Original Article

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Familial hypercholesterolemia is undertreated in clinical practice

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Abstract

Background: Familial hypercholesterolemia (FH) is related with premature coronary heart disease (CHD), while controversial data exist regarding non-coronary cardiovascular disease (CVD). Nevertheless, recent data have indicated underdiagnosis and undertreatment of this high risk condition.
Aim: To compare the prevalence of CVD and target attainment of lipid-lowering therapy between FH and non-FH hyperlipidemic individuals.
Methods: This was a retrospective (from 1999 to 2013) observational study including 1000 consecutive adults treated for hyperlipidemia and followed up for ≥3 years. Dutch Clinic Network criteria were applied for the diagnosis of FH. High-intensity statin therapy was defined according to the expected low-density lipoprotein cholesterol (LDL-C) reduction ≥50%. LDL-C targets were those proposed by the European and Hellenic Atherosclerosis Society guidelines. The following comparisons were performed between FH and non-FH individuals regarding: a) the baseline prevalence of CVD (after adjusting for gender, age, smoking, hypertension, diabetes and family history of premature cardiovascular disease), b) the intensity of statin treatment and the LDL-C target attainment at the most recent visit.
Results: Of 1000 eligible hyperlipidemic adults, 12% were diagnosed with heterozygous FH. A higher prevalence of CHD was noticed in FH individuals compared with the non-FH subjects at the baseline visit (adjusted OR: 2.89, 95% CI: 1.12-7.45, p <0.05), while no differences were found regarding the prevalence of non-coronary CVD. After a median follow-up of 6 years, a non-significant trend towards a higher risk of incident overall CVD (HR 1.14, 95% CI: 0.51-2.54, p >0.05) was noticed. During follow-up FH patients were more likely to receive a high-intensity statin or statin/ezetimibe combina-

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tion treatment (64 vs 28%, p <0.05 and 63 vs 25%, p <0.05, respectively). Among those at high cardiovascular risk, both groups achieved low rates of LDL-C goal achievement (<100 mg/dL, 37 vs 44%, p >0.05). Among those at very high cardiovascular risk, patients with FH were less likely to achieve optimal LDL-C levels <70 mg/dL compared with the non-FH individuals (15 vs 25%, p <0.05).
Conclusions: FH is associated with a higher prevalence of CHD. Almost one third of FH patients do not receive intensive lipid-lowering treatment and a high proportion of them do not achieve LDL-C targets in clinical practice.

Key words: familial hypercholesterolemia; cardiovascular disease; coronary heart disease; low-density lipoprotein cholesterol; target attainment; statin

1. Introduction

Familial hypercholesterolemia (FH) is a common metabolic disease related with premature coronary heart disease (CHD).[1, 2] FH is caused mostly by mutations in genes encoding low-density lipoprotein (LDL) receptor (LDLR), apolipoprotein B (Apo-B), proprotein convertase subtilisin/kexin type 9 (PCSK9) and LDL receptor adaptor protein (LDLRAP1).[3-6] These mutations result in markedly reduced hepatic capacity to clear LDLs from the circulation, with consequent accumulation of LDL cholesterol (LDL-C).[2] If left untreated, males and females with heterozygous FH typically develop CHD before age 55 and 60, respectively, while homozygotes develop CHD very early in life and if untreated many will die before age of 20.[6] Unlike CHD, there is controversial data regarding FH and non-coronary cardiovascular disease (CVD).[7,8] To what extent FH remains underdiagnosed and undertreated in general clinical practice and the setting of a lipid clinic remains unknown.[3, 9, 10]

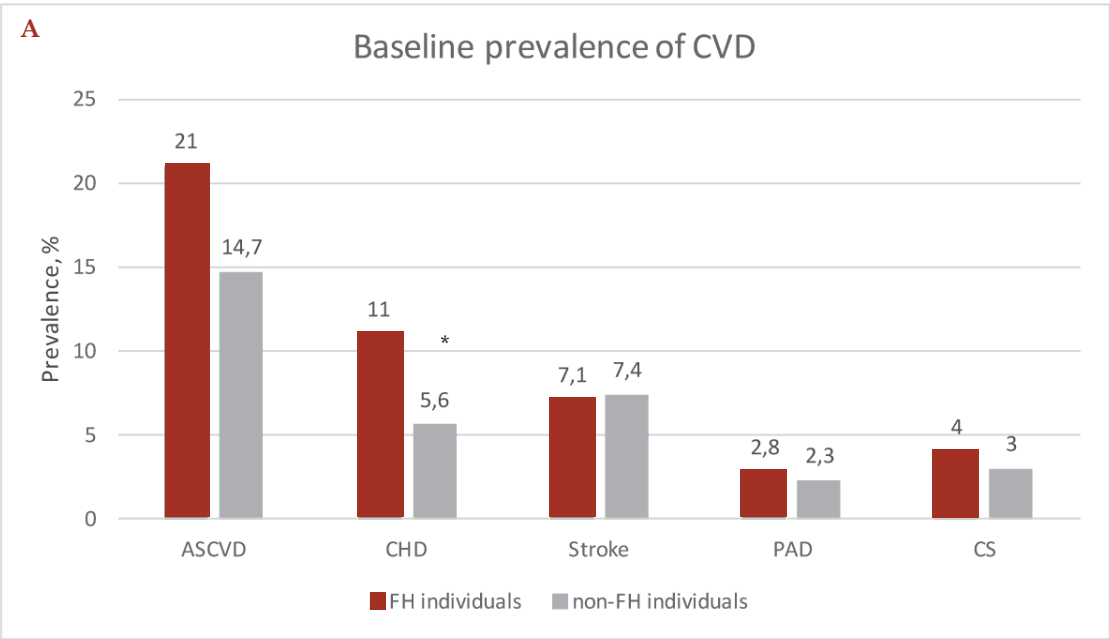
The aim of the present manuscript was to compare CHD/CVD prevalence and target attainment of lipid-lowering therapy between heterozygous FH patients and non-FH individuals in the setting of a lipid clinic.

2. Methods

This was a retrospective observational study as previously described.[11-14] Briefly, hyperlipidemic adults attending the Outpatient Lipid Clinic of the University Hospital of Ioannina in Greece and followed-up for at least 3 years were included. The study protocol was approved by the institutional Ethics Committee.

All subjects were of Greek origin (Caucasians). All participants had a complete assessment of cardiovascular and concomitant diseases. FH was defined according to the diagnostic criteria of Dutch Lipid Clinic Network.[6] Hyperlipidemic individuals fulfilling the criteria of 'definite' or 'probable' FH were considered as heterozygous FH patients in the present study. Demographic characteristics along with clinical data were recorded at baseline and at the most recent (final) visit. These included: a) anthropometric indices [body mass index (BMI), waist], b) age, follow-up duration, gender and smoking status, c) the presence of metabolic syndrome (MetS) and diabetes, and d) family history of diabetes and premature CVD. Laboratory data were also available, such as: a) blood pressure (BP) readings, b) lipidemic and metabolic profile, including all atherogenic indices, fasting glucose and insulin resistance defined by the homeostatic model assessment (HOMA-IR: glucose x insulin/405). CVD comprised of documented CHD, stroke, peripheral arterial disease (PAD) and carotid stenosis (CS) >50%.

Concomitant medications were also recorded with particular emphasis on the lipid-lowering



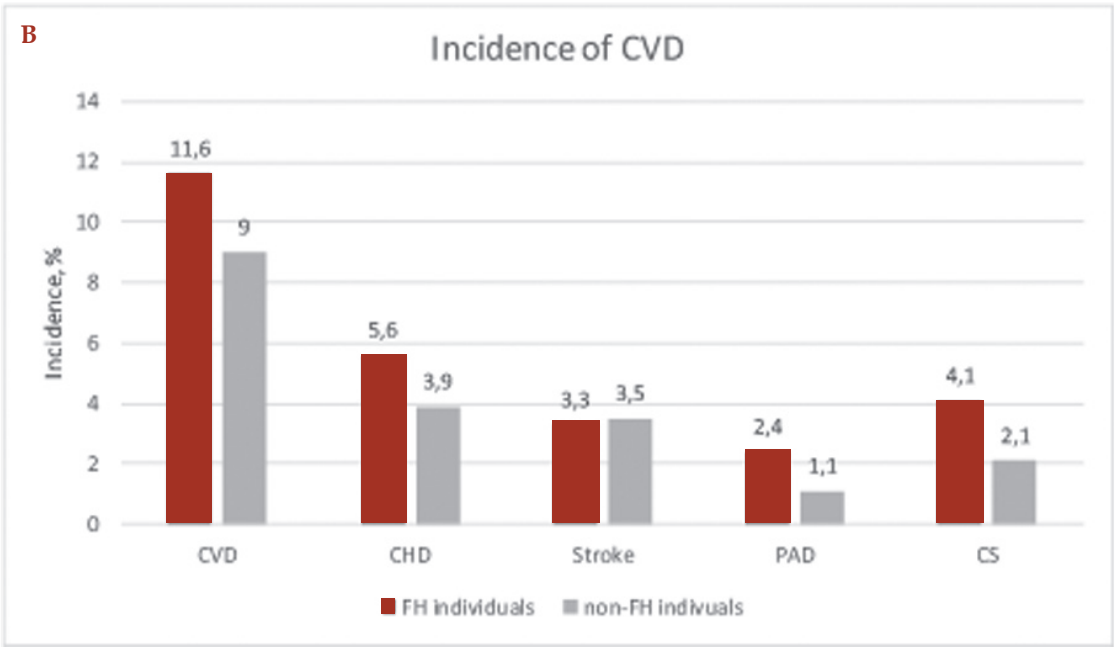


Figure 1.

A. Baseline prevalence of CVD

ANCOVA was performed across 2 groups after adjustment for gender, age, smoking, hypertension, diabetes and family history of premature cardiovascular disease.

* p <0.05 for the comparison with FH individuals

B. Incidence of CVD after a follow-up of 6 years

ANCOVA was performed across 2 groups after adjusting for gender, age, smoking, hypertension, diabetes, family history of premature cardiovascular disease, previous CVD, follow-up duration and untreated LDL-C levels at the most recent visit

* p >0.05 for all comparisons with FH individuals

Abbreviations: FH = familial hypercholesterolemia, CVD = cardiovascular disease, CHD = coronary heart disease, PAD = peripheral arterial disease, CS = carotid stenosis, LDL-C = low-density lipoprotein cholesterol

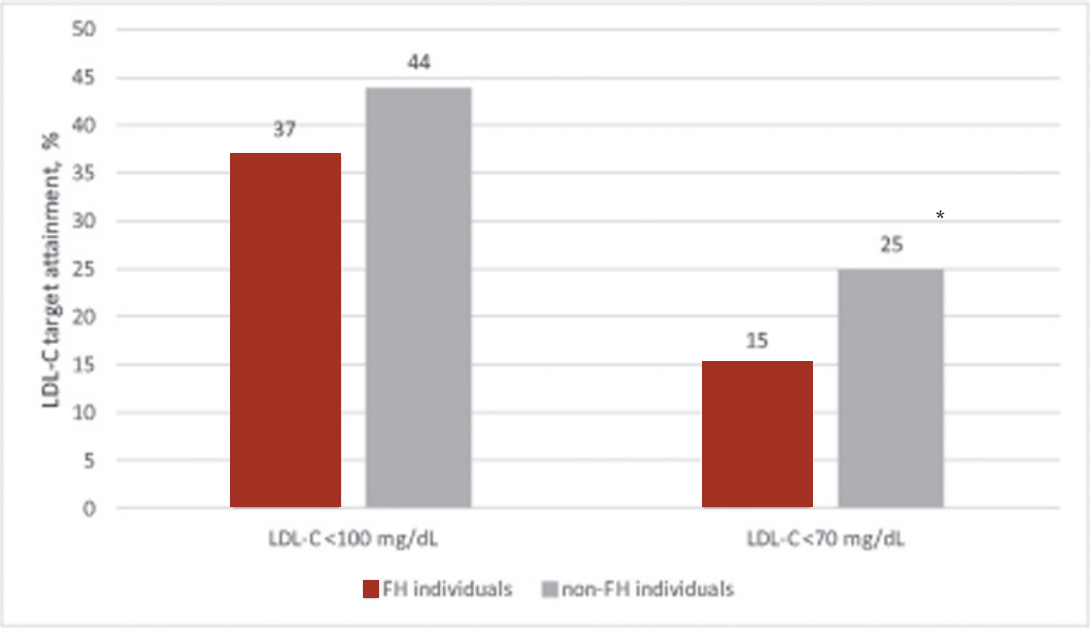


Figure 2. LDL-C target attainment ¥
Chi-square test was performed across 2 groups
¥ LDL-C targets were defined according to the Hellenic and the European Atherosclerosis Society guidelines[16, 17]
* p <0.05 for the comparison with FH individuals

Abbreviations: FH = familial hypercholesterolemia, LDL-C = low-density lipoprotein cholesterol, CV = cardiovascular.

therapy, including the name and dose of each statin and other lipid-lowering drugs (i.e. ezetimibe, colesevelam, fibrates and omega-3 fatty acids). In addition, the intensity of statin therapy was classified as 'high', 'moderate' and 'low' on the basis of the average expected LDL-C lowering of ≥50%, =30 to <50% and <30%, respectively.[15] Atorvastatin 80 mg was not available as a single pill in Greece and therefore was rarely prescribed. As a result, 'high-intensity' treatment included atorvastatin 40 mg/day or rosuvastatin 20-40 mg/day. 'Moderate-intensity' treatment included atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40 mg and fluvastatin 80 mg daily. Simvastatin 10 mg daily was considered as 'low-intensity' treatment. The targets of lipid-lowering therapy were defined according to the guidelines of the Hellenic Atherosclerosis Society (HAS) and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS).[16, 17]

In the present study we performed comparisons between patients diagnosed with FH and non-FH individuals regarding: a) their metabolic and lipidemic profile, b) the baseline prevalence of CVD and diabetes, c) the incidence of CVD, d) the intensity of lipid-lowering therapy and e) the LDL-C target attainment.

2.1 Statistical analysis

Continuous variables were tested for normality by the Kolmogorov-Smirnov test and logarithmic transformations were performed if necessary. Data are presented as mean ± standard deviation (SD) and median [interquartile range (IQR)] for normal and non-normal distributed data, respectively. Chi-square tests were performed for categorical values. The difference of variables between 2 groups was assessed by independent sample t-test. Analysis of covariance (ANCOVA) was performed to present the difference between rates of the variables of interest, after adjusting for confounding factors. The odds ratios (ORs) and 95% confidence intervals (CI) for the prevalence of the variables of interest were calculated on the basis of binary logistic regression,

Table 1. Baseline characteristics of study population

	FH individuals	non-FH individuals
N	120	880
Gender, (male), %	48	45
Age, years	43 (31-54)	57 (50-65) *
Follow-up duration, years	6 (5-11)	6 (4-10)
Smoking, %	15	17
Hypertension, %	13	68 *
Diabetes, %	0	12 *
Metabolic syndrome, %	10	48 *
Fasting Glucose, mg/dL	91 (83-97)	97 (89-108) *
Fasting insulin, μU/mL	6.2 (3.6-9.2)	7.7 (5.0-11.7)
HOMA-IR	1.26 (0.85-2.26)	1.88 (1.11-11.70) *
BMI, kg/m2	24.7 (22.9-26.9)	27.5 (25.4-30.1) *
Waist, cm	90 (85-100)	99 (92-106) *
SBP, mmHg	120 (110-135)	140 (130-155) *
DBP, mmHg	80 (70-87)	88 (80-95) *
TCHOL, mg/dL	308 (276-350)	247 (212-281) *
TG, mg/dL	105 (75-149)	135 (99-195) *
HDL-C, mg/dL	55 (47-64)	51 (44-61) *
LDL-C, mg/dL	227 (195-261)	164 (132-191) *
Apo-AI, mg/dL	143 (127-164)	146 (129-172)
Apo-B, mg/dL	144 (128-169)	120 (101-137) *
Apo-E, mg/dL	47 (40-56)	45 (36-56)
Lp(a), mg/dL	17.7 (10.0-38.3)	10.5 (4.9-22.2) *
Lipid-lowering treatment		
Statins, %	19	16
Ezetimibe, %	1	1
Fibrates, %	1	2
Omega-3 fatty acids, %	0	1
Colesevelam, %	1	1

Values are expressed as median (IQR), unless percentages are shown.
Independent sample t-test and chi-square test were performed across treatment groups (Parametric and non-parametric).
* p <0.05 for the comparison with FH individuals.

Abbreviations: FH = familial hypercholesterolemia, HOMA-IR = homeostatic model assessment of insulin resistance, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, TCHOL = total cholesterol, TG = triglycerides, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Apo = apolipoprotein, IQR = interquartile range

Table 2. **Lipid-lowering treatment at the most recent visit**

	FH individuals	non-FH individuals
Statins, %	98	90
Specific statin, % (median dose, mg)		
Atorvastatin	26 (40)	40 * (20)
Rosuvastatin	66 (40)	24 * (20)
Simvastatin	6 (40)	22 * (40)
Fluvastatin	0	4 * (80)
Intensity of statin treatment a, %		
High intensity statin	64	28 *
Moderate intensity statin	33	59 *
Low intensity statin	1	3
Ezetimibe	61	18 *
Coleveselam	8	0
Fibrates	1	6 *
Omega-3 fatty acids	2	5
Statin plus ezetimibe	63	25 *

[a] Intensity of statin treatment was classified according to the average expected LDL-C reduction as proposed by the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[15]
* p <0.05 for the comparison with FH individuals

Abbreviations: FH = Familial hypercholesterolemia

after adjustment for confounding factors. The hazard ratios (HRs) and their 95% CIs for the incidence of the variables of interest were calculated on the basis of Cox-regression analysis, after adjustment for confounding factors. Two-tailed significance was defined as p <0.05. Analyses were performed with the Statistical Package for Social Sciences (SPSS) v21.0 software (SPSS IBM Corporation, Armong, New York, USA).

3. Results

After screening a total of 1000 subjects, 120 fulfilled the criteria of 'probable' or 'definite' heterozygous FH according to the criteria of Dutch Lipid Clinic Network. Median age of participants were 56 years; 45% were males and their median follow-up duration was 6 years. Baseline and clinical characteristics of study participants are shown in **Table 1**. Briefly, FH individuals had higher levels of atherogenic lipoproteins [ie. such as LDL-C, Apo-B and lipoprotein (a) (Lp(a))] in comparison with the non-FH hyperlipidemic subjects **(Table 1)**. However, the former group exhibited better profile regarding the markers of MetS and glucose homeostasis and exhibited a lower prevalence of diabetes (**Table 1**).

3. 1Prevalence and incidence of CVD

As shown in **Figure 1A**, a non-significant trend towards a higher prevalence of overall CVD was noticed in FH individuals compared with those not fulfilling the criteria of FH at the baseline visit (OR 1.45, 95% CI: 0.68-3.05, p >0.05, after adjusting for

gender, age, smoking, hypertension, diabetes and family history of premature CVD). Importantly, FH was associated with a higher prevalence of CHD in contrast to non-FH individuals (adjusted OR 2.89, 95% CI: 1.12-7.45, p <0.05), while no differences were noticed regarding the prevalence of stroke, PAD and CS (**Figure 1A**).

After a median follow-up of 6 years, a non-significant trend towards a higher risk of incident overall CVD (HR 1.14, 95% CI: 0.51-2.54, p >0.05, after adjusting for gender, age, smoking, hypertension, diabetes, family history of premature cardiovascular disease, baseline CVD and untreated LDL-C levels at the most recent visit) and incident CHD (adjusted HR 1.59, 95% CI: 0.49-5.08, p >0.05) was noticed in FH individuals compared with the non-FH ones (**Figure 1B**). Similarly increased was the risk of incident PAD (adjusted HR 2.08, 95% CI: 0.48-8.97, p >0.05) and CS (adjusted HR 1.98, 95% CI: 0.26-15.03, p >0.05), whereas no noticeable differences were noticed regarding the risk of stroke **(Figure 1B)**.

3.2 Lipid-lowering therapy and LDL-C target attainment

A low proportion (15%) of both FH and non-FH groups were on statin therapy at the baseline visit (**Table 1**). On the other hand, 94% of study participants were receiving lipid-lowering treatment at the most recent visit. As shown in **Table 2**, FH individuals were more likely to receive a high intensity statin or a statin/ezetimibe combination treatment compared with non-FH ones (64 vs 28%, p <0.05 and 63 vs 25%, p <0.05, respectively).

Regarding the target attainment of lipid-lowering therapy, only 1 of 3 study participants had optimal LDL-C levels as proposed by HAS and ESC/EAS guidelines. As shown in **Figure 2**, among those being at high cardiovascular risk, both FH and non-FH individuals exhibited similar low rates of LDL-C target attainment. On the other hand, FH individuals at very high cardiovascular risk were less likely to achieve optimal LDL-C levels <70 mg/dL compared with non-FH subjects (**Figure 2**).

4. Discussion

The present study confirms previously published data demonstrating that untreated FH individuals develop premature CHD, whereas no difference was noticed regarding the prevalence of non-coronary CVD. A high proportion of these patients do not achieve LDL-C targets in clinical practice.

The prevalence of heterozygous FH has been estimated to 1/500, while recent data have shown that the prevalence of FH might be much higher (~1/200-300).[18-20] In Greece, it is estimated that 1 in 250 people have FH.[17] Our data showing a higher prevalence of FH (12%) are explained by the present study conducted in the setting of a lipid clinic.

FH is most often caused by mutations in the LDLR gene, resulting in the absence or dysfunction of LDLR on the surface of hepatocytes. Defects in the genes encoding Apo-B and PCSK9 account for ~5% and <1% of FH cases, respectively. However, 5-30% of cases of phenotypic FH could not be attributed to already known mutations.[3-5, 20] Because DNA testing was not performed in all FH individuals, no data on the FH mutations were available for the present study. Study participants fulfilling the criteria of FH had higher levels of atherogenic indices, such as LDL-C, Apo-B and Lp(a) compared with the non-FH subjects.[3, 21] Nevertheless, FH subjects exhibited a better profile regarding the markers of MetS and glucose homeostasis. These results along with the lower prevalence of diabetes noticed in FH subjects are in agreement with previous studies and could be attributed to the possible role of LDLR in the development of type 2 diabetes.[22, 23]

If left untreated, FH is undoubtedly related with a high risk of premature CHD, while controversial data exist regarding non-coronary CVD.[7, 8, 20] Indeed, our results demonstrate an approximately 3-fold higher prevalence of CHD in FH individuals compared with non-FH subjects, whereas no difference was noticed regarding the prevalence of stroke, PAD and CS. Despite their increased cardiovascular risk, only 1 of 10 FH individuals was on statin therapy at the time of referral. These rates are in agreement with

other studies underlying the undertreatment of such individuals in the general population.[19, 24]

A high proportion of FH individuals, but not all, was on statin treatment at the most recent visit. In addition, these patients were more likely to take a high-intensity statin or a combination treatment of a statin plus ezetimibe compared with the non-FH individuals. These results are in agreement with previous reports of World Health Organization (WHO) and Make Early Diagnosis to Prevent Early Death (MED PED) underlining a significant progress on the treatment of patients with FH during the last 20 years, due to the development of specialized lipid clinics and the use of new lipid-lowering drugs.[25, 26] As a result of those, a satisfactory increase in the percentage of these patients receiving lipid-lowering therapy has been observed.[25, 26] Nevertheless, a high proportion of those remain undertreated.[25, 26] Indeed, a low proportion of both groups in our study achieved optimal LDL-C levels and only 15% of FH individuals with established CVD had optimal LDL-C levels <70 mg/dL. Thus, it seems that the therapeutic gap in treating hypercholesterolemia is even greater in FH individuals with CHD.[27, 28] These results are in agreement with other studies conducted in lipid clinics showing that statin-treated FH individuals are undertreated and remain at high cardiovascular risk and mortality.[9, 10, 27-30] Indeed, in a previous study we showed that 40% of the individuals with LDL-C ≥190 mg/dL receiving high intensity statin monotherapy and 20% of those taking a high intensity statin plus ezetimibe do not achieve the anticipated LDL-C reduction ≥50%, as recently proposed by ESC/EAS guidelines.[13, 31] In this context, novel therapies, such as such as the anti-PCSK9 monoclonal antibodies should be considered in such individuals.[32]

5. Study limitations

Study limitations are the design of our study. This was a retrospective observational study with an extensive follow-up of 6 years in a real-world outpatient lipid clinic. Thus, our findings regarding the incidence of CVD should be interpreted in light of this limitation. Due to the adjustment for potential confounding factors, the trend towards a higher risk of incident CVD in the FH individuals compared with the non-FH subjects could be considered insignificant. Under these circumstances, our results confirm the fact that the cardiovascular risk of statin-treated FH individuals becomes equal to that of the general population. Otherwise, after taking into consideration the low-rates of LDL-C target attainment noticed in our FH study participants and their small sample size, along with the retrospective nature of our study and other potential confounding factors not included in the present analysis, this no-significant trend should be underlined. Nevertheless, our study representing a ''pragmatic study'' provides the real data of the everyday clinical practice and replicates previous findings regarding the undertreatment of patients with FH in Hellenic population.

6. Conclusions

Despite FH being related with increased risk of premature CHD, a high proportion of such individuals do not achieve optimal LDL-C levels. Because of undertreatment of FH, there is an urgent worldwide need for early and aggressive treatment of this high-risk and common condition.[10]

Conflict of interest: ME, EL and GL have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies. ME and EL are editorial members of Hellenic Journal of Atherosclerosis. FB has no conflict of interest to report.

Περίληψη

Η οικογενής υπερχοληστερολαιμία υποθεραπεύεται στην κλινική πράξη

Φ. Μπάρκας, Ε. Λυμπερόπουλος, Γ. Λιάμης, Μ. Ελισάφ

Ιστορικό: Η οικογενής υπερχοληστερολαιμία (FH) συσχετίζεται με πρώιμη στεφανιαία νόσο (ΣΝ), ενώ υπάρχουν αμφιλεγόμενα στοιχεία όσον αφορά τη συσχέτιση με τη μη στεφανιαία καρδιαγγειακή νόσο (ΚΑΝ). Παρ 'όλα αυτά, πρόσφατα στοιχεία έχουν επισημάνει ότι η FH υποδιαγιγνώσκεται στην κλινική πράξη.

Σκοπός: Η σύγκριση του επιπολασμού της ΚΑΝ και της επίτευξης των στόχων της υπολιπιδαιμικής αγωγής μεταξύ υπερλιπιδαιμικών ασθενών με ή χωρίς FH.

Μέθοδοι: Πρόκειται για μια αναδρομική μελέτη παρατήρησης (1999-2013) στην οποία συμμετείχαν 1000 ενήλικοι ασθενείς που ελάμβαναν υπολιπιδαιμική θεραπεία με διάρκεια παρακολούθησης ≥3 έτη. Για τη διάγνωση της FH χρησιμοποιήθηκαν τα Dutch Clinic Network κριτήρια. Ως υψηλής αποτελεσματικότητας στατίνες ορίστηκαν εκείνες που αναμένονται να μειώσουν τη χαμηλής πυκνότητας λιποπρωτεϊνών χοληστερόλη (LDL-C) ≥50%. Οι στόχοι όσον αφορά την LDL-C ορίστηκαν σύμφωνα με τις κατευθυντήριες οδηγίες της Ευρωπαϊκής και της Ελληνικής Εταιρείας Αθηροσκλήρωσης. Οι ακόλουθες συγκρίσεις έγιναν μεταξύ των ασθενών με ή χωρίς FH όσον αφορά: α) το βασικό επιπολασμό της ΚΑΝ (μετά από τη διόρθωση για το φύλο, την ηλικία, το κάπνισμα, την υπέρταση, το διαβήτη και το οικογενειακό ιστορικό πρώιμης ΚΑΝ), β) την επιθετικότητα της αγωγής με στατίνη και την επίτευξη των στόχων όσον αφορά την LDL-C στην πιο πρόσφατη επίσκεψη.

Αποτελέσματα: Από τους 1000 υπερλιπιδαιμικούς ασθενείς, ένα ποσοστό 12% είχε διαγνωστεί με ετερόζυγη FH. Οι ασθενείς με FH εμφάνισαν μεγαλύτερο επιπολασμό ΣΝ σε σύγκριση με τους ασθενείς χωρίς FH στην αρχική επίσκεψη (adjusted OR: 2,89, 95% CI: 1,12 - 7,45, p <0,05), ενώ δεν βρέθηκαν διαφορές όσον αφορά τον επιπολασμό της μη στεφανιαίας ΚΑΝ.

Μετά από μια μέση διάρκεια παρακολούθησης 6 ετών, μια μη στατιστικά σημαντική τάση υψηλότερου κινδύνου για την εμφάνιση ΚΑΝ παρατηρήθηκε στους ασθενείς με FH (HR 1,14, 95% CI: 0,51 - 2,54, p> 0,05) σε σύγκριση με εκείνους χωρίς FH. Κατά τη διάρκεια της παρακολούθησης υψηλότερα ποσοστά ασθενών με FH έπαιρναν στατίνη υψηλής αποτελεσματικότητας ή συνδυασμού υπολιπιδαιμικής αγωγής με στατίνη / εζετιμίμπη σε σύγκριση με τους υπόλοιπους ασθενείς χωρίς FH (64 έναντι 28%, p <0,05 και 63 έναντι 25%, p <0,05, αντίστοιχα). Μεταξύ των ασθενών με υψηλό καρδιαγγειακό κίνδυνο, και οι δύο ομάδες ασθενών εμφάνισαν χαμηλά ποσοστά επίτευξης των στόχων όσον αφορά την LDL-C (<100 mg / dL, 37 vs 44%, p> 0,05). Μεταξύ των ασθενών με πολύ υψηλό καρδιαγγειακό κίνδυνο, οι ασθενείς με FH ήταν λιγότερο πιθανό να επιτύχουν τα επιθυμητά επίπεδα LDL-C <70 mg / dl σε σύγκριση με τους ασθενείς χωρίς FH (15 έναντι 25%, p <0,05).

Συμπεράσματα: Η FH συσχετίζεται με υψηλότερο επιπολασμό ΣΝ. Σχεδόν το ένα τρίτο των ασθενών με FH δεν λαμβάνουν επιθετική υπολιπιδαιμική αγωγή και ένα υψηλό ποσοστό από αυτούς δεν επιτυγχάνουν τους στόχους όσον αφορά την LDL-C στην κλινική πράξη.

Λέξεις ευρετηρίου: οικογενής υπερχοληστερολαιμία, καρδιαγγειακή νόσος, στεφανιαία νόσος, χαμηλής πυκνότητας λιποπρωτεΐνών χοληστερόλη, επίτευξη στόχων, στατίνη

***Στοιχεία υπεύθυνου συγγραφέα: Λυμπερόπουλος Ευάγγελος**
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