Drug Metab Drug Interact 2011;26(1):13–20 © 2011 by Walter de Gruyter • Berlin • New York. DOI 10.1515/DMDI.2011.107

Review

Effect of apolipoprotein E polymorphism on statin-induced decreases in plasma lipids and cardiovascular events

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Abstract

Hypercholesterolemia or dyslipidemia is an independent risk factor for cardiovascular disease and statins (inhibitors of a key enzyme of cholesterol synthesis, 3-hydroxymethyl glutaryl coenzyme A reductase) are the drugs of choice for decreasing plasma cholesterol. It has been estimated that genetic factors can explain 40%–60% of final cholesterol concentrations and approximately 70% of the efficacy of statin treatment. The gene most often analyzed in the context of statin efficacy is the gene for apolipoprotein E (*APOE*). This review summarizes evidence of the association between variations in the *APOE* gene locus and the response of plasma lipids to statin therapy. Although the results are not consistent, carriers of the *APOE4* allele seems to be less responsive to statins than carriers of *APOE2* and *APOE3* alleles. This effect is partially context-dependent (gene-gender interactions; gene-nutrition and gene-smoking interactions have not yet been studied) and the absolute differences vary between different population groups.

Keywords: apolipoprotein E; cardiovascular events; cholesterol; gene; interaction; polymorphism; statin; treatment.

Introduction

High plasma cholesterol is a well-established independent risk factor for cardiovascular disease (CVD) (1). Interindividual variability of plasma cholesterol concentrations can be explained by a number of factors that affect cholesterol metabolism pathways. Lifestyle and dietary factors seem to be the most important, but others, such as season of the year, time of day and overall conditions for blood sampling, also play a role.

Lifestyle in terms of dietary habits and physical activity patterns has a substantial effect, so therapeutic lifestyle changes represent the initial intervention in patients with high plasma lipids or cholesterol. However, the majority of patients do not respond sufficiently to lifestyle interventions or do not comply with the recommendations, and thus require pharmacological treatment to achieve recommended target lipid levels established according to their CVD risk category (generally, the approach "the lower the better" is widely used). Statins (inhibitors of 3-hydroxymethyl glutaryl coenzyme A reductase, the key enzyme in the biosynthesis of the cholesterol) are the drugs of choice to lower plasma cholesterol. Statins impact positively on the entire plasma lipid spectrum and exhibit a number of further antiatherogenic effects (2). However, high interindividual variability [10%–55% decrease in low-density lipoprotein (LDL)-cholesterol, 5%–30% decrease in triglycerides, 0%–10% increase in high-density lipoprotein (HDL)-cholesterol] (3) between individuals treated with the same drug at the same dose is observed. However, the efficacy of statin therapy in an individual is relatively stable over time and seems to be under significant genetic control. Thus, genetic testing could be a helpful tool for the detection of hyper- and hypo-responders to statin therapy.

In studies on siblings and twins it has been estimated that genetic factors can explain approximately 40%–60% of the final concentrations of plasma lipids and up to 70% of the effect of statins (4). It should be noted that besides genetic factors, there are many other important confounders, including sex, age, physical activity, smoking, alcohol intake and type of diet consumed. All these factors can partly modify genetic predisposition and thus analyses of such interactions are of extreme interest and importance. However, so far, gene-environment interactions and statin treatment efficacy have not been analyzed.

To date, more than 40 well-defined different gene loci (if we exclude genome-wide studies, in which markers within the entire genome are screened) have been studied in an effort to detect the most important variants influencing statin treatment efficacy. The candidate genes can be divided into two groups. The first group comprises genes with a potential impact on statin absorption, transport, metabolism and elimination from the body (pharmacokinetics). The second involves genes coding for plasma cholesterol transport proteins and cellular receptors (pharmacodynamics).

In plasma, cholesterol is transported on lipoprotein particles, mostly on LDLs, originating from very-low-density

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Received February 15, 2011; accepted April 19, 2011

lipoproteins (VLDLs). Within lipoproteins, cholesterol is found in the form of esters associated with other lipids and different proteins (mostly with apolipoproteins, APOs). APOs serve as structural components of these particles and as receptor ligands and co-factors for lipid metabolism enzymes. Thus, not surprisingly, variants of the apolipoprotein genes have attracted much attention in the search for the genetic basis of increased plasma lipid levels and statin treatment efficacy.

The gene coding for apolipoprotein E (*APOE*) is one of the best-established and most important genetic factors modulating plasma lipoprotein levels and has been in the focus of pharmacogenetics studies.

APOE gene

The gene coding for APOE is located within the gene cluster for apolipoproteins E-C1-C2 on chromosome 19. APOE is expressed in most tissues. Besides its effect on lipid metabolism and CVD risk, APOE has other so-called pleiotropic effects that are likely to play a role in the development of neurodegerative diseases (association with the risk of Alzheimer's and Parkinson's diseases) (5), end-stage renal disease (6) and an as yet unclear relationship to spontaneous abortions (7) and memory test results (8).

Within the *APOE* gene (gene ID 348, OMIM accession 107741), more than 30 rare mutations have been described (9, 10) and its common three-allelic polymorphism [two individual single-nucleotide polymorphisms (SNPs) located in close proximity to each other] is undoubtedly the most extensively studied *APO* gene variation in the context of genetic determination of CVD (11). APOE is a major protein component of VLDL and HDL particles, but can be found in all lipoprotein species.

The three common *APOE* isoforms (designated *APOE2*, *APOE3* and *APOE4* according to protein positions after isoelectric focusing, used for APOE classification in the pre-PCR era) result from two SNPs. *APOE2* differs from the most common *APOE3* allele by an Arg158→Cys substitution (rs7412) and from *APOE4* by a Cys112→Arg (rs429358) mutation.

In different populations, the most common allele, *APOE3,* occurs at a frequency between 60% and 90%, the *APOE4* allele is detected in 5%–40% of individuals, and the *APOE2* allele frequency usually varies between 0% and 10% (12, 13). *APOE4* carriers tend to have higher total cholesterol levels, whereas subjects carrying the *APOE2* allele have lower cholesterol compared to *APOE3* homozygotes. This association can, to some extent, be influenced by sex, diet and physical activity (14), but has been consistently described in all populations analyzed so far. The association of individual *APOE* alleles with CVD risk is less homogeneous and seems to be significantly modulated by environmental factors (smoking, obesity, diet) (15). In comparison to the *APOE3* and *APOE4* alleles, *APOE2* binding affinity for the LDL-receptor is almost completely abolished.

APOE2 homozygosity is associated with a rare disorder, familial dysbetalipoproteinemia (FD). Interestingly, almost all FD patients are *APOE2* homozygotes, but 95% of *APOE2* homozygotes in the population do not develop FD (16).

Literature search

Public databases (PubMed, MEDLINE, SCOPUS) were searched for all combinations of the keywords apoE/apo E/apolipoprotein E/apolipoproteinE and statin/statins/HMGCoA, hypolipidemic treatment, polymorphism/polymorphisms/variant/mutation. For this review we selected articles in English, German and Spanish. We also examined references within the papers of interest. We did not attempt to perform further analyses of the data obtained. Within the clinical studies, results were considered significant for $p<0.05$. For genome-wide association (GWA) studies, an arbitrary p-value of 1×10^{-7} was used. As most of the studies did not use exact p-values, especially for negative results, we classified such results as non-significant. Of the 351 records primarily screened, 44 studies of interest were finally included in the review.

Pharmacogenetic studies on *APOE* status and statins

Among the candidate genes considered as potential predictors of statin efficacy, *APOE* is the most commonly analyzed. So far there have been almost 50 studies published on this topic. Generally, there are not even two studies that can be directly compared because of significant differences in study design, age, concomitant diseases, selection and number of probands, and statin dose and type. These issues are critical and hamper comparison of study results over a wide time range of more than 20 years since publication of the first study on this topic.

Statins and *APOE* in patients with familial hypercholesterolemia

Familial hypercholesterolemia (FH) is the most common autosomal dominant monogenic disorder of lipoprotein metabolism. It is caused by a mutation in the LDL-receptor gene. The frequency of FH heterozygotes in most populations is approximately 1:500. These individuals have markedly elevated serum total and LDL-cholesterol levels, as well as a risk of premature coronary artery disease (CAD) (17).

The first published study on the effect of *APOE* polymorphism on statin efficacy (simvastatin, 40 mg) was performed in 120 Dutch FH heterozygotes. The authors reported no variation in treatment response in relation to *APOE* polymorphism (18). However, an interesting gene-gender interaction was observed: female *APOE3* homozygotes responded better to the treatment than males with the same genotype.

Soon after, a Finnish group reported a significant modifying effect of *APOE* polymorphism in an FH population (19). Some 67 FH patients with *APOE3E4* genotype treated with lovastatin (20 or 40 mg) exhibited slightly smaller reductions in total- and LDL-cholesterol levels compared to the common *APOE* genotype. Interestingly, in non-FH hypercholesterolemic patients (n=144), no effect of *APOE* genotype was observed.

Following on from previous work, Carmena and co-workers treated 189 patients with the highest dose (80 mg) of lovastatin and described a lower response to treatment in *APOE4* carriers compared to non-carriers (20). Furthermore, another gene-gender interaction was described: the decrease in LDL-cholesterol was significantly lower in male than in female *APOE4* carriers.

The impact of *APOE* polymorphism on treatment efficacy has also been studied in adolescents (21). In this study, *APOE* had a significant impact on the effect of simvastatin (20 mg) only in carriers of LDL-receptor negative mutations (n=33), and not in those with LDL-receptor defective mutations. *APOE2* carriers benefited most from the treatment.

Besides the above publications reporting a positive association between the effect of statin treatment and *APOE* polymorphism, a number of negative studies on this topic have also been published. Studies of 134 FH heterozygotes treated with lovastatin (20 or 40 mg twice daily) (22), of 120 Swedish patients (23) and of 49 individuals treated with atorvastatin (20 mg) (24) detected no significant association between *APOE* genotype and lipid-lowering response to treatment. In the latest study, the benefit of stain treatment was identical in 136 FH heterozygotes, regardless of *APOE* genotype (25).

Non-FH hypercholesterolemic patients

The rare monogenic disorders leading to serious forms of FH (mutations of the LDL-receptor gene, but also of the *APOB, PCSK9, CYP7A1* and *ARH* genes) (26) can explain only a minor portion of hypercholesterolemia cases in the general population. Much more often, plasma cholesterol concentrations increase as a result of negative effects of many common predisposing alleles (and an unhealthy lifestyle), resulting in polygenic hypercholesterolemia or dyslipidemia. The genetic background of polygenic dyslipidemia is likely to lie in hundreds, if not thousands, of combinations of different alleles.

The first study in non-FH hypercholesterolemic patients (27) was published almost 5 years after the report on *APOE* effects on post-treatment lipid levels in FH patients. In a small group of patients (n=97, treated with pravastatin 40 mg daily), a beneficial effect was observed in *APOE2* carriers compared to non-carriers.

The first study was quickly followed by at least 13 (28–40) subsequent publications [most of them reviewed by Nieminen et al. (41)], which we have summarized in Table 1.

The number of individuals analyzed in the studies varies from only 50 (36) to almost 800 (40). Most importantly, not even two studies tested the identical intervention or had comparable response criteria or follow-up time. Approximately one-quarter of the studies did not detect any correlation between *APOE* polymorphism and statin-induced decreases in plasma lipids. This also holds true for one of the largest studies, performed by Peña et al., who analyzed more than 400 patients treated with 20 mg of pravastatin (31).

On pooling the results from positive studies, a relatively homogeneous impact of *APOE* polymorphism on plasma lipid responses after statin therapy can be observed. *APOE4* carriers generally showed a lower response to therapy, regardless of the parameter analyzed (e.g., relative reduction in total or LDL-cholesterol, increase in HDL-cholesterol or the ability to reach the target values).

Statins, *APOE* and cholesterol-lowering in diabetics

Patients with diabetes usually have a substantially higher risk of CVD and thus are commonly treated with statins. Despite the marked difference in the prevalence of diabetes and of FH,

Table 1 Summary of studies investigating the pharmacogenetic effect of *APOE* polymorphism on lipid-lowering in patients with non-FH hypercholesterolemia.

Subjects, n	Ethnicity	Treatment	Follow-up	*APOE* effect	Reference
90	Caucasian	Lovastatin, 40 mg/day	At least 12 weeks	Not significant	(28)
88	Asian	Simvastatin, 5 mg/day	12 weeks	Not significant	(29)
99	Caucasian	Simvastatin, 20 mg/day	6 months	Not significant	(30)
401	Caucasian	Pravastatin, 20 mg/day	16 weeks	Not significant	(31)
222	Caucasian	Different statins	1 year	Not significant	(32)
232	Caucasian	Different statins	3 weeks	Non significant	(33)
67	Caucasian	Fluvastatin, dose not given	12 weeks	Non significant	(34)
66	Caucasian	Simvastatin, gemfibrosil cross-over	Each for 6 weeks	*APOE2* best response (increased HDL-C in just 3 individuals)	(35)
50 patients 50 controls	Caucasian	Different statins	Not given	*APOE2* best response	(36)
123	Asian	Pravastatin, 20 mg/day	12 weeks	*APOE4* carriers with lower efficacy	(37)
160	~90% Caucasians	Fluvastatin	12 weeks	*APOE4* alleles carriers with lower efficacy, no effect on CAD progression	(38)
328	–	Atorvastatin, 10 mg/day	1 year	*APOE4* alleles carriers with lower efficacy, valid for males but not for females	(39)
400 patients 338 controls	Caucasian	Different statins	Different time, unspecified	*APOE4* alleles carriers with lower efficacy	(40)

only three studies on the pharmacogenetics of statin efficacy have been published so far, two of which were performed in Asian populations. In the first study, 42 Japanese patients with type 2 diabetes were treated with 20 mg of pravastatin per day; no significant effect of *APOE* on post-treatment lipid levels was observed (42). In the second study, involving 96 Chinese diabetics treated with simvastatin (10 mg) or atorvastatin (20 mg), a significantly better response was observed in *APOE4* carriers, while *APOE2* subjects showed a rather low response (43).

The largest study so far (Go-DARTS study) analyzed almost 1400 type 2 diabetics treated with different doses of different statins. While the impact of *APOE* on treatment efficacy was inconsistent, *APOE4* carriers were less likely to achieve the target LDL-cholesterol level of 2 mmol/L (44).

APOE, gene-gene and gene-environment interactions and statin efficacy

Interactions between *APOE* polymorphism and other genetic variants have been studied in two studies so far. In the first study, researchers analyzed 337 hypercholesterolemic patients (202 males and 135 females) treated for 52 weeks with 10 mg of atorvastatin (45). The decrease in LDL-cholesterol was lowest in *CYP7A1* C-204C homozygotes carrying the *APOE4* allele. An LDL-cholesterol reduction was observed in *APOE2* individuals with at least one *CYP7A1* A-204 allele. The results are promising; however, despite the relatively large number of subjects, the numbers of patients in distinct subgroups were very low and thus any interpretation requires caution. It is noteworthy that in female patients, no such interaction between these two genes and decreases in plasma LDL-cholesterol was detected.

The second study on interactions between *APOE* variants and *CYP7A1* was performed on a small number (n=33) of individuals with the same ethnicity (46). The lowest efficacy was observed in individuals with the *APOE4* allele and at least one *CYP7A1* C allele.

A gender-dependent effect of *APOE* has been described in other studies (18, 20), but the results are far from being consistent. It should also be mentioned that the analysis of potentially sex-specific effects of *APOE* on statin treatment response was not a primary outcome of any of the above-mentioned studies, so the results should be viewed in this perspective.

Unfortunately, no study on further interactions with nutrition, smoking or physical activity has been published so far.

Large clinical trials

Despite the fact that many large clinical studies have focused on the effects of statins on lipid profile and/or CVD endpoints, only a few have analyzed the genetic background. Some 49 variants in nine genes and their impact on statin efficacy were analyzed in the PROVE IT-TIMI study patients (47). A total of 1378 patients with acute coronary syndrome and relatively low plasma total cholesterol (<240 mg/dL, 6.2 mmol/L) were randomized to atorvastatin 80 mg or pravastatin 40 mg per day and followed for an average of 2 years. The lipid-lowering effect of atorvastatin was highest in *APOE2* carriers and lowest in *APOE4* carriers; *APOE3* homozygotes showed an intermediate response. This association was reproduced in pravastatin-treated patients.

In 2005 the largest study performed so far on *APOE* effects on statin-induced changes in plasma lipids was published by Thompson and co-workers (48). In almost 2700 individuals treated with different types and doses of statins, 43 genotypes within 16 genes (including the *APOE* triallelic polymorphism) were assessed. *APOE* polymorphism was found to be one of two genes with a significant influence on the lipid-lowering response to statins. *APOE2* carriers showed a slightly greater decrease in LDL-cholesterol compared to *APOE3* homozygotes. However, the difference observed (3.5%) was not clinically relevant.

Another large study included 509 patients randomly assigned to low- and high-dose statin phases and almost 500 SNPs within more than 30 genes were analyzed (49). *APOE3* homozygosity was associated with an attenuated LDL-cholesterol reduction in comparison to *APOE2* carriers.

In the REGRESS study, 406 patients on pravastatin (40 mg) and 409 individuals on placebo were followed up for 2 years. Carriers of the *APOE2* allele have the highest increase in HDL-cholesterol and LDL/HDL ratio. However, no significant effect on LDL-cholesterol decreases was observed (50).

The fact that the *APOE* genotype could be used in personalized medicine was confirmed in a study with a different (not strictly pharmacogenetic) design. Very recently, data for 2289 participants were used to calculate the genotype ratio treatment index (GRTI) by dividing the proportion of *APOE3/E2* or *APOE3/E4* participants prescribed a statin by the proportion of *APOE3/E3* participants prescribed a statin. GRTI was lowest in *APOE2E3* individuals (51). This suggest that subjects with low-risk genotypes for LDL-cholesterol are treated with statins at lower frequency and are less likely to be found in treatment groups than in the general population.

Meta analysis

Zintzaras and colleagues used a meta-analytical approach to shed more light on the association between *APOE* polymorphism and lipid-lowering response to statin treatment (52). Pooling data for 24 studies on the topic should have overcome inconsistencies and drawbacks in study design, population selection and interpretation of the results for individual small studies included in the meta-analysis. Division of the population into three groups according to *APOE* genotype revealed that the mean reduction in total cholesterol from baseline was significant for all three *APOE* variants. The magnitude of statin impact on total cholesterol levels differed between genotypes, and was greater in *APOE2* carriers than in those with *APOE3* and *APOE4* alleles. However, the difference did not reach statistical significance. Thus, the authors of the only meta-analysis on *APOE* impact on statin efficacy concluded that there is little reason to consider the use of *APOE* genetic testing to guide statin treatment.

GWA studies

Thompson et al. addressed the issue of genetic determination of statin treatment response using a different approach (53). They performed a GWA study in a large cohort of patients included in the Treating to New Targets cohort. By analyzing almost 300,000 SNPs, they attempted to evaluate the role of known gene markers (e.g., *APOE*) and of newly identified ones. Despite the high power of the study (the original cohort comprised almost 2000 patients and the results were confirmed in another 3750 individuals), none of the SNPs examined was significantly associated with lipid response to statins at an arbitrary GWA significance level (which was set to an extreme 10^{-8}). Nevertheless, among variants with the highest impact, three different *APOE* variants were detected. The result was confirmed using the traditional candidate gene approach by screening for variants in 23 candidate genes in the same population. The previously identified *APOE2* variant showed the greatest modulating effect in terms of lowering LDL-cholesterol. However, the frequency of this *APOE* variant in the population is rather rare, so screening for the variant to individualize statin treatment would not be justifiable.

Pooling data from three studies for 3932 subjects treated with simvastatin, pravastatin or atorvastatin according to slightly different protocols, Barber et al. maximized genome coverage and combined information across studies (54). An SNP encoding rs4420638, located on the *APOC1* gene (neighboring the *APOE* gene), was associated with changes in LDL-cholesterol.

APOE and impact of statin treatment on cardiovascular events and cardiac function

A cardiovascular event is the result of the simultaneous and complex action of different risk factors, with dyslipidemia just one such factor. Even more important than the impact of genome variability on the lipid-lowering efficacy of statins seems to be the contribution of genetic factors to the ability of statins to lower the risk of cardiovascular events. This issue has been studied in several clinical trials.

The influence of *APOE* polymorphism on both lipid levels and clinical outcomes was first studied in the Scandinavian Simvastatin Survival Study (4S study) (55). In a subset of 1000 myocardial infarction (MI) survivors treated with 20–40 mg of simvastatin daily from the 4S study, *APOE* polymorphism was assessed and its impact on lipid parameters and clinical outcomes was evaluated. Similarly to other studies, the cholesterol-lowering effect of the treatment was more pronounced in *APOE4* non-carriers. In the placebo group, mortality was almost twice as high in *APOE4* carriers as in non-carriers. However, this difference disappeared with statin treatment, which suggests that simvastatin lowered mortality twice as effectively in *APOE4* carriers as in non-carriers. This discrepancy (smaller impact of simvastatin on plasma lipids and greater reduction in CVD risk in *APOE4* carriers) could be plausibly explained by non-lipid (pleiotropic) effects, which might play a more important role in *APOE4* carriers.

These results were indirectly confirmed by results simultaneously published for the Lipoprotein and Coronary Atherosclerosis Study (37). More than 300 individuals treated with fluvastatin (40 mg) or placebo were followed for up to 2.5 years. The modifying effect of *APOE* genotype on statin-induced decreases in LDL-cholesterol was confirmed (Table 1). However, angiographic measures of CAD progression and the incidence of clinical events were similar across *APOE* genotypes.

A Rotterdam study included almost 8000 individuals, some of them treated with statins (56). The adjusted relative risk of MI or stoke mortality (but not for total mortality) was significantly lower for subjects treated with statins. The protective effect of statins on MI or stroke mortality was expressed independently of *APOE* genotypes.

A large Italian project, the GISSI-Prevenzione study, yielded contradictory results (57). A total of 3300 post-MI patients were treated with pravastatin (20 or 40 mg/day). In *APOE4* non-carriers this treatment did not significantly reduce mortality compared to the placebo group. By contrast, mortality in patients with at least one *APOE4* allele was reduced almost three-fold in the pravastatin group compared to placebo group. Importantly, the mortality observed in this group was even lower than in pravastatin-treated *APOE4* non-carriers. However, the GISSI-Prevenzione results should not be overestimated, as the study had several important limitations (e.g., different follow-up period in individuals, etc.).

Ilveskoski et al. studied the effect of *APOE* genotype on myocardial blood flow in 22 hypercholesterolemic men treated with pravastatin (40 mg) and the same number of individuals on placebo (58). After treatment, adenosine stimulated an increase in myocardial flow in *APOE3* homozygotes, but not in *APOE4* carriers. The decrease in plasma cholesterol was similar in both groups.

In summary, these studies suggest that the effect of statins on reducing CAD severity or incidence of CAD events does not depend on *APOE* genotype.

APOE and undesirable effects of statin treatment

As shown by an extensive meta-analysis of 35 studies with almost 80,000 patients, statin treatment is associated with a very low, albeit not negligible, risk of undesirable effects (59). The most frequent side effect is myopathy, which occurs in different forms (myalgia, myositis, rhabdomyolysis) in 3%–10% of patients. It is certain that genetic background makes a significant contribution to individual susceptibility to undesirable effects of statins. However, to the best of our knowledge there is no study on the undesirable effects of statins in relation to *APOE* polymorphism. Our own pilot study comparing 45 individuals with statin-induced myopathy and 100 controls without muscle side effects did not reveal any effects of *APOE* polymorphism on the incidence of statin-induced myopathy (Vrablik et al., manuscript in preparation).

Statin compliance and *APOE*

A single study has reported on a significant role of *APOE* genotype in compliance with statin therapy (60). Among 798 patients treated with statins, individuals carrying the *APOE4* allele were more than twice more likely to discontinue their drug. We can speculate about the mechanisms underlying this effect. It might be the difference in susceptibility to side effects and thus poorer tolerance of the treatment in *APOE4* carriers. Another reason may be lower effectiveness of statin treatment in carriers of this allele. The latter argument can be taken *vice versa*. If *APOE4* carriers were more likely not to comply with the treatment, the lower treatment efficacy of statins in *APOE4* carriers might be a result of a lack of compliance rather than of a real reduction in statin efficacy in *APOE4* carriers.

Statin treatment and further *APOE* variants

Even though more common variants have been described for the *APOE* gene, the only one analyzed in relation to statin efficacy is the A-491T variant within the regulatory part of the *APOE* gene (61). In a small number of individuals (n=56) on atorvastatin (10 mg), T-491T homozygotes showed a slightly better response to treatment than carriers of the A-491 allele.

Conclusions

Most studies assessing the impact of genetic background on statin efficacy in the 1990s suffer from a lack of sufficient power (62). Major issues are related to an insufficient number of patients and substantial heterogeneity of concomitant treatment and study population selection.

The interest of the medical community in understanding the genetic determination of statin efficacy is obvious. Genetic information is easy to analyze and the analysis is cheap and less error-prone than biochemical analyses. Moreover, results are valid for the whole lifespan, independent of environmental factors and, most importantly, can be used for exact assessment of the treatment effects of different statins in individual patients. There has recently been a marked improvement in our understanding of the genetics of complex traits (e.g., obesity and diabetes) owing to the availability of high-throughput technologies for rapid sequencing of large parts of the genome.

The other issue will be transformation of results from these studies into clinically meaningful results. For this purpose, results for an individual will have to be compared to reference findings from large cohort and population surveys. Ultimately, this approach will provide very useful information and hopefully will facilitate the tailoring of intervention strategies according to individual needs.

In conclusion, despite some inconsistency in results, the *APOE4* allele is associated with poorer response to statin treatment and individuals with the *APOE2* allele seem to experience the greatest cholesterol-lowering effect. Nevertheless, the absolute impact of *APOE* alleles is context-dependent and relatively modest. There is significant heterogeneity among studies. Given these non-consistent effects of *APOE* genotype on lipid responses, there is little reason to consider the use of *APOE* genetic testing to guide statin treatment at present.

The impact of *APOE* polymorphism observed is scientifically interesting and is mostly statistically significant. However, currently it seems to be too modest to modify the final effect of statins on both the lipoprotein spectrum and CVD risk to a clinically meaningful level.

Acknowledgments

The authors are supported by projects 00023001 (IKEM) and 1M0510 (MEZS, CR) and grants NS10579-3 and NT11307-5 from the IGA of MH CR.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors state that there are no conflicts of interest regarding the publication of this article. Research support played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

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