Apolipoprotein Isoform E4 Does Not Increase Coronary Heart Disease Risk in Carriers of Low-Density Lipoprotein Receptor Mutations

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Background—In humans, the E4 allele of the apolipoprotein E gene is associated with increased coronary heart disease risk. Surprisingly, in rodents, apolipoprotein E4 only accelerates the atherosclerotic process when transgenic for the human low-density lipoprotein receptor (LDLR) protein. We therefore investigated whether the LDLR locus interacted with the apolipoprotein E gene genotype on coronary heart disease risk in patients clinically diagnosed with familial hypercholesterolemia with and without LDLR mutation. We investigated whether the presence of an LDLR mutation diminishing LDLR function was protective in E4/E4 carriers.

Methods and Results—In a cohort of 2400 patients clinically diagnosed with familial hypercholesterolemia, we found an LDLR gene mutation in 1383 patients, whereas in 1013 patients, such mutation was not present. In 92 patients homozygous for the apolipoprotein E4, the presence of an LDLR mutation conferred lower coronary heart disease risk (hazard ratio, 0.16; 95% CI, 0.05–0.58; P=0.005). Mirroring these results, the apolipoprotein E4/E4 genotype was also associated with lower coronary heart disease risk in patients with familial hypercholesterolemia with an LDLR mutation (hazard ratio, 0.26; hazard ratio, 0.08–0.80; P=0.02).

Conclusions—LDLR function is key to the detrimental effects of apolipoprotein E4 in humans. Kinetic studies in humans are now required to study the consequences of our observation for prevention of both coronary heart disease and Alzheimer disease. (Circ Cardiovasc Genet. 2011;4:655-660.)

Key Words: apolipoprotein E coronary heart disease familial hypercholesterolemia

Complications of atherosclerotic vascular disease are the most common causes of death and morbidity in the Western world with coronary heart disease (CHD) as its most prominent manifestation.1 Hereditary predisposition plays an important role in the pathobiology of atherosclerosis. One of the genes best known for its association with CHD risk is the 1 coding for the low-density lipoprotein receptor (LDLR) protein. Mutations in this gene cause an autosomal-dominant disorder called familial hypercholesterolemia (FH), which is characterized by severe hypercholesterolemia and premature CHD.2 Another important gene known to influence CHD risk is apolipoprotein E (APOE).3 Mice completely lacking the ApoE protein are severely hypercholesterolemic and develop extensive atherosclerotic lesions, a process that is accelerated when they are fed a high-fat diet.4,5 Homozygous deficiency of the APOE gene in humans is extremely rare and is also characterized by atherogenic lipid abnormalities and premature CHD.6,7

Clinical Perspective on p 660

In humans, 3 main haplotypes of the APOE gene have been identified: APOE2, APOE3, and APOE4. The encoded ApoE2, ApoE3, and ApoE4 proteins differ in their amino acid sequences at positions 112 and 158. Although these differences are not located in the LDLR binding domain, affinity to the LDLR differs between genotypes: ApoE2 has the lowest affinity for the LDLR, whereas ApoE4 has the highest.8 This leads to lower low-density lipoprotein cholesterol.
terol levels in APOE2 carriers due to upregulation of LDLRs and higher low-density lipoprotein cholesterol levels in APOE4 carriers due to downregulation of LDLRs. Although the APOE4 allele is best known for its strong association with Alzheimer disease, it is also consistently associated with a 26% to 42% higher CHD risk.13,14 This increased CHD risk in APOE4 carriers cannot merely be explained by small differences in low-density lipoprotein cholesterol levels. The LDLR–APOE interaction is, however, central to the increased CHD risk associated with ApoE4: atherosclerosis resulting from specific APOE genotypes can be replicated in rodents, but only when human LDLRs are also abundant.13,14 Notably, mice expressing human ApoE4 develop no substantial atherosclerosis, but they display fulminant disease when the human LDLR is also introduced.14,15

To date, the interaction between ApoE and the LDLR has not directly been examined in humans. A suitable group of patients for investigating this interaction would consist of patients who have a genetic defect in the LDLR gene that results in lower residual function of the LDLR protein. In fact, in 2 earlier studies of modest study size in patients with FH, the APOE4 allele was not associated with CHD risk. We therefore hypothesized that carriers of the E4/E4 genotype might benefit from a reduction in functional LDLRs.16,17 In a large population of persons clinically diagnosed with FH, we investigated whether the presence of an LDLR mutation that reduces LDLR function was protective in E4/E4 carriers.

Materials and Methods

FH Cohort
During 1989 to 2002, we recruited a cohort of 2400 patients with severe hypercholesterolemia from 27 lipid clinics as described in detail previously.18 We selected 2400 unrelated subjects who fulfilled the internationally established FH diagnostic criteria. A well-trained team of 13 data collectors reviewed medical records to establish extensive phenotypic data including CHD events. Total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were measured by standard methods in fasting patients who had been withdrawn from lipid-lowering medication at least 6 weeks before blood collection. Low-density lipoprotein cholesterol concentration was calculated with the Friedewald formula.20 The promoter region and all exons (including exon–intron boundaries) of the LDLR gene were sequenced in all patients and the multiplex ligation-dependent probe amplification technique was used to identify large rearrangements. Exons 26 and 29 of the APOB gene, encoding the major LDLR binding sites, were also sequenced. All known mutations were tested in duplo and sequencing and multiplex ligation-dependent probe amplification was performed twice when no previously known mutation was identified. Therefore, false-negative results for LDLR mutation assessment were unlikely (approximately 0.06%). Genetic variants without a clear effect on LDLR function were filtered using pedigree data from the Dutch screening program as published earlier: if a potential mutation did not segregate with hypercholesterolemia, pathogenicity of this variant is questionable. In the current study, such variants were not considered as a LDLR mutation. Carriers of such mutations were considered to have no LDLR mutation.21 In a later stage, PCSK9 was sequenced in samples in which no mutation was identified, but this analysis did reveal only a limited number of mutations in patients with an FH phenotype in general and none in this cohort.22 The DNA of 2145 unrelated patients was available for APOE genotyping performed in a multiplex genotyping assay.23 All patients gave informed consent, and the ethics Institutional Review Board of each hospital approved the protocol.

CHD Outcome Measures

CHD was defined as the presence of at least 1 of the following: (1) myocardial infarction, proved by at least 2 of the following: (a) classical symptoms (>15 minutes), (b) specific electrocardiographic abnormalities, and (c) elevated cardiac enzymes (>2× upper limit of normal); (2) percutaneous coronary intervention or other invasive procedures; (3) coronary artery bypass grafting; and (4) angina pectoris, diagnosed as classical symptoms in combination with at least 1 unequivocal result of 1 of the following: (a) exercise test, (b) nuclear scintigram, (c) dobutamine stress ultrasound, or (d) >70% stenosis on a coronary angiogram.

Statistical Analysis

General characteristics were compared using analysis of variance for continuous variables (statistical analyses of substantially skewed data were performed after logarithmic transformation) and χ² test for categorical variables. Variables with low frequencies (hypertension, diabetes, CHD) were analyzed using the Fisher exact test comparing each genotype separately with APOE3/E3. In Table 1, P values are given when comparing E3/E3, E3/E4, and E4/E4, whereas in Supplemental Table II (http://circ.ahajournals.org), overall P values comparing all genotypes are given. First, we investigated the effect of having an LDLR mutation on CHD risk in this FH study population using Cox proportional hazards models adjusted for year of birth, sex, and smoking because the Cox proportional hazards modeling seems most powerful in genetic studies.24 Follow-up started at birth and ended at the first occurrence of CHD. Patients without CHD were censored at the date of the last lipid clinic visit or at the date of death attributable to causes other than CHD. The proportional hazards assumption was tested by drawing log minus log plots of the survival function and was met for all Cox proportional hazard models used. Next, we stratified by APOE genotype. We also studied the effect of APOE genotypes on CHD risk in the whole study population as well as stratified according to the presence of an LDLR mutation. Interaction was tested by introducing an interaction term in Cox regression analyses. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 15.0.

Results

In 1383 patients, an LDLR mutation was identified, whereas in 1017 patients, no pathogenic mutation in the LDLR or APOB gene was found by sequencing the complete LDLR gene or by using the multiplex ligation-dependent probe amplification technique. Comparison of individuals with and without LDLR mutation in this cohort showed significant differences as published earlier by Van Aalst-Cohen et al: patients with FH without an LDLR mutation had higher triglyceride levels (1.71 versus 1.39 mmol/L), body mass index (25.6 versus 24.7 kg/m²), and systolic blood pressure (137 versus 133 mm Hg) and were more likely to have ever smoked (79.5% versus 68.7%), whereas patients with FH with an LDLR mutation had higher low-density lipoprotein cholesterol levels (8.18 versus 6.61 mmol/L).25 Successfully genotyping for APOE was assessed in 2061 patients of whom 1150 had an LDLR mutation. The polymorphisms at positions 112 and 158 were in Hardy-Weinberg equilibrium both in the whole population and in the group with an LDLR mutation. Genotype frequencies are shown in Supplemental Table I. General characteristics are shown in Table 1. For the sake of clarity, we only list APOE3/E3, E3/E4, and E4/E4 and P values given are for this comparison; patients carrying genotypes consisting of 1 or 2 APOE2 alleles were not significantly different except that triglyceride levels appeared to be increased by the APOE2 allele in the group without
BMI, kg/m² 25.3
Age statin started, y 46.0
Diabetes (%) 35 (7.0) 16 (5.5) 6 (13.6) NS 33 (4.9) 14 (4.8) 1 (2.0) NS
Hypertension (%) 51 (10.2) 40 (14.2) 4 (9.3) NS 58 (8.7) 24 (8.3) 3 (6.1) NS
Smoking ever (%) 363 (80.7) 212 (80.6) 32 (84.2) 0.86 425 (69.9) 178 (68.7) 29 (67.4) 0.90
Follow-up time, y 50.0
Age at first visit lipid clinic, y 48.9
Lp(a), mg/L 193
Triglycerides, mmol/L 1.72
HDL cholesterol, mmol/L 1.21
LDL cholesterol, mmol/L 6.26
Total cholesterol, mmol/L 8.48

**Table 1. General Characteristics per Genotype With and Without an LDLR Mutation**

<table>
<thead>
<tr>
<th></th>
<th>No LDLR Mutation</th>
<th>LDLR Mutation Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>258 (51.4)</td>
<td>157 (64.3)</td>
</tr>
<tr>
<td>Age at first visit lipid clinic, y</td>
<td>48.9 ±11.8</td>
<td>48.2 ±11.7</td>
</tr>
<tr>
<td>Follow-up time, y</td>
<td>50.0 ±12.0</td>
<td>49.7 ±11.7</td>
</tr>
<tr>
<td>Smoking ever (%)</td>
<td>363 (80.7)</td>
<td>212 (80.6)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>51 (10.2)</td>
<td>40 (14.2)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>35 (7.0)</td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>186 (37.1)</td>
<td>97 (33.6)</td>
</tr>
<tr>
<td>Statin at baseline (%)</td>
<td>118 (23.5)</td>
<td>75 (26)</td>
</tr>
<tr>
<td>Age statin started, y</td>
<td>46.0 ±11.7</td>
<td>46.2 ±11.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.3 ±3.4</td>
<td>25.5 ±3.3</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>8.48 ±12.8</td>
<td>8.56 ±13.6</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>6.26 ±1.16</td>
<td>6.31 ±1.21</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.21 ±0.32</td>
<td>1.18 ±0.32</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.72 ±0.79</td>
<td>1.75 ±0.87</td>
</tr>
<tr>
<td>Lp(a), mg/L</td>
<td>193 ±257</td>
<td>166 ±215</td>
</tr>
<tr>
<td>Lp(a) &gt;3 mg/dL</td>
<td>166 (43.6)</td>
<td>85 (37)</td>
</tr>
</tbody>
</table>

Values are mean ±SD. Follow-up time from birth to event or censoring. LDLR indicates low-density lipoprotein receptor; APOE, apolipoprotein E; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein(a); NS, nonsignificant.

*APOE4/E4 versus APOE3/E3.

**LDLR Mutation Protective in Patients Expressing ApoE4**

The effect of the presence of an LDLR mutation on CHD risk in these patients with FH is shown in Table 2. Within the entire cohort, the presence of an LDLR mutation was not significantly associated with CHD (hazard ratio [HR], 0.88; 95% CI, 0.76–1.02; P = 0.10). The borderline significant protective effect of having an LDLR mutation appeared to be due to the larger burden of classical risk factors such as smoking and hypertension in patients with FH without an LDLR mutation; as published earlier, when adjusting for these additional risk factors, the apparent difference in CHD risk difference did no longer exist.25 However, in E4/E4 genotyped patients with FH, a strong protective effect of an LDLR mutation was observed (HR, 0.16; 95% CI, 0.05–0.58; P = 0.005). Because the groups with and without an LDLR mutation differed with regard to classical risk factors such as smoking and hypertension, we added different covariates to the analyses. None influenced the protective effect of the LDLR mutation (Supplemental Table II; values comparing all genotypes). High-density lipoprotein cholesterol levels also appeared significantly different in the group without LDLR mutation but this association disappeared after adjustment for triglyceride levels.

In the total cohort successfully genotyped for APOE, 603 CHD events occurred of which 547 were in the E3/E3, E3/E4, and E4/E4 genotyped individuals (Table 1). Classical risk factors and lipid levels were not significantly different between subjects carrying the different APOE genotypes except lipoprotein(a) levels in the analysis restricted to patients with FH with an LDLR mutation: E4/E4 genotyped patients with FH with an LDLR mutation displayed the lowest lipoprotein(a) levels, whereas E3/E4 genotyped patients with FH with a mutation were intermediate between E3/E3 and E4/E4. The most striking difference was the prevalence of CHD; this was lowest in the APOE4/E4 genotyped patients, but only in the group with an LDLR mutation (E4/E4 6.1% versus 25.1% in E3/E3; P = 0.009; group without LDLR mutation 36.4% versus 37.1%; P = 0.61).

**Table 2. Protective Effect of an LDLR Mutation on CHD Risk in APOE4/E4 Patients With FH**

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>HR 95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Overall</td>
<td>2400</td>
<td>0.88 0.76–1.02</td>
<td>0.10</td>
</tr>
<tr>
<td>APOE3/E3</td>
<td>1178</td>
<td>0.84 0.68–1.04</td>
<td>0.11</td>
</tr>
<tr>
<td>APOE3/E4</td>
<td>580</td>
<td>1.01 0.74–1.37</td>
<td>0.96</td>
</tr>
<tr>
<td>APOE4/E4</td>
<td>93</td>
<td>0.16 0.05–0.58</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Model I adjusted for gender and year of birth; Model II additionally adjusted for smoking. LDLR indicates low-density lipoprotein receptor; CHD, coronary heart disease; APOE, apolipoprotein E; FH, familial hypercholesterolemia; HR, hazard ratio.
LDLR mutation in APOE4/E4 genotyped individuals in this cohort of individuals with the clinical diagnosis of FH.

**Is APOE4/E4 Protective in the Presence of an LDLR Mutation?**

Because it appeared that the lowest number of events occurred in E4/E4 genotyped patients with an LDLR mutation (Table 1), we tested whether the APOE4 allele was associated with a lower CHD risk using a Cox proportional hazards model (Table 3). In the complete study population, the APOE4/E4 genotype was not significantly related to CHD (E4/E4 versus E3/E3 HR, 0.66; 95% CI, 0.42–1.05; \( P = 0.94 \)). However, separate analyses of patients with and without LDLR mutation showed that a CHD-protective effect was restricted to APOE4/E4 homozygotes who had an LDLR mutation (no LDLR mutation HR, 1.16; 95% CI, 0.69–1.95; \( P = 0.57 \); with LDLR mutation HR, 0.26; HR, 0.08–0.80; \( P = 0.02 \)). We confirmed the interaction by analyzing LDLR mutation status, APOE genotype, and interaction terms for LDLR mutation with APOE genotype. Indeed, the interaction term APOE4/E4*LDLR mutation was highly significant (HR, 0.22; 95% CI, 0.06–0.76; \( P = 0.016 \)). CHD risk in carriers of APOE2 containing genotypes was not significantly different from CHD risk in APOE3/E3 genotyped patients with FH (data not shown).

**Discussion**

We show for the first time in humans that the LDLR plays a key role in the detrimental consequences of ApoE4 carriership that is known to lead to the development of CHD. Our data reveal a protective role for LDLR mutations in FH subjects carrying the APOE4/E4 genotype; in fact, this genotype seems to even reduce CHD risk in patients with FH in contrast to the increased risk that ApoE4 confers in the general population.\(^{11}\) It should be stressed that having an LDLR mutation is detrimental for CHD risk in the first place, and because our study is restricted to analyses within a severely hypercholesterolemic population, we cannot say that CHD risk in patients with FH with an LDLR mutation is normalized by the APOE4/E4 genotype; most likely CHD risk is still increased but to a lesser extent in comparison with other APOE genotypes. This CHD risk reduction might partly be explained by lower lipoprotein(a) levels, but in all likelihood, this cannot be directly deduced from our study.

ApoE3 and ApoE4 differ by only 1 amino acid at position 112, but the effects on the risk of CHD and Alzheimer disease show that the consequences of such a change can be immense. In humans, the interaction between ApoE and the LDLR has been studied only indirectly. Three small studies have previously shown that APOE4/E4 is not a genetic risk factor for CHD in patients with FH despite the observed increased risk in APOE4/E4 carriers in the general population.\(^{16,17,26}\) Similarly, 2 polymorphisms in the LDLR gene were linked to Alzheimer disease, but only in patients carrying at least 1 APOE4 allele.\(^{27}\) To the best of our knowledge, a role of the ApoE–LDLR interaction in the etiology of atherosclerosis in human subjects is a novel concept.

Most studies investigating the interaction between the LDLR and ApoE have been performed in murine models in which the LDLR gene was either knocked out or overexpressed by replacing the mouse LDLR gene by the human LDLR gene. LDLR knockout mice homozygous for the human APOE4 haplotype (Ldlr\(^{-/-}\) Apoe\(^{4/4}\)) display less atherosclerosis in response to a Western-type diet than both Apoe\(^{4/4}\) mice overexpressing the human LDLR and Apoe\(^{3/4}\) mice with physiological murine LDLR levels.\(^{13,14}\) Mice homozygous for the APOE3 isoform did not show different responses to variations in LDLR expression.

We recognize a number of weaknesses of our study. First, all patients in our cohort had hypercholesterolemia, which means that patients in this cohort without an LDLR mutation cannot be considered as healthy control subjects; in fact, they are individuals having another primary lipid disorder, most likely familial combined hyperlipidemia.\(^{25}\) On the other hand, this fact implies that hypercholesterolemia per se cannot be responsible for the interaction. The fact that in our study the APOE4/E4 genotype was not associated with CHD in patients without an LDLR mutation, in contrast to a strong and consistent association in earlier studies and meta-analyses, suggests that the contribution of the APOE4/E4 genotype in patients with severe dyslipidemia is small.\(^{11,12}\) If the control group would have consisted of persons without hypercholesterolemia, the APOE4/E4 genotyped individuals would most likely have been identified as having an increased CHD risk.\(^{11,12}\) The distributions of the different LDLR mutations were similar among APOE genotypes. However, we did not measure residual LDLR activity in all individuals.

A number of artifacts could underlie our remarkable findings. Survival bias was not likely in view of the Hardy-Weinberg equilibrium and similar ages of the different genotype groups. We confirmed the APOE genotype distribution in an additional cohort of patients with FH but the number was too small to consider this as a true replication (\(n=464\); data not shown). Classical CHD risk factors, most

| Table 3. Protective Effect APOE4/E4 Genotype in Patients With FH With an LDLR Mutation |
|----------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Genotype | No. | HR (95% CI) | \( P \)      | No. | HR (95% CI) | \( P \)      |
| APOE3/E3   | 447 | (reference) |        | 603 | (reference) |        |
| APOE3/E4   | 260 | 0.83 (0.64–1.07) | 0.15 | 258 | 0.97 (0.72–1.30) | 0.83 |
| APOE4/E4   | 43  | 1.16 (0.69–1.95) | 0.57 | 43  | 0.26 (0.08–0.80) | 0.02 |

Adjusted gender, birth year, and smoking. APOE indicates apolipoprotein E; FH, familial hypercholesterolemia; LDLR, low-density lipoprotein receptor; HR, hazard ratio.
importantly smoking and untreated total and low-density lipoprotein cholesterol levels, did not differ between APOE genotypes with or without an LDLR mutation. Earlier studies suggested an interaction between APOE4 and smoking.28,29 Adjustment for smoking did not change our results. Differences in risk profiles, especially untreated lipid levels, might have led to earlier statin treatment and consequent risk reduction. However, as expected from the lack of differences in terms of classical risk factors, age of starting statins was similar between different APOE genotypes with or without an LDLR mutation.

The substitution at position 112 of a cystein in ApoE3 by an arginin in ApoE4 causes structural variations. First, the interaction between the N-terminal and C-terminal domain leads to a more compact structure with lower thermal and chemical stability making ApoE4 more prone to aggregation.6,7,8,9,37–39 Second, ApoE4 displays altered preference for lipoproteins and increased affinity to the LDLR.5,9,30–36 There is substantial evidence that the higher binding affinity of ApoE4 to the LDLR leads to unfavorable “trapping” of ApoE, enhancing sequestration of very-low-density lipoprotein at the hepatocyte surface, which consequently delays internalization leading to an increased conversion at the hepatocyte surface of very-low-density lipoprotein and intestine-derived chylomicrons to atherogenic remnants.13,14,37

Our findings might therefore be explained by the interaction between ApoE4 and less functional LDLRs. Alternatively, increased binding to other receptors such as related LDLR family members or proteoglycans could also explain why the presence of an LDLR mutation might be beneficial for APOE4/E4 genotyped persons.38–42 Many of these receptors display favorable effects on atherosclerosis, which might be more pronounced if more ApoE is able to bind to these receptors.38–43

In conclusion, we show that an LDLR mutation is protective in patients with FH with the APOE4/E4 genotype and that this genotype even seems to reduce CHD risk in patients with FH with an LDLR mutation instead of increasing it as observed in the general population. This risk reduction might involve reduced lipoprotein(a) levels. Further studies are needed to unravel the biological basis of our finding and to find therapeutic approaches using this interaction in the prevention of CHD. These results might be extrapolated to an important role of this interaction in Alzheimer disease as well.

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References


26. Eto M, Watanabe K, Chonan N, Ishii K. Familial hypercholesterolemia receptor gene mutation in 1383 patients, whereas in 1013 patients, such mutation was not present. In 92 patients in a cohort of 2400 patients clinically diagnosed with familial hypercholesterolemia, we found a low-density lipoprotein receptor mutation in patients clinically diagnosed with familial hypercholesterolemia was protective in E4/E4 carriers.


**CLINICAL PERSPECTIVE**

In humans, the E4 allele of the apolipoprotein E gene is associated with increased coronary heart disease risk next to its well-known association with Alzheimer disease risk. We investigated whether the presence of a low-density lipoprotein receptor mutation in patients clinically diagnosed with familial hypercholesterolemia was protective in E4/E4 carriers. In a cohort of 2400 patients clinically diagnosed with familial hypercholesterolemia, we found a low-density lipoprotein receptor gene mutation in 1383 patients, whereas in 1013 patients, such mutation was not present. In 92 patients homozygous for APOE4, the presence of a low-density lipoprotein receptor mutation conferred lower coronary heart disease risk (hazard ratio, 0.16; 95% CI, 0.05–0.58; P = 0.005). From these results, we can conclude that the low-density lipoprotein receptor function is key to the detrimental effects of ApoE4 in humans. Further studies are now required to study the consequences of our observation for prevention of both coronary heart disease and Alzheimer disease.
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“Apolipoprotein isoform E4 does not increase coronary heart disease risk in carriers of low-density lipoprotein receptor mutations”

-Supplemental Table 1
-Supplemental Table 2
-Summary for clinicians
-Acknowledgment permission
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<thead>
<tr>
<th>Genotype</th>
<th>Total</th>
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<th>LDLR mutation present</th>
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<tr>
<td>APOE3/E3</td>
<td>1178 (57.2)</td>
<td>502 (55.1)</td>
<td>676 (58.8)</td>
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<td>140 (6.8)</td>
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<td>580 (28.1)</td>
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<td>61 (3.0)</td>
<td>21 (2.3)</td>
<td>40 (3.5)</td>
</tr>
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<td>2 (0.2)</td>
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<tr>
<td>APOE4/E4</td>
<td>93 (4.5)</td>
<td>44 (4.8)</td>
<td>49 (4.3)</td>
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*Values are count (percentage)*