

The effect of apolipoprotein E gene polymorphism and Lp(a) levels on coronary artery disease with atrial fibrillation

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Abstract

Objective: To explore the influence of apolipoprotein E (APOE) genotypes and blood lipid metabolism on coronary artery disease (CAD) with atrial fibrillation (AF).

Methods: Patients with suspected CAD were consecutively enrolled and divided into groups with or without CAD and/or AF. Blood lipid levels and APOE genotypes were determined and analysed for associations with CAD and AF.

Results: A total of 2048 patients were included (400 patients without CAD or AF [controls], 126 patients without CAD but with AF, 1294 patients with CAD without AF, and 228 patients with CAD and AF). Age and lipoprotein (a) (Lp[a]) levels were significantly higher in patients with CAD and AF versus those with CAD without AF. Among patients with CAD, the E3/E3 genotype and ϵ 3 allele frequencies were significantly lower in patients with AF than in those without AF, and the E4/E4 genotype and ϵ 4 allele frequencies were significantly increased. Multivariate logistic regression revealed that increased Lp(a) levels and age were independent risk factors for AF in patients with CAD.

Conclusion: Among patients with CAD, those with AF had increased age, ϵ 4 frequencies and Lp(a) levels. Age and Lp(a) levels may be independent risk factors for AF in patients with CAD.

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Keywords

Apolipoprotein E, Lp(a) levels, coronary artery disease, atrial fibrillation, lipoprotein (a), APOE alleles

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Introduction

Coronary artery disease (CAD) is currently the most common cardiovascular disease, and with a gradually increasing incidence, it has become the main cause of death in developed and developing countries.^{1–3} Of the arrhythmias, atrial fibrillation (AF) is the most prevalent type.⁴ In addition to increasing the incidence of cardiogenic stroke, AF may significantly increase the risk of heart failure and death in patients with CAD,^{5,6} bringing a heavy burden to human health.^{7,8} Thus, AF and CAD have undoubtedly become the two most attention-worthy cardiovascular diseases. While AF is an electrical atrial disease, CAD is a disease of the vascular structure.⁹ However, many studies have shown that AF and CAD are closely related,^{10–12} which may explain the common mechanisms associated with occurrence and development, and their common risk factors, such as dyslipidaemia, fibrosis, inflammation, hypertension, and age.^{13–15} The correlation between dyslipidaemia and the occurrence and development of AF has received increasing attention, however, many controversies remain,^{16–20} resulting in the need for further investigation.

The apolipoprotein E (*APOE*) gene, involved in lipoprotein synthesis and metabolism, has three main subtypes, E2, E3 and E4, encoded by the corresponding $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ alleles, and has six possible genotypes, E2/2, E2/3, E2/4, E3/3, E3/4 and E4/4.²¹ Previous studies have shown that both AF and CAD are related to genetic factors, and there is a strong genetic

component for the diseases.^{22–24} The $\epsilon 4$ allele of *APOE* is related to the incidence of atherosclerosis and CAD,^{25,26} and *APOE* has been shown to be associated with AF in the Alzheimer's disease population.^{27,28} However, few studies have investigated *APOE* and AF in patients with CAD. Thus, the aim of the present study was to explore the effects of *APOE* and blood lipids on CAD with AF.

Patients and methods

Study population

This observational case-control study included consecutively enrolled patients who were admitted to the Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, for suspected CAD between June 2020 and July 2021. Relevant information was collected from the patients' clinical records and all included patients underwent coronary angiography or coronary computed tomography angiography (CTA) examination. The diagnostic criteria for CAD were as follows: typical angina symptoms and a coronary vascular examination showing that the diameter of the subepicardial coronary artery was $>50\%$, or a noninvasive examination showing that the patient had evidence of myocardial ischemia.²⁹ AF was defined as the disappearance of P waves on electrocardiogram, the presence of F waves of different sizes, shapes, and amplitudes, an F wave frequency of 350 to 600 beats per min, and a variable R–R interval.³⁰ The exclusion criteria were as

follows: (1) patients with incomplete clinical data, including the lack of basic clinical data, and unsuccessful completion of coronary angiography or coronary CTA; (2) patients with prehospital use of lipid-lowering drugs, such as statins; (3) patients with severe liver and/or kidney dysfunction (significant damage to liver or kidney structure and function); and (4) patients with thyroid disease (abnormal thyroid function) and multiple organ dysfunction (simultaneous or sequential dysfunction of two or more organs). Enrolled patients were grouped according to the presence or absence of CAD and AF, as follows: control group (CAD- AF-, patients without CAD or AF), CAD- AF+ group (patients without CAD but with AF), CAD+ AF- group (patients with CAD without AF) and CAD+ AF+ group (patients with both CAD and AF).

The study was approved by the Ethics Committee of Xuzhou Medical University, and all enrolled patients provided written informed consent. The reporting of this study conforms to STROBE guidelines.³¹

Clinical and laboratory data

After hospitalization and study enrolment, the demographic and clinical data of all participants were collected, including sex, age, body mass index (BMI [kg/m²]), smoking status, hypertension, and diabetes. Diabetes and hypertension were defined according to the relevant published diagnostic criteria,^{32,33} and smoking was defined as continuous or cumulative smoking for more than 6 months.³⁴

Determination of blood lipids and APOE genotype

Peripheral venous blood was drawn from patients on an empty stomach into tubes containing ethylenediamine tetra acetic

acid (EDTA) anticoagulant and used immediately, with 1 ml of the sample used to evaluate blood biochemistry, as follows: total cholesterol and triglycerides were measured using a blood lipid biochemical test kit (TEGEN, Shanghai, China); high-density lipoprotein cholesterol (HDL-C) was determined by a phosphotungstic precipitation method with reagents from Zhongsheng Beikong Bio-technology (Beijing, China); low-density lipoprotein cholesterol (LDL-C) was obtained by formula calculation; and lipoprotein(a) (Lp[a]) was measured using a sandwich enzyme-linked immunosorbent assay kit (Rayzbio Technology, Shanghai, China), with results evaluated in a plate reader by absorbance readings at 450 nm. All assays were performed according to the manufacturer's instructions.

Single nucleotide polymorphisms in the *APOE* gene were detected using a commercial kit (Beyotime, Shanghai, China). Briefly, DNA as extracted from 2 ml of the patient's blood sample in EDTA using a DNA extraction kit (Beyotime) according to the manufacturer's instructions. Genomic DNA was then subjected to polymerase chain reaction (PCR) with primers specific to the *APOE* gene: sense, 5'-AACAACT GACCCCGGTGGCG-3'; antisense, 5'-ATGGCGCTGAGGCCGCGCTC-3'; and sense, 5'-CCCACCTGCGCAAGCTGCG C-3', using thermal cycling conditions according to Hixson and Vernier.³⁵ In brief, each reaction mixture was heated at 95°C for 5 min for denaturation, then subjected to 30 amplification cycles of primer annealing at 60°C for 1 min, extension at 70°C for 2 min, and denaturation at 95°C for 1 min. An Affymetrix gene chip reader (Subsidiary of Thermo Fisher Scientific; Santa Clara, CA, USA) was used to read the fluorescence curve of the amplified product sample, according to the manufacturer's instructions.

Statistical analyses

Data were statistically analysed using IBM SPSS software, version 22.0 (IBM, Armonk, NY, USA). Continuous variables are presented as mean \pm SD, and were compared between groups with Student's *t*-test. Categorical variables are presented as frequencies and were compared using χ^2 -test or Fisher's exact test. Spearman's rank correlation coefficient was used to compare the correlation between $\epsilon 4$ and Lp(a). Variables were then incorporated into multiple logistic regression analysis to evaluate the independent risk factors that determine the presence of AF in patients with CAD. A *P* value <0.05 was considered statistically significant.

Results

Study population characteristics

The study included a total of 2048 patients who were divided into four groups: control group (CAD- AF-, *n* = 400); CAD- AF+ group (*n* = 126); CAD+ AF- group (*n* = 1294); and CAD+ AF+ group (*n* = 228). The basic clinical and demographic characteristics of the study population are summarized in Table 1. Compared with the control group, patients with CAD and/or AF were significantly older

(*P* <0.05); and BMI, the proportion of male patients, and those with hypertension, diabetes, and who smoked was significantly higher in patients with CAD (*P* <0.05). Patients with both CAD and AF were significantly older than patients with CAD without AF (*P* <0.05 ; Table 1).

Comparison of blood lipids in the study population

Compared with the control group, levels of total cholesterol, LDL-C, and Lp(a) were significantly increased in patients with CAD, and HDL-C was significantly decreased (*P* <0.05); although levels of triglycerides were numerically higher, the difference was not statistically significant. The Lp(a) levels were significantly higher in the CAD+ AF+ group versus the CAD+ AF- group (*P* <0.05 ; Table 2).

Distribution of APOE genotypes among the study population

Compared with the control group, frequencies of the E3/E4 and E4/E4 genotypes and $\epsilon 4$ allele were significantly increased in patients with CAD, and frequencies of the E3/E3 genotype and $\epsilon 3$ allele were significantly decreased. In addition, among patients with CAD, frequencies of the E3/E3 genotype and $\epsilon 3$ allele were significantly

Table 1. Study population characteristics.

Variable	CAD-		CAD+	
	AF- (<i>n</i> = 400)	AF+ (<i>n</i> = 126)	AF- (<i>n</i> = 1294)	AF+ (<i>n</i> = 228)
Age, years	60.69 \pm 11.8	63.6 \pm 10.31*	64.88 \pm 10.69**	66.86 \pm 10.78**,#
Male	191 (47.8)	59 (46.8)	816 (63.1)**	143 (62.7)**
Hypertension	200 (50)	69 (54.8)	745 (57.6)*	140 (61.4)*
Diabetes	58 (14.5)	20 (15.9)	332 (25.7)**	63 (27.6)**
Smoking	88 (22)	26 (20.6)	482 (37.2)**	85 (37.3)**
BMI, kg/m ²	21.61 \pm 3.67	22.53 \pm 3.91	24.95 \pm 3.72*	25.05 \pm 3.5*

Data presented as mean \pm SD or *n* (%) prevalence.

BMI, body mass index; CAD, coronary artery disease; AF, atrial fibrillation.

P* <0.05 versus controls (CAD- AF-); *P* <0.001 versus controls (CAD- AF-); #*P* <0.05 versus CAD+ AF-.

Table 2. Biochemical data of the study population.

Variable	CAD–		CAD+	
	AF– (n = 400)	AF+ (n = 126)	AF– (n = 1294)	AF+ (n = 228)
TC, mmol/L	4.73 ± 1.36	4.81 ± 1.51	4.92 ± 1.45*	5.07 ± 1.32*
TG, mmol/L	1.66 ± 1.35	1.52 ± 1.16	1.71 ± 1.22	1.68 ± 1.14
LDL-C, mmol/L	2.68 ± 1.04	2.74 ± 1.14	2.85 ± 1.18*	2.98 ± 1.17*
HDL-C, mmol/L	1.35 ± 0.43	1.36 ± 0.38	1.29 ± 0.41*	1.27 ± 0.38*
Lp(a), mg/L	231.87 ± 195	263.84 ± 263.43	254.92 ± 222.81*	285.69 ± 170.32*,#

Data presented as mean ± SD.

CAD, coronary artery disease; AF, atrial fibrillation; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; Lp(a), lipoprotein (a).

* $P < 0.05$ versus controls (CAD– AF–); # $P < 0.05$ versus CAD+ AF–.

Table 3. Prevalence of apolipoprotein E (APOE) gene polymorphisms in the study population.

APOE genotype	CAD–		CAD+	
	AF– (n = 400)	AF+ (n = 126)	AF– (n = 1294)	AF+ (n = 228)
E2/E2	3 (0.8)	0 (0)	6 (0.5)	1 (0.4)
E2/E3	42 (10.5)	14 (11.1)	153 (11.8)	25 (11)
E3/E3	268 (67)	84 (66.7)	742 (57.3)*	111 (48.7)**,#
E2/E4	11 (2.8)	1 (0.8)	22 (1.7)	4 (1.8)
E3/E4	56 (14)	20 (15.9)	250 (19.3)*	53 (23.2)*
E4/E4	20 (5)	7 (5.6)	121 (9.4)*	34 (14.9)**,#
ε2	59 (7.4)	15 (6)	187 (7.2)	31 (6.8)
ε3	634 (79.3)	202 (80.2)	1887 (72.9)**	300 (65.8)**,#
ε4	107 (13.4)	35 (13.9)	514 (19.9)**	125 (27.4)**,###

Data presented as n (%) prevalence.

CAD, coronary artery disease; AF, atrial fibrillation.

* $P < 0.05$ versus controls (CAD– AF–); ** $P < 0.001$ versus controls (CAD– AF–); # $P < 0.05$ versus CAD+ AF–;

$P < 0.001$ versus CAD+ AF–.

lower in patients with AF than in those without AF, and frequencies of the E4/E4 genotype and ε4 allele were significantly increased ($P < 0.05$; Table 3).

Correlation between the APOE ε4 allele and Lp(a) levels in patients with CAD with or without AF

Analysis by Spearman's rank correlation coefficient revealed that in patients with CAD, although ε4 and Lp(a) levels were correlated, the correlation was weak

($r = 0.106$ [$P < 0.001$]; Table 4). In patients with CAD, Lp(a) levels were significantly higher in the ε4 group than in patients without ε4 ($P < 0.05$; Figure 1).

Multiple logistic regression analysis of patients with CAD with or without AF

The logistic regression analysis included all potential risk factors, and revealed that increased Lp(a) levels ($P = 0.041$) and age ($P = 0.01$) were independent risk factors for AF in patients with CAD (Table 5).

Discussion

Coronary artery disease and AF, the most common cardiovascular disease and arrhythmia type, respectively, have become significant threats to human health, and many studies have shown

Table 4. Correlation between the apolipoprotein E (APOE) $\epsilon 4$ allele and Lp(a) in patients with CAD.^a

Variable	Lp(a)	
	r	Statistical significance
With $\epsilon 4$	0.106	$P < 0.001$

CAD, coronary artery disease; Lp(a), lipoprotein (a).

^aSpearman's rank correlation coefficient.

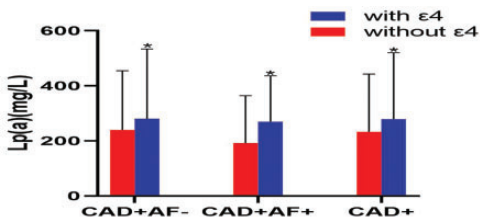


Figure 1. Comparison of Lp(a) between patients with CAD with or without the apolipoprotein E $\epsilon 4$ allele. Lp(a), lipoprotein (a); CAD, coronary artery disease. Data presented as mean \pm SD; * $P < 0.05$ versus patients without $\epsilon 4$.

them to be correlated.^{36–38} The main risk factors for AF are also risk factors for CAD, and include age, race, blood lipid levels, obesity, hypertension, and certain lifestyle factors.^{39–41} Blood lipid levels are an established risk factor for CAD, with the relationship between blood lipid levels and AF becoming a research hotspot.^{16,17} Both CAD and AF show strong genetic correlations, therefore, the present study aimed to explore the internal connection between CAD and AF through assessment of the differences in blood lipid levels and expression of the regulatory gene *APOE* in patients with CAD and AF.

In the present study, comparison of clinical data showed that patients with AF or CAD were significantly older than controls without CAD or AF, and BMI, the proportion of male patients, and those with hypertension, diabetes, and smoking were significantly higher in patients with CAD. Among patients with CAD, those with AF were significantly older than patients without AF. These results concur with the epidemiological manifestations of CAD and AF.^{29,30} The present study also showed that, compared with the control group, levels of total cholesterol, LDL-C, and Lp(a) were significantly increased in patients with CAD, and HDL-C was significantly

Table 5. Multiple logistic regression analysis of potential risk factors for AF in 1522 patients with CAD.

Variable	B	SE	Wald χ^2	Statistical significance	Odds ratio
Constant	-3.410	0.698	23.865	$P < 0.001$	0.033
Male	-0.045	0.174	0.068	NS	0.956
Age	0.018	0.007	6.626	$P = 0.010$	1.018
Hypertension	0.119	0.150	0.630	NS	1.126
Diabetes	0.089	0.163	0.298	NS	1.093
Lp(a)	0.063	0.031	4.187	$P = 0.041$	1.065
Smoking	0.057	0.174	0.107	NS	1.058
BMI	0.006	0.020	0.105	NS	1.006
With $\epsilon 4$	0.148	0.153	0.932	NS	1.160

BMI, body mass index; CAD, coronary artery disease; AF, atrial fibrillation; Lp(a), lipoprotein (a); $\epsilon 4$, apolipoprotein E $\epsilon 4$ allele.

NS, no statistically significant correlation with AF ($P > 0.05$).

reduced. Since the associations between triglyceride levels and CAD have been controversial, it is worth noting that although patients with CAD in the present study were found to have an increasing trend in triglyceride levels, no statistical significance was found. A previously published report attracted much attention by stating that hypertriglyceridemia should not be regarded as a single entity, but should be regarded according to the multiple conditions of total particle number and composition,⁴² which may explain the ongoing controversy over triglycerides in the research of CAD. In addition, research data on the relationship between blood lipid levels and AF remain inconclusive and controversial. Among published research, a more convincing study by Jiang et al.,⁴³ used Mendelian randomization methods to assess the association between blood lipid levels and the risk of AF. Regarding causality, large-scale multivariable Mendelian randomization studies have shown that there is a positive causal relationship between high Lp(a) levels and an increased risk of AF.⁴³ Among patients with CAD in the present study, levels of Lp(a) in patients with AF were significantly higher than in patients without AF. However, in patients without CAD, there were no significant differences in Lp(a) levels between patients with or without AF. This result may have been due to the relatively low sample size in the present study, or differences in comorbid diseases, and requires more data from larger samples for further investigation.

Next, the prevalence of *APOE* genotypes were compared between the present study groups. Compared with controls, the frequency of the E3/E4, E4/E4 genotypes and $\epsilon 4$ allele was significantly increased in patients with CAD, and the frequency of the E3/E3 genotype and $\epsilon 3$ allele was significantly decreased. These results are similar to those of previous studies indicating that the *APOE* genotype is closely related to the

occurrence and development of CAD.^{25,26} It is worth noting that among patients with CAD, the frequency of $\epsilon 4$ was significantly higher in patients with AF than in patients without AF. Published studies on AF and *APOE* are lacking, and currently available studies mainly focus on cerebrovascular diseases, particularly Alzheimer's disease.^{27,28,44,45} Falsetti et al.⁴⁴ showed that in Alzheimer's disease, the $\epsilon 4$ allele in patients with AF was associated with a higher risk of rapid cognitive deterioration. A population-based study from Finland, the CAIDE study,⁴⁵ showed that AF was an independent risk factor for dementia and Alzheimer's disease, and this association was related to the $\epsilon 4$ genotype. Similar to these results, it seems that $\epsilon 4$ plays an important role in patients with CAD and AF.

Carriers of the *APOE* gene $\epsilon 4$ allele have been shown to have higher total cholesterol and Lp(a) levels.^{46,47} The present study found that in patients with CAD, Lp(a) levels were significantly higher in patients with the $\epsilon 4$ allele than in those without $\epsilon 4$. However, subsequent analysis by Spearman's correlation coefficient showed that, although there was a correlation between $\epsilon 4$ carriers and Lp(a) levels, the correlation was weak. Therefore, Lp(a) levels, the $\epsilon 4$ genotype and other possible risk factors were included in multiple logistic regression analysis. The results suggest that age and Lp(a) levels may be independent risk factors for AF in patients with CAD, which is novel information regarding CAD with AF.

The results of the present study may be limited by several factors. First, this was a single-centre study, and the study population was entirely Han ethnicity, thus, the results may not be representative of the general population. In addition, similar results were not observed when comparing AF in patients with CAD versus patients without CAD, and at present, we cannot provide a

satisfactory explanation. Future multi-centre, larger sample studies are needed to further clarify the results.

In conclusion, among patients with CAD, patients with AF had increased age, $\epsilon 4$ frequencies and Lp(a) levels. Age and Lp(a) levels may be independent risk factors for AF in patients with CAD.

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Author contributions

Lei Chen, Yameng Shao, Min Zhang and Li Zhi performed the experiments and analysed the data. Yong Li and Yuan Lu designed the study and wrote the manuscript.

Data accessibility

The original data supporting the conclusions of this manuscript will be provided by the author to any qualified researcher without reservation.


Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

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References

1. Kang Q, Li X, Yang M, et al. Galectin-3 in patients with coronary heart disease and atrial fibrillation. *Clin Chim Acta* 2018; 478: 166–170.
2. Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology [published correction appears in *Eur Heart J* 2014; 35: 2260–2261]. *Eur Heart J* 2013; 34: 2949–3003.
3. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 385: 117–171.
4. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; 285: 2370–2375.
5. Kundu A, O'Day K, Shaikh AY, et al. Relation of atrial fibrillation in acute myocardial infarction to in-hospital complications and early hospital readmission. *Am J Cardiol* 2016; 117: 1213–1218.
6. Mehta RH, Dabbous OH, Granger CB, et al. Comparison of outcomes of patients with acute coronary syndromes with and without atrial fibrillation. *Am J Cardiol* 2003; 92: 1031–1036.
7. Marijon E, Le Heuzey JY, Connolly S, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation* 2013; 128: 2192–2201.
8. Pistoia F, Sacco S, Tiseo C, et al. The epidemiology of atrial fibrillation and stroke. *Cardiol Clin* 2016; 34: 255–268.
9. Theodorakis GN. Coronary artery disease and atrial fibrillation. *Hellenic J Cardiol* 2017; 58: 213–214.
10. Hohnloser SH, Crijns HJ, Van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation [published correction appears in *N Engl J Med* 2009; 360: 2487] [published correction appears in *N Engl J Med* 2011; 364: 1481]. *N Engl J Med* 2009; 360: 668–678.
11. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in

- patients with atrial fibrillation. *N Engl J Med* 2010; 362: 1363–1373.
12. Jabre P, Jouven X, Adnet F, et al. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation* 2011; 123: 2094–2100.
 13. Allessie M, Ausma J and Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002; 54: 230–246.
 14. Burokienė N, Domarkienė I, Ambrozaitytė L, et al. Classical rather than genetic risk factors account for high cardiovascular disease prevalence in Lithuania: a cross-sectional population study. *Adv Med Sci* 2017; 62: 121–128.
 15. Christodoulidis G, Vittorio TJ, Fudim M, et al. Inflammation in coronary artery disease. *Cardiol Rev* 2014; 22: 279–288.
 16. Chamberlain AM, Agarwal SK, Ambrose M, et al. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2010; 159: 850–856.
 17. Watanabe H, Tanabe N, Yagihara N, et al. Association between lipid profile and risk of atrial fibrillation. *Circ J* 2011; 75: 2767–2774.
 18. Lopez FL, Agarwal SK, Maclellan RF, et al. Blood lipid levels, lipid-lowering medications, and the incidence of atrial fibrillation: the atherosclerosis risk in communities study. *Circ Arrhythm Electrophysiol* 2012; 5: 155–162.
 19. Lee HJ, Lee SR, Choi EK, et al. Low lipid levels and high variability are associated with the risk of new-onset atrial fibrillation. *J Am Heart Assoc* 2019; 8: e012771.
 20. Garg PK, Guan W, Karger AB, et al. Lp(a) (lipoprotein [a]) and risk for incident atrial fibrillation: multi-ethnic study of atherosclerosis. *Circ Arrhythm Electrophysiol* 2020; 13: e008401.
 21. Kolovou G, Daskalova D and Mikhailidis DP. Apolipoprotein E polymorphism and atherosclerosis. *Angiology* 2003; 54: 59–71.
 22. Zhou J, Chen X, Ye H, et al. An association study between genetic polymorphism in the interleukin-6 receptor gene and coronary heart disease. *Biomed Res Int* 2014; 2014: 504727.
 23. Gertler MM, Garn SM and White PD. Young candidates for coronary heart disease. *J Am Med Assoc* 1951; 147: 621–625.
 24. Gould WL. Auricular fibrillation; report on a study of a familial tendency, 1920–1956. *AMA Arch Intern Med* 1957; 100: 916–926.
 25. Ilveskoski E, Perola M, Lehtimäki T, et al. Age-dependent association of apolipoprotein E genotype with coronary and aortic atherosclerosis in middle-aged men: an autopsy study. *Circulation* 1999; 100: 608–613.
 26. Lehtinen S, Lehtimäki T, Sisto T, et al. Apolipoprotein E polymorphism, serum lipids, myocardial infarction and severity of angiographically verified coronary artery disease in men and women. *Atherosclerosis* 1995; 114: 83–91.
 27. Ding M, Fratiglioni L, Johnell K, et al. Atrial fibrillation, antithrombotic treatment, and cognitive aging: a population-based study. *Neurology* 2018; 91: e1732–e1740.
 28. Mattsson N, Eriksson O, Lindberg O, et al. Effects of APOE $\epsilon 4$ on neuroimaging, cerebrospinal fluid biomarkers, and cognition in prodromal Alzheimer's disease. *Neurobiol Aging* 2018; 71: 81–90.
 29. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) [published correction appears in *Eur Heart J* 2020; 41: 4242]. *Eur Heart J* 2020; 41: 407–477.
 30. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC [published correction appears in *Eur Heart J* 2021; 42: 507] [published correction appears in *Eur Heart J*

- 2021; 42: 546–547] [published correction appears in *Eur Heart J* 2021; 42: 4194]. *Eur Heart J* 2021; 42: 373–498.
31. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [published correction appears in *Ann Intern Med* 2008; 148: 168]. *Ann Intern Med* 2007; 147: 573–577.
 32. Alberti K and Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539–553.
 33. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension [published correction appears in *Eur Heart J* 2019; 40: 475]. *Eur Heart J* 2018; 39: 3021–3104.
 34. World Health Organization. *Guidelines for controlling and monitoring the tobacco epidemic*. Geneva: World Health Organization, 1998.
 35. Hixson JE and Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 1990; 31: 545–548.
 36. Motloch LJ, Reda S, Larbig R, et al. Characteristics of coronary artery disease among patients with atrial fibrillation compared to patients with sinus rhythm. *Hellenic J Cardiol* 2017; 58: 204–212.
 37. Proietti M, Calvieri C, Malatino L, et al. Relationship between carotid intima-media thickness and non valvular atrial fibrillation type. *Atherosclerosis* 2015; 238: 350–355.
 38. Camm AJ and Obel OA. Epidemiology and mechanism of atrial fibrillation and atrial flutter. *Am J Cardiol* 1996; 78: 3–11.
 39. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2009; 158: 111–117.
 40. Sanoski CA. Prevalence, pathogenesis, and impact of atrial fibrillation. *Am J Health Syst Pharm* 2010; 67: S11–S16.
 41. Marcus GM, Alonso A, Peralta CA, et al. European ancestry as a risk factor for atrial fibrillation in African Americans. *Circulation* 2010; 122: 2009–2015.
 42. Navar AM. The evolving story of triglycerides and coronary heart disease risk [published correction appears in *JAMA* 2019; 321: 1412]. *JAMA* 2019; 321: 347–349.
 43. Jiang Q, Qin D, Yang L, et al. Causal effects of plasma lipids on the risk of atrial fibrillation: a multivariable mendelian randomization study. *Nutr Metab Cardiovasc Dis* 2021; 31: 1569–1578.
 44. Falsetti L, Viticchi G, Buratti L, et al. Interactions between atrial fibrillation, cardiovascular risk factors, and ApoE genotype in promoting cognitive decline in patients with Alzheimer’s disease: a prospective cohort study. *J Alzheimers Dis* 2018; 62: 713–725.
 45. Rusanen M, Kivipelto M, Levälähti E, et al. Heart diseases and long-term risk of dementia and Alzheimer’s disease: a population-based CAIDE study. *J Alzheimers Dis* 2014; 42: 183–191.
 46. Chaudhary R, Likidilid A, Peerapatdit T, et al. Apolipoprotein E gene polymorphism: effects on plasma lipids and risk of type 2 diabetes and coronary artery disease. *Cardiovasc Diabetol* 2012; 11: 36.
 47. De Knijff P, Kaptein A, Boomsma D, et al. Apolipoprotein E polymorphism affects plasma levels of lipoprotein(a). *Atherosclerosis* 1991; 90: 169–174.