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Autosomal Recessive Hypercholesterolemia

Long-Term Cardiovascular Outcomes

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ABSTRACT

BACKGROUND Autosomal recessive hypercholesterolemia (ARH) is a rare lipid disorder characterized by premature atherosclerotic cardiovascular disease (ASCVD). There are sparse data for clinical management and cardiovascular outcomes in ARH.

OBJECTIVES Evaluation of changes in lipid management, achievement of low-density lipoprotein cholesterol (LDL-C) goals and cardiovascular outcomes in ARH.

METHODS Published ARH cases were identified by electronic search. All corresponding authors and physicians known to treat these patients were asked to provide follow-up information, using a standardized protocol.

RESULTS We collected data for 52 patients (28 females, 24 males; 31.1 ± 17.1 years of age; baseline LDL-C: 571.9 ± 171.7 mg/dl). During a mean follow-up of 14.1 ± 7.3 years, there was a significant increase in the use of high-intensity statin and ezetimibe in combination with lipoprotein apheresis; in 6 patients, lomitapide was also added. Mean LDL-C achieved at nadir was 164.0 ± 85.1 mg/dl (−69.6% from baseline), with a better response in patients taking lomitapide (−88.3%). Overall, 23.1% of ARH patients reached LDL-C of <100 mg/dl. During follow-up, 26.9% of patients had incident ASCVD, and 11.5% had a new diagnosis of aortic valve stenosis (absolute risk per year of 1.9% and 0.8%, respectively). No incident stroke was observed. Age (≥30 years) and the presence of coronary artery disease at diagnosis were the major predictors of incident ASCVD.

CONCLUSIONS Despite intensive treatment, LDL-C in ARH patients remains far from targets, and this translates into a poor long-term cardiovascular prognosis. Our data highlight the importance of an early diagnosis and treatment and confirm the fact that an effective treatment protocol for ARH is still lacking. (J Am Coll Cardiol 2018;71:279–88)

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ABBREVIATIONS AND ACRONYMS

ARH = autosomal recessive hypercholesterolemia

ASCVD = atherosclerotic coronary vascular disease

CHD = coronary heart disease

HoFH = homozygous familial hypercholesterolemia

LA = LDL-C apheresis

LLM = lipid-lowering medication

LDL-C = low-density lipoprotein cholesterol

LDL-R = low-density lipoprotein receptor

LDLRAP1 = low-density lipoprotein receptor adaptor protein-1 gene

LOF = loss of function

Autosomal recessive hypercholesterolemia (ARH; Online Mendelian Inheritance in Man [OMIM] catalog number 603813) is a rare genetic disease caused by disruptive variants in both alleles of the low-density lipoprotein receptor (LDLR) adaptor protein-1 (*LDLRAP1*) gene (1). This gene, located on chromosome 1p36.1, encodes a liver-specific LDLR chaperone that plays a crucial role in the endocytic internalization of LDLR-LDL complex in liver cells (2). Therefore, the lack of the functional LDLRAP1 protein markedly impairs the removal of LDL (3) and, thereby, raises plasma concentration of low-density lipoprotein cholesterol (LDL-C) up to 3 to 4 times above average (4–7). ARH is a genetic disease with clinical similarity to homozygous familial hypercholesterolemia (HoFH; OMIM number 143890), a disorder caused by the presence of biallelic disruptive mutations in the *LDLR* gene. Unlike HoFH, ARH is typically characterized by a recessive mode of inheritance as both parents of index cases are normocholesterolemic (8). ARH is considered a rare disease with a worldwide estimated prevalence of <1 in 10^6 population (8).

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However, early investigations revealed a frequency of *ARH* heterozygotes of approximately 1:143 individuals among Sardinians, thus making ARH very common in that population (8). Fellin et al. (9) recently carried out a careful review of published cases that confirmed that ARH, in addition to severe hypercholesterolemia (typically, LDL-C >400 mg/dl), is phenotypically characterized by cutaneous xanthomas, premature atherosclerotic coronary vascular disease (ASCVD), and atheromatous involvement of the aortic valve. It was also reported that in ARH, LDL-C may be lowered up to 65% by statin monotherapy (9–11) and up to 58% to 85% when more potent statins were combined with ezetimibe (9,12).

Despite this wealth of knowledge, several questions in the management and prognosis of ARH remain unanswered. It is not known whether LDL-C control also is improved over time, considering the availability of novel lipid-lowering drugs. More importantly, it is unknown how LDL lowering may influence the occurrence of ASCVD and aortic valve stenosis. Although randomized studies assessing the impact of therapy on clinical events in this disorder are not feasible and unethical, analysis of changes in outcomes by using real-life clinical data may be helpful in answering these questions. Therefore, the goals of the present study were to evaluate the changes and long-term effects of lipid-lowering therapies (LLT) and their impact on cardiovascular risk in the largest cohort of ARH patients collected throughout a worldwide collaboration.

METHODS

PATIENT EVALUATION. Available electronic databases (e.g., PubMed and MEDLINE) were searched up to December 2015 for published ARH cases by using the queries *autosomal recessive hypercholesterolemia* (ARH) and *LDLRAP1*. The only inclusion criterion was molecular confirmation of ARH. This search yielded several publications. All corresponding authors and

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physicians known to treat HoFH were contacted and asked to provide clinical and follow-up information about their published or unpublished ARH patients. The flowchart for patients' identification is shown in Online Figure 1. The collection of data was carried out according to a pre-specified protocol, as described below.

DATA COLLECTION. Demographic characteristics, medical history (with specific reference to previously diagnosed ASCVD and aortic valve stenosis), major coronary risk factors, medications both at referral (baseline) and during follow-up, and information on new ASCVD events were collected. In patients who were referred before the discovery of the *LDLRAP1* gene, the date of definitive diagnosis of ARH was considered part of the baseline data. Plasma lipids obtained at baseline and the best values observed during follow-up (defined as nadir value) were collected. For those patients who were receiving LDL-C apheresis (LA) therapy, pre-apheresis lipid profile was considered.

The follow-up period was defined as the time between the first and last available visit. The mean follow-up was 14.0 ± 7.3 years (range: 1.0 to 28.0 years).

ASCVD was defined as any of the following: 1) myocardial infarction; 2) newly diagnosed angina pectoris; 3) coronary revascularization (percutaneous transluminal coronary angioplasty and/or coronary artery bypass grafting; also grouped as coronary heart disease [CHD]); 4) severe (>70% stenosis) carotid atherosclerosis; 5) nonhemorrhagic stroke; and 6) cardiovascular death. The aortic valve status was evaluated by standard ultrasonographic examination as well as medical history of valve replacement. No data for safety parameters or side effects during treatment were collected.

All procedures were followed in accordance with the ethical standards of the local institutional committees on human experimentation and according to tenets of the Helsinki Declaration of 1964, as revised in 2013. No specific consent was provided for this study, but living patients were appropriately informed and agreed to share their anonymous data for scientific purposes.

GENETIC AND BIOCHEMICAL ANALYSES. Genetic analyses were carried out at each collaborating site by using standard sequencing protocols. Plasma lipids were measured by standard techniques at each site. LDL-C values were calculated by using the Friedewald formula or direct assay according to local procedures. No other biochemical analytes were provided.

STATISTICAL ANALYSIS. All statistical analyses were performed using SPSS/WIN software version 18.0 (SPSS Inc., Chicago, Illinois). Descriptive statistics such as mean ± SD and ranges were estimated for all variables. Continuous variables were compared by Student's *t*-test, whereas categorical variables were compared by chi-square or Fisher exact test. Differences in lipid levels between therapies were tested for significance by using regression analysis, including baseline values as covariates. To estimate the incident rate of ASCVD, the first event occurred during follow-up was considered. We estimated the time to first ASCVD event by using Kaplan-Meier survival curves. Survival curves were compared by age and previous ASCVD events by using the log-rank test. Cox proportional hazards model was applied to investigate the independent predictive role of the following characteristics: sex, age at first visit, previous CHD event, baseline LDL-C value, and smoking. Survival curves for aortic stenosis were not estimated due to the small number of observed events. Results were expressed as hazard ratios (HR) with their 95% confidence intervals (CIs). Finally, incidence rates (IRs) for ASCVD were calculated and expressed as number of events per 10,000 patient-years with their 95% CI. IRs were calculated for the whole study cohort and after categorization for sex, age, and

TABLE 1 Baseline Clinical Characteristics of ARH Patients

	Whole Cohort (N = 52)	Men (n = 24, 46.2%)	Women (n = 28, 53.8%)
Age at first visit, yrs	31.1 ± 17.1 (2–70)	33.1 ± 17.6 (8–70)	29.1 ± 16.8 (2–59)
BMI, kg/m^2	24.4 ± 5.0 (15.4–36.1)	25.4 ± 4.7 (16–33)	23.4 ± 5.2 (15.4–36.2)
Number of xanthomas	47 (90.4)	22 (91.7)	25 (89.3)
Smokers	5 (9.6)	2 (8.3)	3 (10.7)
Hypertension	9 (20.5)	5 (20.8)	4 (14.3)
Diabetes mellitus	2 (3.8)	1 (4.2)	1 (3.6)
ASCVD			
CHD	9 (17.6)	5 (20.8)	4 (14.3)
Stroke	0 (0.0)	0 (0.0)	0 (0.0)
Carotid artery stenosis*	1 (3.5)	0 (0.0)	1 (3.5)
Aortic valve stenosis			
Moderate	8 (15.4)	4 (16.7)	4 (14.3)
Severe	3 (5.8)	2 (8.3)	1 (3.6)
Plasma lipids, mg/dl			
Total cholesterol	638.9 ± 174.0 (282–1,200)	625.8 ± 162.4 (381–1,040)	650.1 ± 185.6 (282–1,200)
LDL-C	571.9 ± 171.7 (208–1,135)	563.7 ± 165.4 (299–986)	578.9 ± 179.6 (208–1,135)
HDL-C	43.2 ± 11.5 (19–71)	40.9 ± 10.7 (26–62)	45.0 ± 11.9 (19–71)
Triglycerides	131.5 ± 77.7 (29–522)	114.3 ± 61.1 (29–329)	146.1 ± 87.9 (57–522)

Values are mean ± SD (range) or n (%). *Patient showed left carotid artery stenosis >70%. The severity of aortic valve stenosis was defined by ultrasonographic examination according to local protocols. CHD was defined as any of the following: myocardial infarction, angina pectoris, or coronary revascularization.

ARH = autosomal recessive hypercholesterolemia; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

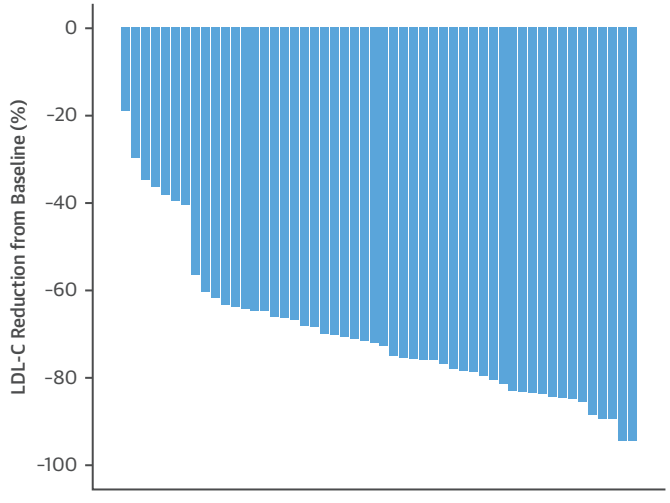
TABLE 2 Changes in Treatment

	ARH		
	Whole Cohort	Men	Women
Follow-up, yrs	14.1 ± 7.3	13.4 ± 7.8	14.6 ± 7
First evaluation			
No Tx	13 (26.5)	4 (19.0)	9 (32.1)
Only LA	27 (55.1)	13 (54.2)	14 (50)
Only LLM	8 (16.3)	4 (19)	4 (14.3)
LA plus LLM	1 (2.0)	0 (0.0)	1 (3.6)
Number of medications	NA	NA	NA
Follow-up			
No Tx	0 (0.0)	0 (0.0)	0 (0.0)
Only LA	1 (1.9)	0 (0.0)	1 (3.6)
Only LLM	24 (46.2)	7 (29.2)	17 (60.7)
LA plus LLM	27 (51.9)	17 (70.8)	10 (35.7)
Medications			
Rosuvastatin (mean dosage: 33.9 mg/day; range: 5–60 mg/day)	10 (19.2)	4 (16.7)	6 (21.4)
Atorvastatin (mean dosage: 55.7 mg/day; range: 20–80 mg/day)	14 (26.9)	4 (16.7)	10 (35.7)
Simvastatin (mean dosage: 40 mg/day; range: 40–40 mg/day)	6 (11.5)	1 (4.2)	5 (17.8)
Ezetimibe, 10 mg/day	23 (44.2)	8 (33.3)	15 (53.6)
Lomitapide (mean dosage: 15.8 mg/day; range: 5–40 mg/day)	6 (11.5)	1 (4.2)	5 (17.9)
Resins, g/day	6 (11.5)	3 (12.5)	3 (10.7)

Values are mean ± SD or n (%). Follow-up therapies are those prescribed at a nadir of low-density lipoprotein cholesterol. Data for LLT at baseline were not available in 4 patients. Types of statins prescribed during follow-up were reported in 35 subjects.

ARH = autosomal recessive hypercholesterolemia; LA = lipoprotein apheresis; LLM = lipid-lowering medications; LLT = lipid-lowering therapies; NA = not available; Tx = therapies.

FIGURE 1 Individual LDL-C Reduction at Nadir



Data are reported as individual percentage reduction from baseline to nadir of LDL-C, observed during follow-up. LDL-C = low-density lipoprotein cholesterol.

previous ASCVD events. IRs in the ARH cohort were compared to those in the Italian general population (13). Due to the exploratory nature of our survey, we did not a priori determine a specific primary endpoint. Therefore, we used a 2-sided p value of <0.05 as the level of statistical significance for all comparisons.

RESULTS

BASELINE CHARACTERISTICS OF ARH COHORT. The study cohort consisted of 52 genetically defined ARH patients (24 men and 28 women) with complete lipid and outcome data. Thirty-three subjects (63.5%) were from Italy, 5 (9.6%) were from the Netherlands, 4 (7.7%) were from Spain, 4 (7.7%) were from Turkey, 3 (5.8%) were from the Turkish-Syrian border, and 3 (5.8%) were from Japan. Genotypes of patients are reported in Online Table 1. None of the patients was carrying mutations in the *LDLR* and *APOB* genes. Twelve different *LDLRAP1* mutations (including 2 major rearrangements) in *LDLRAP1* were detected; 8 of them predict the presence of a truncated ARH protein. Thirty-nine patients were simple homozygotes, and 13 were compound heterozygotes. The most common pathogenic variants were p.(Trp22*) and p.(Ala145Serfs*26), which were present in 26.9% and 53.8% of patients, respectively. This is because these genetic variants are common among Sardinian cases of ARH (4,14), which represented the largest subgroup in our cohort.

Table 1 summarizes the baseline clinical features of study cohort. Age at first visit was 31.3 ± 17.1 years, 46.2% of patients were men, and 90% showed xanthomas. Moreover, 17.6% reported a history of CHD, with a numerically but not statistically higher prevalence in men than in women. Eleven patients (21.1%) showed aortic valve stenosis, which was reported to be severe in 5.8%. As expected, baseline LDL-C levels were markedly elevated without significant differences between sexes. Compared to ARH patients without ASCVD, ARH patients with ASCVD at baseline were older (49.2 ± 15.1 years of age vs. 27.1 ± 15.0 years of age; $p < 0.001$), more often had diabetes (20.0% vs. 0%, respectively; $p = 0.006$), had lower LDL-C concentrations (467.4 ± 138.2 mg/dl vs. 598.0 ± 170.9 mg/dl, respectively; $p = 0.03$), and reported higher usage of LLT (100.0% vs. 68.4%, respectively; $p = 0.05$).

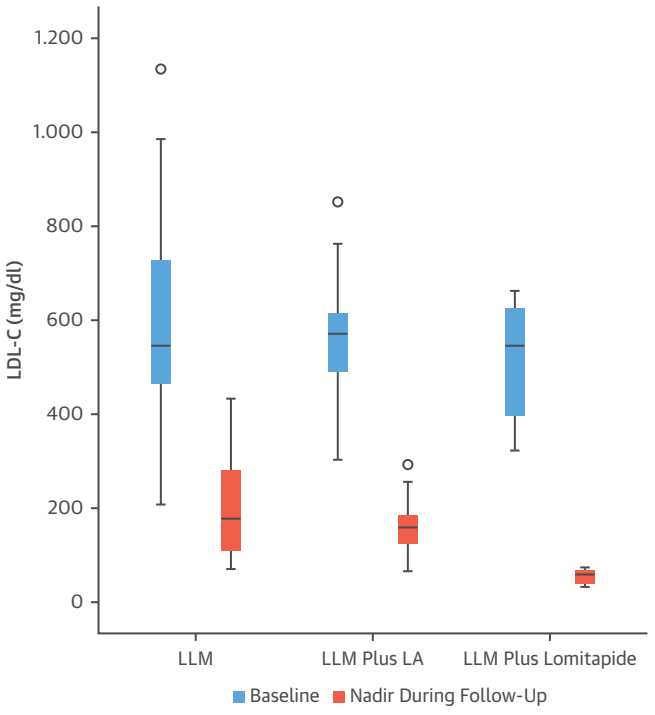
EVOLUTION OF TREATMENT AND LIPID CONTROL. The evolution of treatment in ARH patients is described in Table 2. At baseline, 55.1% were receiving only LA, and 16.3% were receiving only lipid-lowering

medications (LLM). Approximately one-fourth of subjects were not receiving any LLT. No information about the type of medications at baseline could be retrieved. During follow-up, a progressive improvement of treatment was observed. At last visit, 51.9% of ARH patients were taking LLMs in addition to LA, and the remaining 46.2% were treated only with LLMs; in 1 patient, only LA monotherapy was used. In many patients, a high-intensity statin regimen alone or in combination with ezetimibe was used. Six patients were receiving lomitapide in combination with the other LLMs; the mean duration of this combined treatment was 1.3 ± 0.9 years with a mean dosage of 15.8 mg/day (range: 5 to 40 mg/day). It is noteworthy that women were preferentially treated only with LLTs (including lomitapide), whereas the combination with LA was more commonly used in men ($p = 0.05$).

The more intensive treatment was associated with a significant improvement of lipid profile. The nadir of LDL-C during follow-up in the whole ARH cohort was 164.0 ± 85.1 mg/dl, corresponding to a mean reduction of 69.6 ± 16.9% from baseline. The benefit of LLT extended to the whole lipid profile with a significant reduction of total cholesterol (61.9 ± 16.9%; $p < 0.001$) and total triglycerides (21.4 ± 45.3%; $p < 0.01$) at nadir. HDL-C showed a slight improvement, with a nadir mean value of 45.9 ± 11.2 mg/dl compared to the baseline value of 43.1 ± 11.5 mg/dl ($p = 0.07$). However, only 23.1% and 11.5% of ARH patients achieved the LDL-C goals of <100 and 70 mg/dl as recommended for primary and secondary prevention, respectively (15). Comparable changes were observed in men and women (data not shown). However, a large interindividual variability in the lipid-lowering response was seen, as the nadir of LDL-C percentage of reduction ranged from 18.9% to 94.3% (**Figure 1**).

To explore the effects of different LLTs on LDL-C reduction, we divided the cohort into 3 groups according to the use of statin alone or in association with ezetimibe (group 1: n = 18), statin with or without ezetimibe together with LA (group 2: n = 28), and the addition of lomitapide to the other LLTs (group 3: n = 6). It must be noted that 2 of these patients stopped LA 2 to 3 months after the addition of lomitapide and that the reported nadir lipid results were without LA treatment. Compared to baseline, LDL-C nadir values were 62.0 ± 22.3% (range: 18.9 to 88.4) lower in group 1, 70.6 ± 10.3% lower (range: 36.2 to 89.1) in group 2, and 88.3 ± 5.0% (range: 82.7 to 94.3) lower in group 3 (**Figure 2**). The differences in LDL-C lowering among groups were statistically significant ($p = 0.002$ for trend). It is interesting to note, that 100% and 83.3% of ARH patients in group 3 reached a nadir LDL-C value of <100 and 70 mg/dl, respectively. In contrast, in group 1, only 16.7% reached an LDL-C of <100 mg/dl (none: <70 mg/dl), whereas in group 2, 10.7% and 3.6%, respectively, achieved these targets.

FIGURE 2 LDL-C Changes by Lipid-Lowering Therapies



LDL-C values at baseline and at nadir during follow-up were reported. The **box plots** give the median levels **(middle horizontal line in each box)**, the interquartile ranges **(top and bottom of each box)**, and outliers falling below the fifth percentile or above the 95th percentile (**points below or above the vertical lines**, respectively). LLM indicate statins, ezetimibe, and resins. LA = lipoprotein apheresis; LLM = lipid-lowering medications; other abbreviations as in **Figure 1**.

CARDIOVASCULAR OUTCOMES. During follow-up, 12 nonfatal and 2 fatal ASCVD events were recorded in the ARH cohort, giving an overall incidence of 26.9% (1.9% per year) (**Table 3**). Six new events were observed in ARH patients without ASCVD at baseline, thus providing an incidence rate of 14.2% (i.e., 1.0% per year) in this subgroup. One Italian patient died due to the progression of aortic valve stenosis and complications related to replacement surgery, whereas 1 patient from Japan died of non-ASCVD-related cause. The rates of incident ASCVD were comparable in men and women (29.2% and 25%, respectively; $p = 0.73$). The mean age at the time of

TABLE 3 Cardiovascular Outcomes in ARH Cohort During Follow-Up

	Whole Cohort	Men	Women
ASCVD	14 (26.9)	7 (29.2)	7 (25.0)
Fatal	2 (3.8)	0 (0.0)	2 (7.1)
Nonfatal	12 (23.1)	7 (29.2)	5 (17.9)
Type			
MI	5 (9.6)	2 (8.3)	3 (10.7)
Coronary procedures			
PCI	3 (5.8)	3 (12.5)	-
CABG	8 (15.4)	4 (16.7)	4 (14.3)
Cerebrovascular events (TIA, stroke)	0 (0.0)	0 (0.0)	0 (0.0)
Carotid artery stenosis*	1 (3.5)	0 (0.0)	1 (3.5)
Estimated ASCVD IRs			
Overall ARH	203 (97–310)	227 (59–394)	184 (48–321)
ARH without ASCVD	85 (11–160)	90 (0–193)	78 (0–187)
ARH with ASCVD	882 (306–1,459)	833 (17–1650)	926 (114–1,738)
General population	NA	33.9	9.5
Overall relative risk ratio	-	6.7 (1.7–11.6)	19.4 (5.1–33.8)
Without ASCVD	-	2.7 (0–5.7)	8.2 (0–19.7)
With ASCVD	-	24.6 (0.5–48.7)	97.5 (12–182.9)
Aortic valve stenosis†			
Moderate	1 (1.9)	-	1 (3.6)
Severe	5 (9.6)	1 (4.9)	4 (14.3)
Death from complications related to aortic valve stenosis	1 (1.9)	-	1 (3.4)

Values are n (%), n (range), or %. *Patient showed severe bilateral carotid stenosis (>70%) and underwent revascularization. †Evaluation of aortic valve status during follow-up was available in 45 patients. IRs are reported per 10,000 person-years (95% confidence interval). Relative risk was calculated as ARH IRs/IRs general population.

CABG = coronary artery bypass graft; IRs = incidence rates; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; other abbreviations as in Table 1.

the new ASCVD episode was 50.6 ± 13.8 years of age (range: 31 to 72 years). In our population, the most common incident ASCVD event was coronary revascularization (21.2%). For 2 patients with CHD, we did not have information about the treatment given; another patient who experienced CHD during follow-up was currently treated only with medical therapy due to the high risk associated with surgical revascularization. No incident stroke was recorded. All fatal cardiovascular events occurred in women; 2 died of fatal coronary heart disease and 1 because of progression of aortic valve stenosis. The mean age of death in these patients was 52.0 ± 9.1 years.

To estimate the actual ASCVD risk associated with ARH, we compared the incidence rate of ASCVD in our cohort with that reported in the Italian general population standardized for a comparable follow-up period (13). Because the data in the whole general population were not available, we performed the comparison after categorization for sex (Table 3). ARH males showed a 6-fold and females a 19-fold higher risk of incident ASCVD than individuals in the general population.

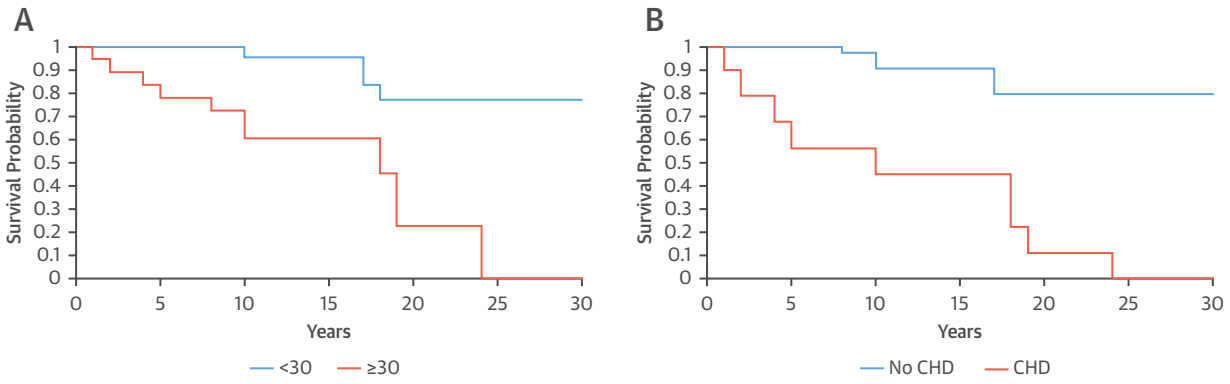
Kaplan-Meier survival analyses showed that the overall median event-free survival in the ARH cohort was 24 years, and this did not differ between men and women (Online Figure 2). However, when patients were categorized according to age and the presence of ASCVD at baseline, event-free survival time was lower in patients at 30 years of age or younger (log-rank test: $p = 0.0003$) (Figure 3A) and in patients with ASCVD at baseline (Figure 3B) (log-rank test: $p < 0.0001$). Finally, the results of the multivariate Cox regression analysis including age, sex, smoking, baseline LDL-C, and history of ASCVD (Online Table 2) demonstrated that age was the only significant independent predictor of recurrent ASCVD ($p = 0.001$), with risk increasing by 8% for each year increase in age. Baseline history of ASCVD was associated with almost 3-fold higher risk of a recurrent ASCVD event, although this association did not reach statistical significance ($p = 0.09$).

During follow-up, 6 new cases of aortic valve stenosis were recorded (1 classified as moderate and 5 as severe), thus giving an overall incidence of this complication of 11.5% (0.8% per year). Among these patients, 3 underwent valve replacement surgery. For the remaining 3 patients, we were not able to retrieve information about the clinical management of aortic stenosis. Of note, 3 times more women than men developed this complication (14.2% vs. 4.2%, respectively; p = NS).

DISCUSSION

The results of this study, involving a large cohort of ARH patients, highlighted 2 major findings. First, the study demonstrated the poor cardiovascular prognosis of these patients. During the 14-year follow-up, 26.9% of them had a new episode of ASCVD, and 11.5% had a new diagnosis of aortic valve stenosis, corresponding to an absolute risk of 1.9% per year and 0.8% per year, respectively (Central Illustration). Moreover, the median ASCVD event-free survival was 24 years in the overall cohort and was dramatically lower (10 years) in ARH patients who had established CHD at entry. Compared to the general Italian population, treated ARH patients showed a 6-fold and 19-fold higher risk of ASCVD in men and women, respectively. The explanation for this sex difference is unclear. The apparently less aggressive LLT in women seems unlikely as the percentage of LDL-C reductions were not different between sexes. The most plausible explanation is that ARH abolishes the cardiovascular protection usually observed in premenopausal women.

FIGURE 3 Kaplan-Meier Survival Curves for Incident ASCVD



Kaplan-Meier survival curves for incident ASCVD according to **(A)** age and **(B)** CHD at baseline. Log-rank test p = 0.0003 for ASCVD according to age at first visit; log-rank test p < 0.0001 for ASCVD according to previous CHD. Label "years" defines the time free of new ASCVD event during follow-up. ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease.

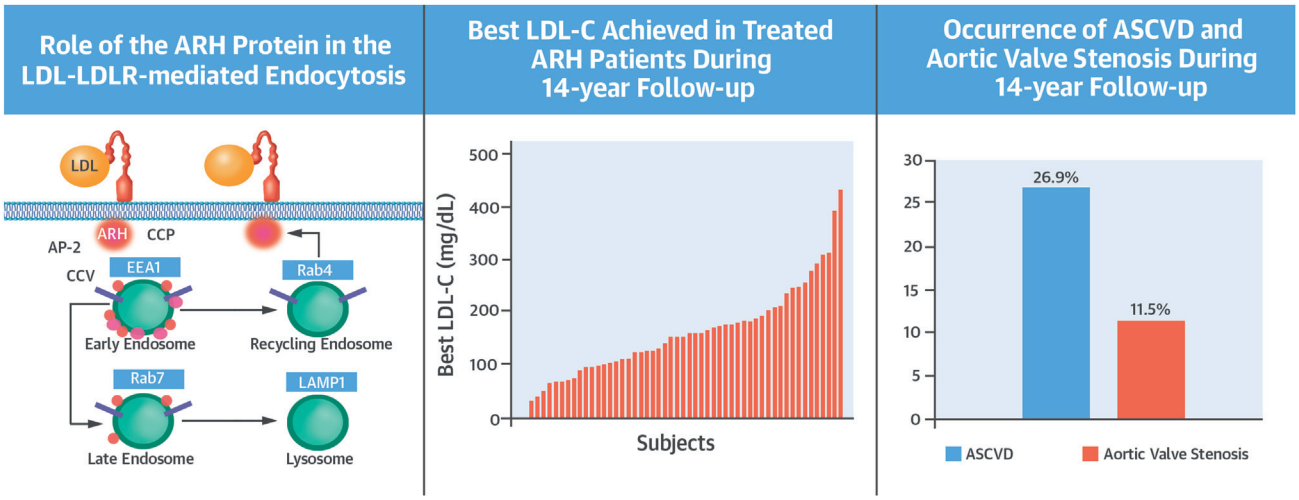
ARH shares clinical similarities with HoFH due to *LDLR* mutations, and previous studies have suggested that the ASCVD risk in ARH may be lower than in HoFH (7,16). A direct comparison between these 2 disorders is not available. However, the exploration for published data may be useful in addressing this question. In a retrospective study by Thompson et al. (17), which included 44 HoFH patients (7 with ARH) followed for 50 years, CAD occurred in 33 patients (75%), thus providing an estimated incident rate of approximately 1.5% per year. Moreover, the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) registry (including also 3 ARH patients) reported ASCVD events in 3 HoFH patients (9.7%) during a follow-up of about 7 years thus giving an incidence rate of about 1.4% per year (18). Finally, in a recent French report considering 53 HoFH patients followed for almost 30 years, the new ASCVD events were 28 (53%), translating into an incidence rate of 1.8% per year (19). The study by Raal et al. (20) provided higher ASCVD incidence rates (3.1% per year), but it must be considered that in that study no HoFH patient received LA and their mean LDL-C concentrations during follow-up remained markedly elevated (451.6 ± 131.2 mg/dl). Taken together with our results, these findings suggest that treated ARH have incident rates of ASCVD, comparable to those of classic HoFH patients.

Another clinical complication that has been reported to be in common between ARH and HoFH is aortic valve stenosis. In our retrospective analysis, we found that 21.2% of patients showed aortic stenosis at baseline and that approximately 11.5% developed it during the follow-up. This provided an estimated incidence rate of 0.8% per year. Remarkably, this complication appeared to be more frequent in women than in men. Comparable estimates in HoFH patients are scanty. In the SAFEHEART registry, the prevalence of aortic stenosis was found to be 19%, but no incidence data were reported (18). In the UK (United Kingdom) HoFH cohort, 21 patients developed aortic valve stenosis during the 50 years of follow-up, with an estimated incidence rate of 0.9% per year (21). This figure is comparable to that in the present study, strongly suggesting that the risk of aortic valve stenosis in ARH is similar to that in HoFH.

It is interesting to note that none of the ARH patients experienced stroke during follow-up. To some extent, this may be surprising, but the lack of a detailed evaluation of atherosclerosis in carotid or cerebral arteries prevents drawing any convincing explanation for this finding. Further studies are needed to clarify this point.

Age and history of ASCVD were found to be significant predictors of incident ASCVD in ARH. In particular, cardiovascular prognosis was the worst in patients who were referred at ≥30 years of age. Conversely, baseline LDL-C did not predict the recurrence of ASCVD. Similar findings have been observed in HoFH (19) and may be explained by the fact that the cumulative cholesterol exposure rather than baseline LDL-C levels determine the risk of new ASCVD in severe forms of hypercholesterolemia (19,22). Unfortunately, we were unable to estimate the total cholesterol burden in our ARH patients. Nevertheless, considering that the best achieved LDL-C was

CENTRAL ILLUSTRATION **Long-Term Outcomes in Patients With Autosomal Recessive Hypercholesterolemia: Retrospective Analysis of a Worldwide Cohort**



D'Erasmo, L. et al. J Am Coll Cardiol. 2018;71(3):279-88.

A summary of clinical and biochemical characteristics of ARH is shown. The role of ARH protein is shown in the liver. The *LDLRAP1* gene is located on chromosome 1p36.11 (exome 9) and encodes an adaptor protein that interacts with the cytoplasmic tail of LDLR, phospholipids, and components of the clathrin mediating the positioning of LDLR to coated pit. It is involved in the endocytic machinery of the LDL-LDLR complex in the liver, mediating internalization of the LDL-LDLR complex **(Left)**. The prevalence of worldwide ARH is estimated to be <1 in 5 × 10^6 population, but in the selected population of Sardinia, Italy, a frequency of *ARH* heterozygotes of approximately 1:143 individuals has been reported. As few clinical data are available for outcomes in these patients, we decided to perform a retrospective collaborative study to answer this question. **(Middle)** The best LDL-C value achieved by each patient during follow-up is reported in Figure 1. As represented, there is large interindividual variability in the response to lipid-lowering therapies, and only the 23.1% of ARH patients achieved the LDL-C target of <100 mg/dl. **(Right)** We reported the prevalence of new ASCVD events and aortic valve stenosis progression during follow-up (Figure 2). AP-2 = adaptor protein complex 2; ARH = autosomal recessive hypercholesterolemia; ASCVD = atherosclerotic cardiovascular disease; CCP = clathrin-coated pit; CCV = clathrin-coated vesicle; LDL-C = low-density lipoprotein cholesterol; LDL-LDLR = low-density lipoprotein–low-density lipoprotein receptor complex; LDLR = low-density lipoprotein receptor.

approximately 164 mg/dl and that only 23.1% of patients reached LDL-C of at least <100 mg/dl, we could speculate that these patients remained exposed to an exceedingly high level of atherogenic LDL-C.

Despite the improvement in lipid-lowering treatment during recent years, the management of LDL-C levels in ARH patients remains far from being satisfactory. However, ARH patients showed a great variability in their lipid-lowering response as some patients displayed up to 90% reduction of their LDL-C levels whereas others did not reach the 20% LDL-C level despite maximum therapy. Given the retrospective nature of this study, there were no reliable data for compliance, which could explain this phenomenon. Nevertheless, it is worth mentioning that ARH patients who received the microsomal triglyceride transfer protein inhibitor lomitapide in addition to the maximal LLM showed a mean LDL-C nadir level of 55.7 ± 17.5 mg/dl (−88% from baseline). Moreover, 83% of them achieved a LDL-C nadir level of <70 mg/dl. These figures are higher than those reported in HoFH subjects, where the addition of lomitapide to conventional treatments allowed achievement of mean percentage of LDL-C changes ranging between −45.5% to −68.2% and an LDL-C level of <70 mg/dl in 47% to 58% of treated patients (23,24). The finding that lomitapide might be a useful drug for improving LDL-C control in ARH warrants further evaluation. An alternative therapeutic option would be the use of PCSK9 inhibitors, but none of the patients in our cohort received these medications. It is noteworthy that the TAUSSIG (Trial Assessing Long Term USe of PCSK9 Inhibition in Subjects With Genetic LDL Disorders) trial reported an LDL-C reduction of 15% in 5 ARH patients receiving 420 mg of evolocumab subcutaneously monthly (25), and more recently, a 32.7% decrease in LDL-C was seen in 1 ARH patient treated with evolocumab, 140 mg twice monthly (26).

STUDY LIMITATIONS. We must acknowledge some strengths and limitations of the present study. To our knowledge, this is the largest longitudinal study

involving ARH that reflects real-life clinical care, and it is the first study to provide information about the ASCVD risk in this rare lipid disorder. Nevertheless, there are several limitations that deserve to be taken into account. Limitations are related mainly to the retrospective nature of our analysis. Clinical data were obtained from medical records, and in some patients, we were not able to retrieve complete clinical data. However, we did not have the possibility to estimate the adherence to treatments as well, as we did not consider that lipid-lowering regimens might have been changed during the observation. ASCVD events were not diagnosed according to a standardized protocol, but they were confirmed by a careful review of clinical records. Moreover, the study design has also limited the use of sophisticated statistical modeling to evaluate the ASCVD risk. We did not a priori identify specific primary endpoints. However, it must be considered that our survey was aimed at describing the natural history of ARH, and it is very difficult to establish a priori power analysis for outcomes in an ultrarare disease such as ARH. The largest proportion of enrolled patients was from Sardinia, thus limiting the possibility to extrapolate present results to all ARH patients. Furthermore, given the rarity of the disease and its recessive inheritance, a subset of patients was related and this may have weakened conclusions about clinical management and outcomes. Finally, the crude comparison between ASCVD risk in ARH and that in the general population should be considered with caution because there are several confounders with this kind of approach. Our rationale for this choice was that most patients included in the study cohort were from Italy. We have standardized the comparison for sex and time period but not for medications or concomitant cardiovascular diseases.

CONCLUSIONS

Our observations indicate that ARH is a serious condition that requires early diagnosis and prompt initiation of an aggressive lipid-lowering therapy. The demonstration that cardiovascular prognosis significantly deteriorates when the diagnosis and therapy are initiated after 30 years of age support this indication. Although the clinical management of ARH has significantly improved in recent years, it is far from optimal. Our findings reinforce the importance of evaluating the effects of new treatments, in addition to optimized established therapies, to improve the cardiovascular prognosis in these high-risk patients.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: ARH is a rare, genetic form of severe hypercholesterolemia caused by mutations in the gene encoding the adaptor protein LDLRAP1 that modulates internalization of the LDL-LDLR. Patients with ARH have inadequate responses to lipid-lowering therapy, which translates to an elevated residual risk of ischemic events.

TRANSLATIONAL OUTLOOK: Clinical trials are needed to determine the optimum long-term management strategy for patients with ARH, including evaluation of novel lipid-lowering therapies.

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KEY WORDS atherosclerotic cardiovascular disease, autosomal recessive hypercholesterolemia, follow-up, lipid-lowering therapies, retrospective analysis

APPENDIX For supplemental figures and tables, please see the online version of this paper.