Clinical Features and Gaps in the Management of Probable Familial Hypercholesterolemia and Cardiovascular Disease

Barak Zafrir, MD; Ayman Jubran, MD; Gil Lavie, MD; David A. Halon, MD; Moshe Y. Flugelman, MD; Chen Shapira, MD

Background: Familial hypercholesterolemia (FH) is associated with premature atherosclerotic cardiovascular disease (ASCVD). The introduction of potent therapeutic agents underlies the importance of improving clinical diagnosis and treatment gaps in FH.

Methods and Results: A regional database of 1,690 adult patients with high-probability FH based on age-dependent peak-low-density lipoprotein cholesterol (LDL-C) cut-offs and exclusion of secondary causes of severe hypercholesterolemia, was examined to explore the clinical manifestations and current needs in the management of ASCVD, which was present in 248 patients (15%), of whom 83% had coronary artery disease (CAD); 19%, stroke; and 13%, peripheral artery disease. ASCVD was associated with male gender, higher peak LDL-C, lower high-density lipoprotein cholesterol (HDL-C), and traditional risk factor burden. Despite high-intensity statin (prescribed in 83% and combined with ezetimibe in 42%), attainment of LDL-C treatment goals was low, and associated with treatment intensity and drug adherence. Multivessel CAD (adjusted hazard ratios (HR), 3.05; 95% CI: 1.65–5.64), myocardial infarction, and the presence of ≥1 traditional risk factor (HR, 2.59; 95% CI: 1.42–4.71), were associated with repeat coronary revascularizations, in contrast with peak LDL-C >300 mg/dL (HR, 1.13; 95% CI: 0.66–1.91).

Conclusions: Main manifestations of ASCVD in FH patients were premature, multivessel CAD with need for recurrent revascularization, associated with classical cardiovascular risk factors but not with peak LDL-C. In spite of intensive therapy with lipid-lowering agents, treatment gaps were significant, with low attainment of LDL-C treatment goals.

Key Words: Adherence; Coronary revascularization; Familial hypercholesterolemia; Low-density lipoprotein cholesterol

Familial hypercholesterolemia (FH) is a common monogenic disorder, with a prevalence of approximately 1:300 in its heterozygous form in the general population. Clinical diagnosis of FH is based on elevated age-dependent low-density lipoprotein cholesterol (LDL-C), characteristic physical stigmata, and premature atherosclerotic cardiovascular disease (ASCVD) due to lifelong exposure of the arterial vasculature to high LDL-C. Given that inheritance is primarily autosomal dominant, evidence of these signs in first- and second-degree relatives strengthens the clinical diagnosis, and gene-environment interactions modulate ASCVD risk.

Although much research has been done in recent years on evaluating gaps in identification, diagnosis and management of FH, data are lacking regarding the clinical manifestations of ASCVD in FH, the associated risk factors mediating the progression of atherosclerosis, and the risk of recurrent interventions and cardiovascular events. In the current study we explored clinical characteristics and current needs in the management of FH patients with prevalent ASCVD, and investigated predictors of repeat coronary revascularization.
regional health-care population of 685,314 insured individuals <75 years who were screened, 1,932 living patients with a high probability of FH were diagnosed (estimated prevalence of probable FH, 1:355 in the insured district population <75 years of age).

The current study is a subanalysis of the adult FH population with a diagnosis of ASCVD. Of the 1,690 adults with FH (after exclusion of 242 children and adolescents under the age of 20 years), 275 had a current diagnosis of ASCVD, defined as coronary artery disease (CAD), ischemic stroke and transient ischemic attack (TIA), or peripheral artery disease (PAD) of atherosclerotic origin. We excluded the cases of TIA diagnosis (n=27), because these cases, clinically defined as a suspicion of transient neurologic deficit, were not reliably proven to be associated with ASCVD. Therefore, the final study group of adult patients with prevalent ASCVD comprised 248 of the 1,690 adult patients (15%). The study was approved by Clalit Health Services community ethics committee, with waiving of the need for individual patient consent.

Clinical and Laboratory Measurements

Demographic and baseline clinical characteristics were recorded from computerized data of patient files and included age, gender and concomitant cardiovascular risk factors such as smoking, diabetes mellitus and hypertension.

Serum LDL-C concentration was calculated using the Friedwald equation, and was classified as peak (highest level documented in patient’s history in the computerized laboratory database), and current (the most recent documented LDL-C level in the computerized laboratory database). Comparison was made between peak and current LDL-C with evaluation of attainment of LDL-C treatment goals. In addition, the most recent high-density lipoprotein cholesterol (HDL-C) level, as well as the lowest HDL-C level of each patient in the computerized database, were documented. High-intensity statins included atorvastatin 40–80 mg or rosuvastatin 20–40 mg/day. Dispensed lipid-lowering medications were defined as prescriptions for lipid-lowering drugs that were filled in the last 6 months.

CAD included acute coronary syndrome (ACS), history of myocardial infarction (MI), as well as unequivocally documented ASCVD on coronary angiography or imaging such as coronary computed tomography (CT) angiography.

Table. Subject Characteristics vs. Presence of ASCVD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=1,690)</th>
<th>No ASCVD (n=1,442)</th>
<th>ASCVD (n=248)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49±15</td>
<td>47±15</td>
<td>58±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>702 (42)</td>
<td>542 (38)</td>
<td>160 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>391 (23)</td>
<td>324 (22)</td>
<td>67 (27)</td>
<td>0.122</td>
</tr>
<tr>
<td>Hypertension</td>
<td>426 (25)</td>
<td>291 (20)</td>
<td>135 (54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>238 (14)</td>
<td>167 (12)</td>
<td>71 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak LDL-C (mg/dL)</td>
<td>277±44</td>
<td>275±43</td>
<td>291±46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak LDL-C &gt;300 mg/dL</td>
<td>338 (20)</td>
<td>261 (18)</td>
<td>77 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current LDL-C (mg/dL)</td>
<td>181±69</td>
<td>186±68</td>
<td>152±72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>49.8±14.0</td>
<td>50.7±14.0</td>
<td>44.6±13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C attainment &lt;100 mg/dL</td>
<td>192 (11)</td>
<td>125 (9)</td>
<td>67 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C reduction &gt;50%</td>
<td>537 (32)</td>
<td>403 (28)</td>
<td>135 (55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High-intensity statin (prescription)</td>
<td>968 (57)</td>
<td>763 (53)</td>
<td>205 (83)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Figure 1. Cumulative atherosclerotic cardiovascular disease (ASCVD)-free survival, according to age and (A) gender, (B) peak low-density lipoprotein cholesterol (LDL-C) >300 mg/dL and (C) lowest high-density lipoprotein cholesterol (HDL-C) <40 mg/dL. P<0.0001 (log-rank test) for all comparisons.
Repeat coronary revascularization was defined as any percutaneous coronary intervention or cardiac surgery (coronary artery bypass grafting: CABG) during the follow-up period, in both the acute and non-acute setting.

**Statistical Analysis**

Continuous data are presented as mean±SD or median (IQR), and categorical variables as numbers and percentages. Independent-samples T-test was used to compare continuous variables, and the Mann-Whitney and Kruskal-Wallis tests were used for skewed data. Chi-squared test was used to compare categorical variables. Fisher’s exact test was used in the case of small sample size. A multivariate forward binary logistic regression analysis was applied to determine independent associations of patient characteristics with ASCVD. Included were variables that were statistically significant on univariate analysis: age, gender, diabetes mellitus, hypertension, smoking, prescription of high-intensity statin, peak LDL-C >300 mg/dL and HDL-C <40 mg/dL.

ASCVD-free survival in the overall FH group according to age and the presence of risk factors, as well as the rate of repeat revascularization over time in patients with CAD, were calculated using the Kaplan-Meier method, and statistical comparison was performed using log-rank test. The association of risk factors with long-term repeat revascularization in patients with CAD was evaluated using the Cox proportional hazards model, calculating hazard ratios (HR) and 95% CI, after adjustment for age and gender.

The results were considered statistically significant for 2-sided P<0.05. SPSS version 20.0 was used to perform all statistical analyses.

**Results**

Of the 1,690 living adults <75 years with probable FH (mean age, 49±15 years), 248 (15%) had a diagnosis of ASCVD and comprised the subject group. CAD was present in 205 patients (83% of those with ASCVD), ischemic stroke in 46 (19%) and PAD in 31 (13%). Mean ASCVD patient age was 58±10 years and 64% were male. Compared with patients without ASCVD, those with ASCVD were currently older, more were men, and they had a significantly higher burden of traditional atherosclerotic risk factors (Table). At least 1 risk factor (diabetes, hypertension or smoking) was present in 174 (70%) of the patients with ASCVD. In addition, those with ASCVD had lower HDL-C and higher peak LDL-C, although their most recent LDL-C level was lower, with better attainment of LDL-C treatment goals (Table). The rates of ASCVD-free survival according to age and the presence of risk factors (gender; LDL-C >300 mg/dL; HDL-C <40 mg/dL) are given in Figure 1.

On multivariate adjusted logistic regression analysis, male gender (OR, 3.93; 95% CI: 2.76–5.60, P<0.001), age (per 10-year increment: OR, 1.99; 95% CI: 1.70–2.34, P<0.001), hypertension (OR, 2.35; 95% CI: 1.66–3.33, P<0.001), smoking (OR, 1.41; 95% CI: 1.01–1.95, P=0.042), peak LDL-C >300 mg/dL (OR, 3.20; 95% CI: 2.21–4.62, P<0.001), HDL-C <40 mg/dL (OR, 2.14; 95% CI: 1.50–3.07, P<0.001), and prescription of high-intensity statin (OR, 2.56; 95% CI: 1.75–3.75, P<0.001), were all independently associated with the presence of ASCVD in FH patients.

High-intensity statin was prescribed in 83% of the patients with ASCVD, and was combined with ezetimibe in 42% of the patients. Overall, 55% of FH patients with ASCVD achieved LDL-C reduction >50%, only 27% achieved LDL-C <100 mg/dL and 5%, LDL-C <70 mg/dL. Lipid-lowering prescriptions were not filled in the last 6 months by 20% of the patients. Attainment rate of the LDL-C treatment goal was directly associated with treatment intensity and drug adherence (P<0.001; Figure 2).

Mean age at ASCVD diagnosis was 50±10 years. Coronary revascularization was required in 184 (90%) of the patients with CAD. Of them, 58% had multivessel CAD and 39% underwent CABG. One-third of the patients required recurrent interventional procedures over a median follow-up of 60 months (IQR, 24–108 months), most of which were performed in the setting of ACS (74%). Repeat coronary revascularization was associated with the presence of ≥1 concomitant traditional risk factors including diabetes mellitus, hypertension or smoking, as well as the presence of multivessel CAD (Figure 3). After adjustment for age and gender, presence of multivessel disease (adjusted HR, 3.05; 95% CI: 1.65–5.64, P=0.0004) and presence of ≥1 concomitant cardiovascular risk factor (HR, 2.59; 95%
ASCVD was significantly associated with higher peak LDL-C in the overall FH group (Table, Figure 1). Similarly, although lower HDL-C was associated with ASCVD in the FH group, HDL-C <40 mg/dL did not predict repeat revascularization (age and gender adjusted HR, 1.47; 95% CI: 0.85–1.52, P=0.168).

Discussion

In the current study we investigated characteristics of ASCVD in a cohort of patients with high clinical probability of FH. The main presentation of ASCVD was premature CAD, associated with traditional cardiovascular risk factors, higher peak LDL-C and reduced HDL-C. A lower prevalence of clinical atherosclerosis was observed in other vascular beds. Combination therapy with high-intensity statin and ezetimibe was correlated with better attainment of lipid goals, in contrast with those recently non-adherent to lipid-lowering therapies. In FH patients with CAD, the burden of traditional cardiovascular risk factors, evidence of multivessel CAD and previous MI, predicted the need for repeat coronary revascularization, while the extent of peak LDL-C elevation was not associated with recurrent coronary interventions.

The main manifestation of ASCVD in the present FH patients was CAD. This is consistent with data from several registries of heterozygous FH patients around the world. In FH patients with CAD, high rates of multivessel coronary atherosclerosis were observed. In past studies, coronary plaque burden identified non-invasively on coronary CT angiography was significantly associated with future coronary events in patients with heterozygous FH. A significant number of the present FH patients with CAD underwent cardiac surgery. A high rate of CABG was similarly seen in a recent FH study on the presence of cardiovascular disease at the time of death, reaching 29% of deceased FH patients. These results emphasize the diffuse and progressive nature of coronary atherosclerosis in FH and are in line with the observation that most hospitalizations of FH patients for cardiovascular disease are due to ischemic heart disease.

The impact of atherosclerosis in FH is not limited to the coronary arteries. Atherosclerosis in cerebral vessels resulting in stroke, and in peripheral arteries leading to limb

---

CI: 1.42–4.71, P=0.002) as well as previous MI, were significantly associated with increased HR for repeat revascularization (Figure 4). In contrast, higher peak LDL-C in patients with diagnosed CAD was not associated with increased risk for repeat revascularization (peak LDL-C above median, Figure 3; >300 mg/dL, Figure 4; HR, 1.13; 95% CI: 0.66–1.91; P=0.663). This was despite the fact that
ischemia, tends to occur at a later age, and is less frequently reported and recognized than CAD in FH literature. In the current patients, CAD was present in 12% of the overall adult FH group aged 20–75, ischemic stroke in 2.7% and PAD in 1.8%. These results are similar to those reported recently in the SAFEHEART registry of patients with molecularly defined heterozygous FH in Spain (12% CAD, 1.6% stroke/TIA and 1.4% PAD in an FH population of similar mean age). In a meta-analysis of observational studies, FH was associated with a higher risk of cerebrovascular disease compared with the general population in the pre–statin era, which was significantly reduced after the introduction of statin therapy. A recent study on the association of heterozygous FH with PAD reported that the diagnosis of FH was associated with an almost 6-fold greater adjusted prevalence of PAD detected on reduced ankle-brachial index (ABI) in comparison with normo-lipidemic subjects. Although it is likely that effective lowering of serum LDL-C in FH patients is associated with lower rates of non-coronary clinical atherosclerosis, the aforementioned data may support the need for screening for obstructive atherosclerotic disease of the carotid and peripheral arteries in middle-age heterozygous FH individuals.

Significant treatment gaps were observed in the present FH patients with prevalent ASCVD. Although high-intensity statins were prescribed to most of the patients, fewer than half had received combination therapy with ezetimibe, and a very low number achieved the LDL-C treatment goal of <70 mg/dL. In addition, the fact that 20% of the patients with diagnosed ASCVD were not filling their lipid-lowering prescriptions in recent months is concerning, and is reflected by the direct association between treatment intensity, drug adherence and attainment rate of the LDL-C treatment goal.

In a recent analysis from Norway, most FH patients had established cardiovascular disease at the time of death, and approximately 70% had experienced one or more MI. Although, however, it is suggested that most FH patients will experience cardiovascular events at some time if untreated, some FH patients may have normal life expectancy. The onset of clinical ASCVD varies significantly among FH patients, even in carriers of the same mutations. The heterozygous FH population is heterogeneous in the clinical manifestations due to the variance in genetic background, the presence of concomitant traditional risk factors, the cholesterol burden throughout life and the history of drug treatment. In the current study, traditional cardiovascular risk factors, including male gender and age as well as diabetes mellitus, hypertension, smoking, and low HDL-C, were independently associated with the presence of ASCVD in the FH population. This is consistent with previous reports such as on FH patients from Dutch lipid clinics, emphasizing these factors as important risk predictors for cardiovascular disease in FH. Moreover, these classical risk factors were recently shown to be more prevalent in FH patients who died at a younger age. Therefore, healthy lifestyle habits and regular risk factor screening and modulation should be routinely implemented at an early age in individuals with FH.

Detection of high-risk index FH patients with prevalent ASCVD on screening regional electronic databases may facilitate rapid identification of affected relatives through clinical FH registries and active cascade screening. It is reasonable to assume that affected family members of patients with FH and ASCVD will have a similar lifelong risk for ASCVD, and therefore preventive measures and initiation of lipid-lowering therapies at a young age are of paramount importance.

Higher peak LDL-C, both above the median and >300 mg/dL, was associated with the development of ASCVD in the present overall FH group. Patients with higher peak LDL-C may have increased risk of cardiovascular disease because of the length of exposure to non-treated extreme LDL-C, and, accordingly, the cumulative burden of plasma cholesterol over the years. Interestingly, for any observed LDL-C level, FH mutation carriers were shown in research studies to have substantially increased risk for CAD. Besseling et al, however, also showed that patients with molecularly diagnosed “severe” heterozygous FH, defined as LDL-C above the 90th percentile in their FH group, are at increased cardiovascular risk compared with non-severe FH patients with lower LDL-C.

In patients referred for coronary angiography due to ACS, the rate of recurrent MI was higher in patients with FH compared with those unlikely to have FH. Also, in additional studies, patients with FH and ACS had a >2-fold adjusted risk of coronary event recurrence within the first year after discharge than patients without FH, despite the widespread use of high-intensity statins. We have recently shown that by screening a cardiac catheterization database, severe FH patients with premature CAD can be identified, suggesting that screening existing cardiovascular databases of populations at risk will promote identification and management of severe FH patients and their affected family members. A novel observation of the present study was the evaluation of parameters associated with recurrent coronary revascularizations over time in FH patients with CAD. Evidence of multivessel coronary disease at first catheterization, previous MI and the presence of at least 1 traditional risk factor (smoking, hypertension or diabetes), were independently associated with the need for recurrent revascularization. Of note, although peak LDL-C was significantly associated with the presence of ASCVD in the overall FH group, higher peak LDL-C did not predict recurrent coronary revascularization in those patients with established CAD. This finding that classical risk factors but not the extent of peak LDL-C elevation are associated with recurrent coronary interventions, highlights the importance of regular assessment and modulation of concomitant risk factors in FH patients with CAD, rather than solely relying on LDL-C reduction for decreasing cardiovascular risk. Future studies should evaluate the association of cumulative cholesterol burden throughout life with repeat coronary revascularizations in FH patients.

Several limitations to our study deserve consideration. The FH cohort included only living patients. Therefore, the actual rate of ASCVD would probably be higher if patients with premature death secondary to ASCVD had not been excluded. Moreover, only patients under the age of 75 years were included. Physical findings, family history, and lipoprotein(a) levels are strong risk factors for cardiovascular disease in FH, and were not evaluated in the current study, because these data were not available for all patients in the electronic database. In addition, it is possible that a lack of complete revascularization at initial presentation with clinical ASCVD, may have affected the results. We also did not evaluate the presence of aortic valve and root disease, which are known to be associated with severe FH. In addition, measures of treatment status...
and cholesterol levels were not evaluated repeatedly over the years and therefore their cumulative lifetime impact on cardiovascular risk could not be assessed. Moreover, the lack of access to FH mutation testing did not enable us to evaluate the association of mutation type with the risk for ASCVD and recurrent coronary revascularization. Finally, the current analysis was performed before the widespread use of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors in FH patients. PCSK9 inhibitors markedly reduce LDL-C in high-risk patients with hypercholesterolemia on stable statin therapy. The availability and utilization of these novel and potent medications in the present FH patients will need future assessment.

Conclusions

The main manifestation of ASCVD in patients with probable FH is premature multivessel CAD in middle age, which is associated with baseline abnormalities in plasma LDL-C and HDL-C as well as with the burden of traditional cardiovascular risk factors. In spite of the presence of ASCVD diagnosis, treatment gaps are still significant, with very low attainment of lipid treatment goals. The present study underscores the significant impact of classical cardiovascular risk factors, and not solely the extent of peak LDL-C, on recurrent coronary revascularization in FH subjects, and hence emphasizes the importance of early education for healthy lifestyle habits, as well as routine clinical assessment and modulation of cardiovascular risk factors in this high-risk population.

Acknowledgments

Funding for this project was provided by Sanofi Israel. The company played no role in the study design, analysis, or preparation of the manuscript.

Disclosures

The authors declare no conflict of interest.

References


