Atherosclerosis 250 (2016) 144–150

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Predictors of cardiovascular events after one year of molecular screening for Familial hypercholesterolemia

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ARTICLE INFO

Article history:
Received 17 March 2016
Received in revised form
9 May 2016
Accepted 11 May 2016
Available online 15 May 2016

Keywords:
Familial hypercholesterolemia
Cascade screening
Cardiovascular diseases
Cardiovascular disease predictors
Index patient

ABSTRACT

Background and aims: This study reports the first year follow-up of individuals enrolled in Brazil's genetic cascade screening program for Familial Hypercholesterolemia (FH), Hipercol Brasil. Predictors for the occurrence of cardiovascular (CV) events in individuals screened for FH were studied. *Methods*: This is an open prospective cohort of individuals who were included in a cascade genetic screening program for FH. The first prospective follow-up was carried out one year after patients received their genetic test result. Individuals included in this study were index cases (probands) and relatives with identified (M +) or not genetic mutations (M −). Logistic regression analysis was performed to determine predictive variables for the occurrence of CV events censored at one-year of follow-up.
Results: A total of 818 subjects were included, 47 first CV events were ascertained, with 14 (29.7%) being fatal. For index cases, the only factor independently associated with increased risk of CV events was the presence of corneal arcus (OR: 9.39; 95% CI: 2.46–35.82). There was an inverse association of CV events with higher HDL-cholesterol levels (OR: 0.95; 95% CI: 0.90–0.99). For M+ relatives, risk factors associated with increased CV events risk were diabetes mellitus (OR: 7.97; 95% CI: 2.07–30.66) and tobacco consumption (OR: 3.70; 95% CI: 1.09–12.50).
Conclusions: A high one-year incidence of CV events was found in this cascade-screening cohort. Predictors of events differed between index cases and relatives and can be useful for the development of preventive efforts in this highly susceptible group of individuals.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disease clinically characterized by elevated levels of serum low-density lipoprotein-cholesterol (LDL-C) and the occurrence of early cardiovascular disease (CVD) [1–5]. The worldwide prevalence varies from 1:200 to 1:500 in the heterozygous form. The homozygote form is rare and its prevalence is around 1:300,000–1,000,000. In Brazil, it is estimated that there are 402,000 to 670,000 cases of FH and less than 1% are diagnosed and treated appropriately [6–8].

HipercolBrasil program [7] is a nation-wide initiative to provide molecular FH screening for in-risk probands and first-degree relatives. Initially, the Index Case (IC) is clinically identified (LDL-C $\geq$ 210 mg/dL without lipid-lowering drugs) and molecularly tested for a mutation in one of the three known genes that cause heterozygous FH (*LDLR*, *PCSK9* and *APOB*). Once a mutation is detected in an IC, all first-degree relatives (regardless of their cholesterol levels) are invited to participate in the screening program. First-degree relatives have a 50% chance of having the disease [8,9].

FH patients are at high risk for early cardiovascular disease (CVD), since they are exposed to elevated LDL-C levels since birth [10,11]. The risk of cardiovascular (CV) events in these patients may be increased by 20 times if FH is not diagnosed and treated properly [11]. Other factors may increase the risk of CV events in these individuals, such as smoking, hypertension, diabetes, high body mass index (BMI), family history of premature CVD and low levels of HDL cholesterol (HDL-C) [12–16]. However, most studies evaluating the impact of risk factors in FH patients included only probands and

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http://dx.doi.org/10.1016/j.atherosclerosis.2016.05.023
0021-9150/

were derived from retrospective or cross sectional evaluations, thus making the predictors of CV events in relatives still uncertain. In addition, it is tempting to speculate that clinical and demographic determinants of cardiovascular events will vary depending on the final result of the molecular screening program and that this may have important consequences for the care of these individuals. Therefore, the aim of this study was to identify the main CV event predictors in individuals included in a cascade screening cohort for FH, for both probands and relatives.

2. Materials and methods

2.1. Study design

This study evaluated prospectively a cohort of patients who were included in the genetic cascade screening program, HipercolBrasil [7] and was conducted at the Laboratory of Genetics and Molecular Cardiology of the Heart Institute (InCor), University of São Paulo Medical School Hospital, São Paulo, Brazil. The study was approved by the Institutional Ethics Committee (CAPPesq number 3757/12/013).

2.2. Study population and inclusion criteria

The cascade screening program for FH was previously reported by Jannes et al. [7] Index Cases (IC) and relatives summoned by HipercolBrasil program were oriented by trained professionals about the importance of familial genetic screening and written informed consent was obtained from all IC and relatives. For underage individuals (<18 years old), written informed consent was obtained from their legal responsible. The genetic test results were delivered privately in the presence of patients only. In that occasion, patients were instructed about the genetics of FH and the importance of mutation detection. Along with the report, participants received informative folders about FH, cardiovascular disease and the importance of cholesterol control. All patients who agreed to enter the program were registered in the Lipid Clinic of the Heart Institute (InCor/HC-FMUSP), which is the reference tertiary center for treatment and follow-up.

Individuals older than 15 years which were participating in the cascade-screening program were included in the follow-up study once they received the genetic screening report (T0). Study subjects were: IC with suggestive clinical and presenting a definitive genetic diagnosis of FH (M+); IC with suggestive clinical diagnosis but no identified mutations (M−); and relatives with and without identified causal mutations (rM+ and rM−, respectively). Although it is not expected that rM-present a higher risk for CV events when compared to M+ or rM+, these were maintained in the follow-up study so we could assess whether they indeed present no higher risk for CV events, as well to serve as a family-adjusted control group.

2.3. One-year follow-up

To collect data from individuals included in the study, a standardized questionnaire was applied by phone by a trained professional one year after the patient received the result of the genetic test. The follow-up questionnaire ascertained whether the patient presented or not a cardiovascular event during the follow-up. In addition, the questionnaire inquired about previous CVD; presence of risk factors for atherosclerosis; history of early CVD in first-degree relatives (e.g. male <55 and female <60 years-old); current biochemical exams; follow-up with specialists; which medication the patient was using and if there were changes in prescription; adherence to treatment; onset of additional risk factors for cardiovascular events (hypertension, diabetes, smoking); physical activity, and patient's general health. Incomplete treatment adherence was defined as patients failing to take their medication at least 5 times a month.

First cardiovascular events during follow-up were defined as: acute myocardial infarction, unstable angina with hospitalization, coronary angioplasty, coronary artery bypass surgery, ischemic stroke, ischemic heart disease, or congestive heart failure. Cardiovascular events, plasma lipids, presence of CVD risk factors, and use of lipid-lowering drugs were adjudicated from patients' medical records.

2.4. Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 13.0). Initially, a descriptive analysis of the variables was carried out. For continuous variables the mean and standard deviation were calculated. Categorical variables were calculated as frequencies. The differences between frequencies were compared using the chi-square test. The differences between means were compared with Student t or Analysis of variance (ANOVA) tests if necessary. Significance was considered at a p value < 0.05. The logistic regression analysis was performed to determine predictive variables for the occurrence of CV events. The magnitude of the association was estimated using the odds ratio (OR) with 95% confidence intervals (95% CI).

3. Results

3.1. Clinical and laboratory parameters

A total of 818 subjects were included in the study. Tables 1 and 2 show clinical and laboratory characteristics of the subjects in the first year of follow-up, respectively. Of all ICs (n = 299) included in the analysis, 167 (55.8%) were M+ while 132 were M−. Of interest, after one year of follow-up, although 11% of M- IC had their dose of lipid-lowering agents increased, overall this group presented a trend for decrease in the prevalence of lipid-lowering treatment (LLT). For M+, in 18.5% the prescribed doses were increased, without a significant change in the overall prevalence of LLT.

Regarding the lipid profile, Table 2 shows that both M+ and M- IC presented a decrease in total and LDL-C, and an increase in HDL-C levels after one year ($p < 0.05$).

The numbers of relatives included in the analysis were 348 rM+ (67%) and 171 rM−. Table 1 shows that rM + had an increase in the prevalence of diabetes diagnosis, in the use of lipid-lowering drugs and a decrease in tobacco consumption ($p < 0.05$) after one year. Among rM + individuals that were under LLT during the follow-up, 29.8% presented changes in the drug dosage (21.2% with dose increase). However, of all patients under LLT 25.1% reported incomplete adherence to treatment. Table 2 shows that there was no significant alteration in lipid profile of relatives after one year.

3.2. Cardiovascular events during follow-up

During follow-up a total of 47 first new CV events occurred, being 33 (70%) nonfatal: 21.2% myocardial infarction, 15.5% angina, 12.1% coronary artery bypass surgery, 24.2% coronary angioplasty, 12.1% congestive heart failure, 3% ischemic stroke, and 10% ischemic heart disease. Fourteen events (30%) were fatal: 71.4% myocardial infarction, 21.4% congestive heart failure, and 7.1% ischemic stroke. Of all CV events (fatal or non-fatal) in the group of mutation positive individuals (IC and relatives) 24.3% refer to coronary angioplasty and 10.8% to coronary artery bypass surgery.

A total of 37 (7.2%) and 10 (3.3%) events occurred respectively in

Table 1
Clinical characteristics of index cases presenting or not familial hypercholesterolemia causing mutations (M +, n = 167; M −, n = 132) and their respective relatives (M +, n = 348; M−, n = 171) at the time of genetic test result deliver (T_0) and one-year follow-up (T_1).

	Mutation +					Mutation −				
	T_0		T_1			T_0		T_1		
		n		n	*p* value		n		n	*p* value[b]
Index cases										
Age (years)	50 ± 16	167	52 ± 15	167	0.01	56 ± 12	132	57 ± 12	132	0.01
BMI (kg/m^2)	27 ± 5	134	27 ± 4	134	0.42	28 ± 4	129	27 ± 5	129	0.07
Hypertension (%)	28.7	48	31.1	52	0.52	49.6	66	51.1	68	0.75
Diabetes (%)	8.4	14	11.4	19	0.30	16.5	22	22.6	30	0.20
Tobacco consumption										
Current	6.0	10	5.4	9		18.0	24	15.8	21	
Former	28.7	48	29.3	49	0.96	31.6	42	33.8	45	0.85
Never	51.5	86	50.3	84		48.9	65	48.1	64	
Pharmacological treatment[a] (%)	80.8	135	90.4	151	0.97	89.5	119	83.5	111	0.06
Relatives										
Age (years)	46 ± 17	348	48 ± 16	348	0.01	47 ± 16	171	49 ± 17	171	0.01
BMI (kg/m^2)	26 ± 5	333	26 ± 5	333	0.68	28 ± 14	162	27 ± 6	162	0.19
Hypertension (%)	30.5	106	32.8	114	0.47	25.0	43	25.0	43	0.94
Diabetes (%)	9.8	34	14.9	52	0.03	9.9	17	12.2	21	0.46
Tobacco consumption										
Current	12.1	42	8.6	30		9.3	16	9.3	16	
Former	21.0	73	24.7	86	0.21	23.3	40	23.8	41	0.99
Never	66.4	231	65.5	228		67.4	116	66.9	115	
Pharmacological treatment[a] (%)	68.7	239	79	275	0.04	25.6	44	23.8	41	0.11

[a] Medications for cholesterol treatment were statins, ezetimibe, resins, fibrates and niacin.
[b] *p* value < 0.05.

Table 2
Plasma lipids of index cases presenting or not familial hypercholesterolemia causing mutations (M +, n = 167; M −, n = 132) and of their relatives (M +, n = 348; M −, n = 171) at the period of genetic test result deliver (T_0) and at 1 year follow-up (T_1).

	Mutation +				Mutation −			
	T_0	T_1	n	*p* value	T_0	T_1	n	*p* value[a]
Index cases								
TC (mg/dL)								
All individuals	259 ± 95	241 ± 86	115	0.01	236 ± 71	218 ± 61	96	0.01
LDL-C (mg/dL)								
All individuals	188 ± 90	170 ± 84	119	0.01	156 ± 65	135 ± 51	95	0.01
HDL-C (mg/dL)								
All individuals	46 ± 14	48 ± 15	115	0.02	51 ± 15	53 ± 15	96	0.13
TG (mg/dL)								
All individuals	119 ± 57	113 ± 57	111	0.21	156 ± 103	155 ± 94	95	0.95
Relatives								
TC (mg/dL)								
All individuals	232 ± 61	229 ± 64	206	0.47	200 ± 39	203 ± 50	20	0.69
LDL-C (mg/dL)								
All individuals	162 ± 57	158 ± 60	200	0.39	126 ± 34	127 ± 39	18	0.91
HDL-C (mg/dL)								
All individuals	47 ± 13	48 ± 14	202	0.05	54 ± 16	56 ± 16	19	0.43
TG (mg/dL)								
All individuals	111 ± 70	107 ± 61	201	0.29	128 ± 54	120 ± 57	20	0.63

[a] *p* value < 0.05.

those presenting or not a mutation ($p < 0.05$). There were respectively 20 (11.9%) and 4 (3%) cardiovascular events in IC presenting or not a mutation ($p < 0.05$). Among M+ and M−relatives there was no difference in the rate of CV events, 4.8% and 3.5% respectively ($p > 0.05$).

Table 3 shows the clinical characteristics of IC presenting or not a CV event during follow-up. Comparing M+ IC with and without events, those presenting a CV event, had a higher prevalence of corneal arcus, previous CVD and, higher total and LDL-C and triglycerides with lower concentrations of HDL-C. For M− IC with CV events, only the prevalence of corneal arcus was significantly higher when compared to M−IC without events. There were no differences on the prevalence of LLT at baseline among the groups.

Table 4 shows characteristics of relatives presenting or not a CV event. Among rM+, those presenting CV events were older and mostly male with a higher prevalence of hypertension, diabetes, tobacco consumption and corneal arcus ($p < 0.05$). For rM− with a CV event, levels of total and LDL-C were higher when compared to rM− without events.

When performing univariate analysis, factors associated with increased risk of CV events in IC (M+ and M−) were the presence of a causal FH mutation and corneal arcus. After multivariable adjustment, corneal arcus presence was significantly associated with increased risk for CV events (Table 5). On the contrary there was an independent association of higher HDL-C levels with a reduced risk of CVD.

Table 6 shows the univariate associations with increased risk for CV events in rM+. Older age, male sex, hypertension, diabetes,

Table 3
Characteristics of the index cases according to the presence or absence of cardiovascular (CV) events.

	Mutation + (n = 167)					Mutation− (n = 132)				
	Presence of CV events[a]					Presence of CV events				
	Yes (n = 20)		No (n = 147)		*p* value	Yes (n = 4)		No (n = 128)		*p* value[d]
		n		n			n		n	
Age (years)	56 ± 19	20	50 ± 15	147	0.08	63 ± 10	4	55 ± 12	128	0.22
Males (%)	55.0	11	42.2	62	0.27	25.0	1	25.0	32	0.99
Females (%)	45.0	9	57.8	85		75.0	3	75.0	96	
Hypertension (%)	35.0	7	27.9	41	0.25	50.0	2	50.0	64	0.97
Diabetes (%)	0	0	9.5	14	0.17	0	0	17.2	22	0.42
Previous CVD (%)	60.0	12	37.4	55	0.05	50.0	2	29.5	38	0.37
Family history of CVD[b] (%)	40.0	8	35.4	52	0.21	50.0	2	48.2	62	0.80
Pharmacological treatment[c] (%)	70.0	14	82.3	121	0.74	100	4	89.1	114	0.53
BMI (kg/m^2)	27 ± 6	14	27 ± 5	126	0.96	27 ± 3	4	28 ± 4	126	0.55
Tobacco consumption (current and former) (%)	35.0	7	34.7	51	0.59	25.0	1	50.0	64	0.31
Corneal arcus (%)	50.0	10	24.5	36	0.01	50.0	2	13.3	17	0.04
Xanthelasmas (%)	20.0	4	10.2	15	0.09	0	0	7.0	9	0.58
Tendon xanthoma (%)	15.0	3	9.5	14	0.26	0	0	2.3	3	0.78
TC (mg/dL)	351 ± 175	13	264 ± 93	124	0.01	254 ± 121	4	240 ± 67	114	0.68
LDL-C (mg/dL)	274 ± 161	13	193 ± 90	126	0.01	174 ± 101	4	160 ± 63	112	0.66
HDL-C(mg/dL)	37 ± 8	13	47 ± 13	126	0.01	52 ± 14	4	50 ± 14	114	0.78
TG (mg/dL)	182 ± 137	13	122 ± 57	122	0.01	140 ± 103	4	163 ± 108	113	0.67

[a] Patients who had a cardiac event in the first year of follow-up.
[b] Family first degree who had some early cardiovascular event: male < 55 and female < 60 years-old.
[c] Medications for cholesterol treatment were statins, ezetimibe, resins, fibrates and niacin.
[d] *p* value < 0.05. TC: total cholesterol; TG: triglycerides.

Table 4
Characteristics of the relatives according to the presence or absence of cardiovascular (CV) events.

	Mutation + (n = 348)					Mutation− (n = 171)				
	Presence of CV events[a]					Presence of CV events				
	Yes (n = 17)		No (n = 331)		*p* value	Yes (n = 6)		No (n = 165)		*p* value[d]
		n		n			n		n	
Age (years)	55 ± 16	17	46 ± 16	331	0.02	66 ± 6	6	47 ± 16	165	0.01
Males (%)	64.7	11	36.9	122	0.02	50.0	3	36.4	60	0.49
Females (%)	35.3	6	63.1	209		50.0	3	63.6	105	
Hypertension (%)	64.7	11	28.7	95	0.01	66.7	4	23.6	39	0.01
Diabetes (%)	47.1	8	7.9	26	0.01	33.3	2	9.1	15	0.05
Previous CVD (%)	76.5	13	35.0	116	0.01	50.0	3	10.2	17	0.01
Family history of CVD[b] (%)	47.1	8	50.2	166	0.47	66.7	4	47.3	78	0.49
Pharmacological treatment[c] (%)	94.1	16	67.4	223	0.04	16.7	1	26.1	43	0.39
BMI (kg/m^2)	28 ± 7	16	26 ± 5	328	0.34	27 ± 3	6	28 ± 14	165	0.92
Tobacco consumption (current and former) (%)	70.6	12	31.1	103	0.01	50.0	3	32.1	53	0.35
Corneal arcus (%)	41.2	7	16.9	56	0.01	0	0	4.2	7	0.63
Xanthelasmas (%)	11.8	2	8.8	29	0.67	0	0	3.0	5	0.69
Tendon xanthoma (%)	11.8	2	7.6	25	0.68	0	0	0	0	0.84
TC (mg/dL)	234 ± 74	14	238 ± 68	223	0.82	249 ± 6	2	190 ± 39	25	0.04
LDL-C (mg/dL)	174 ± 72	14	164 ± 58	214	0.55	166 ± 11	2	115 ± 36	23	0.06
HDL-C(mg/dL)	43 ± 13	14	47 ± 13	219	0.28	54 ± 18	2	51 ± 15	24	0.84
TG (mg/dL)	86 ± 39	14	125 ± 131	219	0.27	149 ± 111	2	129 ± 64	25	0.69

[a] Patients who had a cardiac event in the first year of follow-up.
[b] Family first degree who had some early cardiovascular event: male <55 and female <60 years old.
[c] Medications for cholesterol treatment were statins, ezetimibe, resins, fibrates and niacin.
[d] *p* value < 0.05. TC: total cholesterol; TG: triglycerides.

previous CVD, tobacco consumption (current or former) and corneal arcus were all associated. In the multivariate analysis only diabetes and tobacco consumption remained significantly associated with the risk of CV events.

4. Discussion

This study reports the first follow-up in individuals enrolled in the cascade genetic screening program for FH in Brazil, one year after they received their genetic test results. Different from previous reports, this is not a sole description of early events in a cohort of FH patients. Since we are following all individuals that were submitted to a genetic screening cascade our results allow us to derive estimates of risk for a broader variety of risk subgroups that are commonly seen in this type of program. As reported, a high risk of CV events is not only seen in probands of such a cohort, but rather in all different substrata analyzed. Predictors of this risk are, however, different.

4.1. Cardiovascular events and their predictors in index cases and relatives

As previously described [14], the incidence of CV events in M+ individuals was higher than in M−, and the incidence of fatal or

Table 5
Variables associated with CV events in index cases presenting or not mutations after univariate and multivariate logistic regression.

	OR[a]	95% CI	*p* value[c]	OR[b]	95% CI	*p* value
Mutation +	4.35	1.45–13.07	0.01			
Age (years)	1.02	0.99–1.05	0.10			
Gender (male)	1.93	0.83–4.47	0.12			
Hypertension	1.28	0.50–3.27	0.59			
Previous CVD	2.75	1.17–6.43	0.01			
Tobacco consumption (current and former)	0.87	0.34–2.25	0.77			
Family history of CVD	1.84	0.55–6.07	0.31			
Xanthelasmas	2.70	0.82–8.86	0.10			
Corneal arcus	7.33	2.63–20.44	0.01	9.39	2.46–35.82	0.01
Tendon xanthomas	2.93	0.76–11.22	0.11			
TC	1.00	0.99–1.01	0.88			
LDL-C	1.01	1.00–1.02	0.01			
HDL-C	0.95	0.91–0.99	0.01	0.95	0.90–0.99	0.04
TG	1.00	0.99–1.01	0.20			

[a] Univariate Logistic Regression Analysis.
[b] Multivariate Logistic Regression Analysis (Adjusted for age, gender, HDL-C, corneal arcus, previous CVD).
[c] p value < 0.05.

Table 6
Variables associated with CV events in relatives with positive mutations after univariate and multivariate logistic regression.

	OR[a]	95% CI	*p* value[c]	OR[b]	95% CI	*p* value
Age (years)	1.03	1.01–1.06	0.02			
Gender (male)	3.14	1.13–8.70	0.02			
Hypertension	4.41	1.58–12.29	0.01			
Diabetes	10.25	3.65–28.82	0.01	7.97	2.07–30.66	0.01
Previous CVD	6.02	1.92–18.89	0.01			
Tobacco consumption (current and former)	5.26	1.80–15.33	0.01	3.70	1.09–12.50	0.03
Family history of CVD	0.67	0.22–2.00	0.47			
Xanthelasmas	1.37	0.29–6.37	0.68			
Corneal arcus	4.03	1.40–11.57	0.01			
Tendon xanthoma	1.37	0.29–6.36	0.68			
TC	0.99	0.99–1.01	0.99			
LDL-C	1.01	0.99–1.01	0.54			
HDL-C	0.97	0.93–1.02	0.28			
TG	0.99	0.97–1.01	0.99			

[a] Univariate Logistic Regression Analysis.
[b] Multivariate Logistic Regression Analysis (Adjusted for age, hypertension, diabetes, previous CVD, tobacco consumption and corneal arcus).
[c] p value < 0.05.

nonfatal CV events in the first year of follow-up was more than twice in M + IC than in affected relatives. The occurrence of coronary artery bypass surgery and coronary angioplasty among M + IC and rM+ was 35%, suggesting that the cascade screening could have in part contributed to the occurrence of these events. After genetic diagnosis affected individuals were indeed referred to a tertiary cardiology center. Needless to say that the sole fact that these individuals were molecularly diagnosed as having FH may have led to increased use of diagnostic procedures to diagnose subclinical atherosclerosis that is frequently encountered in FH patients [2] and, consequently, led to more revascularization procedures. It is not the scope of the present work to discuss the evidence-based indication of revascularization procedures for coronary artery disease. It should be realized, nonetheless, that individuals that received new revascularization procedures were perceived by their clinicians as having increased cardiovascular risk.

FH phenotype presents great variability within the same family and among different mutations [17,18]. However, through the analysis of risk factors association with CV events, it is possible to infer that exposure time to elevated levels of LDL-C in the IC seems to be the most important factor that influenced CV event occurrence. In M + IC who suffered a CV event, mean baseline LDL-C levels were 274 mg/dL, being 29% higher than in IC who did not have a CV event. Previously, LDL-C levels ≥260 mg/dL have been shown to increase in 8.29 times the risk of a CV event is FH individuals [18–21]. Indeed, xanthelasmas and corneal arcus formation, important markers of long term exposition to high levels of LDL-C [22], were significantly higher in the M + IC who had a CV event and the latter was independently associated with occurrence of CVD in the follow-up.

On the other hand, as previously seen in cross sectional evaluations [13,14] higher HDL-C concentrations were independently associated with a reduced risk of CV events.

Of importance, in the rM+ who had a CV event, predictors where different from those of index cases. We have observed, as predictors, a higher prevalence of lifestyle-related factors such as diabetes, hypertension, tobacco consumption, resembling the factors related to CV events in the non-FH populations [23]. This highlights the importance of early detection and reemphasizes the need for cascade screening of FH probands' first-degree family members [24].

4.2. Life-style changes after genetic screening

Another important question we have addressed was regarding the effects of going through FH genetic screening upon lifestyle changes. This is particularly important since once FH screening programs are well established they will constitute golden opportunities to impact the cardiovascular health of high-risk individuals in a community. Understanding the dynamics of its impact is, thus,

paramount for the better overall use of this resource.

In general, FH index cases present higher prevalence and duration of statin use than their relatives [17,18]. In the first year of follow-up, there was a significant decrease in total and LDL-C levels in M+ IC. Although 81% of M+ ICs were already under LLT treatment when enrolled in the study, the genetic test result might have contributed to treatment adherence and adjustment of drug dosage. This justifying the significant decrease in the lipid levels of these individuals, despite the overall majority of them being already on treatment at baseline.

In the rM+, there was a significant increase in LLT prevalence. When they received the genetic result, 68.7% of rM+ where under treatment and after the program guiding and referral to specific care, the prevalence increased to 79%. However, there was no significant decrease in lipid levels after one year probably due to the fact that many rM+ were still adjusting their treatment, both for dose and type of medication. In addition, one in four referred incomplete adherence to proposed treatment. A follow-up study with FH individuals, performed in the Netherlands [25], has shown that when they got in the screening program, only 37.6% of patients follow the LLT and one year after they were enrolled in the program, that percentage increased to 92.5%.

Unexpectedly, in this one year of follow-up there was a significant increase in diabetes prevalence on rM+. It is difficult to infer in a one-year follow-up period the main reason for this augmented prevalence, being this one of the limitations of this study. However, we must take into account the use of statins in the incidence of diabetes, as pointed by Preiss et al. [26] who have shown that the use of statins seems to be associated with the increase in diabetes incidence. We could not associate the observed increased incidence with dose augmentation or statin initiation. Another possibility is that, since diabetes information was self-referred, the noted increased is mainly secondary to increased awareness and search for health care resources by individuals exposed to the program's information on cardiovascular related risks.

In conclusion, after one-year follow-up of individuals enrolled in the HiperCol Brasil genetic cascade screening program we were able to detect a high prevalence of CV events after this small follow-up period. Moreover, we could identify that in IC the long-term exposition to high levels of LDL-C, indicated by the presence of corneal arcus, seem to be the most important predictor of short-term risk for a CV event, while in relatives of positive ICs one was able to associate CV events occurrence to an increased number of modifiable risk factors. Longer follow-up will help to better characterize the importance of risk factors for CVD onset in a population receiving contemporary lipid lowering therapy.

Conflict of interest

The authors declared that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Acknowledgments

We thank the patients who participated in the cohort study, the technical assistance of the Laboratory of Genetics and Molecular Cardiology group, Heart Institute (InCor) University of Sao Paulo Medical School Hospital. The funding of Sociedade Hospital Samaritano and Ministério da Saúde (PROADI-SUS; SIPAR: 25000.180.672/2011-81) are gratefully acknowledged.

RDS refers receiving honoraria for consulting or speaker activities from Amgen, Aegerion, Astra Zeneca, Akcea, Boehringer-Ingelheim, Cerenis, Genzyme, Kowa, Eli-Lilly, Merck, Prizer, Sanofi/Regeneron, Torrent and Unilever.

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