logistic regression (for categorical variables) or ANOVA and general linear models (for continuous variables). Hardy-Weinberg equilibrium was tested by \( \chi^2 \) tests. Differences between the 3 genotypes in the effects of active treatment on blood pressure were investigated by ANOVA (1) during the run-in phase of the trial, including all subsequently randomized patients with known genotype, comparing baseline with prerandomization blood pressure measurements; and (2) during the entire study period, including all randomized patients assigned to active treatment with known genotype, comparing baseline with final postrandomization blood pressure measurements. Average postrandomization differences in blood pressure between the randomized groups were also estimated by fitting linear mixed models, by using baseline and all available postrandomization blood pressure measurements with an interaction term to compare the effects in the 3 subgroups defined by genotype.

Longitudinal associations between ACE genotypes and events were investigated with the Cox proportional-hazards models for those outcomes for which a specific event date was available (all stroke and coronary outcomes) and logistic regression models for those outcomes for which a specific event date was not available (dementia and cognitive decline). Hazard ratios and odds ratios were calculated by using the II genotype as the reference group. All analyses were carried out first without adjustment and then with adjustment for potential confounding variables (treatment allocation, assignment to combination or single-drug therapy, Asian or non-Asian ethnicity).

The effects of randomized treatment on events for each individual genotype were also estimated by using Cox and logistic regression models. Because the overall effect of treatment on stroke was greater among participants treated with combination therapy than among those treated with single-drug therapy,\(^{10}\) treatment effects were standardized for the proportions of the study population for whom combination (58%) or single-drug (42%) therapy was planned by taking weighted averages of the estimates obtained for the 2 therapies. Homogeneity of the effects of treatment among different genotypes was tested by adding interaction terms to the relevant statistical models.\(^{13}\)

Results

Study Population and Baseline Characteristics

A total of 6105 individuals were randomized into PROGRESS. The current analyses include the 5688 randomized participants for whom ACE I/D genotyping was successful: of these, 2828 were in the active treatment group and 2860 were in the placebo group. These 5688 participants were representative of the total study participants in terms of their principal sociodemographic and clinical characteristics.\(^{10}\)

The 2132 Asian subjects (individuals recruited from the People’s Republic of China or Japan) were younger (60.9 vs 65.7 years), had a lower body mass index (24.6 vs 26.4 kg/m\(^2\)), consumed less alcohol (18% vs 47%, \( \simeq 1 \) U per week) were more likely to have a history of stroke (92% vs 79%), and less likely to have a history of TIA or amaurosis fugax (12% vs 29%) than the 3556 non-Asian participants (all \( P<0.0001 \)). The DD genotype was also significantly (\( P<0.0001 \)) less frequent in Asian subjects (\( II 41.0\%, ID 44.3\%, DD 14.7\% \)) than in non-Asian subjects (\( II 21.2\%, ID 46.8\%, DD 32.0\%)\), but in both groups, genotypes were in Hardy-Weinberg equilibrium. Therefore, Table 1 provides baseline characteristics by genotype in Asian and non-Asian subjects separately. There were no significant differences in any of the baseline variables listed in Table 1 between the 3 genotypes. In particular, there were no differences in baseline systolic or diastolic blood pressure levels between the 3 genotype groups. This was true overall and separately for males and females and for participants who were and were not taking blood pressure–lowering medications at study entry (data not shown). The proportions assigned to each randomized treatment and the proportions managed with combination compared with single-drug therapy were well balanced between the 3 genotypes (Table 1).

The effects of randomized treatment on events for each individual genotype were also estimated by using Cox and logistic regression models. Because the overall effect of treatment on stroke was greater among participants treated with combination therapy than among those treated with single-drug therapy,\(^{10}\) treatment effects were standardized for the proportions of the study population for whom combination (58%) or single-drug (42%) therapy was planned by taking weighted averages of the estimates obtained for the 2 therapies. Homogeneity of the effects of treatment among different genotypes was tested by adding interaction terms to the relevant statistical models.\(^{13}\)
Effects of ACE Genotype on Blood Pressure Reduction Achieved

During the 4-week run-in period, treatment with perindopril reduced the overall mean blood pressure from baseline to follow-up by 8.8/4.7 mm Hg (Table 2) among the randomized participants genotyped. The mean reduction in blood pressure during run-in did not differ between the 3 participant groups defined by each genotype (P = 0.30 for systolic and diastolic blood pressure). This was true in both males and females separately, those participants already taking blood pressure-lowering medication and those who were not, and in both Asian and non-Asian participants separately (data not shown). Similar analyses of the effects of perindopril±indapamide on blood pressure during the mean 3.9-year postrandomization phase in the 2828 actively treated participants showed a mean 14.4/7.4 mm Hg reduction in blood pressure from baseline to final assessment (Table 2). Once again, there was no evidence that the effects of treatment varied between the participant groups defined on the basis of genotypes (P = 0.57 for systolic and diastolic blood pressure).

Associations of ACE Genotypes With the Risk of Vascular Events

Three-way analyses of the ACE genotypes identified no significant associations of ACE genotype with major outcomes in either unadjusted or adjusted analyses (Table 3). Pairwise comparisons of ID and DD against the II reference...
group identified only small to moderate differences in the relative risks of events, with estimates of effect ranging between 0.70 (30% reduced risk) and 1.23 (23% increased risk) for the 9 outcomes. The only pairwise comparisons to provide statistically significant results were for the outcomes major vascular events and major coronary heart disease. In each case, the DD group had lower risks than the II group, although both were only borderline significant at the 5% level. There was no evidence that the associations of ACE genotype with the risks of vascular events were different between Asian and non-Asian participants (results not shown). No association between ACE genotype with the risks of vascular events were observed when the placebo group was considered alone (data not shown).

**Associations of ACE Genotypes With the Effects of Active Treatment on the Risk of Vascular Events**

The main study analyses showed overall beneficial effects of randomized treatment on the risks of all of the 8 outcomes studied here except for dementia, for which there was only a nonsignificant trend toward benefit. There was no evidence that the beneficial effects of study treatment observed overall varied between the 3 participant groups defined by genotype. Although the confidence intervals about the estimates for individual genotypes were generally wide, all estimates for all outcomes were suggestive of benefit, except for a slight and nonsignificantly increased risk of death among participants with the ID genotype (Table 4). However, neither for this nor for any other outcome was there any statistical evidence that the effects of treatment varied between ACE genotype subgroups (All P homogeneity ≥0.18).

**Discussion**

The PROGRESS study clearly demonstrated that among individuals with previous stroke or TIA, a perindopril-based blood pressure–lowering regimen reduced blood pressure and the risks of stroke, coronary heart disease, and cognitive decline. Although the activity of the ACE enzyme is to a significant extent determined by the ACE genotype in Asian and white subjects, we could find no evidence of any association between the ACE II/ID and DD genotypes and the effects of the ACE inhibitor on study outcomes.

There is little evidence that ACE genotype is a major determinant of hypertension or blood pressure variation, and this was confirmed by the PROGRESS study. Despite the large size of the study and the precise estimates of blood pressure levels afforded, there were no identifiable associations of ACE genotype with baseline blood pressure levels. Similarly, although there has been debate as to whether ACE genotype might influence the reduction in blood pressure achieved with ACE inhibitor therapy, the PROGRESS study provides no evidence to support this hypothesis. In PROGRESS, the estimates of treatment effect obtained for each genotype were very precise and provided extremely good statistical power to detect, with 90% power, a difference in blood pressure reduction (last recorded minus baseline reading) of 3.5, 2.5, and 3.2 mm Hg. Moreover, the ACE genotype was not useful in predicting the significant falls in systolic and diastolic pressures during the 4-week run-in phase, during which all patients were exposed to perindopril, or among the 2828 of these patients assigned to active perindopril-based treatment during the approximate 4-year follow-up period. This was so, whether or not patients were receiving other (non–ACE inhibitor) antihypertensive therapy at the time. Nor was there any association between ACE genotypes and the mean postrandomization differences in blood pressure between participants assigned to active treatment and those assigned to placebo.

Although no association between ACE genotype and blood pressure could be identified, it remained possible that postulated blood pressure–independent effects of ACE inhibition might be associated with the ACE genotype. We were able to test for longitudinal associations between ACE genotypes and the incidence of predefined cerebrovascular outcomes. There was no evidence that the likelihood of a recurrent stroke (total, ischemic, or hemorrhagic) was any different for those
with a particular ACE genotype. In PROGRESS, the estimates of treatment effect obtained for each genotype were precise; we had sufficient numbers to detect, with 90% power, relative risk reductions of 41%, 29%, and 35% (for DD, ID, and II, respectively) for stroke and of 35%, 23%, and 29% for major vascular disease. Although some studies suggested associations between the ACE D allele and increased carotid intima-media thickness,19 carotid plaque,20 carotid stenosis,21 and ischemic stroke,22 the findings of PROGRESS confirm other negative association analyses.23–26

Patients with cerebrovascular disease, though at very high risk of stroke, also have substantially elevated risks of myocardial infarction and other cardiac events.27 In the PROGRESS study, 150 incident cases of nonfatal myocardial infarction and a total of 255 major coronary events were observed in the genotyped subjects. Earlier reports of the association of ACE genotype with myocardial infarction were somewhat variable,28 and in PROGRESS, there was no overall association between these events and ACE genotype. Pairwise comparisons did identify participants with the ACE DD genotype as being at slightly lesser risk of major coronary events and major vascular events compared with those with the ACE II genotype, although these differences were of borderline significance.

Prior studies had also suggested that the ACE gene might contribute to complications of cerebrovascular disease, such as vascular dementia,29 and the ACE gene has been associated with both cognitive decline30 and Alzheimer’s disease.31 In the PROGRESS study, careful assessment of cognitive function32 identified several hundred patients who developed dementia and more with cognitive decline. However, there was no evidence that the likelihood of these events occurring during follow-up was associated with the ACE genotype. It has also been suggested that the ACE DD genotype might be associated with increased overall death rate.32 However, in PROGRESS, rates of death during the 4-year follow-up were

### TABLE 3. Associations Between ACE I/D Genotypes and Risks of Stroke, Vascular Events, Mortality, Dementia, Cognitive Decline, and Disability

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Genotype</th>
<th>Events, n (%)</th>
<th>Unadjusted Estimated RR* (95% CI)</th>
<th>Adjusted Estimated RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stroke</td>
<td>DD</td>
<td>167 (12)</td>
<td>0.97 (0.79–1.19)</td>
<td>0.98 (0.80–1.22)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>317 (12)</td>
<td>1.01 (0.85–1.21)</td>
<td>0.89 (0.68–1.23)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>198 (12)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>DD</td>
<td>132 (9)</td>
<td>0.98 (0.78–1.23)</td>
<td>0.96 (0.75–1.22)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>244 (9)</td>
<td>1.00 (0.82–1.22)</td>
<td>0.98 (0.81–1.22)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>155 (10)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>DD</td>
<td>21 (2)</td>
<td>0.77 (0.44–1.33)</td>
<td>1.08 (0.61–1.89)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>48 (2)</td>
<td>0.96 (0.61–1.50)</td>
<td>1.16 (0.74–1.82)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>15 (2)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Major coronary heart disease</td>
<td>DD</td>
<td>60 (4)</td>
<td>0.92 (0.65–1.29)</td>
<td>0.70 (0.50–0.99)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>119 (5)</td>
<td>1.00 (0.75–1.33)</td>
<td>0.86 (0.64–1.15)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>76 (5)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>DD</td>
<td>38 (3)</td>
<td>0.90 (0.59–1.38)</td>
<td>0.69 (0.45–1.07)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>63 (2)</td>
<td>0.82 (0.57–1.19)</td>
<td>0.71 (0.49–1.04)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>49 (3)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Major vascular events</td>
<td>DD</td>
<td>233 (16)</td>
<td>0.90 (0.76–1.07)</td>
<td>0.84 (0.70–1.00)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>463 (18)</td>
<td>0.99 (0.85–1.14)</td>
<td>0.96 (0.82–1.11)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>296 (18)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total mortality</td>
<td>DD</td>
<td>161 (11)</td>
<td>1.23 (0.98–1.53)</td>
<td>1.07 (0.85–1.34)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>273 (10)</td>
<td>1.14 (0.94–1.39)</td>
<td>1.06 (0.87–1.30)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>154 (9)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>DD</td>
<td>97 (7)</td>
<td>0.99 (0.75–1.32)</td>
<td>0.92 (0.69–1.32)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>181 (7)</td>
<td>1.03 (0.81–1.32)</td>
<td>0.99 (0.77–1.27)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>110 (7)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>DD</td>
<td>156 (11)</td>
<td>1.20 (0.95–1.52)</td>
<td>1.06 (0.83–1.36)</td>
</tr>
<tr>
<td></td>
<td>ID</td>
<td>269 (10)</td>
<td>1.14 (0.93–1.41)</td>
<td>1.08 (0.87–1.33)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>149 (9)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval.
*Hazard ratio except for dementia and cognitive decline, where an odds ratio is shown.
†Test of the null hypothesis of no difference between the 3 genotypes.
‡Adjusted for treatment (active/placebo), therapy (single drug/combination), and race (Asian/not).
Perspectives

These analyses of PROGRESS are among the most comprehensive assessment of the effects of ACE genotype on outcome to date. The ACE gene I/D polymorphisms do not appear to translate into significant phenotypic effects of ACE inhibitor treatment. These genotype analyses of PROGRESS provide no rationale for using ACE genotype to guide treatment decisions or to provide prognostic information relevant to cerebrovascular, cardiovascular, or cognitive function end points.

Appendix

PROGRESS Collaborative Group
A complete list is given in Reference 10. Management Committee: John Chalmers (coprincipal investigator), Stephen MacMahon (coprincipal investigator), Craig Anderson, Marie-Germaine Bousser, Jeffrey Cutler, Stephen Davis, Geoffrey Donnan, Lennart Hansson (deceased), Stephen Harrap, Kennedy Lees, Liu Lisheng, Giuseppi Mancia, Bruce Neal, Teruo Omae, John Reid, Anthony Rodgers, Roberto Sega, Andreas Terent, Christophe Tzourio, Charles Warlow, and Mark Woodward. End-point Adjudication Committee: Geoffrey Donnan (chair), Neil Anderson, Christopher Bladin, Brian Chambers, Gary Gordon, and Norman Sharpe. Denen-
tia Adjudication Committee: Craig Anderson and Yogni Ratna-
sabapathy. Data Monitoring Committee: Rory Collins (chair), Peter
Sandercok, John Simes, and Peter Sleight. Statistical Analysis:
Samuel Colman, Lesley Francis, Arier Lee, and Mark Woodward.

Acknowledgments
PROGRESS was funded by grants from Servier, the Health Research
Council of New Zealand, and the National Health and Medical
Research Council of Australia. The study was designed, conducted,
analyzed, and interpreted by the investigators, independent of all
sponsors.

References
Latchaw RE, Todd HW, Viste K, Starke R, Gurgus MS, Marler J, Enr M,
Hart N. Advances in the genetics of cerebrovascular disease and stroke.
2. Gretarsdottir S, Sveinbjornsdsottir S, Jonsson HH, Jakobsson F,
Einarsdottir E, Agnarsson U, Shkodin D, Einarsson G, Gudjonsdottir HM,
Valdimarsson EM, Einarsson OB, Thorgerisson G, Hadzic R, Jonsdottir
S, Reynolds ST, Bjarnadottir SM, Gudmundsdottir T, Gudjonsdottir GJ,
Gill R, Lindpaintner K, Sainz J, Hannesson HH, Sigurdsson GT,
Frugge ML, Kong A, Gudnason V, Stefansson K, Gulcher JR. Local-
ization of a susceptibility gene for common forms of stroke to Sq12. Am J
Hum Genet. 2002;70:593–603.
3. Zhu X, McKenzie CA, Forrester T, Nickerson DA, Broeckel U,
Schunkert H, Doering A, Jacob HJ, Cooper RS, Rieder MJ. Localization
of a small genomic region associated with elevated ACE. Am J Hum
4. Rigat B, Hubert C, Alhec-Gelas F, Cambien F, Corvol P, Soubrier F. An
insertion/deletion polymorphism in the angiotensin I-converting enzyme
gene accounting for half the variance of serum enzyme levels. J Clin
Iwasaki R, Hiramori K. Deletion polymorphism of the angiotensin I-converting enzyme gene is associated with serum ACE concentration and increased risk for CAD in the Japanese. Circulation. 1994;90:
2199–2202.
Lack of association of the angiotensin converting enzyme polymorphism
7. Bloem LJ, Manatunga AK, Pratt HJ. Racial difference in the relationship
of an angiotensin I-converting enzyme gene polymorphism to serum
CJW, Watt GCM. The angiotensin I-converting enzyme gene and pre-
disposition to high blood pressure in man. Hypertension. 1993;21:
455–460.
9. Danser AH, Schalekamp MA, Bax WA, van den Brink AM, Saxena PR,
Riegger GA, Schunkert H. Angiotensin-converting enzyme in the human
92:1387–1388.
10. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood pressure lowering regimen among 6,105 indi-
viduals with previous stroke or transient ischaemic attack. Lancet. 2001;
358:1033–1041.
11. PROGRESS Collaborative Group. Effects of a perindopril-based blood
pressure lowering regimen on cardiac outcomes among patients with
12. PROGRESS Collaborative Group. Effects of blood pressure lowering
with perindopril on dementia and cognitive decline in patients with
13. Woodward M. Epidemiology: Study Design and Data Analysis. Boca
of linkage between the angiotensin converting enzyme locus and human
Kim K, Yung Lee H, Suk Han D. ACE DD genotype is more susceptible
than ACE II and ID genotypes to the antiproteinemic effect of ACE
inhibitors in patients with proteinuric non-insulin-dependent diabetes
16. Todd GP, Chadwick IG, Higgins KS, Yeow WW, Jackson PR, Ramsay LE.
Relation between changes in blood pressure and serum ACE activity after
a single dose of enalapril and ACE genotype in healthy subjects. Br J Clin
17. Stavroulakas GA, Makris TK, Krespi PG, Hatzizacharias AN, Gialeraki
AE, Anastadiadis G, Tripoposkis P, Kyriakidas M. Predicting response to
Prediction of patient responses to antihypertensive drugs using genetic
1996;14:259–262.
M, Reunanen A, Kesanenien YA. Association between angiotensin con-
verting enzyme gene polymorphism and carotid atherosclerosis.
20. Watanabe Y, Ichigami T, Kawano Y, Umahara T, Nakamori A,
Mizushima S, Hibi K, Kobayashi I, Tamura K, Ochiai H, Umemura S,
Association between angiotensin I-converting enzyme genotypes, extracranial
22. Margaglione M, Celentano E, Grandone E, Vecchione G, Cappucci G,
Giuliani N, Colaizzo D, Panico S, Mancini FP, Di Minno G. Deletion
polymorphism in the angiotensin-converting enzyme gene in patients
16:304–309.
23. Hung J, McQuillan BM, Nidorf M, Thompson PL, Beilby JP. Angioten-
sin-converting enzyme gene polymorphism and carotid wall thickening in
a community population. Arterioscler Thromb Vasc Biol. 1999;19:
Folsom AR, Heiss G, Higginson M. Angiotensinogen and angiotensin con-
verting enzyme genotypes and carotid atherosclerosis: the atherosclerosis
risk in communities and the NHLBI family heart studies. Atherosclerosis.
25. Ueda S, Weir CJ, Inglis GC, Murray GD, Muir KW, Lees KR. Lack of
association between angiotensin converting enzyme gene insertion/
Prospective evaluation of the angiotensin-converting enzyme insertion/
deletion polymorphism and the risk of stroke. Circulation. 1999;99:
340–343.
27. Hartmann A, Rundek T, Mast H, Mohr JP. Mortality and causes of death
after first ischaemic stroke: the Northern Manhattan Stroke Study. Neu-
28. Butler R. The DD-ACE genotype and cardiovascular disease. Pharma-
associated with dementia in subjects with cerebrovascular disease. Archiv
Effect of the angiotensin I-converting enzyme I/D polymorphism on
73–80.
31. Narain Y, Yip A, Murphy T, Brayne C, Easton D, Evans JG, Xuereb J,
Cairns N, Esiri MM, Farlong RA. Rubinsztein DC. The ACE gene and
32. Morris BJ, Zee RY, Schrader AP. Different frequencies of angiotensin-
converting enzyme genotypes in older hypertensive individuals. J Clin
The ACE Gene I/D Polymorphism Is Not Associated With the Blood Pressure and Cardiovascular Benefits of ACE Inhibition

Stephen B. Harrap, Christophe Tzourio, François Cambien, Odette Poirier, Segolene Raoux, John Chalmers, Neil Chapman, Samuel Colman, Solenn Leguennec, Stephen MacMahon, Bruce Neal, Takayoshi Ohkubo and Mark Woodward

for the PROGRESS Collaborative Group

Hypertension. 2003;42:297-303; originally published online August 18, 2003;
doi: 10.1161/01.HYP.0000088322.85804.96

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/42/3/297

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/