Current Atherosclerosis Reports
https://doi.org/10.1007/s11883-022-01019-5

CARDIOMETABOLIC DISEASE AND TREATMENT (R. SANTOS, SECTION EDITOR)

Familial Hypercholesterolemia and Lipoprotein(a): Two Partners in Crime?

Rodrigo Alonso[1,2] · Rosa Argüeso[3] · Pilar Álvarez-Baños[4] · Ovidio Muñiz-Grijalvo[5] · Jose Luis Diaz-Diaz[6] · Pedro Mata[2]

Accepted: 9 March 2022

Abstract

Purpose of Review Familial hypercholesterolemia is a high cardiovascular risk disorder. We will review the role of lipoprotein(a) in cardiovascular risk and in aortic valve stenosis in familial hypercholesterolemia, as well as its association with their phenotype, and strategies to identify this high-risk population.

Recent Findings Patients with familial hypercholesterolemia have higher lipoprotein(a) levels mainly due to an increased frequency of LPA variants, and the cardiovascular risk is increased twofolds when both conditions coexist. Also, an increased risk for aortic valve stenosis and valve replacement has been observed with high lipoprotein(a) levels. Assessment of lipoprotein(a) during the cascade screening for familial hypercholesterolemia is a good opportunity to identify this high-risk population.

Summary High cardiovascular risk in familial hypercholesterolemia is increased even more when lipoprotein(a) is also elevated. Measurement of lipoprotein(a) in these patients is crucial to identify those subjects who need to intensify LDL-cholesterol reduction pending availability of lipoprotein(a)-specific treatments.

Keywords Familial hypercholesterolemia · Lipoprotein(a) · Atherosclerotic cardiovascular risk · Aortic valve stenosis · Cascade screening

Introduction

Familial hypercholesterolemia (FH) and high lipoprotein(a) [Lp(a)] are two prevalent genetic disorders associated with premature atherosclerotic cardiovascular disease (ASCVD). Individuals with FH have high low-density lipoprotein cholesterol (LDL-C) levels since birth, usually over 190 mg/dL, leading to a high ASCVD risk at early ages. The disorder is caused by mutations in genes related to the clearance of LDL particles, principally *LDLR* gene, and less frequently by mutations in apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes. It is inherited as an autosomal dominant pattern; therefore, the chance of transmitting to children is 50% [1•]. The prevalence of the heterozygous FH is approximately 1 case in 250 individuals of the general population. On the other hand, homozygous

✉ Rodrigo Alonso
rodrigoalonsok@gmail.com

Rosa Argüeso
rosa.argueso.armesto@sergas.es

Pilar Álvarez-Baños
mpalvarezb@gmail.com

Ovidio Muñiz-Grijalvo
omunizg@gmail.com

Jose Luis Diaz-Diaz
jose.luis.diaz.diaz@sergas.es

Pedro Mata
pmata@colesterolfamiliar.org

1 Center for Advanced Metabolic Medicine and Nutrition, Av. Las Condes 9460, of 501. , Santiago, Chile

2 Fundación Hipercolesterolemia Familiar, Madrid, Spain

3 Department of Endocrinology, Hospital Universitario Lucus Augusti, Lugo, Spain

4 Department of Endocrinology, Hospital Universitario de Burgos, Burgos, Spain

5 Internal Medicine Department, Hospital Virgen del Rocío, Sevilla, Spain

6 Internal Medicine Department, Hospital Abente Y Lago, A Coruña, Spain

Published online: 07 April 2022

FH (HoFH) is a rare condition affecting approximately 1 in 300,000 individuals in the population. In this very severe condition, ASCVD and the compromise of the aortic valve can be evident during the first decade of life. A high variability in FH phenotype, especially in LDL-C levels, age of onset, and type of cardiovascular disease, has been described in different series of FH patients explained in part by the type of mutation and the presence of other cardiovascular risk factors [2–5].

In the last decades, high Lp(a) concentrations, found in 10 to 20% of the general population, have been long linked to an increased risk of ASCVD and calcific aortic valve disease in the general population and in FH patients, and also, it has been shown that it can influence in the FH phenotypes in some patients [6–8, 9••, 10]. Although FH and elevated Lp(a) are both inherited disorders associated with an increased risk of ASCVD, they have distinct genetic bases.

Patients with FH are considered to have high or very high CV risk because of their high LDL-C levels, and depending on the presence of another CV risk factor or the occurrence of ASCVD (11). In this sense, a patient with FH and high Lp(a) is a special and unique situation in which two genetic risk factors, LDL-C and Lp(a), are independently associated with a high lifetime ASCVD burden and premature coronary artery disease. Reducing LDL-C in FH patients with high Lp(a) does not reduce the risk associated to Lp(a) [7].

The objective of this review is to analyze the relationship between FH and Lp(a) levels, the contribution of Lp(a) in ASCVD risk in this population, and the association of Lp(a) with FH phenotype.

Cardiovascular Risk in Familial Hypercholesterolemia

In earlier studies in the pre-statin era, the cumulative risk of fatal and non-fatal coronary events by age 60 years was 50% in men and 30% in women, if they were not treated [12]. Further and later studies from different populations confirmed the high risk of fatal and non-fatal premature ASCVD in FH [13, 14]. In the SAFEHEART study, the prevalence of ASCVD was threefold higher in molecularly confirmed FH patients compared with their unaffected relatives, showing significant differences in the coronary (11.8% in FH vs. 3.6% in non-FH) and peripheral arteries (3.6% in FH vs. 0.2% in non-FH) clinical manifestations [5]. Other studies, with different inclusion criteria and methodology, like the CASCADE-FH registry in the USA or the analysis of the Copenhagen General Population Study, showed a higher prevalence and risk of CAD [4, 15]. Khera et al. showed that for any observed LDL-C level, individuals with molecularly defined FH have four times increased risk for CAD compared with those individuals without mutation [16]. The reduction in CV risk observed in the follow-up of patients recruited in the Simon Broome registry in the UK and the Dutch cohort can be explained in part by the use of more effective drugs such as statins [17, 18].

Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein-like particle containing ApoB that is covalently bound with a highly polymorphic glycoprotein, apolipoprotein(a) [Apo(a)]. Plasma levels of Lp(a) are principally determined by the *LPA* gene that encodes apo(a) and affects its production [6]. This apolipoprotein consists of two kringle domains, IV (KIV) with 10 subtypes and V (KV), and an inactive protease domain. The kringle IV type 2 (KIV2) is the unique that expands from 1 to more than 40 copies, and the number of these repeats determines the isoform size of apolipoprotein(a) and plasma levels of Lp(a) in an inverse relationship manner. The number of kringle 4 repeats in the apo(a) gene accounted for almost 70 to 90% of the variation in Lp(a) levels [19]. Lp(a) levels are highly skewed toward low levels, with a high inter-individual and ethnic, ranging from < 0.1 mg/dL to more than 200 mg/dL [6]. No consensus has been reached about the threshold value to define elevated levels of Lp(a). Some guidelines consider Lp(a) > 30 mg/dL as a risk factor, a threshold where the risk started to rise [20]. An alternative threshold value of 50 mg/dL, corresponding to the 80 percentile of the Danish population was proposed by the European Atherosclerosis Society as an optimal value, meaning that there are 20% of the general population with Lp(a) levels over 50 mg/dL (125 nmol/L) [6].

Epidemiological and genetic studies have shown that high plasma Lp(a) levels increase the risk of myocardial infarction, stroke, peripheral arterial disease, and calcified aortic valve disease (CAVD) [6]. Many mechanisms by which Lp(a) may increase the risk of atherosclerosis, thrombosis, and aortic valve calcification have been described. The pro-atherogenic effect is similar to that described to LDL-C resulting in cholesterol deposition in the intima, endothelial dysfunction, and promotion of an inflammatory response. The prothrombotic effects are related to the structural homology of apo(a) with plasminogen and plasmin. For CVAD, the proposed and identified mechanisms include the deposition of oxidized phospholipids transported by Lp(a) and delivery of autotaxin to aortic valve tissue that can promote inflammation and calcification [21].

Lipoprotein(a) Levels in Familial Hypercholesterolemia

Patients with FH have shown to have elevated plasma levels of Lp(a); however, the mechanisms involved and the role of LDL-R in the clearance of Lp(a) are still a matter of debate and controversy [7, 22, 23].

Earlier studies in patients with a clinical diagnosis of FH showed that patients with FH had threefold higher Lp(a) levels compared with a random general population and that this difference was not related to apo(a) phenotype frequencies, suggesting a possible role of LDLR in the catabolism of Lp(a) [22]. Also, Kraft et al. reported that homozygous FH patients had twofold higher Lp(a) levels than heterozygous FH, and the latter had also significantly higher Lp(a) levels compared with non-FH subjects [23]. This increase in Lp(a) levels was not explained by differences in apo(a) allele frequencies, excluding the effect of different apo(a) isoforms; moreover, the results showed a significant gene-dosage effect. This study pointed to a possible role of LDL-R in the clearance of Lp(a) from the circulation [23]. In a cross-sectional analysis of the SAFEHEART study including 1960 FH patients, and 957 unaffected relatives, median Lp(a) levels and percentage of cases with Lp(a) > 50 mg/dL was higher in FH patients, compared with their unaffected relatives (23.6 mg/dL vs. 21.9 mg/dL, and 29.3% vs. 22.2%, $p < 0.0001$, respectively). In addition, a nonsignificant trend toward higher Lp(a) levels in patients carrying null mutations compared with those carrying defective mutations was observed [7]. Later studies have shown that patients with a clinical diagnosis of FH have greater Lp(a) levels compared with the general population, as well as compared with non-FH hypercholesterolemic subjects; however, no differences in Lp(a) levels were observed among patients with or without a pathogenic variant in LDLR or other related genes [24–26].

Elevated Lipoprotein(a) and Clinical Diagnosis of Familial Hypercholesterolemia

Lipoprotein(a) contains approximately 30 to 45% cholesterol in each molecule, and in individuals with Lp(a) > 50 mg/dL, the Friedewald formula used to estimate LDL-C levels can overestimate levels by 20 to 40% in those with very high Lp(a) levels [27, 28]. This is important in FH since patients are usually diagnosed based on LDL-C levels above a threshold. Therefore, high Lp(a) levels can contribute not only to the high risk in FH, but also be the cause of the FH phenotype. Langsted et al. determined that almost 25% of individuals registered in the Copenhagen General Population Study (CGPS) with a clinical diagnosis of FH using different modified clinical criteria was due to high Lp(a) levels. Besides, after adjusting LDL-C for Lp(a) cholesterol content (30 to 45%), no differences in Lp(a) concentration were observed between individuals with or without the clinical diagnosis, and also in the few cases in whom a causative mutation was found in LDLR and/or APOB genes [10].

Recently, Trinder et al. reported higher Lp(a) levels in clinically diagnosed FH patients from the British Columbia Familial Hypercholesterolemia cohort compared to the general population and to patients with non-FH dyslipidemia [25]. In addition, no differences were observed in Lp(a) levels between individuals carrying a pathogenic variant in *LDLR* or *APOB* genes and those non-carriers. In this cohort, the elevated levels of Lp(a) were mostly explained by an increased frequency of the rs10455872-G LPS risk allele. As in the Langsted study, when LDL-C levels were adjusted for Lp(a) cholesterol content, the likelihood of a clinical diagnosis of FH was reduced by 16% [25].

Lipoprotein(a) and Atherosclerosis Cardiovascular Disease in Familial Hypercholesterolemia

The consequence of lifelong exposure to high LDL-C levels in FH is the early development of ASCVD that is enhanced with the concomitant high Lp(a). It is of importance that patients with FH have significantly higher Lp(a) levels especially those with ASCVD, and also higher levels of Lp(a) are more prevalent in FH than in the general population or their unaffected relatives (Table 1) [7, 10, 26, 29]. In a large retrospective multi-center study in the Netherlands, Jansen et al. analyzed 2400 individuals with strict clinical diagnosis or genetic diagnosis (50%) and found that Lp(a) > 30 mg/dL was an independent predictor of cardiovascular disease [29]. In addition, high Lp(a) worsened the prognosis from age 30 years. In a cross-sectional study in Norway, Nenseter et al. classified 112 patients with a genetic diagnosis of FH, in susceptible or resistant to coronary heart disease (CHD) according to the age of onset of CHD. They found that Lp(a) levels were significantly higher in the CHD-susceptible group (median values: 67.1 mg/dL vs. 24.4 mg/dL, $p < 0.001$, respectively) that was evident in females. In the CHD-susceptible women group, 42% had Lp(a) levels > 100 mg/dL vs. 0% in the CHD-resistant woman group that had mostly levels < 30 mg/dL [30].

Later, our group with data of the SAFEHEART study showed that Lp(a) levels and percent of individuals with Lp(a) levels > 50 mg/dL were significantly higher in FH patients with ASCVD than patients without ASCVD (43.4 mg/dL vs. 21.3 mg/dL, and 46.2% vs.26.9%, $p < 0.00001$, respectively). In the multivariable analysis, Lp(a) was an independent predictor of CVD and although this effect was independent of the type of mutation, those patients with severe mutations and high Lp(a) have the highest CVD risk [7].

In the CGPS study, a higher cumulative incidence of myocardial infarction was observed in those patients with a clinical diagnosis of FH and Lp(a) > 50 mg/dL or KIV-2 repeat numbers above 20% and was similar for all clinical criteria used (10). Finally, a recent meta-analysis including

Table 1 Selected studies showing high Lp(a) levels in familial hypercholesterolemia and its association with cardiovascular risk in this population

Author (reference)	Size (*n*)	Type of study	Lp(a) levels mg/dL		*p*	Outcome	CV risk, *OR*/*RR*, (95% *CI*)
			FH	Non-FH			
Jansen AC, 2004 (29)	2400, clinical Dx, 50% genetic	Retrospective	23.0	15.0	< 0.001	Total CVD (including CV mortality)	Lp(a) > 30 mg/dL *RR*, 1.50 (1.20–1.79, $p = 0.0001$)
Nenseter M, 2011 (30)	112, genetic Dx	Cross-sectional	67.1 mg/dL in susceptible CHD FH vs. 24.4 mg/dL in resistant CHD FH		0.0001		- -
Alonso R, 2014 (7)	2917 (1960 FH) Genetic Dx	Cross-sectional	23.6	21.0	< 0.0001	Non-fatal CVD	*OR*, 1.007 (1.004–1.011, $p < 0.0001$)
Langested A, 2016 (10)	46,200 clinical Dx (DLCN, MEDPEPD, Simon Broom) 37 definite 147 probable 3082 possible 42,934 unlikely	Prospective cohort study	35.0 21.0[A]	23.0 24.0[A]	0.0001 0.46	Myocardial infarction	*HR* 5.3 (3.6–7.6) in FH and Lp(a) > 50 mg/dL vs. HR 3.2 (2.5–4.1) in FH and Lp(a) ≤ 50 mg/dL
Perez de Isla L, 2017 (32)	2404 FH (genetic Dx)	Prospective	38.2	-		Fatal and non-fatal CVD	Lp(a) > 50 mg/dL *HR* 1.52 (1.05–2.21, $p = 0.028$)
Cao YX et al. 2019 (50)	393 patients Clinical Dx, DLCN score > 6	Prospective	33.5	N.A	-	CVD: fatal and non-fatal MI or stroke, coronary revascularization, cardiac death	*HR* 2.03 (1.28–3.21, $p = 0.002$) with plasma Lp(a) per log unit increase *HR* 6.96 (2.24–9.32, $p = 0.001$) upper vs. lower Lp(a) tertiles
Ellis K, 2019 (26)	3682 (2699 FH, genetic Dx; 983 non-FH relatives)	Prospective	84.0[B] 11.6[C]	77.0[D] 11.2[E]	< 0.001	Non-fatal CVD	Neither, reference *HR* 4.40 (1.92–10.07) FH + high Lp(a) ($p < 0.001$) *HR* 2.47 (1.06–5.74) FH ($p = 0.036$) *HR* 3.17 (1.16–8.64) high Lp(a) ($p = 0.024$)
Trinder M, 2020 (25)	391 from BCFH cohort Clinical diagnosis (DLCN) 221 with positive genetic testing. From 37,486 participants in UK Biobank	Prospective	28.7 10.7	13.0 8.7	0.0008 0.24	-	-

FH, familial hypercholesterolemia; *DLCN*, Dutch lipid clinical score; *MEDPED*, make early diagnosis to prevent early death criteria; *BCFH*, British Columbia Familial Hypercholesterolemia cohort

[A]Adjusted LDL-cholesterol for Lp(a) cholesterol content; median Lp(a) levels in relatives with FH and Lp(a) > 50 mg/dL[B]; relatives with FH alone[C]; in non-FH relatives with high Lp(a)[D], and neither FH and high Lp(a)[E]

8 studies with 8378 participants and 1458 CV outcomes revealed that high Lp(a) levels are positively associated with CVD compared to low Lp(a) levels [31].

Two different scores have been developed to predict fatal and non-fatal CV events in different FH populations, and in both, Lp(a) contribute independently to the development of incidental ASCVD events [32, 33]. In the SAFEHEART study, the analysis of 2404 genetically confirmed FH subjects ≥ 18 years in primary (87%) or secondary prevention (13%) followed up for a mean of 5.5 years permitted the development of an accurate risk-equation (SAFEHEART-RE) to predict 5-year and 10-year risk of incidental ASCVD. Along with other 7 clinical variables, Lp(a) levels > 50 mg/dL were an independent predictor [32]. Recently, the analysis of 3881 patients from 5 different registries, with a clinical diagnosis of FH (74% genetically confirmed) and in primary prevention, showed that Lp(a) is together with other 5 clinical variables an independent predictor of 10-year ASCVD risk [33].

The role of Lp(a) in the risk of ASCVD in older FH individuals has been demonstrated recently in another analysis of the SAFEHEART study [34]. From 5262 FH patients, 930 individuals were 65 years old or older or would have had this age if a cardiovascular fatal event had not occurred. Those individuals without ASCVD were classified as Resilient FH (R-FH, 579), and the other 351 were considered non-R-FH. Median follow-up was 8.4 years, and the mean age at the end of follow-up was almost 74 years old. Median Lp(a) levels in R-FH patients were significantly lower than in non-R-FH patients and among other clinical variables including SAFEHEART-RE. Lower Lp(a) levels were also an independent predictor related to resilient FH [34].

Cascade Screening for Lp(a) in FH Patients

Due to the additive high CV risk in patients with FH and high Lp(a), identification of these subjects should be a priority. Therefore, a good option is to take advantage of determining Lp(a) levels while conducting a cascade screening from an index case with FH [26, 35]. Ellis et al. evaluated the effectiveness of Lp(a) cascade screening and the association between elevated Lp(a) and incidental ASCVD events in the SAFEHEART study (26). The authors showed that testing for elevated Lp(a) during cascade screening for FH is highly effective in identifying new cases with high Lp(a). Thirty percent of relatives of probands with genetically defined FH and high Lp(a) inherited both conditions. Moreover, screening for elevated Lp(a) in relatives using this systematic approach (index case with both conditions) has a higher yield of detection than an opportunistic approach (index case with FH but not high Lp(a) levels). One new case of high Lp(a) was detected every 2.4 individuals using the systematic cascade screening approach compared to 1 case in 5.8 individuals using the opportunistic approach. Similarly, the yield of detection of both conditions was higher with the systematic approach (1 in 3.4 individuals) [26]. The detection of these cases with high Lp(a) is important because these individuals are at high risk, especially if they also have FH. In this study, patients with FH and high Lp(a) had the greatest ASCVD risk (H.R: 4.40, $p < 0.001$) compared to each condition alone (Fig. 1). A recent publication from Australia, using a similar systematic approach in a small population, showed similar results [35].

Lipoprotein(a) and Aortic Valve Damage in FH

High LDL-C concentration has been associated with aortic valve stenosis (AVS) in observational studies [36]; however, randomized clinical trials with high-intensity lipid-lowering therapy have failed to demonstrate the benefit of lowering LDL-C on the progression of the disease [37, 38]. On the other hand, Mendelian randomization studies have demonstrated that genetic elevation in LDL-C, as determined by a genetic risk score, is associated with both the presence of aortic valve calcium and incident aortic stenosis, suggesting a causal association between LDL-C and aortic valve disease [39]. In addition, Mendelian randomization studies also showed the association between genetic variations in *LPA* locus, mediated by Lp(a) levels with aortic valve calcification, and with incident clinical aortic stenosis [40]. Lp(a) is the principal carrier of oxidized phospholipids and may contribute to the deposition and accumulation of these phospholipids in the aortic valve promoting inflammation and calcification [41, 42]. The development of AVS is a frequent complication in homozygous FH patients, especially in children and in those patients carrying more severe null mutations [43, 44]. Few studies have analyzed the impact of heterozygous FH in aortic valve disease and the role of Lp(a) in this population. Ten Kate et al. have demonstrated a higher prevalence and extent of aortic valve calcification assessed by cardiac computed tomography in 145 asymptomatic heterozygous FH patients when compared with non-related control individuals [45]. In this study, Lp(a) levels were not available. Two larger prospective studies have given more information about the risk of AVS in FH patients [9••, 46]. Mundal et al. reported an increased risk of AVS and aortic valve replacement (AVR) (mean age, 65 years) in genetically defined FH patients in Norway compared with the general population [46]. As in the Ten Kate study, Lp(a) levels were not available in this study. In recently published data from the SAFEHEART study, a 5.71-fold increase in the need for AVR was observed in FH patients compared with their non-affected relatives after a mean follow-up of

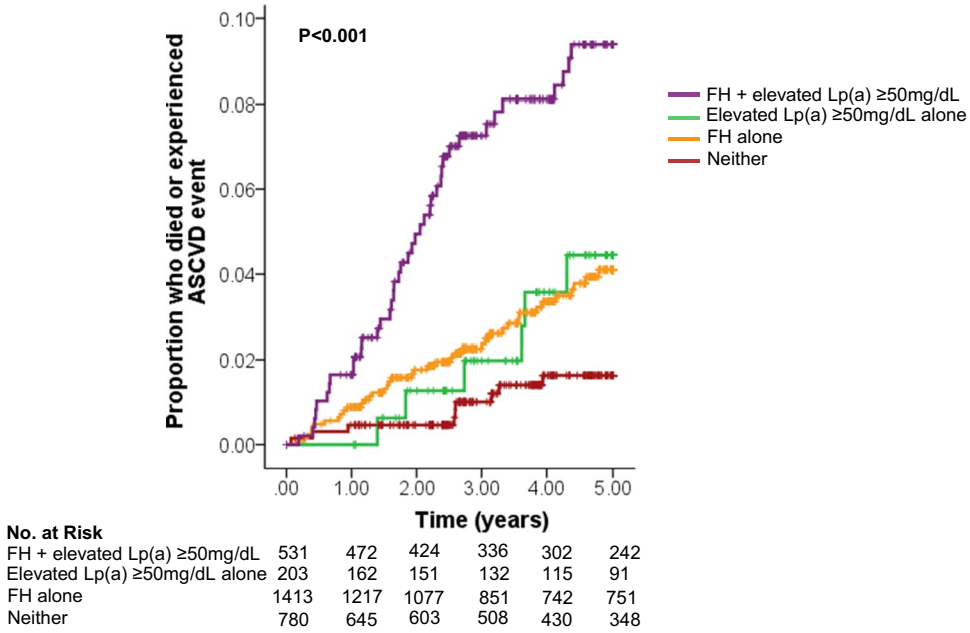

Fig. 1 Kaplan–Meier survival analysis in screened relatives according to their condition: FH, elevated Lp(a), both conditions or neither (reprinted from Ellis K, et al. J Am Coll Cardiol 2019; 73:1029–1039, with permission from Elsevier) [26]

7.5 years [9••]. In addition, the incidence rate of AVR was 4.36 times higher in patients with FH, and the average incidence of AVR in patients with FH was 1.7 cases for 1000 patients-year compared with a corresponding incidence of 7.7-fold for ASCVD [47]. Patients requiring valve replacement had higher median Lp(a) levels compared with those who did not require (58.5 vs. 23.6 mg/dL, respectively, $p < 0.001$). In multivariable analysis, independent predictors for AVR were age, history of ASCVD, hypertension, elevated Lp(a) levels, and sustained elevation in LDL-C levels determined as LDL-cholesterol year score corrected for Lp(a) cholesterol[9]. These results suggest an integrated management of LDL-C, hypertension, and if possible Lp(a) to retard the progression of AS in FH; however, this needs to be tested in a clinical trial.

Therapeutic Approach in FH Patients with High Lp(a)

Current management of FH is combined treatment with high-intensity statins, ezetimibe, and PCSK9 inhibitors (PCSK9i). There is enough evidence about the effectiveness and safety of these therapies in the FH population. Recent ESC/EAS guidelines classified FH patients with ASCVD or with at least one major risk factor as very high risk and those without major CV risk factors as high risk (11). In the first case, a reduction ≥ 50% in LDL-C levels and an LDL-C goal < 55 mg/dL should be considered; in the high-risk group, a reduction ≥ 50% in LDL-C levels and an LDL-C goal < 70 mg/dL are recommended. These more stricter goals are more difficult to achieve with statins and ezetimibe; however, the incorporation of PCSK9i has improved significantly the achievement of these goals [48].

On the other hand, the management of patients with elevated Lp(a) is a therapeutic challenge. PCSK9 inhibitors may moderately decrease Lp (a) levels, but intensive reductions in Lp(a) levels have been achieved with specific apo(a) antisense therapy that targets hepatic apo(a) mRNA and reduces Lp(a) concentrations in patients with and without established cardiovascular disease, at least in shorter-term follow-up [49••]. While we await the outcomes of the selective Lp(a) lowering therapies to assess the potential clinical benefit, we must strictly control LDL-C levels and other risk factors in subjects with FH and high Lp (a) levels.

Conclusions

Familial hypercholesterolemia and high Lp(a) are two prevalent genetic disorders associated with premature ASCVD. The association of FH and high Lp(a) levels is frequent and increases the ASCVD risk up to twofold compared to FH alone. Therefore, the detection of these cases with high Lp(a) is crucial because these individuals are at high risk. Detecting FH early and decreasing LDL-C levels are the two pillars for effective ASCVD prevention in FH. Combination treatment, including emerging therapies, may lower ASCVD risk in patients with FH. While we await the outcomes of the new anti-Lp(a) trials to assess the potential clinical benefit of lowering Lp(a) levels, we must strictly control LDL-C levels and other risk factors in subjects with FH and high Lp(a) levels.

The implementation of the search and measure of Lp(a) levels in individuals with FH is mandatory and, like Sherlock Holmes deductive reasoning, does apply not only to the scene and partners in crime, but also to the medical fields. Indeed, an ideal detective and an ideal clinician share the same qualities: observation, deduction, and knowledge.

Declarations

Human and Animal Rights and Informed Consent. This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Dr. Alonso reports personal fees from Tecnofarma and Teva, outside the submitted work.
The other authors declare that they have no conflict of interest.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.• Watts GF, Gidding S, Mata P, Pang J, Sullivan DR, Yamashita S, et al. Familial hypercholesterolemia: evolving knowledge for designing adaptive models of care. Nat Rev Cardiol. 2020;17:360–77. (**This publication summarizes recent advances in the knowledge of FH related to diagnosis, cardiovascular risk stratification, LDL-C targets, and management.**)
2. Sijbrands EJ, Westendorp RG, Lombardi MP, Havekes LM, Frants RR, Kastelein JJ, et al. Additional risk factors influence excess mortality in heterozygous familial hypercholesterolemia. Atherosclerosis. 2000;149:421–5.
3. Alonso R, Mata N, Castillo S, Fuentes F, Saenz P, Muñiz O, et al. Cardiovascular disease in familial hypercholesterolaemia: influence of low-density lipoprotein receptor mutation type and classic risk factors. Atherosclerosis. 2008;200:315–22.
4. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolemia: screening of 98098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. Eur Heart J. 2016;37:1384–94.
5. Perez de Isla L, Alonso R, Mata N, Saltijeral A, Muñiz O, Rubio-Marin P, et al. Coronary heart disease peripheral arterial disease, and stroke in familial hypercholesterolemia Insights from the SAFEHEART Registry. Arterioscler Thromb Vasc Biol. 2016;36:2004–10.
6. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, et al. European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31:2844–5853.
7. Alonso R, Andres E, Mata N, Fuentes-Jiménez F, Badimón L, López-Miranda J, et al. SAFEHEART Investigators. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. J Am Coll Cardiol. 2014;63:1982–9.
8. Vongpromek R, Bos S, Ten Kate GJ, Yahya R, Verhoeven AJ, de Feyter PJ, et al. Lipoprotein(a) levels are associated with aortic valve calcification in asymptomatic patients with familial hypercholesterolaemia. J Intern Med. 2015;278:166–73.
9.•• Perez de Isla L, Watts GF, Alonso R, Díaz-Díaz JL, Muñiz-Grijalvo O, Zambón D, et al. Lipoprotein(a), LDL-cholesterol, and hypertension: predictors of the need for aortic valve replacement in familial hypercholesterolemia. Eur Heart J. 2021;42:2201–11. (**This study shows that aortic valve replacement due to AV stenosis is significantly increased in FH, and predictors are older age, history of ASCVD, hypertension, high lipoprotein(a) levels, and LDL-C adjusted Lp(a) burden.••**)
10. Langsted A, Kamstrup P, Benn M, Tybjaerg-Hansen A, Nordestgaard B. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolemia: a prospective cohort study. Lancet Diabetes Endocrinol. 2016;4:577–87.
11. Mach F, Baigent C, Catapano A, Koskinas KC, Casula M, Badimón L, et al. 2019 ESC/EAS guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–88.
12. Slack J. Risks of ischaemic heart disease in familial hyperlipidemic states. Lancet. 1969;II:1380–2.
13. Hopkins P, Stephenson S, Wu L, Riley WA, Xin Y, Hunt SC. Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia. Am J Cardiol. 2001;87:547–53.
14. Scientific Steering Committee on behalf of the Simon Broome Register Group. The risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ. 1991;303:893–6.
15. Duell PB, Gidding S, Andersen R, Knickelbine T, Anderson L, Gianos E, et al. Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: the CASCADE FH registry. Atherosclerosis. 2019;289:85–93.
16. Khera A, Won HH, Peloso G, Lawson KS, Bartz TM, Deng X, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. 2016;67:2578–89.
17. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J. 2008;29:2625–33.
18. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ. 2008;337:a2423.
19. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest. 1992;90:52–60.
20. Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB. Lipoprotein Lp(a) and the risk for myocardial infarction. Atherosclerosis. 1981;38:51–61.
21. Tsimikas S. A test in context: lipoprotein(a). Diagnosis, prognosis, controversies and emerging therapies. J Am Coll Cardiol. 2017;69:692–711.
22. Utermann G, Hoppichler F, Dieplinger H, Seed M, Thompson G, Boerwinkle E. Defects in the low density lipoprotein receptor gene affect lipoprotein (a) levels: multiplicative interaction of two gene loci associated with premature atherosclerosis. Proc Natl Acad Sci USA. 1989;86:4171–4.
23. Kraft HG, Lingenhel A, Raal FJ, Hohenegger M, Utermann G. Lipoprotein(a) in homozygous familial hypercholesterolemia. Arteriosclerr Thromb Vasc Biol. 2000;20:522–8.

24. Li S, Wu NQ, Zhu CG, Zhang Y, Guo YL, Gao Y, et al. Significance of lipoprotein(a) levels in familial hypercholesterolemia and coronary artery disease. Atherosclerosis. 2017;260:67–74.
25. Trinder M, DeCastro M, Azizi H, Cermakova L, Jackson LM, Frohlich J, et al. Ascertainment bias in the association between elevated lipoprotein(a) and familial hypercholesterolemia. J Am Coll Cardiol. 2020;75:2682–93.
26.•• Ellis K, Perez de Isla L, Alonso R, Fuentes F, Watts G, Mata P. Value of measuring lipoprotein(a) during cascade testing for familial hypercholesterolemia. J Am Coll Cardiol. 2019;73:1029–39 (**This study shows the feasibility and effectiveness of testing Lp(a) levels during FH cascade screening. Those FH patients with FH and high Lp**. (**This study shows the feasibility and effectiveness of testing Lp(a) levels during FH cascade screening. Those FH patients with FH and high Lp(a) levels have the highest risk of ASCVD compared to each disorder separately.••**)
27. Kinpara K, Okada H, Yoneyama A, Okubo M, Murase T. Lipoprotein(a)-cholesterol: a significant component of serum cholesterol. Clin Chim Acta. 2011;412:1783–7.
28. Saeedi R, Li M, Allard M, Frohlich J. Marked effects of extreme levels of lipoprotein(a) on estimation of low-density lipoprotein cholesterol. Clin Biochem. 2014;47:1098–9.
29. Jansen AC, van Aalst-Cohen ES, Tanck MW, Trip MD, Lansberg PJ, Liem AH, et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. J Intern Med. 2004;256(6):482–90.
30. Nenseter M, Lindvig HW, Ueland T, Langslet G, Ose L, Holven KB, et al. Lipoprotein(a) levels in coronary heart disease-susceptible and-resistant patients with familial hypercholesterolemia. Atherosclerosis. 2011;216:426–32.
31. Watanabe J, Hamasaki M, Kotani K. Risk of cardiovascular disease with lipoprotein(a) in familial hypercholesterolemia: a review. Arch Med Sci Atheroscler Dis. 2020;5:e148–52.
32. Pérez de Isla L, Alonso R, Mata N, Fernández-Pérez C, Muñiz O, Díaz-Díaz JL, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study). Circulation. 2017;135:2133–44.
33. Paquette M, Bernard S, Cariou B, Hegele RA, Genest J, Trinder M, et al. Familial hypercholesterolemia-risk-score: a new score predicting cardiovascular events and cardiovascular mortality in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2021;41:2632–40.
34. Pérez de Isla L, Watts GF, Muñiz-Grijalvo O, Díaz-Díaz JL, Alonso R, Zambón D, et al. A resilient type of familial hypercholesterolemia: case-control follow-up of genetically characterized older patients in the SAFEHEART cohort. Eur J Prev Cardiol. 2021;2:zwab185. https://doi.org/10.1093/eurjpc/zwab185.
35. Chakraborty A, Pang J, Chan D, Ellis K, Hooper AJ, Bell DA, et al. Cascade testing for elevated lipoprotein(a) in relatives of probands with familial hypercholesterolemia and elevated lipoprotein(a). Atherosclerosis. 2021;S0021–9150(21):01417–9. https://doi.org/10.1016/j.atherosclerosis.2021.11.004.
36. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease: Cardiovascular Health Study. J Am Coll Cardiol. 1997;29(3):630–4.
37. Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Investigators SEAS. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008;359:1343–56.
38. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J, ASTRONOMER Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation. 2010;121:306–14.
39. Smith JG, Luk K, Schulz CA, Engert JC, Do R, Hindy G, et al. Association of low-density lipoprotein-cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. JAMA. 2014;312:1764–71.
40. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med. 2013;368:503–12.
41. Capoulade R, Chan KL, Yeang C, Mathieu P, Bossé Y, Dumesnil JG, et al. Oxidized phospholipids, lipoprotein(a), and progression of calcific aortic valve stenosis. J Am Coll Cardiol. 2015;66:1236–46.
42. Mata P, Alonso R, Perez de Isla L, Badimón L. Dyslipidemia and aortic valve disease. Curr Opin Lipidol. 2021;32:349–54.
43. Alonso R, Díaz-Díaz JL, Arrieta F, Fuentes-Jiménez F, de Andrés R, Saenz P, et al. Clinical and molecular characteristics of homozygous familial hypercholesterolemia patients: insights from SAFEHEART registry. J Clin Lipidol. 2016;10:953–61.
44. Alves AC, Alonso R, Díaz-Díaz JL, Medeiros AM, Jannes CE, Merchan A, et al. Phenotypical, clinical, and molecular aspects of adults and children with homozygous familial hypercholesterolemia in Iberoamerica. Arterioscler Thromb Vasc Biol. 2020;40:2508–15.
45. Ten Kate GR, Bos S, Dedic A, Neefjes LA, Kurata A, Langendonk JG, et al. Increased aortic valve calcification in familial hypercholesterolemia: prevalence, extent, and associated risk factors. J Am Coll Cardiol. 2015;66:2687–95.
46. Mundal LJ, Hovland A, Igland J, Veierod MB, Holven KB, Bogsrud MP, et al. Association of low-density lipoprotein cholesterol with risk of aortic valve stenosis in familial hypercholesterolemia. JAMA Cardiol. 2019;4:1156–9.
47. Perez de Isla L, Arroyo-Olivares R, Alonso R, Muñiz-Grijalvo O, Díaz-Díaz JL, Zambón D, et al. Incidence of cardiovascular events and changes in the estimated risk and treatment of familial hypercholesterolemia: the SAFEHEART registry. Rev Esp Cardiol. 2020;73:828–34.
48. Alonso R, Muñiz-Grijalvo O, Díaz-Díaz JL, Zambón D, de Andrés R, Arroyo-Olivares R, et al. Efficacy of PCSK9 inhibitor in the treatment of heterozygous familial hypercholesterolemia: a clinical practice experience. J Clin Lipidol. 2021;15:584–92.
49.•• Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. N Engl J Med. 2020;382:244–55. (**This RCS shows a dose-dependent reduction in Lp(a) levels ranging 35 to 80% using weekly subcutaneous infection of antisense oligonucleotide AKCEA-APO(a)-LRX. The most common adverse event was injection-site reactions.••**)
50. Cao YX, Jin JL, Guo YL, Sun D, Liu HH, Wu NQ, et al. Baseline and on-statin treatment lipoprotein(a) levels for predicting cardiovascular events in patients with familial hypercholesterolemia. Atherosclerosis. 2019;291:27–33.