

Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes

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Aims

We aimed to assess the prevalence and management of clinical familial hypercholesterolaemia (FH) among patients with acute coronary syndrome (ACS).

Methods and results

We studied 4778 patients with ACS from a multi-centre cohort study in Switzerland. Based on personal and familial history of premature cardiovascular disease and LDL-cholesterol levels, two validated algorithms for diagnosis of clinical FH were used: the Dutch Lipid Clinic Network algorithm to assess possible (score 3–5 points) or probable/definite FH (>5 points), and the Simon Broome Register algorithm to assess possible FH. At the time of hospitalization for ACS, 1.6% had probable/definite FH [95% confidence interval (CI) 1.3–2.0%, $n = 78$] and 17.8% possible FH (95% CI 16.8–18.9%, $n = 852$), respectively, according to the Dutch Lipid Clinic algorithm. The Simon Broome algorithm identified 5.4% (95% CI 4.8–6.1%, $n = 259$) patients with possible FH. Among 1451 young patients with premature ACS, the Dutch Lipid Clinic algorithm identified 70 (4.8%, 95% CI 3.8–6.1%) patients with probable/definite FH, and 684 (47.1%, 95% CI 44.6–49.7%) patients had possible FH. Excluding patients with secondary causes of dyslipidaemia such as alcohol consumption, acute renal failure, or hyperglycaemia did not change prevalence. One year after ACS, among 69 survivors with probable/definite FH and available follow-up information, 64.7% were using high-dose statins, 69.0% had decreased LDL-cholesterol from at least 50, and 4.6% had LDL-cholesterol ≤ 1.8 mmol/L.

Conclusion

A phenotypic diagnosis of possible FH is common in patients hospitalized with ACS, particularly among those with premature ACS. Optimizing long-term lipid treatment of patients with FH after ACS is required.

Keywords

Familial hypercholesterolaemia • acute coronary syndrome • premature atherosclerosis • quality of care • cardiovascular prevention

Introduction

Heterozygous familial hypercholesterolaemia (FH) is an autosomal-dominant genetic disorder with an estimated prevalence of 1/200–1/500 in the general population.^{1,2} Early identification of patients with FH is important, because appropriate treatment may reduce

the risk of premature atherosclerosis.^{3,4} Mainly two diagnosis algorithms are used to diagnose FH in the general population. The Dutch Lipid Clinic Network algorithm is a scoring system based on clinical factors endorsed by many guidelines worldwide, such as the European Society of Cardiology, the National Lipid Association in the USA, the International FH Foundation, and the European

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Atherosclerosis Society.^{1,5–7} The Simon Broome Register criteria from NICE guidelines in the UK requires both an elevated LDL-cholesterol >4.9 mmol/L (or total cholesterol >7.5 mmol/L) along with history of premature atherosclerosis.^{8,9}

Underdiagnosis of FH in the general population has recently been recognized as an important issue, and for many patients with FH who are unaware of their disease, the first clinical manifestation is an acute coronary syndrome (ACS).¹⁰ Identifying FH during hospitalization for ACS would allow specific counselling for diet and cardiovascular risk factors, ensure high-dose statin prescription at discharge as well as appropriate referral to lipid clinics for identification of family members.^{11–13} In addition, new lipid-lowering drugs inhibiting proprotein convertase subtilisin/kexin 9 (PCSK9) might be particularly promising in addition to maximal statin dose among patients with FH.¹⁴ However, the proportion of patients hospitalized with ACS who have FH remains uncertain, with prevalence ranging from 12% to >50% in patients <60 years old according to two small previous studies.^{15,16} To fill these gaps, we aimed to assess the prevalence of FH and its 1-year management in a large multi-centre cohort of patients with ACS.

Methods

Study population

This study was performed within the framework of the SPUM-ACS (Special Program University Medicine-Acute Coronary Syndromes) cohort study designed to evaluate the determinants and consequences of ACS in the general population. Details regarding the methods of the SPUM-ACS study were previously reported,^{17–19} and are provided in Supplementary material online. Of the 5713 patients in the SPUM-ACS study hospitalized between 2009 and 2014, we excluded 935 patients with missing values for total cholesterol, HDL-cholesterol, and triglycerides (Supplementary material online, *Figure S1*). Thus, the final sample for this analysis was 4778.

Ethics statement

The study protocol was approved by the institutional review board of all participating centres and all patients provided written, informed consent.

Diagnosis of familial hypercholesterolaemia

We assessed the presence of FH based on age, personal and family history of premature atherosclerosis, and LDL-cholesterol levels. We used the validated Dutch Lipid Clinic Network algorithm recommended by many guidelines to diagnose FH in the general population in central European countries.^{1,5–7} Clinical signs of lipid accumulation in the tissue, as well as family history of elevated LDL-cholesterol were not available in our study sample and missing information was counted as zero in the Dutch Lipid Clinic algorithm. A possible diagnosis was considered when the Dutch Lipid Clinic Network score was 3–5, and a probable/definite FH when the score was 6 or higher.²⁰ We also used the Simon Broome Register criteria from NICE guidelines in the UK. The diagnosis of possible FH requires both an elevated LDL-cholesterol >4.9 mmol/L (or total cholesterol >7.5 mmol/L) along with family or personal history of premature atherosclerosis.^{8,9} Because signs of lipid accumulation in the tissue or genetic tests for monogenic anomalies were not available, a confirmed diagnosis of definite FH according to the Simon Broome algorithm could not be evaluated. Details regarding

measurement of covariates and the proportion of patients eligible for each criteria are provided in Supplementary material online, *Tables S1* and *S2*.

Statistical analysis

One-way ANOVA and χ^2 tests or the Kruskal–Wallis rank test were used for comparisons of clinical characteristics between those with/without FH, for each diagnosis algorithm. Estimates of prevalence were also reported for patients with premature ACS, defined by the occurrence of ACS <55 years of age for men and <60 years of age for women. Stratified analyses for the prevalence of FH were reported according to the use of lipid-lowering drugs before hospitalization. Sensitivity analyses were done after excluding those with >3 days between symptoms onset and lipid measurements, to take into account changes in lipid levels after ACS. Further sensitivity analyses excluding patients with severe hyperglycaemia >9 mmol/L at admission, or those under dialysis or with acute renal failure with an estimated glomerular filtration rate <60 mL/min, or those consuming >14 units of alcohol were conducted to exclude secondary causes of hyperlipidaemia. All hypothesis tests are two-sided and the significance level set at 5%. Statistical analyses were performed using STATA statistical software[®] (Version 13, STATA Corp, College Station, TX, USA).

Results

Among 4778 patients hospitalized for ACS, 78 [1.6%, 95% confidence interval (CI) 1.3–2.0%] had a probable/definite FH, and 852 (17.8%, 95% CI 16.8–18.9%) had possible FH using the Dutch Lipid Clinic Network algorithm (*Figure 1*). The Simon Broome algorithm identified 259 (5.4%, 95% CI 4.8–6.1%) patients with possible FH. Combining both algorithms, a total of 977 patients were identified with either Dutch or Simon Broome criteria, and 77 (1.6%, 95% CI 1.3–2.0%) had both probable/definite Dutch and Simon Broome criteria. Most patients with possible FH identified with the Simon Broome algorithm were also identified with the Dutch Lipid Clinic algorithm (Supplementary material online, *Figure S2*). Among 1451 young patients with premature ACS, the Dutch Lipid Clinic algorithm identified 70 (4.8%, 95% CI 3.8–6.1%) with probable/definite FH, and 684 (47.1%, 95% CI 44.5–49.7%) patients with possible FH (*Figure 1*). The Simon Broome Register algorithm identified 203 (14.0%, 95% CI 12.2–15.9) patients with possible FH among patients with premature ACS.

Stratified analysis in 3353 patients not using lipid-lowering drugs before hospitalization yielded about similar prevalence of 1.3% (95% CI 1.0–1.8%) for probable/definite FH, and 19.4% (95% CI 18.0–20.7%) for possible FH according to the Dutch Lipid Clinic algorithm (Supplementary material online, *Figure S3A*). Among 1425 patients using lipid-lowering drugs before hospitalization, the prevalence of probable/definite FH reached 2.4% (95% CI 1.7–3.3%) (Supplementary material online, *Figure S3B*). Sensitivity analysis in 3493 patients with blood draw within 72 h after symptoms onset, or in 4165 patients without acute renal failure or dialysis, or in 3677 patients without severe hyperglycaemia at admission, or in 4186 patients without alcohol excessive use yielded similar results for prevalence of FH (Supplementary material online, *Figure S4*).

Baseline characteristics of the 4778 participants with respect to FH diagnosis are presented in *Table 1*. Compared with patients

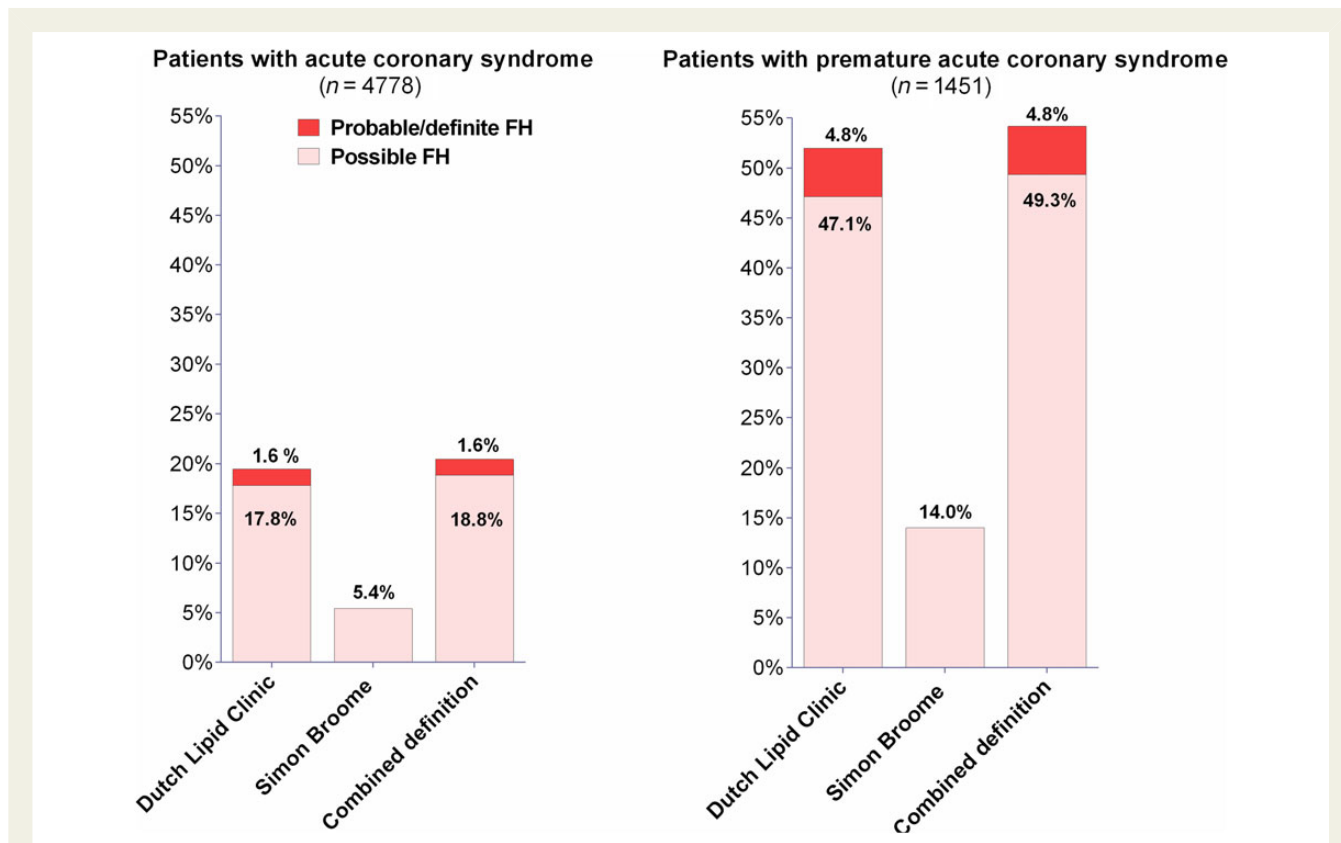


Figure 1 Prevalence of clinical familial hypercholesterolaemia among patients with acute coronary syndrome ($n = 4778$). FH, familial hypercholesterolaemia.

without FH, patients with FH were younger, had higher proportion of personal or family history of premature coronary heart disease (CHD), were more frequently smokers, but were less frequently suffering from hypertension, diabetes, or pre-existing cardiovascular disease. Baseline characteristics with respect to the use of lipid-lowering drugs before hospitalization are presented in Supplementary material online, *Table S3*. Compared with patients not using lipid-lowering drugs before hospitalization, those with lipid-lowering drugs were older, had more frequently pre-existing cardiovascular disease or diabetes, but were less frequently current smokers.

Quality of care during and 1-year after hospitalization for ACS in 977 patients with possible FH according to either Dutch or Simon Broome algorithm is shown in *Tables 2* and *3*. Among 78 patients with probable/definite FH according to the Dutch Lipid Clinic algorithm, 61.8% had an ST-segment elevation myocardial infarction, and 69.7% were prescribed high-dose statins at discharge (*Table 2* and *Figure 2*). After 1 year, 879 patients with possible FH were alive and had available follow-up visit information, including a subsample of 508 patients with measured LDL-cholesterol levels. Among the 69 patients with probable/definite FH according to the Dutch Lipid Clinic algorithm, 44 (64.7%) had high-dose statins (*Table 3* and *Figure 2*). In the subsample of 43 patients with probable/definite FH and 1-year LDL-cholesterol available, 29 (69.0%) had decreased their LDL-cholesterol of at least 50% over the year, and 2 (4.6%) had an LDL-cholesterol levels of 1.8 mmol/L or below (*Table 3*).

Discussion

In this large cohort study of patients with ACS, the prevalence of probable/definite FH reached 1.6 and 4.8% when considering only younger adults with premature ACS. These estimates are three to six times higher than those of the general population using similar diagnosis algorithms.² More than a fourth of patients with probable/definite FH were not discharged or were not using high-dose statins 1-year after their hospitalization, or could not reach 50% reduction of their LDL-cholesterol as recommended after ACS.

The prevalence of FH has never been studied in large cohorts of patients with ACS. Previous studies had very small sample size, included patients 20 years ago, and used heterogeneous definition for FH, considering either genetic mutation rates or clinical criteria.^{15,16,21,22} Studying 292 patients younger than 60 years old with myocardial infarction in 1995, Dorsch et al. found a prevalence of FH of 12.3%, based on LDL-cholesterol levels only.¹⁶ Using genetically confirmed criteria for FH, about similar prevalence of 16.4% was reported in 412 men younger than 60 years who underwent coronary angiography for chest pain in the French part of Canada between 1993 and 1995.²¹ In another study examining 102 patients with CHD before the age of 60 years between 1986 and 1987, 54% showed familial lipoprotein disorders, defined as elevated LDL-cholesterol in the index cases and family members.¹⁵ In 33 families with two or more siblings with premature CHD before 55 years of age studied in Utah, USA in the 1980s, 75% had elevated lipids,

Table 1 Baseline characteristics of patients with acute coronary syndrome and familial hypercholesterolaemia, by diagnosis algorithm (n = 4778)

	Dutch Lipid Clinic Network			P-value	Simon Broome Register		
	Probable/definite FH (>5 points)	Possible FH (3–5 points)	No FH		Possible FH	No FH	P-value
Number	78	852	3848		259	4519	
Percentage (95% CI)	1.6 (1.3–2.0)	17.8 (16.8–18.9)			5.4 (4.8–6.1)		
Demographics							
Age (years)	49.5 (9.3)	52.4 (10.0)	64.8 (11.5)	<0.001	51.6 (9.8)	63.8 (12.2)	<0.001
Female	18 (23.1)	172 (20.2)	818 (21.3)	0.7	62 (23.9)	946 (20.9)	0.25
Caucasian	72 (92.3)	791 (92.8)	3632 (94.4)	0.003	239 (92.3)	4256 (94.2)	0.18
Higher education ^a	22 (30.1)	236 (30.4)	906 (27.1)	0.16	68 (28.8)	1096 (27.7)	0.7
Premature CHD ^b	70 (89.7)	684 (80.3)	697 (18.1)	<0.001	203 (78.4)	1248 (27.6)	<0.001
Family history ^c	62 (79.5)	471 (55.5)	680 (17.9)	<0.001	128 (49.4)	1085 (24.3)	<0.001
Smoking status							
Never	19 (24.4)	212 (25.0)	1261 (33.2)	<0.001	68 (26.2)	1424 (31.9)	<0.001
Former	16 (20.5)	159 (18.8)	1223 (32.2)		55 (21.2)	1343 (30.1)	
Current	43 (55.1)	476 (56.2)	1318 (34.7)		136 (52.5)	1701 (38.1)	
Elevated alcohol consumption ^d	10 (13.7)	96 (12.3)	486 (14.2)	0.37	25 (10.5)	567 (14.1)	0.13
Comorbidities							
Hypertension ^e	29 (37.2)	329 (38.6)	2294 (59.7)	<0.001	105 (40.5)	2547 (56.4)	<0.001
Diabetes mellitus ^f	4 (5.1)	89 (10.4)	763 (19.8)	<0.001	30 (11.6)	826 (18.29)	0.006
Pre-existing CVD ^g	9 (11.5)	147 (17.2)	1084 (28.2)	<0.001	36 (13.9)	1204 (26.7)	<0.001
Objective measures							
Total cholesterol (mmol/L)	7.4 (1.6)	5.7 (1.2)	4.7 (1.1)	0.04	7.1 (1.2)	4.8 (1.1)	<0.001
LDL-cholesterol (mmol/L) ^h	6.6 (1.6)	4.3 (1.1)	3.2 (0.9)	<0.001	5.8 (1.1)	3.3 (1.0)	<0.001
HDL-cholesterol (mmol/L)	1.1 (0.3)	1.1 (0.3)	1.2 (0.4)	<0.001	1.1 (0.3)	1.2 (0.4)	0.03
Triglycerides (mmol/L)	1.3 (0.5)	1.5 (1.2)	1.4 (1.1)	<0.001	1.7 (1.3)	1.4 (1.1)	<0.001
Body mass index (kg/m ²)	28.1 (4.9)	27.3 (4.4)	27.0 (4.3)	0.01	27.5 (4.5)	27.1 (4.3)	0.08
eGFR (mL/min)	93.5 (20.3)	98.6 (24.9)	88.6 (27.0)	<0.001	93.9 (23.5)	88.5 (27.1)	0.002
Medication use at admission							
Aspirin	27 (34.6)	174 (20.4)	1265 (32.9)	<0.001	65 (25.1)	1401 (31.0)	0.045
Lipid-lowering drugs	34 (43.6)	203 (23.8)	1188 (30.9)	<0.001	88 (34.0)	1337 (29.6)	0.13
Statins	31 (39.7)	199 (23.4)	1155 (30.0)	<0.001	84 (32.4)	1301 (28.8)	0.2
Anti-hypertensives	23 (29.5)	242 (28.4)	1939 (50.4)	<0.001	75 (29.0)	2129 (47.1)	<0.001

Data are given as number (percentage) or mean (SD). P-values are results of one-way ANOVA, χ^2 tests, or Kruskal–Wallis rank tests, as appropriate. CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia.

^aDefined as a high school or university graduation or higher.

^bAge of onset for ACS before 55 years in males and before 60 in females.

^cBased on major cardiovascular event in a brother or father younger than 55 years old, or a mother or sister younger than 60 years old.

^dMore than 14 units per week.

^eDefined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of blood pressure lowering drugs.

^fBased on patients self-report, use of anti-diabetic medication/insulin, or haemoglobin A1c of $\geq 6.5\%$.

^gDefined as CHD, ischaemic cerebrovascular disease, or periphery artery disease.

^hIncluding 65 missing values because of elevated triglycerides level of 4.5 mmol/L or above.

and 3% had monogenic alteration found in FH.²² More recently, a 2% rate of rare genetic alteration in LDL-cholesterol receptor was reported in young patients with premature myocardial infarction.²³

In our study of >4700 patients with ACS, we found a high prevalence of 1.6% for probable/definite FH. As expected, prevalence of probable/definite FH was higher in patients using statins before hospitalization (2.4%), than those not taking statins (1.3%). These estimates are higher than the prevalence of probable/definite FH

thought to be 0.2% (1/500) in the general population.¹ In a large population-based study in Denmark of nearly 70 000 participants, probable/definite FH based on Dutch Lipid Clinic Network criteria was identified in 0.5% (1/200) of participants,² and genetically confirmed heterozygous FH reached 0.3% (1/244) in a recent Dutch Study.²⁴

Identification of FH is important as the disorder is associated with early onset of CHD,^{3,4} but systematic screening of healthy adults

Table 2 Treatment initiated during and after an acute coronary syndrome, by presence of possible familial hypercholesterolaemia (n = 977)

	Dutch Lipid Clinic probable/definite FH (>5 points)	Dutch Lipid Clinic possible FH (3–5 points)	Simon Broome Register possible FH	Simon Broome and Dutch Lipid Clinic FH (>5 points)
Diagnosis (n = 943)				
STEMI	47 (61.8)	459 (55.9)	147 (59.0)	46 (61.3)
NSTEMI	26 (34.2)	325 (39.6)	95 (38.1)	26 (34.7)
Unstable angina	3 (3.9)	37 (4.5)	7 (2.8)	3 (4.0)
Revascularization procedures (n = 941)				
Stent implantation	64 (84.2)	724 (88.4)	222 (89.5)	63 (84.0)
Balloon dilatation only	2 (2.6)	31 (3.8)	8 (3.2)	2 (2.7)
CABG	0 (0.0)	13 (1.6)	1 (0.4)	0 (0.0)
Medical treatment	10 (13.2)	51 (6.2)	17 (6.8)	10 (13.3)
Medication at discharge (n = 935)				
Statins	73 (96.0)	807 (98.9)	244 (98.0)	72 (96.0)
High-dose statins ^a	53 (69.7)	617 (75.6)	195 (78.3)	52 (69.6)
Other hypolipemians ^b	6 (7.9)	21 (2.6)	12 (4.8)	6 (8.0)
Aspirin	76 (100.0)	814 (99.6)	248 (99.6)	75 (100.0)
Anti-hypertensives ^c	71 (93.4)	779 (95.3)	229 (92.0)	70 (93.3)
Cardiac rehabilitation (n = 950)				
	50 (64.9)	548 (66.0)	176 (69.3)	50 (65.8)

Data are given as number (percentage).

STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; CABG, coronary artery bypass grafting; FH, familial hypercholesterolaemia.

^aAtorvastatin 40–80 mg or rosuvastatin 20–40 mg.

^bFibrates, ezetimibe, niacin, and resins.

^cAngiotensin converting enzyme inhibitors, or angiotensin II receptor blockers, or β -blockers, or calcium-channel blockers, or diuretics.

Table 3 Quality of care among patients with possible familial hypercholesterolaemia 1 year after hospitalization for acute coronary syndrome (n = 879)

	Dutch Lipid Clinic probable/definite FH (>5 points)	Dutch Lipid Clinic possible FH (3–5 points)	Simon Broome Register possible FH	Simon Broome and Dutch Lipid Clinic FH (>5 points)
Medication at 1-year (n = 858)				
Statins	64 (94.1)	710 (94.2)	212 (94.6)	63 (94.0)
High-dose statins ^a	44 (64.7)	454 (60.2)	151 (67.4)	43 (64.2)
Other hypolipemians ^b	13 (19.1)	63 (8.4)	33 (14.7)	13 (19.4)
Aspirin	68 (100.0)	744 (98.5)	222 (99.1)	67 (100.0)
LDL-cholesterol targets reached (n = 508)				
≤1.8 mmol/L	2 (4.6)	98 (22.4)	12 (9.3)	2 (4.6)
≤2.6 mmol/L	16 (37.2)	287 (65.7)	61 (47.3)	16 (37.2)
LDL-cholesterol 50% reduction from baseline without treatment (n = 473)				
	29 (69.0)	170 (41.8)	75 (61.0)	29 (69.0)

Data are given as number (percentage).

FH, familial hypercholesterolaemia.

^aAtorvastatin 40–80 mg or rosuvastatin 20–40 mg.

^bFibrates, ezetimibe, niacin, and resins.

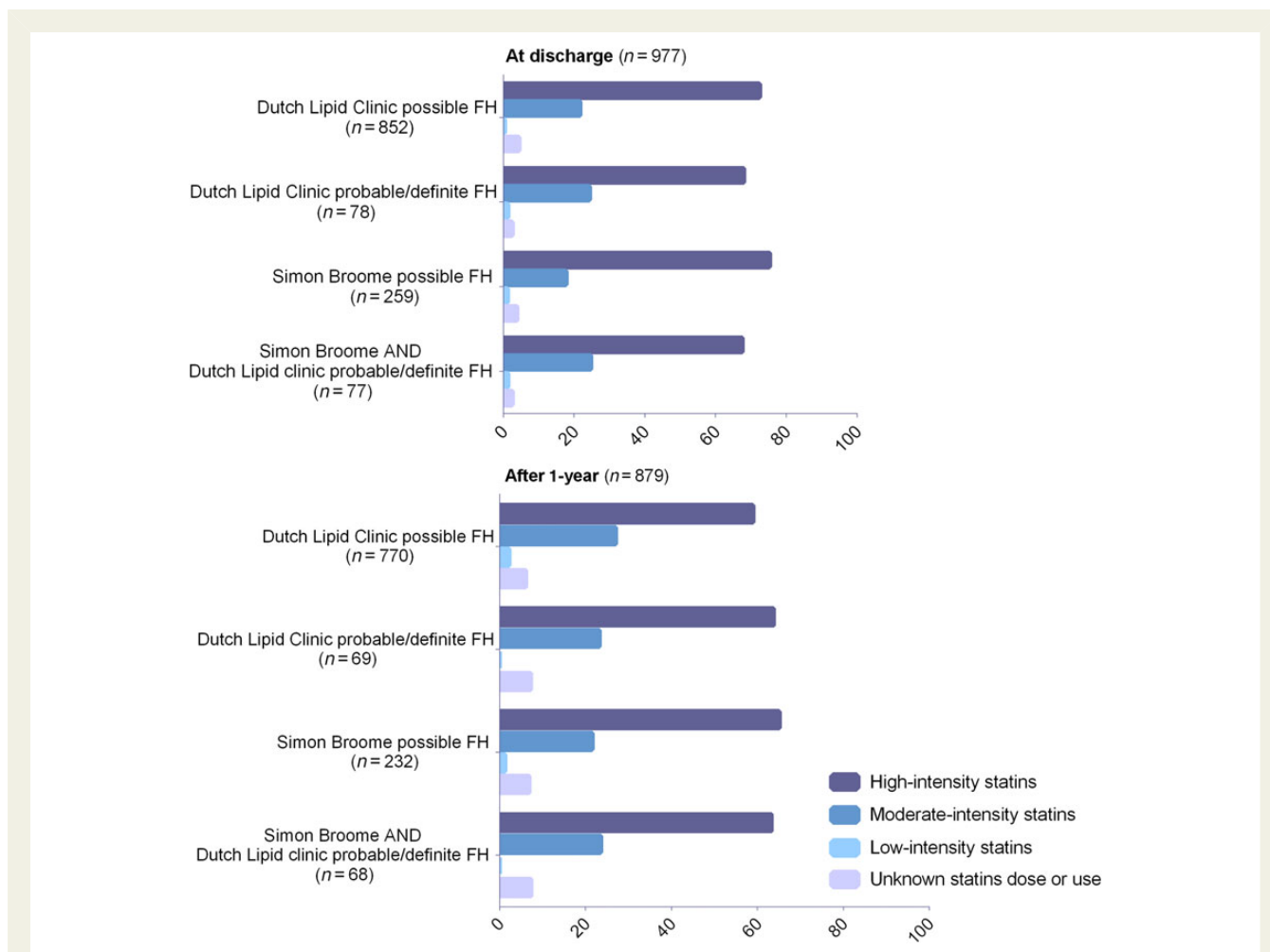


Figure 2 Type of statins used at discharge and after 1-year according to presence of familial hypercholesterolaemia. FH, familial hypercholesterolaemia.

remains a challenge.²⁵ We found that among patients with possible FH that were not using statins but aspirin before hospitalization for ACS, 86% of them used statins 1-year after discharge, confirming that in most cases, undertreatment of FH is due to underdiagnosis rather than statins intolerance. During hospitalization for ACS, screening for FH can be performed at low cost, by assessing familial history of premature CHD and LDL-cholesterol levels. At hospital discharge and after 1-year, we reported that more than a fourth of patients with probable/definite FH and ACS were not using optimal statin doses, and that nearly all could not reach 1.8 mmol/L for LDL-cholesterol 1-year after their ACS. As future perspectives, new lipid-lowering drugs targeting PCSK9 have shown large reduction of LDL-cholesterol levels compared with placebo in FH patients with maximal tolerated statin doses, and phase III placebo-controlled clinical trials examining long-term clinical outcomes are ongoing.¹⁴ If efficacy for cardiovascular prevention is confirmed, many patients with both ACS and FH might benefit from PCSK9 inhibitors, providing they are identified during the hospitalization.

Our study has several limitations. First, we did not perform genetic molecular analysis to identify monogenic mutations associated with FH. The detection rate for monogenic disorder is ~25%

among patients with a diagnosis of possible FH, and ~75% in patients with probable/definite FH.^{26,27} Thus, our estimates should not be compared with prevalence studies of genetically confirmed FH. However, the aim of our study was to estimate the prevalence of clinical FH, because in patients with ACS and a phenotype diagnosis of FH, high-dose statins will be indicated, as recommended by guidelines.^{1,5,7} In the setting of ACS, genetic tests might be used for screening family members.⁷ Second, we were not able to assess all clinical criteria of diagnosis algorithms, such as Achilles xanthoma or LDL-cholesterol in family members. This is a limitation of previous studies about FH prevalence^{2,15,16} and this would likely underestimate the true prevalence of FH. However, when measurement of LDL-cholesterol is systematically performed, such as in patients with ACS, the importance of clinical signs of lipid accumulation in the tissue to help identify patients with FH might be limited. In addition, when family history of premature CHD is known, the importance missing information about LDL-cholesterol levels in family members may be limited, as 85% of families with premature CHD have lipid abnormalities at the 95% percentile.²² Third, clinical diagnosis algorithms for diagnosis of FH have never been validated in patients with ACS. However, accuracy of self-reported information

regarding family history was similar in patients with and without pre-existing cardiovascular disease.²⁸ Finally, cholesterol levels have been shown to decrease 24 h after admission for ACS. However, blood samples were measured from the first blood draw in the emergency department or at coronary angiography, and our sensitivity analysis performed only in patients with a short time interval between symptom onset and blood draw yielded similar results.

Conclusions

The high prevalence of FH in patients presenting with ACS may advocate for better identification of the disorder during the hospital stay, in order to organize specific referral to lipid clinics or primary care physicians for diet counselling, long-term maintenance of high-dose statins, and identification of family members. In addition, new lipid-lowering drugs targeting PCSK9 might represent a promising therapeutic option in addition to statins for many patients with ACS and FH.

Supplementary material

Supplementary Material is available at *European Heart Journal* online.

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