Impact of Apolipoprotein E Polymorphism on Lipoproteins and Risk of Myocardial Infarction

The ECTIM Study

Gérald Luc, Jean-Marie Bard, Dominique Arveiler, Alun Evans, Jean-Pierre Cambou, Annie Bingham, Philippe Amouyel, Paul Schaffer, Jean-Bernard Ruidavets, François Cambien, Jean-Charles Fruchart, Pierre Ducimetiere

Abstract Human apolipoprotein (apo) E, a polymorphic protein with three common alleles, e2, e3, and e4, plays an important role in lipoprotein metabolism. This article describes the association of this polymorphism with lipids, apolipoproteins, and lipoproteins with a particular regard to lipoprotein particles, as defined by their apolipoprotein content, as well as the risk of myocardial infarction in a multicenter population-based case-control study (ECTIM study). In the ECTIM study, 574 male patients aged 25 to 64 were examined 3 to 9 months after myocardial infarction in four regions participating in the World Health Organization MONICA project: Belfast (Northern Ireland) and Lille, Strasbourg, and Toulouse (France). Control subjects (n=722) were randomly selected from the regional populations. The distribution of apoE phenotypes was significantly different across the four control samples (P=.04), with a higher frequency of the e4 allele in Belfast (14.3%) than in Toulouse (8.2%). The association of apoE polymorphism with biological measurements was studied in the control groups (n=640) after men with coronary heart disease or those taking hypolipidemic drugs were omitted, with the apoE3/3 phenotype as a reference after adjustment for concomitant factors. Individuals carrying the e2 allele had lower levels of plasma cholesterol, low-density lipoprotein cholesterol (LDL-C), and apoB and higher levels of triglycerides, very-low-density lipoprotein cholesterol (VLDL-C), apoC-III, apoE, lipoprotein (Lp) C-III:B, and Lp E:B. However, the effect of the e2 allele on triglyceride, VLDL-C, apoE, and Lp E:B parameters was heterogeneous across the populations. The magnitude of these effects was large and statistically significant in Lille and Strasbourg, whereas only apoE was increased in Toulouse, and no effect of the e2 allele appeared in Belfast. The e4 allele was associated with increased triglyceride, VLDL-C, apoB, and Lp C-III:B levels and a decreased LpA-I level, but apoC-III, apoE, and Lp E:B levels were similar to those with the apoE3/3 phenotype. The relative risk of myocardial infarction associated with apoE phenotypes compared with E3/3 was found to increase in the following order: E2/2 < E3/2 < E3/3 (relative risk=1) < E4/2 < E4/4 (P<.05). The presence of e2 and e4 alleles carried a relative risk of 0.73 (P=.05) and 1.33 (P=.02), respectively, in a codominant logistic model, and no heterogeneity between centers was demonstrated. In conclusion, men carrying the e4 allele present an atherogenic lipid and lipoprotein profile compared with E3/3 and are at higher risk of coronary heart disease in the populations under study. Men carrying the e2 allele have lower apoB levels and appear to be at lower risk despite higher triglyceride and Lp E:B levels, at least in some regions. This suggests that other genes or environmental factors play an interactive role with the e2 allele on lipid metabolism. ApoE polymorphism, however, seems to explain a modest proportion, 12%, of myocardial infarction cases at the population level.

Key Words • lipoproteins • apolipoproteins • myocardial infarction • apolipoprotein E polymorphism

Apolipoprotein E (apoE) is a structural component of triglyceride-rich lipoproteins, chylomicrons, and very-low-density lipoproteins (VLDLs), and high-density lipoproteins (HDLs). The structural gene locus of this apolipoprotein is polymorphic. Three common alleles designated e2, e3, and e4 code at a single locus from three isoforms, E2, E3, and E4. These three isoforms lead to six apoE phenotypes in plasma that can be identified by isoelectric focusing on a polyacrylamide gel. Numerous studies have shown a relation between the apoE phenotype and plasma lipid and lipoprotein levels, the apoE phenotype being, for example, a determinant of interindividual differences of total and low-density lipoprotein cholesterol (LDL-C). In vivo and in vitro investigations have shown functional differences between apoE alleles that are thought to modulate lipid levels. Indeed, apoE plays an important role in the metabolism of lipoproteins because it can bind to the apoB,E receptor and to the hepatic remnant receptor. Therefore, the affinity of the apoE2 isoform for the LDL receptor is lower than that of the apoE3 and results in reduced in vivo catabolism of apoE2-containing lipoproteins, whereas apoE4 shows an increased in vivo catabolism compared with apoE3. Lipoproteins play a central role in the appearance and development of atherosclerotic cardiovascular disease in humans, so the modifications of lipid parameters...
related to apoE phenotypes could influence the development of atherosclerosis. Therefore, the hypothesis of the association of the apoE polymorphism with atherosclerosis was tested in a number of epidemiological studies. However, these different studies showed conflicting results, which could be related to differences in sample size; to patient and control subject selection, such as age of included subjects and definition of coronary heart disease (CHD) (eg, survivors of myocardial infarction [MI] or atherosclerosis defined by coronary angiography); and to the confounding effect of major risk factors for atherosclerosis.

The World Health Organization MONICA Project is currently studying trends in CHD incidence and mortality in various regions. To investigate the large differences in CHD incidence between the French MONICA centers of Strasbourg, Toulouse, and Lille and the Northern Ireland center of Belfast, a coordinated population-based case-control study on MI was set up in each region (the Etude Cas-Témoins sur l’Infarctus du Myocarde [ECTIM] study). The case-control analysis of lipids, lipoproteins, and lipoprotein particles measured in the study has already been published. In the present work we report on the associations of apoE polymorphism with the same set of measurements as in the control population of the ECTIM study. Particular emphasis is placed on the study of lipoprotein particles. These particles are characterized on the basis of their apolipoprotein composition. The development of immunoassays allows the determination of the plasma levels of several types of particles that differ in their metabolic and atherogenic properties. This article also considers the question of whether apoE is protective (E2 carriers) or increases the risk (E4 carriers) of MI.

Methods

Subjects

The populations are those covered by the MONICA registers participating in the ECTIM study: Belfast and its surroundings in Northern Ireland, Lille and its surroundings in the north of France, Strasbourg and its surroundings in the northeast of France, and Toulouse and its surroundings in the southwest of France. Only 25- to 64-year-old men whose four grandparents had been born in Europe were eligible for inclusion in the study. In Belfast, the grandparents had to have been born in the historical entity of Ulster. The control subjects were obtained from electoral rolls in France and from the lists of general practitioners held by the Central Services Agency in Belfast. Among the eligible control subjects, 40% in Belfast, 47% in Lille, 54% in Strasbourg, and 49% in Toulouse refused to participate, did not respond, or could not be contacted. The names of MI survivors were obtained from the MONICA registers. MI was defined as corresponding to at least two of the following: chest pain of at least 20 minutes' duration, increase in cardiac enzymes, and typical electrocardiogram changes during the acute attack. The age distribution of the random control samples in French centers was chosen to match that of the MI patients as determined by the MONICA register in each area. In Belfast, an age-matched control subject was chosen for each case. Informed consent was obtained from the subjects and their family doctors. Each subject was examined by a specially trained doctor or nurse. The presence of disease, drug intake, and cigarette and alcohol consumption were recorded. Body weight was measured to the nearest 200 g for subjects without shoes using scales that were regularly checked and calibrated; height was determined to the nearest centimeter with a measuring tape on subjects without shoes standing with their backs to a wall. Epidemiological data and blood samples from MI survivors were obtained between 3 and 9 months after the event.

The total number of control subjects was 722, from whom 194 were recruited in Belfast, 155 in Lille, 185 in Strasbourg, and 188 in Toulouse. Among these, 648 were without CHD and were not taking hypolipidemic drugs. An additional group of 4 subjects had triglyceride levels higher than 800 mg/dL. Thus, 644 subjects were included in the analysis of the association of apoE phenotype with lipoproteins. For the second part of the study concerning the determination of the relative risk (RR) for MI, only control subjects with CHD were included. Therefore, 680 control subjects and 574 MI survivors were included.

Methods

Venous blood obtained from subjects was collected in EDTA-containing tubes after an overnight fast. The blood was kept at 4°C and separated within 3 hours by centrifugation at 4°C. e-Aminocaproic acid, chloramphenicol, and glutathione at final concentrations of 0.9, 0.6, and 0.3 mmol/L, respectively, were added to plasma. The plasma was sent at 4°C to the central laboratory at the Pasteur Institute in Lille within 5 days.

Cholesterol and triglyceride levels were then determined by automated enzymatic procedures (Boehringer Mannheim) adapted to a Hitachi 705 analyzer. Cholesterol was measured in VLDL separated by ultracentrifugation and in the HDL-containing supernatant after phosphotungstate/magnesium chloride precipitation of apoB-containing lipoproteins (Boehringer Mannheim). LDL-C was calculated by subtracting VLDL-C and HDL-C from total cholesterol. ApoA-I and apoB were quantified by laser immunonephelometry (Behring). ApoA-II, apoC-III, and apoE were measured by noncompetitive immunoassays. Lipoprotein particles, defined by their apolipoprotein composition and containing apoA-II and apoA-I (Lp A-I:A-II), apoE and apoB (Lp E:B), and apoC-III and apoB (Lp C-III:B), were measured by two-site immunoenzymatic assays as described elsewhere. Particles containing apoA-I but free of apoA-II were quantified by differential immunoelectroimmunoassay on ready-to-use plates. The apoE phenotype was determined from total plasma by isoelectric focusing followed by transfer onto a nitrocellulose sheet and then by incubation with anti-mouse IgG labeled with peroxidase.

Statistical Analysis

Results were analyzed with SAS statistical software (SAS Institute Inc). Comparison among the four centers of allele frequencies was tested by χ2 test. The relations between each biological measurement and apoE phenotypes in the control population were established by multiple linear regression models (GLM procedure) with the recruitment center and other variables as covariates. For that purpose, the six apoE phenotypes were coded by five (0-1) dummy variables allowing for a direct estimation of each phenotype versus E3/3 differential effect.

The e2 and e4 allelic effects with E3/3 chosen as the reference were obtained by a reduced model with two (0-1-2) dummy variables coding respectively for the number of e2 and e4 alleles in each phenotype. This model specifies a codominant additive effect of e2 and e4 on the level of the independent variable. The goodness of fit of the reduced model was tested by an approximate F ratio. The homogeneity of residuals and e4 effects across populations was tested by introducing specific population effects as interaction terms in the model. For some biological measurements with a highly skewed distribution (ie, triglycerides, VLDL-C, apoC-III, apoE, Lp...
Table 1. Age, Body Mass Index, Alcohol Intake, Tobacco Consumption, and Frequency of Apolipoprotein E Polymorphism Alleles in Control Groups of the ECTIM Study

<table>
<thead>
<tr>
<th>Region</th>
<th>Parameter</th>
<th>Belfast (n=175)</th>
<th>Lille (n=139)</th>
<th>Strasbourg (n=159)</th>
<th>Toulouse (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age, y</td>
<td>54.3±7.8</td>
<td>53.9±7.8</td>
<td>52.7±7.3</td>
<td>50.4±8.4</td>
</tr>
<tr>
<td></td>
<td>Body mass index, kg/m²</td>
<td>25.8±3.6</td>
<td>25.8±3.8</td>
<td>27.4±3.6</td>
<td>26.5±4.1</td>
</tr>
<tr>
<td></td>
<td>Alcohol intake, g/d</td>
<td>35.1±48.1</td>
<td>59.0±47.8</td>
<td>36.0±36.8</td>
<td>35.7±33.4</td>
</tr>
<tr>
<td></td>
<td>Cigarettes, No. per day</td>
<td>5.0±10.4</td>
<td>7.6±12.2</td>
<td>5.4±9.6</td>
<td>4.7±9.7</td>
</tr>
<tr>
<td></td>
<td>Allele frequency, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e2</td>
<td></td>
<td>10.3</td>
<td>11.9</td>
<td>8.5</td>
<td>5.6</td>
</tr>
<tr>
<td>e3</td>
<td></td>
<td>75.4</td>
<td>79.1</td>
<td>80.8</td>
<td>86.3</td>
</tr>
<tr>
<td>e4</td>
<td></td>
<td>14.3</td>
<td>14.0</td>
<td>10.7</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Values are mean±SD. Subjects with coronary heart disease or taking hypolipidemic drugs or those with triglycerides >800 mg/dL were excluded.

C-III:B, and Lp E:B), a logarithmic transformation was first carried out.

The associations of apoE phenotypes with MI were analyzed according to the same strategy as defined above for quantitative traits but using multiple logistic regression models (LOGIST procedure). Adjusted odds ratios for each phenotype compared with E3/3 were first obtained. The corresponding reduced model can be interpreted as a codominant multiplicative model for the e2 and e4 allele-specific RRs (RR associated with a given phenotype is the product of the respective RRs of its two alleles). The goodness of fit of the reduced model and the homogeneity of the allelic RRs across populations were tested by the likelihood ratio statistic.

Results

The distribution of apoE phenotypes in the entire control population was compatible with Hardy-Weinberg equilibrium ($\chi^2_3=1.3$).

Association of ApoE Phenotypes With Lipoproteins

Table 1 shows the general characteristics of the population included in this analysis (N=644). Globally, no large difference was apparent among the four samples for any variable. However, the higher mean alcohol and tobacco consumption levels in Lille and the higher mean body mass index in Strasbourg are noteworthy. The frequency of apoE alleles (Table 1) was significantly different among the four centers ($G^2=18.8$, $P<.01$), with a higher frequency of e2 and e4 in Belfast and Lille, respectively, and e3 in Toulouse.

Table 2 shows crude mean values of plasma lipids, apolipoproteins, and lipoprotein particles in the total population according to the six apoE phenotypes after adjustment for center, age, body mass index, cigarette use, and alcohol intake. The apoE phenotype significantly ($P<.05$) influenced the plasma lipid, lipid of lipoprotein, apolipoprotein, and lipoprotein particle levels except for cholesterol, apoA-II, and Lp A-I:A-II. The low level of cholesterol in phenotype E2/2, E3/2, and E4/2 subsets and its high level in phenotype E4/4 were mainly consequences of a variation in LDL-C. The variation of apoB was parallel to that of LDL-C, but if apoE polymorphism highly modulated LDL-C, the significance level of .05 was not reached for cholesterol. Triglycerides and VLDL-C were highest in subjects homozygous for E2 and E4. The same finding was noticed for Lp E:B and Lp C-III:B levels. In contrast, although the apoE level was highest in the E2/2 subjects, it was lowest in the subjects bearing apoE4. The most important effect of apoE phenotype on HDL particles was for HDL-C and LpA-I levels, which were increased in E2/2 and E3/2 and decreased in E4/4 subjects compared with E3/3 subjects.

Adjusted estimates of the average allelic excess of e2 and e4 when compared with E3/3 were obtained by a codominant additive model that was at first sight compatible with the phenotypic effects depicted in Table 2.
The results are shown in Fig 1: for triglycerides, VLDL-C, apoC-III, apoE, Lp C-III:B, and Lp E:B levels that displayed a skewed distribution in the population, the regression model was applied to log-transformed values. For this reason the reported allelic effects on these measurements would in fact have been multiplicative and not additive if they had been expressed in absolute concentrations. No statistically significant departure from this codominant model for allelic effects was found for any measurements except for apoA-I (P=.05) and log Lp C-III:B (P=.01), so the validity of the estimated effects in these two cases is doubtful. In this sample, e2 was associated with lower total cholesterol, LDL-C, and apoB and higher triglycerides, VLDL-C, apoE, Lp C-III:B, and Lp E:B. Similarly, e4 was associated with higher triglycerides, VLDL-C, and Lp C-III:B but also had a positive effect on apoB. The e2 allele was also associated with lower LpA-I when compared with the apoE3/3 phenotype group. Total cholesterol and LDL-C increased with the e4 allele, but this increase did not attain statistical significance.

The homogeneity of the e2 and e4 effects among the four population samples was tested using the same codominant models. No difference in the magnitude of the e4 effect on the biological measurements was found. In contrast, e2 effects were significantly different among the samples for some measurements listed in Table 3, which gives their estimates obtained separately within each population. No effect of the e2 allele was found on the level of triglycerides, VLDL-C, apoE, and Lp E:B in Belfast and on triglycerides, VLDL-C, and Lp E:B in Toulouse. However, e2 had a significant effect of an increase on these variables in Lille and Strasbourg and on apoE level in Toulouse.

### TABLE 3. Estimates of Average Effect of e2 Allele on Triglyceride, VLDL-C, ApoE, and Lp E:B Levels (After Log Transformation) in the Control Group of the ECTIM Study

<table>
<thead>
<tr>
<th>Region</th>
<th>Triglycerides</th>
<th>VLDL-C</th>
<th>ApoE</th>
<th>Lp E:B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belfast</td>
<td>.040</td>
<td>-.007</td>
<td>.037</td>
<td>-.003</td>
</tr>
<tr>
<td>Lille</td>
<td>.175*</td>
<td>.241†</td>
<td>.365†</td>
<td>.201†</td>
</tr>
<tr>
<td>Strasbourg</td>
<td>.346†</td>
<td>.353†</td>
<td>.476†</td>
<td>.389†</td>
</tr>
<tr>
<td>Toulouse</td>
<td>.010</td>
<td>.205</td>
<td>.315*</td>
<td>.012</td>
</tr>
</tbody>
</table>

VLDL-C indicates very-low-density lipoprotein cholesterol; ApoE, apolipoprotein E; and Lp, lipoprotein. Values are expressed as log milligrams per deciliter. Subjects with coronary heart disease or taking hypolipidemic drugs or those with triglycerides >800 mg/dL were excluded. *P<.05, †P<.01, ‡P<.001.
Table 4. Frequency of Apolipoprotein E Phenotypes in Myocardial Infarction Survivors and Control Subjects in the ECTIM Study

<table>
<thead>
<tr>
<th>Region and Subjects</th>
<th>ApoE Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2/2</td>
</tr>
<tr>
<td>Belfast MI (n=183)</td>
<td>2</td>
</tr>
<tr>
<td>Belfast C (n=176)</td>
<td>2</td>
</tr>
<tr>
<td>Lille MI (n=64)</td>
<td>0</td>
</tr>
<tr>
<td>Lille C (n=150)</td>
<td>2</td>
</tr>
<tr>
<td>Strasbourg MI (n=187)</td>
<td>1</td>
</tr>
<tr>
<td>Strasbourg C (n=172)</td>
<td>2</td>
</tr>
<tr>
<td>Toulouse MI (n=140)</td>
<td>0</td>
</tr>
<tr>
<td>Toulouse C (n=182)</td>
<td>0</td>
</tr>
</tbody>
</table>

ApoE indicates apolipoprotein E; MI, myocardial infarction survivors; and C, control subjects. Control subjects with coronary heart disease were excluded.

(Fig 2, right). However, no specific risk (compared with E3/3) reached statistical significance even after adjustment for the covariates.

Allelic-specific risks for e2 and e4 were computed by the codominant model for RR. The RR 95% confidence interval was 0.73 (0.53 to 1.00) (P = 0.05) and 1.33 (1.05 to 1.68) (P = 0.02) for e2 and e4, respectively, after adjustment for age and other covariates (Fig 2, right). The risks were at the level of significance (RR, 0.75 and 1.29 for e2 and e4, respectively) when no adjustment other than for center was carried out (Fig 2, left). The decreased risk associated with e2 and increased risk associated with e4 did not differ significantly among the four populations (data not shown).

Discussion

ApoE plays an important role in lipoprotein metabolism, so the possible association between the different apoE phenotypes and a number of plasma lipoprotein parameters and the RR for MI was explored in the ECTIM study, a multicenter study designed to identify genotypes predisposing to MI. The possible biases displayed by this case-control study, particularly involving the selection of patients with MI and appropriate control subjects, have been previously discussed in detail.11

A geographical difference appeared in the frequency of apoE alleles among the four control populations. If the allele frequency in Belfast and Lille was close to that already reported in Caucasian populations,8 that of Toulouse, whose ethnic background was probably different from the other regions, was closer to the distribution described in the Chinese or Japanese.20,21

A number of studies have demonstrated a consistent relation between apoE phenotype and plasma lipid levels. This relation was confirmed by Dallongeville et al10 using the powerful tool of meta-analysis. As in most of the previous studies, we have found a lower concentration of cholesterol22-31 and/or LDL-C23,26.27,29,30 for the e2 allele. Conversely, in contrast with most previous studies, which have shown that cholesterol and/or LDL-C levels are increased in e4 allele carriers compared with E3/3 subjects,23-26,28,32 the estimates of this allelic effect on these parameters were of relatively low magnitude and not significant, at least partly because of the much lower levels seen in E4/2 subjects (Table 2) and perhaps because of the exclusion of subjects taking hypolipidemic drugs and subjects having a higher frequency of hypercholesterolemia in relation to the effect of the e4 allele on cholesterol.

The most striking findings of this study were the influence of apoE alleles on triglycerides, apoE, and apolipoprotein (apo) E phenotype and allele compared with apoE3/3 in the ECTIM study. Control subjects without coronary heart disease and survivors of myocardial infarction were included. Left, population-adjusted relative risk; right, covariate (center, age, body mass index, alcohol intake, and tobacco consumption)—adjusted relative risk.
study between e2 effects and body mass index, alcohol intake, or tobacco use within each population.

A metabolic mechanism of the increase of these triglyceride-rich particles in subjects carrying the e2 allele in Lille and Strasbourg could be the delayed catabolism of remnant particles that could be represented in plasma by Lp E: B and Lp C-III: B. Indeed, in subjects with type III hyperlipidemia, a disease caused by a high level of remnants in plasma, plasma Lp E: B and Lp C-III: B levels were particularly high.37

The elevated triglyceride levels were noticed in 30 of 36 subsets of subjects bearing apoE4/3 included in the meta-analysis of Dalongeville et al,3 whereas these levels were lower or higher in apoE4/4 subjects. In the present study the e4 allele was associated with an increase of triglycerides and Lp C-III: B (Fig 1). A defect in lipolysis of triglyceride-rich lipoproteins could delay the disappearance of these particles from the plasma. In support of this hypothesis, previous reports have indicated that the e4 allele might be implicated in the pathogenesis of type V hyperlipoproteinemia.38-40 It is therefore tempting to hypothesize that apoE4 interferes with the triglyceride-rich particle catabolism. However, only the accumulation in plasma of particular types of triglyceride-rich particles, such as those containing apoC-III and apoB but without surficial apoE, seemed to explain the increase of triglycerides (Fig 1). The absence of an increase in Lp E: B could be explained by the fact that apoE4 has been shown to be preferentially associated with VLDL.41 Therefore, the delay of lipolysis of apoE4- and apoB-containing lipoproteins present in the fraction of VLDL density could be compensated by a faster in vivo catabolism of apoE4-containing particles of VLDL or LDL density than that of particles containing apoE3, as suggested by a rapid catabolism of apoE4 compared with that of apoE3.8

In the present multicenter case-control study, an association between the apoE polymorphism and the risk of MI was evident, but despite a large number of cases and control subjects, this association was of only borderline statistical significance. The presence of the e2 and e4 alleles compared with E3/3 genotype leads to a lower and higher risk of MI, respectively, but the strength of the relation (RR 0.73 and 1.33, respectively) was relatively low. Calculation of the attributable risk42 suggested that the apoE polymorphism could have an influence on the expression of this disease independently of the effect on LDL-C levels. This seems to be confirmed by the results of a prospective study, the MRFIT study, which demonstrated that significant differences among apoE phenotypes in CHD risk persist after adjusting for LDL-C.43 Therefore, the apoE polymorphism could modulate other risk factors such as lipoprotein particles, as described in the present study. Lower LDL-C and apoB levels associated with e2 were in accord with a diminished CHD risk in e2 carriers. Control subjects with the e2 allele, however, had higher triglyceride, VLDL-C, and Lp E: B levels on average, and these parameters have been shown to be higher in control subjects living in a region (Northern Ireland) with a higher incidence of CHD (348 per 100 000) than in those living in France, a country with a relatively low CHD incidence (78 to 105 per 100 000).10

These results, complicated by the finding of a heterogeneous e2 metabolic effect on VLDL particles across the centers, are difficult to reconcile, as the numbers of cases and control subjects in this study were too low to
analyze an apoE phenotype–associated risk on a regional basis with an acceptable power.

Finally, the present evidence, together with most previously published data, is in favor of an increasing CHD risk gradient associated with apoE polymorphism in the allelic order e2<e3<e4, but the proportion of MI cases attributable to this polymorphism appears modest at the population level (12%). A more precise assessment of the apparently protective e2 effect would require both experimental work and larger population studies, preferably with a prospective cohort design.

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