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APOE GENE POLYMORPHISM AS A DETERMINANT OF HYPERLIPIDEMIA RISK AND EFFECTIVENESS OF STATIN DRUG THERAPY

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ПОЛИМОРФИЗМЪТ НА ГЕНА *APOE* КАТО ФАКТОР, ОПРЕДЕЛЯЩ РИСКА ОТ ХИПЕРЛИПИДЕМИЯ И ЕФЕКТИВНОСТТА НА ТЕРАПИЯТА СЪС СТАТИНИ

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Abstract.

Introduction: Hyperlipidemia is a medical condition characterized by high levels of lipids, including total cholesterol, low-density lipoprotein (LDL), and triglycerides in the blood. This condition plays a major role in the pathogenesis of cardiovascular diseases, such as atherosclerosis, coronary heart disease, and stroke, which are the leading causes of death and disability globally. The risk factors for hyperlipidemia involve a complex interaction between environmental, lifestyle, and genetic factors. Among these genetic factors, the apolipoprotein E (*APOE*) gene has long been identified as one of the major determinants of lipid metabolism. This study aims to analyze the impact of *APOE* gene polymorphisms on hyperlipidemia risk and statin therapy response using a bioinformatics approach, providing insights into personalized lipid-lowering treatments. **Material and methods:** This study used a bioinformatics approach to analyze genetic and clinical data available in several database sources, including PharmGKB, Ensembl, and GTEx Portal. **Results:** *APOE* gene polymorphisms play a significant role in determining the risk of hyperlipidemia and the effectiveness of statin therapy. Genetic variations such as rs7412, rs429358, rs449647, and rs71352238 affect lipid metabolism and patient response to various types of statins, including atorvastatin, pravastatin, simvastatin, and rosuvastatin. The results showed that

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individuals with certain genotypes, such as CT or TT, tend to have a better response to lowering LDL-C levels compared to other genotypes. Conversely, some alleles, such as the C allele in rs7412 and rs429358, are associated with lower therapy response or increased cardiovascular risk, but these risks can be reduced by selecting appropriate therapy, such as simvastatin. **Conclusions:** Pharmacogenomic approaches may guide more personalized management of statin therapy to improve clinical outcomes and minimize the risk of side effects. This study highlights the importance of understanding genetic interactions in the management of hyperlipidemia to prevent broader cardiovascular complications.

Key words: *APOE*, statin, Snp, rs7412, rs429358, rs449647, rs71352238, hyperlipidemia

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Резюме: **Въведение:** Хиперлипидемия е заболяване, което се характеризира с високи нива на липиди, включително общ холестерол, липопротеини с ниска плътност (LDL) и триглицериди в кръвта. Това състояние играе важна роля в патогенезата на сърдечно-съдовите заболявания, като атеросклероза, коронарна болест на сърцето и инсулт, които са водещите причини за смърт и инвалидност в световен мащаб. Рисковите фактори за хиперлипидемията включват сложно взаимодействие между факторите на околната среда, начина на живот и генетичните фактори. Сред тези генетични фактори генът на аполипопротеин Е (*APOE*) отдавна е идентифициран като един от основните детерминанти на липидния метаболизъм. **Целта** на това проучване е да се анализира влиянието на полиморфизмите на гена *APOE* върху риска от хиперлипидемия и отговора на терапията със статин, като се използва биоинформатичен подход, предоставящ информация за персонализирано лечение за понижаване на липидите. **Материал и методи:** В това проучване е използван биоинформатичен подход за анализ на генетични и клинични данни, налични в няколко бази данни, включително PharmGKB, Ensembl и GTEx Portal. **Резултати:** Полиморфизмите на гена *APOE* играят важна роля в определянето на риска от хиперлипидемия и ефективността на терапията със статини. Генетични вариации като rs7412, rs429358, rs449647 и rs71352238 влияят върху липидния метаболизъм и отговора на пациентите към различни видове статини, включително аторвастатин, правастатин, симвастатин и розувастатин. Резултатите показват, че индивидите с определени генотипове, като CT или TT, са склонни да имат по-добър отговор на понижаването на нивата на LDL-C в сравнение с други генотипове. Обратно, някои алели, като алел C в rs7412 и rs429358, се свързват с по-нисък терапевтичен отговор или повишен сърдечно-съдов риск, но тези рискове могат да бъдат намалени чрез избор на подходяща терапия, като например симвастатин. **Заключение:** Фармакогеномните подходи могат да насочат по-персонализирано управление на терапията със статини, за да се подобрят клиничните резултати и да се сведе до минимум рискът от странични ефекти. Това проучване подчертава важността на разбирането на генетичните взаимодействия при управлението на хиперлипидемията за предотвратяване на по-големи сърдечно-съдови усложнения.

Ключови думи: *APOE*, статин, Snp, rs7412, rs429358, rs449647, rs71352238, хиперлипидемия

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Introduction

Hyperlipidemia is a medical condition characterized by high levels of lipids, including total cholesterol, low-density lipoprotein (LDL), and triglycerides in the blood [1, 2]. This condition plays a major role in the pathogenesis of cardiovascular diseases, such as atherosclerosis, coronary heart disease, and stroke, which are the leading causes of death and disability globally [3]. Risk factors for hyperlipidemia involve a complex interaction between environmental, lifestyle, and genetic factors [4]. Among these genetic factors, the apolipoprotein E (*APOE*) gene has long been identified as one of the main determinants of lipid metabolism. The *APOE* gene is located on chromosome 19 and encodes the *APOE* protein, which plays a role in the transport of lipids through the blood and tissues [5, 6]. Genetic polymorphisms in *APOE* produce three major protein isoforms: *APOE*2, *APOE*3, and *APOE*4 [7, 8]. These variations originate from single nucleotide substitutions at positions rs429358 and rs7412. The *APOE*3 isoform is the most common form and is considered the reference because it has normal physiological functions [8, 9]. In contrast, *APOE*2 is typically associated with lower LDL levels, but may increase the risk of certain types of dyslipidemia, while *APOE*4 is known to be associated with increased total and LDL cholesterol levels, which in turn increases the risk of atherosclerosis and coronary heart disease [10, 11].

The influence of *APOE* polymorphisms is not only limited to genetic predisposition to hyperlipidemia but also affects the response to lipid-lowering therapy, especially statins [12, 13]. Statins are the first-line therapy widely used to lower LDL cholesterol levels and reduce

cardiovascular risk [14, 15]. The main mechanism of action of statins is to inhibit the enzyme HMG-CoA reductase, which plays a role in cholesterol synthesis in the liver [16]. However, the efficacy of statins is known to vary greatly between individuals, which is largely due to genetic factors, including variations in the *APOE* gene. Previous studies have shown that individuals with the *APOE*4 allele have a lower response to statin therapy than individuals with the *APOE*3 or *APOE*2 allele. Conversely, certain genotype combinations, such as CT or TT at rs7412, can increase more significant LDL reduction after statin therapy [17]. These findings emphasize the importance of a pharmacogenomic approach in the management of hyperlipidemia, where therapy can be tailored to the patient's genetic profile to improve treatment efficacy and reduce the risk of side effects [18, 19].

However, despite the growing evidence on the association between *APOE* polymorphisms, hyperlipidemia, and statin response, many aspects remain incompletely understood. For example, the molecular mechanisms underlying the effects of *APOE* polymorphisms on lipid metabolism and statin signaling pathways require further investigation. In addition, additional research is needed to understand the interactions between genetic and non-genetic factors, such as diet, physical activity, and other comorbidities, in determining statin therapy outcomes [20]. Thus, understanding the role of *APOE* polymorphisms as determinants of hyperlipidemia risk and statin therapy outcomes is not only scientifically important but also has significant clinical implications. This knowledge may pave the way for more personalized and effective treatment approaches, allowing for better management of hyperlipidemia and reduction of cardiovascular risk in the global population.

This study aims to investigate the impact of *APOE* polymorphisms on hyperlipidemia risk and statin therapy response using a bioinformatics approach. By integrating genetic and clinical data from multiple databases, this study seeks to provide insights into how specific genetic variations influence lipid metabolism and individual responses to statin treatment. The findings are expected to contribute to the development of personalized lipid-lowering therapies, ultimately improving clinical outcomes and reducing cardiovascular complications.

Material and Methods

This study used a bioinformatics approach to analyze genetic and clinical data available in several database sources, including *PharmGKB, Ensembl*, and *GTEx Portal* [21, 22]. The research steps include:

Identification of *APOE* Polymorphisms Associated with Hyperlipidemia

Using the Ensembl database to search the *APOE* gene sequence and search for polymorphisms associated with blood lipid levels. These polymorphisms were then associated with total cholesterol, LDL, HDL, and triglyceride levels in a population with hyperlipidemia [23, 24].

APOE Gene Expression Analysis in Various Tissues

Data from the GTEx Portal were used to explore *APOE* gene expression in various body tissues, especially liver and blood vessel tissues, which play an important role in lipid metabolism. Comparison of gene expression between individuals with different *APOE* genotypes was performed to see differences in expression patterns that may affect response to statin therapy [25, 26].

Statin Therapy Response Analysis Based on *APOE* Genotype

Data from PharmGKB were used to identify associations between *APOE* polymorphisms and statin therapy effectiveness. The analysis was performed by comparing therapy outcomes (changes in lipid levels) between individuals with different *APOE* genotypes receiving statin treatment [27, 28].

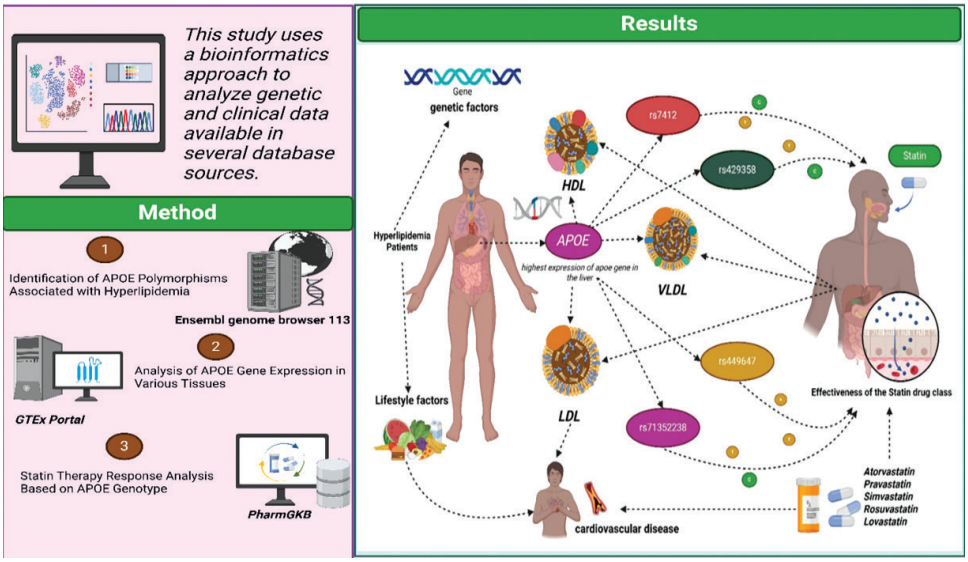

Fig. 1. Mechanism of action of the *APOE* gene and its influence on lipid metabolism and efficacy of statin therapy. Polymorphisms in the *APOE* gene, such as rs7412 and rs429358, affect cholesterol metabolism and response to lipid-lowering therapy. Created in https://BioRender.com

Results

The results of the study using the ensemble approach successfully identified a total of 62 SNPs located in the *APOE* gene. Further selection process was carried out by eliminating SNPs that did not have a significant relationship with the response to statin therapy. After a more in-depth analysis, finally 4 SNPs were found which can be seen in (Table 1) which have a strong relationship with the mechanism of action of statins, which can provide new insights into the potential of pharmacogenomics in statin therapy in certain populations.

Polypoprotein E (*apoe*) is a protein produced primarily in the liver and plays an important role in lipid metabolism, particularly in regulating blood cholesterol levels. In (Fig. 2) High expression of the *APOE* gene in the liver contributes to significant *apoe* production, which then interacts with receptors in the liver to regulate circulating lipoprotein levels. One of the main functions of *apoe* is as a high-affinity ligand for several receptor systems in the liver, including the low-density lipoprotein (LDL) receptor [29, 30]. This interaction is important for the uptake and clearance of lipoproteins containing apoB-100 and/or *apoe*, such as LDL and intermediate-density lipoprotein (IDL), from the circulation. Thus, *apoe* helps reduce blood LDL levels, which if excessive can lead to atherosclerosis or plaque buildup in the arteries. Research by Van Eck et al. (2001) showed that LDL receptors in the liver play an important role in the reduction of serum cholesterol levels mediated by *apoe* produced by macrophages. In this study [31] , *apoe*-deficient mice showed significant reductions in VLDL and LDL cholesterol levels after reintroduction of *apoe* production by macrophages, but this effect depended on the presence of a functional LDL receptor in the liver [32, 33]. Thus, high expression of the *APOE* gene in the liver results in abundant production of *apoe*, which interacts with the LDL receptor to regulate and lower LDL levels in the blood. This mechanism is important for maintaining lipid balance and preventing cardiovascular disease associated with high LDL levels [34, 35].

The association between the *APOE* gene and hyperlipidemia is important, as genetic variations in *APOE* are associated with disorders of lipid metabolism [36]. The *APOE* gene influences cholesterol levels and is associated with various forms of hyperlipidemia, including familial hypercholesterolemia and dysbetalipoproteinemia. This association is confirmed by several studies highlighting the role of specific *APOE* variants in lipid profiles and disease susceptibility [37]. The *APOE* gene has common polymorphisms (e.g., *APOE*2, *APOE*4) that influence lipid metabolism and contribute to hyperlipidemia. Rare variants, such as p.(Leu167del) and p.(Arg163Cys), have been identified in patients with isolated hypercholesterolemia and combined hyperlipidemia, suggesting a role in dyslipidemia [37]. A meta-analysis found that specific *APOE* alleles (e2 and e4) are risk factors for hyperlipidemia, with odds ratios showing a significant association [38]. The *APOE* protein facilitates the clearance of lipoproteins from the bloodstream, and mutations can disrupt this process, leading to increased cholesterol levels. Studies in Apoe mice have shown that the absence of *APOE* causes severe hyperlipidemia, highlighting its important role in lipid homeostasis. Although the *APOE* gene is a major contributor to hyperlipidemia, it is important to consider that other genetic and environmental factors also play important roles in lipid metabolism and cardiovascular health. Further research is needed to fully understand the complex interactions involved [39].

Discussion

Genetic variations in the *APOE* gene have a significant influence on an individual's response to drug therapy used to treat hyperlipidemia. This can be seen in Fig. 3.

Variant rs7412

Individuals with the C allele had a lower response to atorvastatin, pravastatin, and simvastatin compared to those with the T allele [40]. This suggests that therapy with these drugs may be less effective in individ-

Table 1. Allele frequencies of *APOE* gene variants in various populations

Gene	SNP	Allele Frequency in Different Populations									
		EAS		SAS		Africa		Europe		American	
APOE	rs7412	C: 0.900 (907)	T: 0.100 (101)	C: 0.956 (935)	T: 0.044 (43)	C: 0.897 (1186)	T: 0.103 (136)	C: 0.937 (943)	T: 0.063 (63)	C: 0.952 (661)	T: 0.048 (33)
APOE	rs429358	T: 0.914 (921)	C: 0.086 (87)	T: 0.913 (893)	C: 0.087 (85)	T: 0.732 (968)	C: 0.268 (354)	T: 0.845 (850)	C: 0.155 (156)	T: 0.896 (622)	C: 0.104 (72)
APOE	rs449647	A: 0.973 (981)	T: 0.027 (27)	A: 0.807 (789)	T: 0.193 (189)	A: 0.668 (883)	T: 0.332 (439)	A: 0.835 (840)	T: 0.165 (166)	A: 0.742 (515)	T: 0.258 (179)
APOE	rs71352238	T: 0.903 (910)	C: 0.097 (98)	T: 0.876 (857)	C: 0.124 (121)	T: 0.993 (1313)	C: 0.007 (9)	T: 0.867 (872)	C: 0.133 (134)	T: 0.906 (629)	C: 0.094 (65)

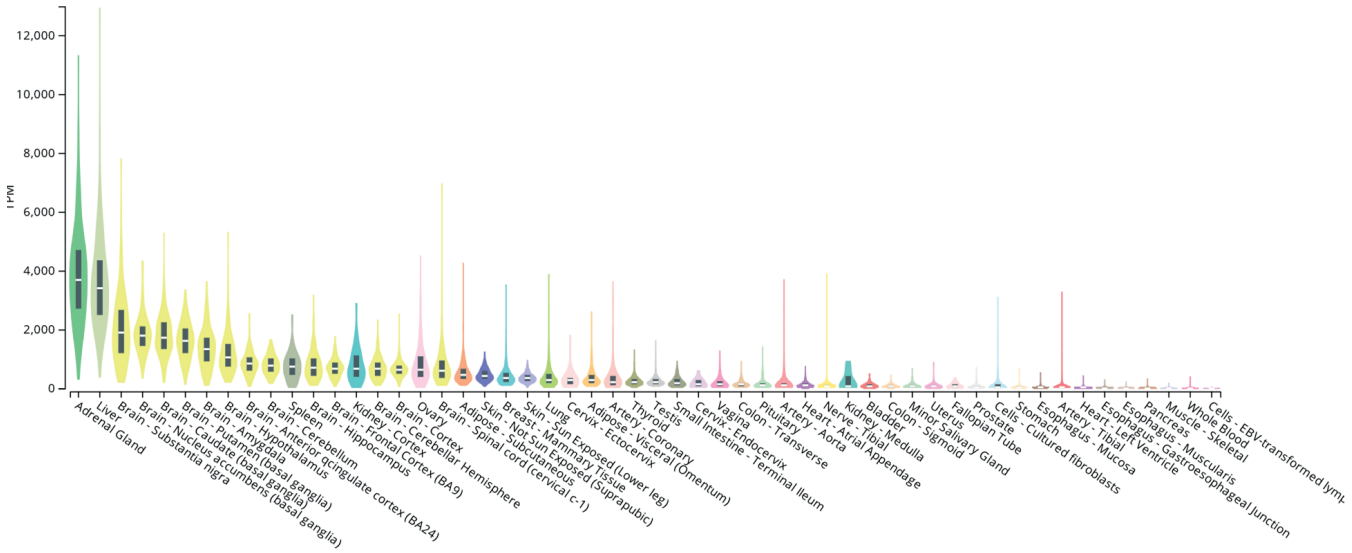

Fig. 2. *APOE* gene expression in human body tissues (ENSG00000130203.10)

Table 2. Genetic Variants of *APOE* and Their Association with Drug Efficacy in Lipid Disorders and Cardiovascular Conditions

Variants	Drugs	Significance	of Cases	Phenotype Categories	Genes	Association
rs7412	atorvastatin; pravastatin; simvastatin	yes	509	Efficacy	*APOE*	Allele C is associated with decreased response to atorvastatin, pravastatin or simvastatin in people with Hyperlipidemias as compared to allele T.
rs429358	Simvastatin	yes	966	Efficacy	*APOE*	Allele C is associated with increased risk of mortality after myocardial infarction, however this can be eliminated when treated with simvastatin as compared to allele T.
rs7412	atorvastatin; pravastatin	yes	692	Efficacy	*APOE*	Genotypes CT + TT are associated with increased percent reduction in LDL-cholesterol when treated with atorvastatin or pravastatin in people with Acute coronary syndrome as compared to genotype CC.
rs449647	atorvastatin; bezafibrate	yes	54	Efficacy	*APOE*	Genotypes AT + TT are associated with increased lipid-lowering effect when treated with atorvastatin or bezafibrate in people with Hyperlipidemias as compared to genotype AA.
rs7412	Rosuvastatin	yes	6989	Efficacy	*APOE*	Genotypes CT + TT are associated with increased response to rosuvastatin as compared to genotype CC.
rs71352238	Rosuvastatin	yes	6989	Efficacy	*APOE*	Genotypes CC + CT are associated with decreased response to rosuvastatin as compared to genotype TT.
rs429358	Atorvastatin	yes	5745	Efficacy	*APOE*	Allele T is associated with LDL-C response when treated with atorvastatin in people with Coronary Disease.
rs429358	Atorvastatin	yes	139	Efficacy	*APOE*	Genotype CT is associated with decreased response to atorvastatin in people with Hypercholesterolemia as compared to genotype TT.
rs7412	Atorvastatin	yes	1263	Efficacy	*APOE*	Genotype CT is associated with increased response to atorvastatin as compared to genotype CC.
rs429358	Lovastatin	no	301	Efficacy	*APOE*	The CC genotype is not associated with response to lovastatin as compared to the TT genotype.

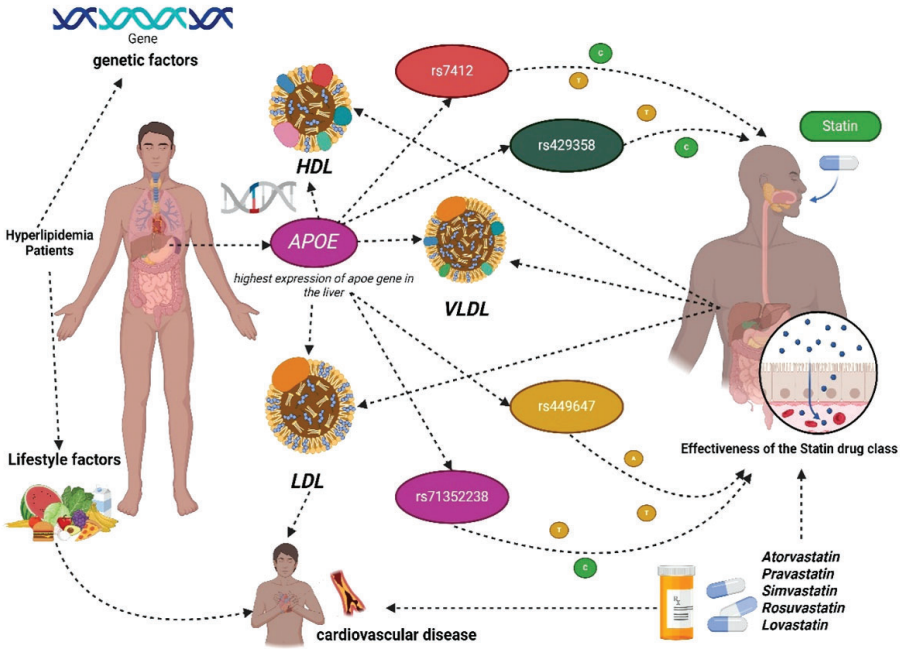

Fig. 3. Apoe gene mechanism and gene expression in the liver affect the metabolism of statin drugs

uals with the C allele in cases of hyperlipidemia. The CT + TT genotype showed a higher reduction in LDL compared to the CC genotype when using atorvastatin or pravastatin. This suggests that individuals with this genotype tend to get a greater benefit in lowering LDL cholesterol. The CT + TT genotype was also associated with a better response to rosuvastatin compared to the CC genotype. This makes rosuvastatin a more effective option for individuals with this genotype [41].

Variant rs429358

The C allele of this variant is associated with a higher risk of death after myocardial infarction. However, this risk can be reversed by therapy with simvastatin, making it an important option for post-infarction treatment in individuals with this allele. The T allele has been shown to be associated with lower LDL-C when treated with atorvastatin in individuals with coronary heart disease. The CT genotype is associated with a lower response to atorvastatin compared with the TT genotype, which may require dose adjustment or selection of an alternative drug. The CC genotype has not been shown to be associated with response to lovastatin compared with the TT genotype, suggesting that lovastatin may be similarly effective without this genetic variation [40].

Variant rs449647

The rs449647 variant in the *APOE* gene plays an important role in determining the effectiveness of combination therapy with atorvastatin or bezafibrate in the treatment of hyperlipidemia [42]. Studies have shown that individuals with the AT + TT genotype have a better response to this treatment than individuals with the AA genotype. This better response is seen from a more significant lipid-lowering effect, including a decrease in low-density lipoprotein (LDL) cholesterol and triglycerides. The AT + TT genotype appears to provide pharmacogenomic advantages, possibly due to variations in the structure or function of the *apoe* protein that affect lipid metabolism. In this genotype, atorvastatin and bezafibrate may be more effective in increasing lipid clearance from the blood through metabolic pathways involving *apoe*. Atorvastatin, as an HMG-CoA reductase inhibitor, helps reduce cholesterol synthesis in the liver, while bezafibrate, as a PPARα agonist, increases fatty acid oxidation and clearance of triglyceride-rich lipoproteins. This combination provides a synergistic effect, which seems to be more optimal in individuals with the AT + TT genotype. Conversely, individuals with the AA genotype may have a lower response to this therapy. This may be due to the lack of efficiency in the interaction of *apoe* with the metabolic pathways affected by both drugs, so that the lipid-lowering effect becomes less significant [42].

Variant rs71352238

The rs71352238 variant in the *APOE* gene plays an important role in determining patient response to treatment with rosuvastatin, a statin drug used to lower LDL cholesterol levels [43]. Based on research, individuals with the CC + CT genotype showed a lower response to rosuvastatin compared to individuals with the TT genotype. This means that in individuals with the CC or CT genotype, the ability of rosuvastatin to lower LDL-C levels and improve overall lipid profiles is less effective compared to individuals with the TT genotype. This lower response may be due to differences in the affinity of the *apoe* protein produced by the *APOE* gene for lipid metabolism, including lipoprotein transport and processing. Individuals with the CC + CT genotype may have a less efficient metabolic mechanism to utilize rosuvastatin in lowering LDL cholesterol, either due to changes in the receptors that interact with lipids or the efficiency of lipid clearance from the blood. In contrast, the TT genotype appears to provide more

optimal results when using rosuvastatin. Individuals with this genotype may have a lipid metabolism profile that is more responsive to the pharmacological effects of rosuvastatin, resulting in a more significant reduction in LDL-C. Thus, the TT genotype may be considered a genetic marker indicating a better therapeutic response to rosuvastatin [44].

Conclusion

APOE gene polymorphisms play a significant role in determining the risk of hyperlipidemia and the effectiveness of statin therapy. Genetic variations such as rs7412, rs429358, rs449647, and rs71352238 affect lipid metabolism and patient response to various types of statins, including atorvastatin, pravastatin, simvastatin, and rosuvastatin. The results showed that individuals with certain genotypes, such as CT or TT, tended to have a better response to lowering LDL-C levels compared to other genotypes. Conversely, some alleles, such as the C allele in rs7412 and rs429358, were associated with lower therapeutic response or increased cardiovascular risk, but these risks could be reduced by selecting appropriate therapy, such as simvastatin. This study emphasizes the importance of a pharmacogenomic approach in the management of hyperlipidemia to improve therapeutic efficacy and minimize the risk of side effects. By understanding the role of *APOE* polymorphisms, treatment can be tailored to the patient's genetic profile, providing opportunities for more personalized and effective lipid management and reducing the risk of cardiovascular disease in diverse populations.

No conflict of interest was declared

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