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CLINICAL INVESTIGATIONS

Prevalence and pharmacologic management of familial hypercholesterolemia in an unselected contemporary cohort of patients with stable coronary artery disease

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Introduction: Familial hypercholesterolemia (FH) is an inherited disorder characterized by elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) associated with premature cardiovascular disease.

Methods: Using the data from the START (STable Coronary Artery Diseases RegisTry) study, a nationwide, prospective survey on patients with stable coronary artery disease (CAD), we described prevalence and lipid lowering strategies commonly employed in these patients. The study population was divided into "definite/probable FH," defined as a Dutch Lipid Clinic Network (DLCN) score ≥6, "possible FH" with DLCN 3-5, and "unlikely FH" in presence of a DLCN <3.

Results: Among the 4030 patients with the DLCN score available, 132 (3.3%) were classified as FH (2.3% with definite/probable and 1.0% with possible FH) and 3898 (96.7%) had unlikely FH. Patients with both definite/probable and possible FH were younger compared to patients not presenting FH. Mean on-treatment LDL-C levels were 107.8 ± 41.5, 84.4 ± 40.9, and 85.8 ± 32.3 ($P < 0.0001$) and a target of ≤70 mg/dL was reached in 10.9%, 30.0%, and 22.0% ($P < 0.0001$) of patents with definite/probable, possible FH, and unlikely FH, respectively. Statin therapy was prescribed in 85 (92.4%) patients with definite/probable FH, in 38 (95.0%) with possible FH, and in 3621 (92.9%) with unlikely FH ($P = 0.86$). The association of statin and ezetimibe, in absence of other lipid-lowering therapy, was more frequently used in patients with definite/probable FH compared to patients without FH (31.5% vs 17.5% vs 9.5%; $P < 0.0001$).

Conclusions: In this large cohort of consecutive patients with stable CAD, FH was highly prevalent and generally undertreated with lipid lowering therapies.

KEYWORDS

familial hypercholesterolemia, management, PCSK-9 inhibitors, stable coronary artery disease, statin, survey, treatment

1 | INTRODUCTION

Familial hypercholesterolemia (FH) is a common monogenic disorder mainly caused by mutations in the low-density lipoprotein (LDL) receptor inherited in a codominant fashion.[1] FH may also results from defects in two other major genes, apolipoprotein B and proprotein convertase subtilisin/kexin 9 (PCSK-9), which influence plasma LDL clearance by affecting the efficiency of ligand-receptor interaction.[1] The inadequate LDL clearance manifested in all FH genotypes leads to marked elevations of plasma LDL-cholesterol (LDL-C) levels, thus

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causing accelerated atherosclerosis and premature cardiovascular (CV) disease.[1] Indeed, it has been clearly demonstrated that FH substantially increase the risk of recurrence of CV events in patients with established coronary artery disease (CAD).[2]

Despite the wealth of knowledge on this disorder, FH remains underdetected and undertreated in most countries.[1,3–8] In particular, the diagnosis of FH in patients with CAD is even less recognized, so that a key opportunity for detecting FH has not been embedded in the routine clinical care. Using the data from the STable Coronary Artery Diseases RegisTry (START) study,[9] a nationwide registry on patients with stable CAD presenting to cardiologists, we sought to describe the prevalence of FH and the use of lipid lowering therapies in these high-risk patients.

2 | METHODS

The design and main results of the START registry have been published elsewhere.[9] Briefly, the START was a prospective, observational, nationwide study aimed to evaluate the current presentation, management, treatment, and quality of life of stable CAD patients as seen by cardiologists in clinical practice in Italy, during a 3-month period.[9] Enrolment was made at the end of outpatient or day-hospital visit or at hospital discharge.

The Italian Association of Hospital Cardiologists (ANMCO) invited to participate all Italian cardiology wards, including university teaching hospitals, general and regional hospitals, and private clinics following stable CAD patients. No specific protocols or recommendations for evaluation, management, and/or treatment have been put forth during this observational study. However, current guidelines for the management of patients with stable CAD have been discussed during the investigator meetings.

All patients were informed of the nature and aims of the study and asked to sign an informed consent for the anonymous management of their individual data. Local Institutional Review Boards (IRB) approved the study protocol according to the current Italian rules.

One-hundred eighty-three cardiology centers included consecutive patients in the survey in different periods of 3 months between March 2016 and February 2017.[9]

2.1 | Diagnosis of familial hypercholesterolaemia

We assessed the presence of FH based on age, personal and family history of premature atherosclerosis, and LDL-C levels. We used the validated Dutch Lipid Clinic Network (DLCN) algorithm; it is a scoring system based on clinical factors endorsed by many guidelines worldwide, including the European Society of Cardiology and the European Atherosclerosis Society.[10–13]

A definite/probable diagnosis of FH was considered when the DLCN score was 6 or higher, and a possible FH when the score was 3 to 5.[14] Patients with a DLCN score <3 were classified as "no/unlikely" FH.[14]

To estimate the pretreatment LDL-C level, we multiplied the on-treatment LDL-C level by a correction factor based on the potency of their treatment regimen as described in detail before.[15] In brief, we determined the estimated LDL-C lowering potency of a specific lipid-lowering drug and dose. We multiplied the on-treatment LDL-C level with that treatment potency, yielding an estimated pretreatment LDL-C level. In case of concomitant use of ezetimibe, we increased the relative LDL-C reduction by 15%, based on a previously reported estimation.[16]

2.2 | Statistical analysis

The study cohort was stratified according to FH: definite/probable FH; possible FH and unlikely FH. Categorical variables are presented as number and percentages and compared by the χ^2 test. Continuous variables are presented as mean and SD, except for triglycerides levels and dosage of statins, which are reported as median and interquartile range (IQR). Continuous variables were compared by the *t* test, if normally distributed, or by the Mann-Whitney *U* test, if not. Multiple comparisons between FH groups (unlikely FH vs possible FH; possible FH vs definite/probable FH; definite/probable FH vs unlikely FH) were performed, considering the Bonferroni correction. A *P*-value <0.05 was considered statistically significant. All tests were two-sided. Analyses were performed with SAS system software, version 9.4: SAS Institute Inc., Cary, NC, USA.

3 | RESULTS

Among the 5070 consecutive stable CAD patients enrolled, 1040 (20.5%) were not classified with the DLCN score due to data missing and therefore excluded from the analysis. These patients presented more frequently high-risk features such as hypertension, peripheral artery disease, history of atrial fibrillation or heart failure, and prior stroke/transient ischemic attack (TIA) compared to patients in whom the DLCN score was assessed (Table S1, Supporting Information).

Among the remaining 4030 patients with the DLCN score assessed, 132 (3.3%) were classified as FH (2.3% with definite/probable and 1.0% with possible FH) and 3898 (96.7%) had no/unlikely FH.

Baseline characteristics of patients with definite/probable, possible FH and without FH are shown in Table 1. Those with both definite/probable and possible FH were younger compared to patients not presenting FH. In addition, patients with definite/probable FH presented higher levels of total cholesterol compared to patients with possible FH and unlikely FH, at the time of enrolment (Table 1). Notably, among patients with data available, mean LDL-C levels were 107.8 ± 41.5, 84.4 ± 40.9, and 85.8 ± 32.3 ($P < 0.0001$) and a target of ≤70 mg/dL was reached in 10.9%, 30.0%, and 22.0% ($P < 0.0001$) of patents with definite/probable, possible FH and unlikely FH, respectively. After adjustment for different statins and dosages, mean LDL-C values resulted as 217.9 ± 97.0, 172.2 ± 88.8, and 162.3 ± 71.9 ($P < 0.0001$) for patents with definite/probable, possible FH and unlikely FH, respectively.

The number of coronary vessels with significant stenoses among the 110 (83.3%) patients with FH (76 with definite/probable and 34 with possible FH) and the 3380 (86.7%) without FH who underwent coronary angiography was not statistically different (Figure S1).

TABLE 1 Baseline clinical characteristics, hemodynamic and laboratory variables of patients with and without FH

	No FH *n* = 3898	FH possible *n* = 40	FH definite/probable *n* = 92	*P* value
Age (years), mean ± SD	68 ± 11[e]	61 ± 10	61 ± 10[g]	<0.0001
Age >75 years, *n* (%)	1028 (26.4)[e]	2 (5.0)	7 (7.6)[g]	<0.0001
Females, *n* (%)	765 (19.6)	8 (20.0)	15 (16.3)	0.73
BMI (kg/m^2), mean ± SD	27.3 ± 4.0	28.0 ± 5.4	26.6 ± 4.2	0.14
Active smokers, *n* (%)	677 (17.4)	9 (22.5)	17 (18.5)	0.67
Diabetes mellitus, *n* (%)	1186 (30.4)	12 (30.0)	22 (23.9)	0.41
Hypertension,[a] *n* (%)	3056 (78.4)	32 (80.0)	69 (75.0)	0.71
History of atrial fibrillation, *n* (%)	515 (13.2)	2 (5.0)	12 (13.0)	0.31
Chronic renal dysfunction,[b] *n* (%)	477 (12.2)	2 (5.0)	9 (9.8)	0.30
Peripheral artery disease,[c] *n* (%)	329 (8.4)	3 (7.5)	9 (9.8)	0.88
COPD, *n* (%)	423 (10.9)	3 (7.5)	7 (7.6)	0.49
Malignancy, *n* (%)	256 (6.6)	3 (7.5)	3 (3.3)	0.43
Depression, *n* (%)	404 (10.4)	4 (10.0)	6 (6.5)	0.49
Previous stroke/TIA, *n* (%)	200 (5.1)	2 (5.0)	4 (4.4)	0.94
History of major bleeding events,[d] *n* (%)	74 (1.9)	1 (2.5)	0 (0.0)	0.39
History of heart failure, *n* (%)	507 (13.0)	3 (7.5)	9 (9.8)	0.39
Prior ACS, *n* (%)	2643 (67.8)	31 (77.5)	65 (70.7)	0.36
Previous revascularization, *n* (%)	3019 (77.5)	35 (87.5)	79 (85.9)	0.05
Ejection fraction (%), mean ± SD (available for 3657 [90.7%] pts)	54 ± 9	55 ± 10	56 ± 11	0.06
SBP (mm Hg), mean ± SD	130 ± 17	126 ± 17	129 ± 15	0.30
HR (bpm), mean ± SD	66 ± 11	66 ± 10	65 ± 9	0.94
Hb (g/dL), mean ± SD (available for 3252 [80.7%] pts)	13.6 ± 1.7	14.0 ± 2.0	13.9 ± 1.5	0.09
Creatinine (mg/dL), mean ± SD (available for 3252 [80.7%] pts)	1.1 ± 0.6	1.0 ± 0.2	1.0 ± 0.3	0.12
Total cholesterol (mg/dL), mean ± SD (available for 2889 [71.7%] pts)	153.6 ± 37.8	157.4 ± 44.8[f]	177.1 ± 43.6[g]	<0.0001
Triglycerides (mg/dL), median (IQR) (available for 2800 [69.5%] pts)	111 [83-151]	130 [117-149]	125 [82-161]	0.07
Glycemia (mg/dL), mean ± SD (available for 2971 [73.7%] pts)	113.6 ± 35.9	124.6 ± 41.9[f]	101.5 ± 23.8[g]	0.0009

Abbreviations: ACS, acute coronary syndrome (STEMI or NSTE-ACS) occurred at least 30 days from enrolment; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FH, familiar hypercholesterolemia; Hb, hemoglobin; HR, heart rate; IQR, interquartile range; SBP, systolic blood pressure; TIA, transient ischemic attack.

[a] Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of blood pressure lowering drugs.

[b] Dialysis, history of renal transplant or creatinine levels >1.5 mg/dL.

[c] History of claudication; amputation for arterial insufficiency; aorta-iliac occlusive disease reconstruction surgery; peripheral vascular bypass surgery, angioplasty, or stent; documented abdominal aortic aneurysm, aneurysm repair or stent; and documented positive noninvasive testing such as abnormal ankle-brachial index or pulse volume recording.

[d] Fatal bleeding or clinically evident bleeding with hemoglobin reduction ≥2 g/dL or requiring transfusion or hospitalization.

[e] $P < 0.017$ for comparison between possible FH and No FH patients (by Bonferroni correction).

[f] $P < 0.017$ for comparison between possible FH and definite/probable FH patients (by Bonferroni correction).

[g] $P < 0.017$ for comparison between definite/probable FH and No FH patients (by Bonferroni correction).

3.1 | Lipid-lowering drugs and lifestyle recommendations

At the time of discharge or at the end of the visit, a statin was prescribed in 85 (92.4%) patients with definite/probable FH, in 38 (95.0%) with possible FH, and 3621 (92.9%) without FH ($P = 0.86$). A low dose of statin (atorvastatin ≤10 mg/d, fluvastatin ≤40 mg/d, lovastatin ≤20 mg/d, pravastatin ≤20 mg/d, rosuvastatin ≤5 mg/d, or simvastatin ≤20 mg/d) was prescribed in 518 (12.9%) patients (16.3% with definite/probable, 17.5% with possible FH, and 12.7% without FH; $P = 0.72$). The main reasons for the lack of statins prescription or for their low dose prescription in 804 patients are depicted in Figure 1.

Atorvastatin was the mainly employed statin compound, especially among patients without FH or with possible FH, while rosuvastatin were prescribed more frequently in patients with FH, especially among those with definite/probable FH (Figure 2). The mean dosages of statins prescribed did not differ between the three groups (Table 2). Concerning the other lipid-lowering agents, ezetimibe alone was used in 2.2% of patients with definite/probable FH, none of possible FH patients, and 1.3% of those without FH ($P = 0.58$), while omega-3 fatty acids alone and fibrates alone were prescribed in patients without FH only (0.5% and 0.1% of cases, respectively).

The association of statin and ezetimibe in the absence of other lipid-lowering therapy was more frequently used in patients with

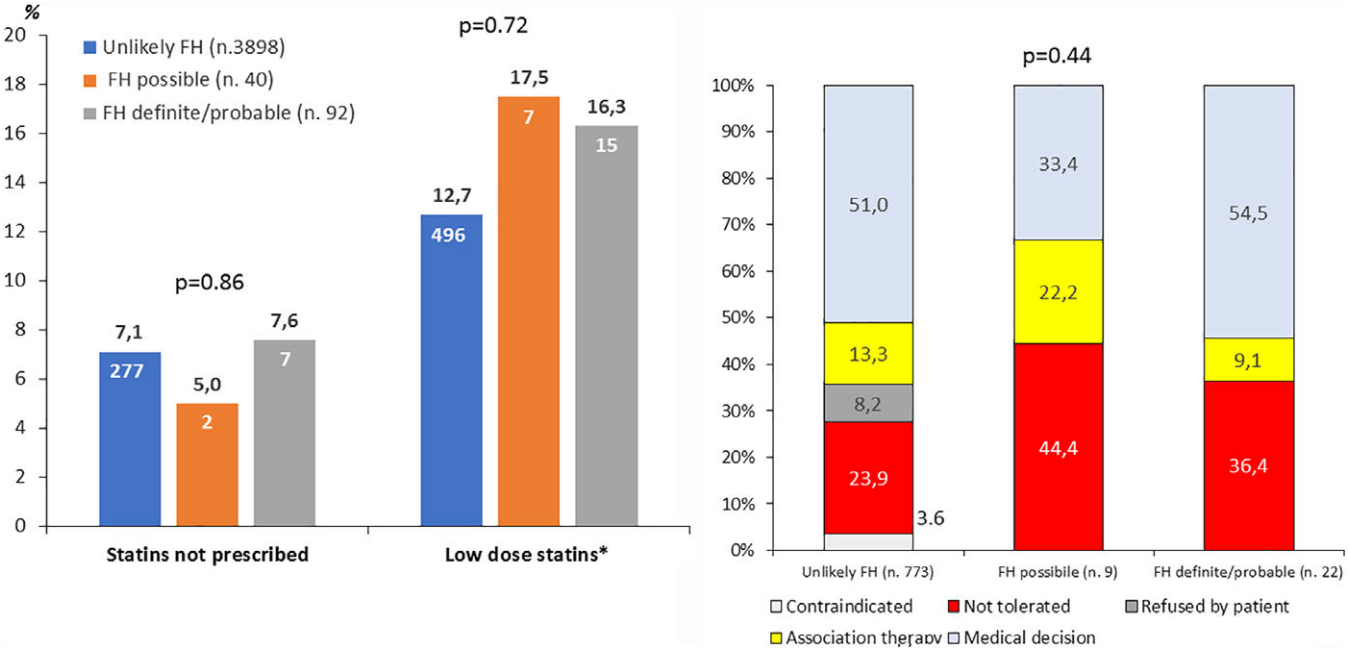

FIGURE 1 Patients with definite/probable, possible FH and without FH not receiving or receiving low dose statins (Atorvastatin ≤10 mg/d, Fluvastatin ≤40 mg/d, Lovastatin ≤20 mg/d, Pravastatin ≤20 mg/d, Rosuvastatin ≤5 mg/d, Simvastatin ≤20 mg/d) at the time of discharge/end of the visit (left panel). Reasons for lack of statins or low dose statins prescription (right panel)

definite/probable FH compared to other groups, while omega-3 fatty acids in association with statins or ezetimibe were frequently employed in patients with possible FH (Figure 3). As a whole, high-intensity lipid-lowering medications (atorvastatin 40-80 mg or rosuvastatin 20-40 mg or simvastatin/ezetimibe combination) were used in 59 (64.1%) with definite/probable FH, 22 (55.0%) with possible FH, and 2327 (59.7%) patients with unlikely FH (P = 0.43).

Finally, a personalized diet was prescribed in 79.4%, 85.0%, and 56.8% (P < 0.0001) and physical activity programs were suggested in 83.7%, 75.0%, vs 64.2% (P = 0.0002), of patients with definite/probable FH, possible FH, and unlikely FH, respectively.

4 | DISCUSSION

In this large cohort study of patients with stable CAD, the prevalence of definite/probable FH was 2.3% and, including possible FH, the rate reached 3.3%, a number approximately 8 to 10 times higher than estimates made in the general population using similar diagnosis algorithms.[3–8,15,16] The prevalence of FH has been also investigated in an unselected population of patients with acute coronary syndromes[6] or in cohort of patients with early-onset manifestation of coronary ischemic events,[7,8] thus not providing a reliable representation of FH frequency in the real word patients with stable CAD. To the best of our knowledge, this is the first study assessing the prevalence of FH in

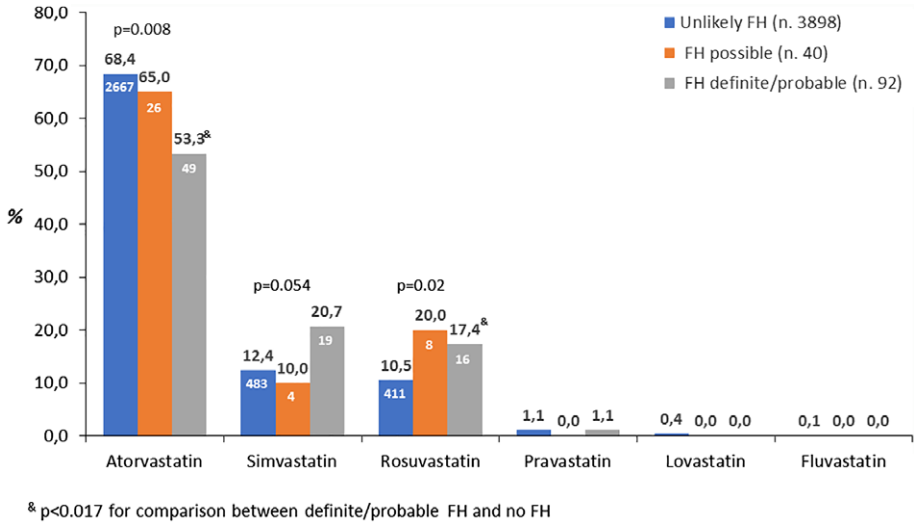

FIGURE 2 Statin compounds prescribed at the time of discharge/end of the visit in patients with definite/probable, possible FH and without FH. &P < 0.017 for comparison between definite/probable FH and unlikely FH

TABLE 2 Dosages of statins prescribed at the end of the visit/discharge in patients with or without FH

	No FH *n* = 3898	FH possible *n* = 40	FH definite/probable *n* = 92	*P* value
Atorvastatin (mg/d), mean ± SD Median [IQR]	41.7 ± 20.9 40 [20-40]	44.2 ± 21.9 40 [40-40]	40.6 ± 20.1 40 [20-40]	0.80
Simvastatin (mg/d), mean ± SD Median [IQR]	25.9 ± 11.6 20 [20-40]	20.0 ± 0.0 20 [20-20]	27.9 ± 16.9 20 [20-40]	0.70
Rosuvastatin (mg/d), mean ± SD Median [IQR]	14.1 ± 7.0 10 [10-20]	15.0 ± 11.6 10 [7.5-20]	16.9 ± 7.9 20 [10-20]	0.28
Pravastatin (mg/d), mean ± SD Median [IQR]	31.5 ± 11.1 40 [20-40]	–	40[a]	0.47
Lovastatin (mg/d), mean ± SD Median [IQR]	30.7 ± 10.3 40 [20-40]	–	–	–
Fluvastatin (mg/d), mean ± SD Median [IQR]	62.5 ± 35.0 80 [45-80]	–	–	–

Abbreviations: FH, familiar hypercholesterolemia; IQR, interquartile range.
[a] Only one patient treated with pravastatin.

patients with stable CAD. In our study, patients with FH were younger and presented a higher prevalence of previous revascularization procedures compared to patients without FH. This finding is in accordance with the known finding that premature CAD is an established phenomenon of FH, with the average mean age of onset of coronary symptoms shown to be 45 years in men and 55 years in women.[17] In this regard, there are several evidences suggesting that the extent of atherosclerosis is likely to be higher in patients with FH, especially in those with definite FH, compared to other patients. This finding is most likely to be due to the fact that subjects with definite FH have had severely elevated LDL-C level since birth, and thus, have a greater cumulative "LDL-C burden".[10]

The standardized mortality rate of CAD and risk of a coronary event are increased in people with untreated FH.[2,12] The specific evidence for treating hypercholesterolemia in FH is based on selected observational studies showing that long-term statin medication decreases CAD events and mortality in FH to a level comparable to or approaching that of the reference population. In addition, primary prevention with statin treatment in FH is more effective in terms of absolute number of prevented deaths than interventions in the setting of secondary prevention.[18] Therefore, high-intensity statins and combination therapy with ezetimibe are the mainstay of treatment that should be started as early as the diagnosis of FH is made.[1] Consistently with previous reports[4,6] our data indicated that CAD patients with FH, despite statin use comparable with that observed in non-FH, attained 2 to 3 times less frequently LDL-C targets. This phenomenon was mainly remarkable in CAD patients with definite/ probable FH, as the vast majority (approximately 90%) of them presented LDL-C levels above 70 mg/dL. This may be due to the low rate of prescription of high-intensity statin alone or in association with ezetimibe. In our cohort, a high intensity statin regimen was used in approximately 60% of definite/probable FH patients and an association of statin with ezetimibe was employed in only 32% of them. We have identified that no prescription or low dose statin prescription in FH patients was mainly

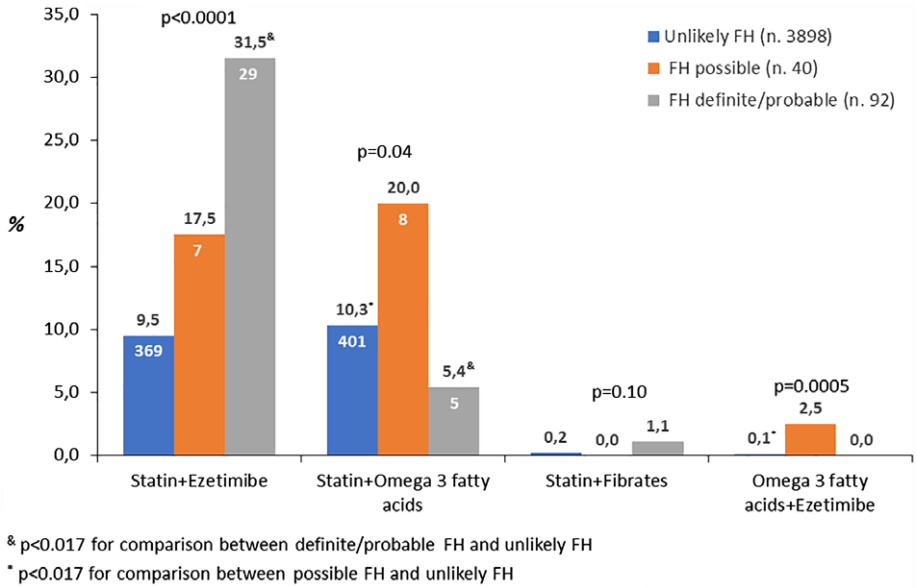

FIGURE 3 Associations of lipid lowering strategies in patients with definite/probable, possible FH and without FH (other possible combinations not shown were used in <0.5% of cases). $^{\&}P < 0.017$ for comparison between definite/probable FH and unlikely FH. $^{*}P < 0.017$ for comparison between possible FH and unlikely FH

due to medical decision or because the drugs were not tolerated by the patient. These findings underline the fact that we still need education and implementation of guidelines recommendations in this setting, as cardiologists seem to underscore the importance of FH recognition in patients at already high/very high risk due to clinically manifest CAD.

Nevertheless, our data further underlying the difficulties in the treatment of FH CAD patients with standard medications. The recently available monoclonal antibodies inhibiting the PCSK-9 have been reported to be particularly promising in the treatment of FH patients requiring additional lipid-lowering.[19–22]

In addition, recent large clinical trials have demonstrated the benefit of these agents on top of high intensive statin therapy in reducing adverse CV outcomes among patients with CV disease.[23–25] In our cohort, patients eligible to PCSK-9 inhibitors according to recent European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommendations,[26] were 9% of those with LDL-C values available. It is worth to mention that the PCSK-9 inhibitors become available in Italy from March 2017, immediately after the conclusion of the START registry. In addition, in Italy the criteria for the reimbursement of these medication are based on different criteria, as only CAD patients taking high potency statins (atorvastatin >40 mg/d and over or rosuvastatin >20 mg/d) in association with ezetimibe must be considered eligible for these therapies. Therefore, our estimate cannot representative of clinical setting in Italy.

4.1 | Study limitations

Our study must be evaluated in the light of some limitations. First, we were not able to assess the prevalence of FH using the DLCN score in around 20% of patients included in the survey, therefore the actual incidence of FH could be underestimated. In addition, DLCN score was assessed by researchers and not all clinical criteria of diagnosis algorithms, such as Achilles xanthoma or LDL-C in family members, have been evaluated. This is a limitation of previous studies about FH prevalence[8,10,16,23] and this would likely underestimate the true prevalence of FH. Another reason for a possible underestimation of FH in our series is that lipid profiles were missing in around 30% of enrolled patients, especially in those with unlikely FH (Table S2). Second, we used a phenotypic diagnosis of FH that may not accurately identify monogenic FH[27,28] . However, in a recent study[29] that confirmed genetically the diagnosis of FH in patients with acute coronary syndromes, about 1/3 were classified as polygenic, thus suggesting that only a minority of CAD patients may show a nonmonogenic form of FH. Third, the data reported in the present analysis are limited to the time of the visit or hospitalization period and we do not have data on long-term persistence to prescribed therapies, their changes and relative outcomes. However, a clinical follow-up at 1 year from enrolment is ongoing. Finally, even if the participating centers were asked to include in the registry all consecutive patients admitted with stable CAD, we were not able to verify the enrolment process, due to the absence of administrative auditing. We believe that it is unlikely, however, that selective enrolment in few sites may have substantially changed the study results.

5 | CONCLUSIONS

In a large cohort of consecutive patients with stable CAD managed by cardiologists, we found a high prevalence of FH. Only a minority of patients with FH received recommended doses or associations of lipid lowering therapies, advocating for better identification of this disorder and specific organization pathways for these high-risk patients.

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Conflict of interest

All authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX A

Committees and participating centers

Steering committee

L De Luca (Chairman), MM Gulizia (co-chairman), PL Temporelli, C Riccio, F Colivicchi, AF Amico, D Formigli, G Geraci, A Di Lenarda.

Executive committee

L De Luca, AP Maggioni, D Lucci.

Coordinating center

ANMCO Research Center (AP Maggioni, D Lucci, A Lorimer, G Orsini, L Gonzini, G Fabbri, P Priami).

Participating centers and investigators

Trieste, Maggiore (P Maras, F Ramani); Pavia, Istituto di Cura Città di Pavia (C Falcone, I Passarelli, S Mauri); Napoli, AORN Colli-Monaldi, UOC Cardiologia-SUN (P Calabrò, R Bianchi, G Di Palma); Caserta, AO S. Anna e S. Sebastiano, UO Cardiologia-UTIC (F Mascia, A Vetrano, A Fusco); Piedimonte Matese (E Proia); Roma, San Filippo Neri (F Colivicchi, A Aiello); Roma, European Hospital (F Tomai, R Licitra, A Petrolini); Santa Maria Capua Vetere (B Bosco); Lecce, V. Fazzi, UO Cardiologia (F Magliari, M Callerame, T Mazzella); Vittoria (GV Lettica, G Coco, F Incao); Città di Castello (L Marinacci, S D'Addario); Sanremo (SN Tartaglione, S Ubaldi, FA Sanchez); Avola (P Costa, G Manca, M Failla); Benevento, AO G. Rummo (M Scherillo, V Procaccini, D Formigli); Bergamo, ASST Papa Giovanni XXIII (M Senni, EM Luminita); Cagliari, SS Trinità (P Bonomo, C Mossa, S Corda); Campobasso, Cardarelli (AR Colavita, G Trevisonno, G Vizzari); Cariati (N Cosentino, C Formaro); Corato (C Paolillo, IL Nalin); Cosenza, Annunziata (FM De Rosa, F Fontana, GF Fuscaldo); Cremona (E Passamonti, E Bertella, EV Calvaruso); Faenza (E Varani, F Tani, G Cicchitelli); Fermo (D Gabrielli, P Paoloni, A Marziali); Ferrara (G Campo, M Tebaldi, S Biscaglia); Foggia, Riuniti (M Di Biase, ND Brunetti, AM Gallotta); Gorizia (L Mattei, R Marini, F Balsemin); Magenta (M D'Urbano, R Naio, P Vicinelli); Massa, Apuane (G Arena, M Mazzini, N Gigli); Melito di Porto Salvo (B Miserrafiti, A Monopoli); Monza, Policlinico (A Mortara, P Delfino, MM Chioffi); Novara, AOU Maggiore della Carità, SCDU Clinica Cardiologica-Cardiologia I (P Marino, M Gravellone, L Barbieri); Palermo, AOR Villa Sofia-Cervello (A Ledda, G Geraci, MG Carmina); Pavia, IRCCS Policlinico San Matteo (AE Raisaro, C Di Giacomo, A Somaschini); Potenza, San Carlo, SSD Card. Riab. (ML Fasano, M Sannazzaro, R Arcieri); Reggio Emilia, S.M. Nuova (M Pantaleoni, C Leuzzi, G Gorlato); Roma, Santo Spirito (G Greco, A Chiera); Rozzano (TA Ammaturo, G Malanchini, MP Del Corral); Battipaglia (L Tedesco); Lecce, Casa di Cura Petrucciani (S Pede, LG Urso); Salerno (F Piscione, G Galasso); Varese, Circolo e Fond. Macchi (S Provasoli); Aversa (L Fattore, G Lucca); Grosseto (A Cresti); Caserta, AO S. Anna e S. Sebastiano, Cardiologia e Riabil. Cardiol. (A Cardillo); Pomezia (MS Fera, F Vennettilli); Roma, Umberto Primo, Cardiologia B - Cardiologia e Angiologia (C Gaudio, V Paravati); Bari, San Paolo (P Caldarola, N Locuratolo); Camposampiero (R Verlato, F De Conti); Conegliano (G Turiano, G Preti); Ascoli Piceno (L Moretti, S Silenzi); Lecce, V. Fazzi, UO Card. Interventistica-Emod. (G Colonna, A Picciolo); Ragusa (A Nicosia, C Cascone); Roma, Campus Biomedico (G Di Sciascio, F Mangiacapra); San Giovanni Rotondo (A Russo, M Villella); Carate Brianza (G Esposito); Cortona (F Cosmi, S D'Orazio); Jesi (C Costantini, A Lanari); Giugliano In Campania (P De Rosa, L Esposito); Arzignano (C Bilato, C Dalla Valle); Pavia, ICS Maugeri (M Ceresa, E Colombo); Reggio Calabria, Bianchi Melacrino Morelli (V Pennisi, G Casciola); Udine, Santa Maria Misericordia (M Driussi, T Bisceglia); Lumezzane (S Scalvini, F Rivadossi); Roma, Sant'Andrea (M Volpe, F Comito); Tradate, Galmarini (D Scorzoni, P Grimoldi); Cassano delle Murge (R Lagioia, D Santoro); Osio Sotto (N De Cesare, T Comotti); Legnano (A Poli, P Martina); Locri (MF Musolino, EI Multari); Feltre (G Bilardo, G Scalchi); Isernia (C Olivieri, F Caranci); San Vito al Tagliamento (D Pavan, G Ganci); Senigallia (A Mariani, E Falchetti); Avellino (T Lanzillo, A Caccavale); Novara, AOU Maggiore della Carità, Cardiologia II (AS Bongo, A Rizzi); Siena (R Favilli, S Maffei); Napoli, San Gennaro (M Mallardo, C Fulgione); Thiene (F Bordin); Trento, Santa Chiara (R Bonmassari, E Battaia); Troina (A Puzzo); Chioggia (G Vianello); Poggibonsi (A D'Arpino, M Romei); Albano Laziale, Albano-Genzano (G Pajes, S Petronzelli); Cesena (F Ghezzi); Monfalcone (S Brigido, L Pignatelli); Torino, Maria Pia Hospital (E Brscic, P Sori); Barletta (M Russo, E Biancolillo); Brindisi (G Ignone, NA De Giorgio); Formia (C Campaniello, P Ponticelli); Milano, San Raffaele (A Margonato, S Gerosa); Agrigento (A Cutaia, C Casalicchio); Andria (F Bartolomucci, C Larosa); Molfetta (T Spadafina, A Putignano); Orvieto (R De Cristofaro, L Bernardi); Viterbo (L Sommariva, A Celestini); Alessandria, Clinica Città di Alessandria (CM Bertucci, M Marchetti); Belluno (E Franceschini Grisolia, C

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