Abstract and keywords

Background: Current treatment goals for familial hypercholesterolemia (FH) recommended by the European Atherosclerosis Society (EAS) are LDL-C ≤2.5 mmol/L (~100 mg/dL), or ≤1.8 mmol/L (~70 mg/dL) in very-high-risk subjects.

Objective: The objective of the present study was to investigate characteristics and treatment status in subjects with genetically verified FH followed at specialized lipid clinics in Norway.

Methods: Data from treatment registries of 714 adult (>18 years) subjects with FH.

Results: Fifty-seven percent were female. Mean age (SD) at last visit was 44 (16.3) years, and the subjects had been followed at a lipid clinic for 11.1 (7.9) years. Two-hundred-forty-five (34%) were classified as very-high-risk, and 44% of these had established coronary heart disease (CHD). Very-high-risk FH subjects more often received maximal statin dose (54 vs. 33%, P<0.001), ezetimibe (76 vs. 48%, P<0.001) or resins (23 vs. 9%, P<0.001), and achieved LDL-C was lower (3.2 vs. 3.5 mmol/L [124 vs. 135 mg/dL], P=0.003) than normal-risk FH. LDL-C treatment goal was achieved in 25% and 8% of subjects with normal-risk and very-high-risk FH, respectively. Lp(a) levels were available in 599 subjects, and they were divided into two groups; ≥90 mg/dL (n=96) and <90 mg/dL (n=503). Despite similar lipid levels, body mass index, smoking status, presence of diabetes, and blood pressure, prevalence of CHD was doubled in the high- compared to low-Lp(a) group (30 vs. 14%, P<0.001).

Conclusion: Too few FH subjects achieve their LDL-C treatment goal. New treatment modalities are needed. Independent of LDL-C and other risk factors, high Lp(a) seem to be an important additional risk factor in genetically verified FH.

Keywords: Familial hypercholesterolemia, LDL-cholesterol, treatment goal achievement, proprotein convertase subtilisin/kexin type 9 (PCSK9), lipoprotein (a)

Highlights

- 714 adult FH subjects followed at a lipid clinic for 11.1 (7.9) years
- LDL-C ≤2.5 mmol/L [~100 mg/dL] was achieved in 25% of FH subjects.
- LDL-C ≤1.8 mmol/L [~70 mg/dL]) was achieved in 8% of very-high-risk FH subjects.
- Prevalence of CHD was doubled in FH subjects with high Lp(a) levels.

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder resulting in reduced capacity to clear low-density lipoprotein (LDL) from the circulation. LDL-cholesterol (LDL-C) levels are elevated from birth resulting in substantially increased life-long cholesterol burden and increased risk of premature cardiovascular disease (CVD).(1, 2) We have recently shown that more than 90% of FH subjects in a Norwegian cohort experienced CVD during life, and that mean age of first myocardial infarction was 44 years.(3) Further, mean age for CVD death was 62 years which is ~15 and ~21 years earlier for men and women, respectively, than in the Norwegian general population.(4) Of note, the risk of death by CVD in FH subjects younger than 40 years of age was four–fold increased compared to the general population.(5) It is the total cholesterol burden during lifespan that defines the risk of FH.(2) Cholesterol lowering treatment to reduce (or possibly normalize) life-long cholesterol burden should ideally start in childhood.(6) Delayed diagnosis and late initiation of treatment requires that LDL-C is reduced to extra-low levels to compensate for the high cholesterol exposure earlier in life. Current treatment goals in FH primary prevention for adults recommended by the European Atherosclerosis Society (EAS) consensus statement is LDL-C ≤2.5 mmol/L (~100 mg/dL).(2) If treatment is initiated late (e.g. >40 years of age), the patient is considered to be at very high-risk due to the accumulated cholesterol burden, and an even lower treatment goal of ≤1.8 mmol/L (~70 mg/dL). is recommended, as for coexisting diabetes or in the presence of coronary heart disease (CHD).

Conventional lipid-lowering therapy (LLT) includes statins, ezetimibe and resins, but even when these drugs are combined in maximal doses, treatment goals may not be reached due to the high pretreatment LDL-C levels in FH subjects. Also, side effects or other adherence issues

are important factors in subjects not reaching treatment goal. Adherence to statin treatment is generally low,(7) and even in FH subjects up to one fourth is not taking any LLT although being prescribed.(8) Previous reports on treatment goal achievement in FH have shown on-treatment LDL-C levels above current recommendations.(9, 10) Add-on treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to be effective in reaching treatment goals,(11) and is well tolerated,(12) but the use of these drugs is currently limited due to high costs.

CVD risk in FH subjects is influenced by LDL-C levels and other classical risk factors like smoking and lipoprotein (a) [Lp(a)]. Lp(a) is an LDL-like particle to which apolipoprotein (a), a plasminogen-like kringle-structured glycoprotein, is bonded by a disulphide bridge.(13) Elevated levels of Lp(a) is a strong and independent risk factor for myocardial infarction (MI), stroke and aortic valve stenosis in the general population,(14-16), also including FH subjects.(17-19) It is, however, challenging to isolate the role of elevated Lp(a) in FH since Lp(a) has been suggested to contribute to the clinical FH diagnosis by adding to the LDL-C level in addition to being a possible cause of premature CVD.(20)

The objective of the present study was to investigate characteristics and treatment status in genetically verified FH subjects followed at specialized lipid clinics in Norway.

Methods

Data was collected from treatment-quality-registries of FH subjects at three regional specialized lipid clinics in Norway (Oslo University Hospital; Nordland Hospital Bodø; and Vestfold Medical Centre). Data were collected retrospectively to the registries from electronic medical

charts in 2014 - 2015. Only subjects with at least one previous visit to the clinics were included in the study in order to obtain both pretreatment and follow-up data. Collected data were; patient demographics, FH diagnosis and peripheral lipid deposits, presence of coronary heart disease (CHD), diabetes and hypertension, lipid-lowering therapy (LLT) and side effects, dietary information, and lipids (total cholesterol [TC], LDL-C, high-density lipoprotein cholesterol [HDL-C], triglycerides [TG] and Lp[a]). CHD information in the medical charts was physicians' description as either angina (verified by the findings of stenosis on angiography in all except one case) or MI, but without ICD-10 code or any other detailed specifications. For subjects with both angina and MI, CHD type would be registered only as MI as this was considered a more severe end point. Dietary data were collected by SmartDiet™, a validated questionnaire on diet and lifestyle.(21) Diet and lifestyle habits were categorized in three categories according to the SmartDiet™ scoring system; either as a "non-heart-healthy" diet (the most unhealthy category), a diet with room for improvement, or a "heart-healthy" diet (the most healthy category). For Lp(a), in the case of several measurements, only the highest measured values were recorded. We wanted to compare the FH subjects in the top percentile (e.g. 90^{th} percentile) of Lp(a) to the FH subjects in the lower percentiles with regard to presence of CVD. The Lp(a) concentrations in the present cohort were measured at different laboratories. In one of these laboratories the upper cut-off concentration for measurement was 900 mg/L, and Lp(a) values >900 mg/L from this laboratory was reported as 900 mg/L. It was therefore not possible to use a cut-off above 900 mg/L, and we therefore decided to use an Lp(a) concentration of 900 mg/L as the cut-off comparing the prescence of CVD. This corresponds to the 85^{th} percentile in this cohort. Samples below the detection limit (e.g. <6 mg/dL) were set to the detection limit (e.g. 6 mg/dL).

The treatment-quality-registries had been individually established and approved at each lipid clinic according to applicable regulations (by the Data Protection Official at Oslo University Hospital and Nordland Hospital Bodø, and by the Medical Center in Vestfold). Data-analysis was evaluated by the Regional Committee of Medical and Health Research Ethics, South-East region of Norway, as being "quality-assurance" and not requiring further approval from the research ethics committee. By recommendation from the Data Protection Official at Oslo University Hospital, the individual patient data were anonymized at each lipid clinic before analysis was performed.

Results are presented as mean (standard deviation [SD]) for continuous variables when normally distributed, and as median (range) when non-normally distributed. Categorical variables are presented as frequencies and percentages. Comparisons between two groups were performed using Student's t-test or Mann-Whitney U test for continuous variables, depending on the distribution, and chi-square test or Fisher's exact test for categorical variables depending on the expected cell frequencies. Statistical analyses were conducted in SPSS (version 21). All tests were two-sided. A 5% level of significance was used.

Results

Data from 714 adult (>18 years at last visit at lipid clinic) heterozygous FH subjects were available in the treatment-quality-registries and included in the data analysis.

Patient demographics, FH diagnosis and pretreatment lipid levels

Fifty-seven percent of the FH subjects were female. Mean age (SD) at diagnosis was 29 (15.6) years. The FH diagnosis was genetically verified in 94% of subjects, most often caused by mutations in the LDL-receptor gene (97%). Two-hundred-forty-five (34%) subjects were classified (according to the EAS consensus statement) as very-high-risk FH, and 44% of these had established CHD. The very-high-risk group was characterized by higher pretreatment TC, LDL-C and Lp(a) levels, later diagnosis, higher prevalence of males, smokers, hypertension, and higher body mass index (BMI) compared to the normal-risk FH subjects (table 1). There were no differences between the groups in pretreatment HDL-C or triglyceride (TG).

Follow-up, treatment data and on-treatment lipid levels

Mean age (SD) at last visit were 44 (16.3) years, and the subjects had been followed at a lipid clinic for 11.1 (7.9) years. Eighty-nine percent of subjects were treated with statin, and 58% received ezetimibe. Achieved LDL-cholesterol was mean (SD) 3.4 (1.3) mmol/L (131 mg/dL). Maximal statin dose was defined as treatment with rosuvastatin 40 mg or atorvastatin 80 mg. Compared to normal-risk FH subjects, the very-high-risk FH subjects more often received maximal statin dose (54 vs. 33%, P<0.001), ezetimibe (76 vs. 48%, P<0.001) or resins (23 vs. 9%, P<0.001), and obtained LDL-C was lower (3.2 vs. 3.5 mmol/L [124 vs. 135 mg/dL], P=0.003) (table 2). An LDL-C treatment goal of ≤2.5 mmol/L (~100 mg/dL) or ≤1.8 mmol/L (~70 mg/dL) was achieved in 25% and 8% of subjects in normal-risk and very-high-risk FH groups, respectively. Overall, up-titration of LLT was recommended for 46% of subjects at the last visit. In subjects, not up-titrated at the last visit, LDL-

C was 3.0 and 2.9 mmol/L (116 and 112mg/dL, ns.) in normal-risk and very-high-risk FH, respectively, and an LDL-C goal of ≤2.5 (~100 mg/dL) or ≤1.8 mmol/L (~70 mg/dL) was achieved by 41 and 13% of subjects, respectively.

Side effects

Overall, 36% of the subjects reported to have experienced side effects of LLT at any time during follow-up (table 2). However, side-effects were not reported as being the reason for not increasing LLT.

Dietary counselling

Overall, 87% of subjects had received dietary counselling. Dietary pattern was measured according to the SmartDiet™ scoring system with three categories. Among those with a diet score in the healthiest category at last visit, LDL-C levels was lower than in subjects with a score in the most unhealthy category (3.2 [1.2] vs. 4.4 [2.1] mmol/L [124 vs. 170 mg/dL], P<0.001). The number of subjects with a diet score in the healthiest diet category doubled during follow-up at the lipid clinics.

PCSK9-inhibitor treatment in a subgroup of subjects

Thirty-eight of the very-high-risk FH subjects (number limited due to reimbursement policies) not achieving LDL-C treatment goal ≤1.8 mmol/L on maximal tolerable dose of conventional LLT, were later initiated on PCSK9-inhibitor treatment. Except two subjects who reduced their statin

dose (one due to statin scepticism, and one due to misunderstanding), all subjects continued conventional LLT in unchanged doses in addition to the PCSK9-inhibitor treatment. One subject stopped the PCSK9-inhibitor due to an adverse event (myalgia without elevated creatinine kinase). After addition of PCSK9-inhibitor, LDL-C levels was reduced by 54% from mean (SD) 3.5 (1.1) [135 mg/dL] to 1.6 (1.2) mmol/L [62 mg/dL] (P<0.001). Individual LDL-C for the 38 subjects before and after addition of PCSK9-inhibitor treatment are shown in figure 1. After add-on PCSK9-inhibitor treatment, 26 (68%) of the subjects achieved LDL-C goal ≤1.8 mmol/L after and Lp(a) levels were reduced from median (range) 29.8 (2.5-318) to 18.4 (3.4-90) mg/dL (P<0.034).

Lp(a) and CHD

Subjects in which Lp(a) levels were available (n=599), were divided into two groups according to Lp(a) levels (table 3); a high-Lp(a) group defined as Lp(a) ≥90 mg/dL (n=96), and a low-Lp(a) group defined as Lp(a) <90 mg/dL (n=503). Lp(a) levels in the high- and low-Lp(a) groups, were median (range) 119.0 (90.0-318.0) and 19.5 (1.0-89.4) mg/dL, respectively. There were more males in the high-Lp(a) group compared to the low-Lp(a) group (55 vs. 43%, P<0.05) (not shown in table). Except for the gender difference, the high- and low-Lp(a) group were similar in terms of BMI, smoking status, presence of diabetes, blood pressure, age at FH diagnosis, lipid levels and years of follow-up at a lipid clinic. CHD was significantly more common among FH subjects in the high-Lp(a) group compared with the low-Lp(a) group (30 vs. 14%, P<0.001) (table 3). Both angina and MI, separately, were higher in the high-Lp(a) group compared with the low-Lp(a) group. In males, but not in females,

CHD was significantly more common in the high-Lp(a) group compared to the low-Lp(a) group (38 vs. 20%, P<0.01 and 21 vs. 10%, P=0.080) (not shown in table).

Discussion

Despite follow-up at specialist lipid clinics for 11.1 years and a high adherence to LLT only 25 and 8% of FH subjects achieved LDL-C treatment goals of ≤2.5 or 1.8 mmol/L, respectively, on conventional LLT. This low treatment goal achievement is in line with another recent registry study in subjects with FH.(22) The lack of treatment goal achievement could be due to insufficient effect of available medication, and/or failure of the doctor to prescribe available medication, and/or intolerance or other adherence issues in the patient. In addition to delays in diagnosis and initiation of treatment, the relatively high on-treatment LDL-C levels is likely contributing to the high morbidity and mortality still seen among FH subjects.(3-5)

Almost half of the subjects in the present study had their dose of conventional LLT up-titrated at the last visit at the lipid clinics. Some subjects having been followed for a shorter time might still have been in an up-titration phase of conventional LLT. However, a registered up-titration in LLT at last visit may more often only represent some kind of re-prescribing due to adherence, tolerance or efficacy issues, i.e. switching to another statin with slightly better lipid-lowering effect, or switching in an attempt of achieving better tolerance rather than a *de facto* increased treatment effect. Also, the fact that 89% were treated with a statin and 58% were treated with ezetimibe does not necessarily mean that 11 and 42% of subjects respectively, never were prescribed a statin or ezetimibe by the doctor, but rather suggest that adherence and/or

tolerance issues towards the treatment plays an important role. Due to the long duration of follow-up, and reimbursement of most treatment costs in Norway, we believe that the achieved LDL-C level reported here, probably represent the maximal achievable effect of conventional LLT in FH subjects during continuous follow-up at a lipid specialist clinic in a real-life setting. This is also supported by the fact that treatment goal attainment was also low in subjects with documented stable treatment (those not up-titrating LLT at last visit); 42 and 13% in normal-risk and very high-risk FH subjects, respectively. After adding PCSK9 inhibitor 68% reached the treatment goal underlining the need for this additional therapy in FH patients.

Although 36% of the subjects had reported presence of side-effects of treatment during follow-up, side-effects was not indicated as main reason for not up-titrating LLT at follow-up. This probably represents a limitation in the registration of side-effects and the treatment-consequences for the patient in the registry design. In general, side effects of statins have been the subject of much attention in mass media and are suggested to be a major cause of low adherence. Reported prevalence of side effects caused by statins range from equal to placebo in randomized clinical trials,(23) to 18% in clinical practice (not placebo controlled).(24) Sorting out true side effects from common complaints occurring on statin treatment, represent a major challenge.(25) In a recent blinded placebo controlled study, only 209 of 472 (44%) subjects were able to correctly identify atorvastatin from placebo.(26) This may partly explain the large gap between side effects reported in unblinded uncontrolled clinical practice and the difference between side effects in placebo and statin group in randomized controlled studies.

A pathogenic FH mutation was confirmed in 94% of the subjects in our study. Traditionally FH have been diagnosed clinically and based on different scoring systems. The genetic basis for FH is well etablished and genetic testing is widely available. The value of genetic testing in

individual risk-prediction has recently been demonstrated by Khera et al.(1), showing that the odds ratio for CHD was up to 3.4 times higher in subjects with an FH-mutation, compared to subjects without a mutation, with similar lipid levels. Still clinical diagnosis (based on various scoring systems) are much used due to cost of genetic testing, and/or in populations in which genetic diagnosis is not available or not possible to obtain.(27)

In the Copenhagen City Heart study, it was recently shown that in subjects with a clinical diagnosis of possible, probable or definite FH according to Dutch Lipid Clinic Network (DLCN) score, subjects with Lp(a) >50 mg/dL had a hazard ratio for MI of 5.3 compared to subjects with Lp(a) <50 mg/dL. High Lp(a) levels have been suggested to promote a clinical FH diagnosis by DLCN score by adding to the LDL-C level, in addition to being a possible cause of premature CVD in the patient or family.(20) In genetically verified FH, however, the additive effect of Lp(a) on LDL-C do not influence the diagnosis. In the present study we show that genetically verified FH subjects with high Lp(a) levels, but with otherwise similar risk profile, have twice the prevalence (30 vs. 14%) of CHD. This is in line with previous reports indicating that Lp(a) is an important and independent risk factor for CHD risk in FH.(19)

A major strength of the present study is the well-characterized population with 94% of the subjects having genetically verified FH and the long-term follow-up of all the subjects in specialized lipid clinics. A major limitation of the study is the retrospective collection of data from the electronic medical charts, with possible incomplete information and lack of complex nuances. Also the fact that Lp(a) levels were collected and measured at different laboratories must be pointed out as a limitation of the study.

In conclusion, too few FH subjects, especially those with very-high-risk, achieve LDL-C treatment goals, despite being treated and followed-up in specialized lipid clinics for several years. Despite similar lipid levels and other risk factors, subjects with high levels of Lp(a) had increased prevalence of CHD. New treatment modalities including PCSK9-inhibitors are needed to improve treatment goal attainment in this patient group.

Author Contributions

M.P.B. and K.B.H. designed the study, acquired data, performed the statistical analyses, and drafted the manuscript. A.G., A.H.and D.J. participated in the design of the study, acquired data, and made critical revision of the manuscript for key intellectual content. G.L., K.E.A., L.M., K.R., C.W. made critical revision of the manuscript for key intellectual content. All authors have approved the final article.

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Figure legends

Figure 1. LDL-C before and after add-on therapy with PCSK9-inhibitor in 38 individual very-high-risk FH subjects**.**

Table 1. Patient demographics, FH diagnosis, and pretreatment lipid levels.

Characteristics	n	Normal-risk FH	n	Very-high-risk FH	*P*
Total number of patients, n (%)	469		245		
Male		187 (39.9)		123 (50.2)	.010
EAS risk classification, n (%)	469		245		
Diabetes		0		51 (20.8)	<.001
CHD		0		108 (44.1)	<.001
Treatment start >40 y		0		170 (69.4)	<.001
Smoking status, n (%)	464		245		<.001
Never		339 (73.1)		134 (54.7)	
Former		82 (17.7)		89 (36.3)	
Current		43 (9.3)		22 (9.0)	
BMI, kg/m^2, mean (SD)	384	25.5 (4.5)	200	27.3 (4.5)	.017
Hypertension, n (%)	469	26 (5.5)	245	107 (43.7)	<.001
Age at FH diagnosis, y, mean (SD)	382	21.2 (11.0)	210	44.0 (11.6)	<.001
Genetic FH diagnosis, n (%)	469	437 (93.2)	245	233 (95.1)	
Mutation gene, n (%)	437		233		
LDLR		426 (97.5)		220 (94.4)	
APOB		8 (1.8)		10 (4.3)	
PCSK9		3 (0.7)		3 (1.3)	
Pretreatment lipids, mean (SD)					
TC, mmol/L	392	8.6 (1.9)	153	10.0 (2.3)	<.001
LDL-C, mmol/L	294	6.5 (1.7)	98	7.1 (2.2)	.004
HDL-C, mmol/L	341	1.3 (0.3)	116	1.3 (0.4)	
TG, mmol/L	322	1.1 (0.7)	111	1.5 (1.2)	
Lp(a), mg/dL	376	24.2 (1.0-275.0)	231	29.8 (1.9-318.0)	.003
Peripheral lipid deposits, n (%)					
Xanthomas[a]	469	188 (40.1)	245	166 (67.8)	<.001

Xanthelasma	469	30 (6.4)	245	28 (11.4)	.028
Arcus cornea	469	50 (10.7)	245	94 (38.4)	<.001

FH; familial hypercholesterolemia, EAS; European Atherosclerosis Society, CHD; coronary heart disease, y; years, BMI; body mass index, SD; standard deviation, *LDLR*; LDL-receptor gene, *APOB*; apolipoportein B gene, *PCSK9*; proprotein convertase subtilisin/kexin type 9 gene, TC; total cholesterol, LDL-C; LDL-cholesterol, HDL-C; HDL-cholesterol, TG; triglycerides, Lp(a); lipoprotein (a), P; P-value.

[a]Including thickened or rough achilles tendon.

Table 2. Follow-up, treatment data, and on-treatment lipid levels.

Characteristics	n	Normal-risk FH	n	Very-high-risk FH	*P*
Follow-up at a lipid clinic, y, mean (SD)					
Age at first visit	468	25.1 (14.3)	245	49.2 (11.7)	<.001
Age at last visit	469	36.8 (13.3)	245	58.8 (10.8)	<.001
Years of follow-up	464	11.8 (8.0)	245	9.7 (7.6)	.001
Time to next visit planned	458	1.3 (0.6)	229	1.1 (0.6)	.007
Treatment at last visit, n (%)	469		245		
Any statin dose		405 (86.4)		230 (93.9)	.004
Maximal statin dose[a]		155 (33.0)		133 (54.3)	<.001
Ezetimibe		225(48.0)		186 (75.9)	<.001
Resins		42 (9.0)		57 (23.3)	<.001
Years of statin treatment, mean (SD)	271	11.9 (8.1)	146	16.1 (8.4)	<.001
Age at statin start, y, mean (SD)	271	24.9 (8.7)	146	42.9 (9.7)	<.001
Up-titration of LLT at last visit	469	233 (49.7)	245	93 (38.0)	
No up-titration of LLT at last visit	469	236 (50.3)		152 (62.0)	<.001
Reasons for no up-titration of LLT, n (%)	236		152		
Close to target		88 (37.3)		31 (20.4)	
Receiving maximal LLT[b]		88 (37.3)		105 (69.1)	
Lifestyle advice		34 (14.4)		9 (5.9)	
Other		26 (1.0)		7(4.6)	

Side effects on LLT[c], n (%)		136 (29.0)	245	119 (48.6)	<.001
LDL-C at last visit, mmol/L, mean (SD)					
All	465	3.5 (1.3)	242	3.2 (1.3)	.003
Up-titration of LLT at last visit	233	4.0 (1.4)	92	3.7 (1.5)	
No up-titration of LLT at last visit	239	3.0 (1.1)	150	2.9 (1.2)	
LDL-C treatment goal		≤2.5 mmol/L		≤1.8 mmol/L	
Reaching treatment goal, n (%)					
All	465	118 (25)	242	19 (7.8)	
Up-titration of LLT at last visit	233	19 (8.2)	92	0	
No up-titration of LLT at last visit	239	99 (41.4)	150	19 (12.7)	
Close to treatment goal[d], n (%)					
All	465	201 (43.2)	242	41 (16.9)	
Up-titration of LLT at last visit	233	50 (21.5)	92	5 (5.4)	
No up-titration of LLT at last visit	239	151 (63.2)	150	36 (24.0)	

FH, familial hypercholesterolemia; SD, standard deviation; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; TG, triglycerides; LLT, lipid-lowering therapy; P, P-value.

[a]Atorvastatin 80 mg or rosuvastatin 40 mg.
[b]Maximal tolerable statin dose and ezetimibe.
[c]Any side effect on any LLT, either present or previous.
[d]Allowing for up to 15% measuring variation in cholesterol this was defined as LDL-C ≤2.9 mmol/L in normal-risk and ≤2.1 mmol/L in very-high-risk FH.

Table 3. Lp(a) and CHD

	n	Lp(a) <90 mg/dL	n	Lp(a) ≥90 mg/dL	*P*
Lp(a), mg/dL, median (range)	503	19.5 (1.0-89.4)	96	119.0 (90.0-318.0)	
CHD, n (%)	503	72 (14.3)	96	29 (30.2)	<.001
Angina		39 (7.8)		16 (16.7)	<.05
MI		33 (6.6)		13 (13.5)	<.05
Males with CHD, n (%)	214	42 (19.6)	53	20 (37.7)	<.01
Females with CHD, n (%)	289	30 (10.4)	42	9 (20.9)	

CHD, coronary heart disease; MI, myocardial infarction; Lp(a), lipoprotein (a); P, P-value.