PREVALENCE AND MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE: THE HEREDITY SURVEY

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ABSTRACT

Background and aims. Familial hypercholesterolemia (FH) is a genetic disorder characterized by high levels of low density lipoprotein cholesterol (LDL-C) predisposing to premature cardiovascular disease. Its prevalence varies and has been estimated around 1 in 200-500. The Heredity survey evaluated the prevalence of potential FH and the therapeutic approaches among patients with established coronary artery disease (CAD) or peripheral artery disease (PAD) in which it is less well documented.

Methods. Data were collected in patients admitted to programs of rehabilitation and secondary prevention in Italy. Potential FH were estimated using Dutch Lipid Clinic Network (DLCN) criteria. Potential FH were defined as having a total score ≥6.

Results. Among the 1438 consecutive patients evaluated, the prevalence of potential FH was 3.7% . The prevalence was inversely related to age, with a putative prevalence of 1:10 in those with <55yrs of age (male) and <60yrs (female). Definite FH (DLCN score >8) had the highest percentages of patients after an ACS (75% vs 52.5% in the whole study population). At discharge, most patients were on high intensity statin therapy, but despite this, potential FH group still had a higher percentages of patients with LDL-C levels not at target and having a distance from the target higher than 50%.

Conclusions. Among patients with established coronary heart disease, the prevalence of potential FH is higher than in the general population; the results suggest that a correct identification of potential FH, especially in younger patients, may help to better manage their high cardiovascular risk.

KEYWORDS: familial hypercholesterolemia; coronary artery disease; lower extremities peripheral disease; prevalence; statins.

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic-based disease characterized by premature atherosclerotic disease due to the presence of high low density lipoprotein cholesterol (LDL-C) levels from birth[1-3]. Mutations in the gene encoding the receptor for LDL (LDLR) are the most common cause of FH, but mutations in other genes involved in LDL metabolism, including proprotein convertase subtilisin/kexin type 9 (PCSK9) and apolipoprotein B, may lead to similar phenotypes[4]. In the general population, the frequency of homozygous FH, requiring therapeutic intervention in the first decade of life, is very low (1:1,000,000)[2, 4]. On the contrary, heterozygous FH in Caucasians is more common; historically, its prevalence was estimated at 1 in 500, but more recent studies suggest a higher frequency, up to 1 in 200-250[5]. Because of the exposure to high levels of LDL-C from birth (200-400 mg/dL; 5-10 mmol/L), FH subjects have a significantly greater risk of cardiovascular disease and, if untreated, they may experience cardiovascular events early in the life[6]. Thus, the identification of FH subjects is critical for the prevention of coronary heart disease through early and effective therapeutic approaches. Despite this, the identification of patients with heterozygous FH is still partial in Europe, in particular in Italy[2].

Different criteria have been proposed to allow the detection of FH patients, including the Simon Broome Register Diagnostic criteria[7], the MedPed/WHO criteria[8] and the Dutch Lipid Clinic Network (DLCN) Diagnostic criteria[9]. These algorithms are mainly based on the blood LDL-C levels, a positive family history of coronary artery disease (CAD), personal CAD history and physical signs[7-9].

Recently, it was shown that among patients with CAD or other atherosclerotic diseases the frequency of FH is significantly higher than in general population and that these patients are at particularly elevated risk of recurrent events[10-12]. In particular, the *post hoc* analysis of EUROASPIRE IV reported an increased prevalence of potential FH in coronary patients from 24 European countries by means of standardized interview and biochemical and clinical examination using an adapted version of the DLCN criteria[10]. However, this study did not include Italian patients; to overcome this lack, we designed the "HEterozigous familial hypeRcholesterolemia in patiEnts admitted to carDiac rehabilitaTion programs in Italy"

(HEREDITY) survey through Italy's national network of cardiac rehabilitation and secondary prevention (CRP) centres. This survey aimed at investigating the prevalence of heterozygous FH using the DLCN criteria among "real world" patients with CAD or peripheral artery disease (PAD) admitted to programs of rehabilitation and secondary prevention. Potential FH patients, defined as having a Dutch score ≥6, were compared with the other patients and evaluated at discharge. Moreover, this study evaluated the therapeutic approaches and the results obtained in terms of recommended lipid target values.

METHODS

Study design

The HEREDITY survey was an observational multicentre nationwide survey involving 26 in- and out-patients CRP units. Each participating centre was asked to provide clinical and biochemical data of at least 50 consecutive patients discharged (between February and March 2015), in order to ensure the expected sample size (more than 1000 patients), after a CRP program (4-8 weeks of duration) for recent (within 2 weeks) acute coronary syndrome (ACS) and/or percutaneous/ surgical myocardial revascularization or stable angina with medical therapy or for lower extremity PAD with or without recent acute event.

Electronic case report forms (eCRF) were used for data entry, and data were transferred via web to a central database. Patients' anonymity was ensured. The eCRF were collected and data were analysed in relation to the characteristics of patients (sex, age, BMI), admission diagnosis, CRP setting (inpatients or outpatients), co-morbidities, global risk profile, drug therapy and biochemical parameters including total cholesterol, LDL-C, HDL-C, triglycerides (TG) and glycaemia values at discharge. Total cholesterol, HDL-C and TG were measured by local laboratories, all accredited by ISO 15189:2003 (Medical Laboratories- Particular requirement for quality and competence). LDL-C was calculated according to the Friedewald's formula. The prevalence of FH was estimated using the DLCN criteria[2] .

Since a large majority of the patients (80.3%) was on statin therapy for at least four weeks at the moment of blood sampling at admission to CRP program, the LDL-C levels obtained were adjusted by correction factors taking into consideration the type and dose of statin[11, 13].

The results of the algorithm were interpreted as follows: unlikely FH, total score 0-2; possible FH, total score 3-5; probable FH, total score 6-8; definite FH, total score>8. Potential FH were defined as having a total score ≥6.

Local Ethical committees approved the study. All patients provided written informed consent. The survey involved no diagnostic tests, care interventions or pharmacological treatments that were not part of the routine clinical practice of each participating centre, and each physician enrolling a patient was fully responsible for his/her management. The survey was independently conducted and the data were analysed under the scrutiny of the Steering Committee of the study.

Statistical methods

We expected to enrol a total sample of approximately 1,000 patients. According to the literature data, we hypothesized a prevalence of heterozygous FH of approximately 5% in our study population, thus allowing to obtain a sample of about 50 patients with probable-definite FH. All data collected in the online database underwent data cleaning and quality control. Continuous variables were expressed as mean±standard deviation (SD) and median (range), categorical variables as number and percentage. Enrolled patients were analysed both as a whole population and by single FH probability class . Patients were also analysed by comparing the group of potential FH having a Dutch score ≥6 (probable FH+definite FH) with all the other patients (unlikely FH+possible FH).

Differences between these groups were tested by the Fischer's exact test or Chi Square (categorical data) and by Student's t-test (continuous numeric data). All computations were carried out with SAS® statistical software (SAS Institute, Cary, NC, USA – version 9.2) and a $p<0.05$ was considered significant.

RESULTS

This survey included a total of 1438 patients recruited from 26 CRP centres (Appendix). Clinical characteristics of the patients participating in this study are presented in Table 1. Men were 83.7% of the sample; mean age of the whole study population was 65.9±10.6 years, and more

than one fourth of total population (429 out of 1438, 29.8%) was ≤60 years old. Recent ACS, with or without percutaneous myocardial revascularization, was the most common clinical presentation (52.5%), followed by stable CAD on medical therapy (26.5%) and symptomatic chronic CAD undergoing surgical or percutaneous myocardial revascularization (18%); isolated lower extremity PAD was the least common presentation (3.1%) (Table 1).

Table 2 reports the prevalence for the different categories of FH according to DLCN criteria by gender, age and entry diagnosis. Considering the whole population, 53 patients (3.7%) had a score ≥6 (potential FH) and 12 (0.8%) had a score>8 (definite FH). Patients with potential FH (probable+definite) were younger compared with the other group (unlikely/possible) (58.3y±11.5 vs 66.2±10.5, p<0.001) (Table 2). The younger population (i.e. men <55 years and women <60) had a significantly higher prevalence of potential FH compared with older patients (10.4% vs 2.3%, p<0.001)

The prevalence of potential FH was higher in women (5.5%) than in men (3.3%); the analysis by age subgroups showed that this finding was valid in patients aged 50-69 years, while among patients aged <50 years or >70 years the prevalence was higher in men. Among potential FH patients, 30.2% had <50 years and 58.5% had <60 years, compared with 8% and 28.7%, respectively, among unlikely/possible FH patients. Among subjects aged <50 years, 12.6% were potential FH but this percentage was drastically reduced in the other classes of age (51-60y: 5%; 61-70y: 2.7%; >70y: 1.6%, P<0.001). About half of the patients enrolled presented with an ACS with or without revascularization (52.5%); when analysed within the single groups, definite FH had the highest percentages of patients presenting with an ACS (75%) (Table 2).

Considering the whole population, a higher number of patients was taking statins at discharge compared to the admission to CRP program (from 80.3% to 87.7%, p<0.001). The percentage of patients taking statin therapy was very high in probable FH (97.6% at discharge) and in definite FH (100%); in potential FH there was a 98.1% of patients taking statins, compared with to 87.3% in the unlikely/possible FH group.

High intensity lipid-lowering approach (atorvastatin 40-80 mg, rosuvastatin 20-40 mg or simvastatin/ezetimibe combination) was used in 80.0% of whole population and in 92.2% of

potential FH patients. Atorvastatin (82.4%) and rosuvastatin (15.7%) were the most used statins in potential FH. None of the potential FH and very low percentage (2.4%) of unlikely/possible FH was discharged with low-intensity statin therapy. Also the use of ezetimibe therapy increased at the end of the survey (from 5.6% to 9.1%). The increase was more evident in probable FH (from 7.3% to 22.0%) and in definite FH groups (from 0% to 25%).

At discharge, the percentages of patients with LDL-C levels at target (LDL-C<70 mg/dL) differed significantly among groups, being higher in the unlikely FH group (45.6%) and very low in the potential FH group (2.2%), due to the fact that only 1 patient of probable FH group and none of definite group had LDL-C levels at target (Figure 1). Among patients not at target, distance from target was higher than 50% in 2.8% of total population and in 36.6% of potential FH patients, despite high intensity therapy (Figure 2). When analyzed based on the distance from target, we observed that most patients were discharged with high-intensity statin therapy (80.9% of those with distance from target ≤50% and 76.7% of those with distance from target >50%), and only a minority was taking moderate-intensity statin therapy (Table 3)

DISCUSSION

The main finding of this study is to contribute, with Italian data, to the epidemiological evidence that FH condition may be highly probable within special groups of patients (such as those with cardiovascular disease) and to suggest a preferred context for the diagnosis of FH patients. In fact, we reported that, among patients with CAD and/or LE-PAD admitted to a structured program of CRP, the prevalence of FH is significantly higher than that observed in the general population, having found a 3.7% patients with a Dutch score ≥6 (potential FH) and 0.8% with a Dutch score>8 (definite FH).

Despite the numerical difference, this finding is in agreement with the observations reported in other recent studies[10-12]. In the EUROASPIRE IV survey, the prevalence of potential FH in coronary patients was 8.3%, while definite FH were 1.1%[10], with large difference between countries. Our results on potential FH were very similar to those observed in South Europe countries (Spain 4.1%; Greece 3.8%; France 4.4%). These data, observed in post-acute phase

of coronary and peripheral artery disease, were different from those observed in the acute phase: in the study of Pang et al., the prevalence of potential FH in patients with early-onset coronary artery disease was 14.3% and definite FH was 2.3%[11]; Nanchen et al. reported a 1.6% prevalence of potential FH among patients with acute coronary syndromes[12]. Altogether, these observations suggest that, although the prevalence of FH in the general population is relatively low, among patients with cardiovascular-related events this prevalence is several folds higher.

In our survey, the prevalence of potential FH was inversely related to age, and more so in men that in women as observed also in other studies[10, 12]. This association with age may be explained by the weight given to younger age at the time of first CAD event in the DLCN criteria. The difference in the prevalence of potential FH by gender may partially be artificial due to the difference in defining premature CAD in men and women. It must be acknowledged, however, that the FH prevalence here reported cannot be compared to that of the general population, as in the sample selected for this survey (post-CAD/PAD patients) women and young people are obviously less represented.

According to our data, more than 1 out of 10 patients younger than 55 years (male) or 60 years (female) with previous atherosclerotic events is a potential FH, with obvious clinical implications for an adequate management. In fact, the higher prevalence of potential FH in patients with cardiovascular disease-related events, especially in those aged <55-60 years, opens the opportunity to increase the detection rate among family members. When a suspect case is detected, family screening protocols are warranted. All those identified with potential FH should receive high-intensity statins; even then, a large proportion will probably not reach the LDL-C goals recommended from international guidelines and combination therapies or new therapies should be considered in these patients.

Furthermore, considering the different entry diagnoses recorded in our study population, a higher percentage of potential FH was observed among patients with a recent acute coronary syndrome compared with subjects with stable symptomatic CAD undergoing medical therapy or elective myocardial revascularization.

Another relevant finding of this study is that, both in the whole population and in the potential FH group, the percentage of patients under statin therapy increased significantly at discharge from cardiac rehabilitation program, compared with the admission, particularly those at high-intensity statin therapy; it is worth noting that the therapeutic approach at discharge was driven by the incident cardiovascular event and not by the presence/absence of FH condition. Differently from data reported for other countries included in the Euroaspire IV study, the present study retrospectively showed that 92.2% of the patients with potential FH were on high-intensity statin therapy at discharge; despite that, only a minority of potential FH patients reached the desired LDL-C target <70 mg/dL, according to secondary prevention guideline recommendations, due to their higher baseline LDL-C levels. It is worth noting that, although the combination statin-ezetimibe has been established as an effective therapeutic approach for FH patients leading to an additional reduction of LDL-C levels of about 10-15% compared with statin alone[14-16], in this study a very low number of patients received statin in combination with ezetimibe at discharge. This observation, together with the low proportion of patients reaching the recommended LDL-C levels suggested by their DLCN score established retrospectively (<70 mg/dL in the presence of CVD)[17], suggests that, in the absence of a clinical evaluation of their possible FH condition, it may be difficult to set an appropriate pharmacological approach for these patients. The SAFEHEART study, a large ongoing registry of molecularly defined patients with heterozygous FH treated in Spain, reported that, despite the use of intensified lipid-lowering therapies, many FH patients do not achieve the recommended LDL-C levels[18]. This suggests that, despite a genetic confirmation of their FH status, the most part of these subjects are not treated properly.

Study limitations

This study has several limitations: first, the lipid measurements were performed in different laboratories, although certified according to ISO rules; inter-laboratory variability may have conditioned the prevalence of potential FH; second, the DLCN questionnaires were frequently lacking for data on family and biochemical history, thus reducing the individual DLCN score and the probability to detect a potential FH case; third, most patients were on therapy at the time

of this evaluation, accordingly the "untreated LDL-C levels" were not measured but estimated using a correction formula based on literature data, although it was validated; and last, the survey was retrospective and genetic analysis was not performed in potential FH patients to confirm the diagnosis. In addition, in this survey, the diagnosis was performed through well established criteria, but genetic test was not performed. However we believe that the major issue is to detect patients with a high probability of having FH who are characterized by a very high cardiovascular risk and thus need an immediate and appropriate pharmacological approach to reduce the risk of secondary cardiovascular events. As also suggested by the results reported by the SAFEHEART registry[18], the presence of a genetic confirmation of the FH status does not guarantee the management of these patients with proper pharmacological approaches and the subsequent attainments of LDL-C goals.

Clinical implications

The analysis of our data, extracted from a large population of patients with previous atherosclerosis-related cardiovascular events, indicates that potential FH is relatively common, especially in those 50 years old or younger and in those with a recent acute coronary syndrome. However, being patients suffering from peripheral artery disease only a marginal part of the evaluated population, we would not extrapolate our results to this subpopulation. We should also acknowledge that the results presented in this paper confirm the observations in other pathological populations and extend this finding also to the Italian population, and represent a further proof of the relevance of investigating the possible presence of FH patients within these groups. Accordingly, clinicians involved in care should have a high grade of suspicion in these patients and their families, for an early detection and treatment of this disease. Despite a large use of appropriate high-intensity lipid-lowering therapies, such as high dose statins and combination with ezetimibe, only a minority of treated patients usually reach the recommended targets of LDL-cholesterol (<70 mg/dL), thus emphasizing the need of appropriate pharmacological approaches, including high intensity statin and ezetimibe in combination.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest regarding the publication of this paper

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TABLE 1. Characteristics of patients participating in the study.

		Total patients	
N		1438	
Men		1203	83.7 %
Women		235	16.3 %
Mean age (y±sd)	Total	65.9±10.6	
	Male	65.0±10.3	p<0.0001
	Female	70.2±10.9	
Setting			
	Outpatients	750	52.2 %
	Inpatients	688	47.8 %
Entry diagnosis			
	LE-PAD	46	3.2 %
	Stable CAD	381	26.5 %
	Post-ACS	755	52.5 %
	PCI/CABG without ACS	259	18.0 %
Co-morbidities:	No	490	34.1 %
	Yes	948	65.9 %
Risk factors			
	None	22	1.5 %
	Dislipidemia	1265	88.0 %
	Family history of CAD	549	38.2 %
	Hypertension	1010	70.2 %
	Diabetes	424	29.5 %
	Smoking	880	62.2 %
	Sedentary habits	670	46.6 %
	Obesity	368	25.6 %

LE-PAD: lower extremity peripheral arterial disease; CAD: coronary artery disease; PCI/CABG: percutaneous coronary intervention/coronary artery bypass surgery; ACS: acute coronary syndrome

TABLE 2. Prevalence for the different categories of FH for all patients, by gender, age and entry diagnosis.

		FH classification					
	Total patients	**Unlikely** (DLCNS 0-2)	**Possible** DLCNS 3-5	**Probable** DLCNS 6-8	**Definite** DLCNS >8	**Potential** DLCNS≥6	
Total	1438	1070 (74.4%)	315 (21.9%)	41 (2.9%)	12 (0.8%)	53 (3.7%)	
Mean age (y±s.d.)	65.9±10.6	68.0±9.5	59.9±11.1	60.1±11.9	52.1±7.9	58.3±11.5	Analysis of variance (ANOVA)
Men	1203	886 (73.6%)	277 (23.0%)	30 (2.5%)	10 (0.8%)	40 (3.3 %)	P<0.0442
Women	235	184 (78.3%)	38 (16.2%)	11 (4.7%)	2 (0.8%)	13 (5.5%)	
Age M<55; F<60	250	99 (39.6%)	125 (50.0%)	17 (6.8%)	9 (3.6%)	26 (10.4%)	P<0.0001
Age M≥55; F≥60	1188	971 (81.7%)	190 (16.0%)	24 (2.0%)	3 (0.3%)	27 (2.3%)	
LE-PAD	46	37 (80.4%)	7 (15.2%)	2 (4.3%)	0 (0.0%)	2 (4.3%)	P=0.5773
Stable CAD	381	283 (74.3%)	84 (22.1%)	12 (3.1%)	2 (0.5%)	14 (3.7%)	P=0.8586
Post-ACS	755	543 (71.9%)	178 (23.6%)	25 (3.3%)	9 (1.2%)	34 (4.5%)	P=0.0754
PCI/CABG without ACS	259	209 (80.7%)	47 (18.1%)	2 (0.8%)	1 (0.4%)	3 (1.2%)	P=0.0256

DLCNS: Dutch Lipid Network Criteria Score; LE-PAD: lower extremity peripheral arterial disease; CAD: coronary artery disease; ACS: acute coronary syndrome; M: male; F: female

Table 3. Intensity of statin therapy at discharge based on distance from target.

Statin intensity	All patients		Distance from target			
			≤50%		>50%	
	N	%	N	%	N	%
Low intensity	20	1.9	20	2.0	-	-
Moderate intensity	178	17.3	171	17.1	7	23.3
High intensity	832	80.8	809	80.9	23	76.7

Figure 1. LDL-C levels at discharge. See the text for details.

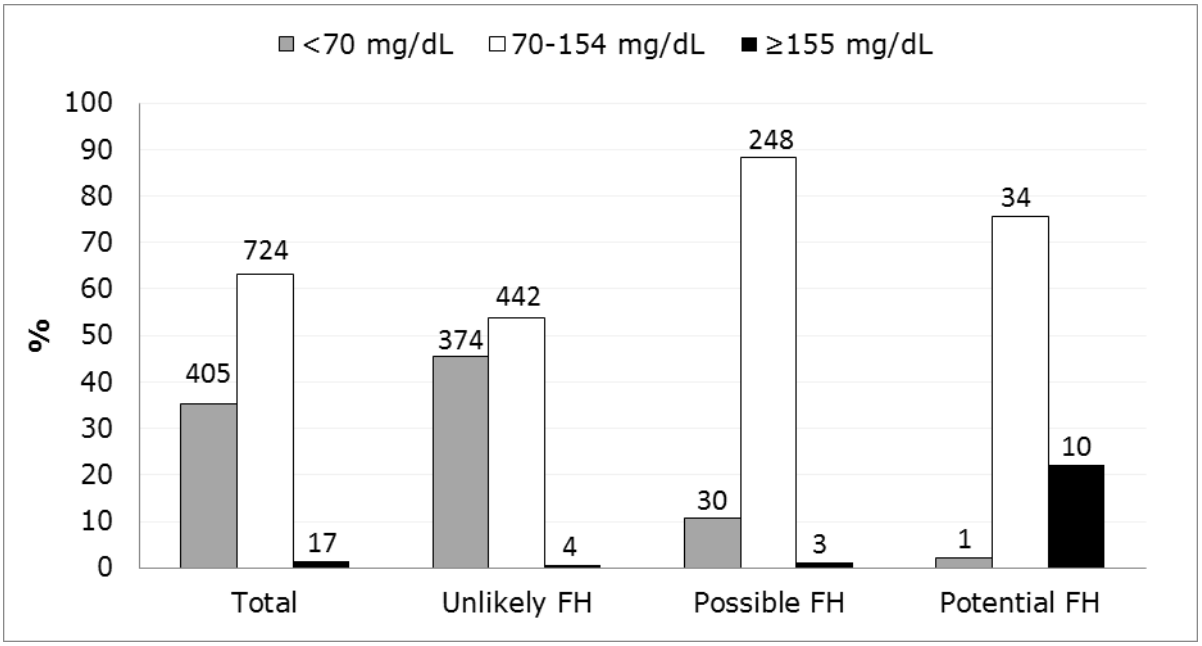
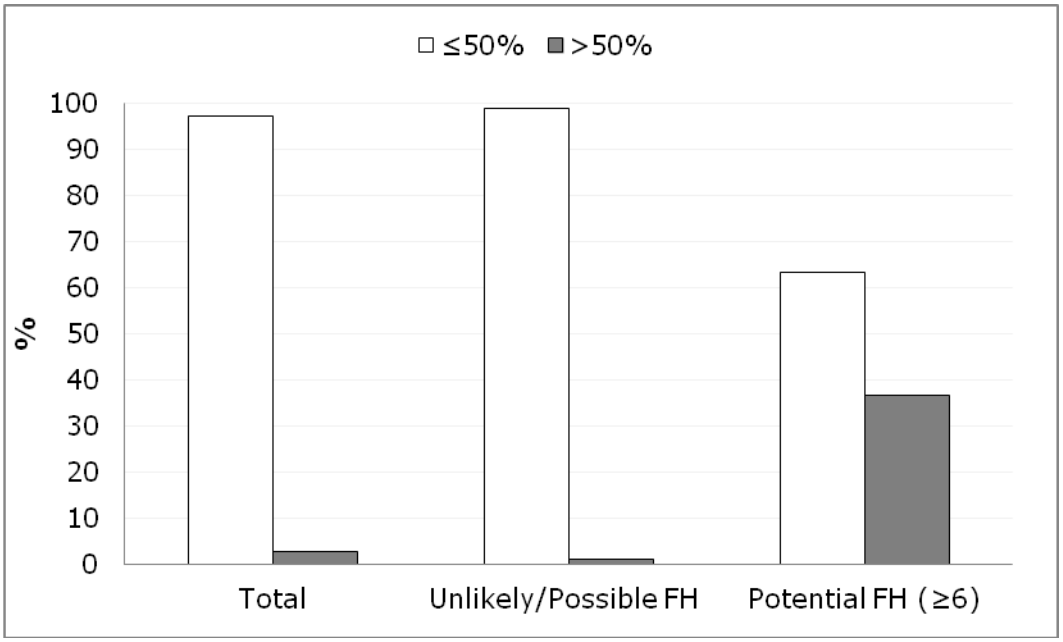


Figure 2. Distance from target, expressed as %. See the text for details.



APPENDIX. CRPs participating to the survey

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