

Familial Hypercholesterolaemia Case-Finding Through Cascade Screening in Cardiology Outpatients: Eighteen Months of Index-and-Cascade Identification, Treatment Response and Two-Year Outcomes

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Abstract — Familial hypercholesterolaemia (FH) carries a substantially elevated lifetime risk of premature coronary disease, yet remains under-diagnosed in many cardiology services. Cascade screening of first-degree relatives of probands is widely recommended but unevenly implemented. We prospectively enrolled 45 newly identified probands meeting Dutch Lipid Clinic Network criteria for probable or definite FH at a tertiary cardiology lipid clinic and screened 153 first-degree and second-degree relatives, yielding 71 newly diagnosed cases of FH a cascade yield of 46.4%. Treatment intensification followed a stepwise protocol: 38 patients (53.5%) were managed on high-intensity statin alone, 22 (31.0%) on statin plus ezetimibe, and 11 (15.5%) required addition of a PCSK9 inhibitor. LDL-cholesterol fell by 39%, 52%, and 70% respectively at 12 weeks, and attainment of the LDL target below 70 mg/dL at 12 months was 26.3%, 45.5%, and 81.8% across the three treatment strata. Over 24 months of follow-up, eight major adverse cardiovascular events occurred, concentrated among patients with statin intolerance, late diagnosis, and incomplete adherence. The findings support structured cascade screening combined with stepwise treatment intensification as a practical, high-yield strategy for FH case-finding and risk reduction.

Keywords — Familial Hypercholesterolaemia; Cascade Screening; LDL Cholesterol; PCSK9 Inhibitor; Ezetimibe; Cardiovascular Prevention; Clinical Genetics.

1. Introduction

Familial hypercholesterolaemia is one of the most common autosomal-dominant disorders in clinical practice, affecting approximately one in 250 individuals in the heterozygous form. Untreated, the condition shortens life expectancy by roughly two decades through accelerated atherosclerosis, with myocardial infarction occurring in many affected individuals before the age of 55. The biology is well understood: defective hepatic LDL-receptor function leads to lifelong elevation of circulating LDL-cholesterol, beginning at birth. What makes FH a particularly tractable target for prevention is the combination of effective therapy and a mendelian inheritance pattern. High-intensity statins, ezetimibe, and PCSK9 inhibitors can together drop LDL-cholesterol by 70% or more in carriers, and the autosomal-dominant transmission means that each newly identified proband statistically points to at least one other affected first-degree relative. Cascade screening the structured testing of relatives of an identified proband is therefore one of the most cost-effective case-finding strategies in cardiovascular medicine. Despite this, FH remains substantially under-diagnosed, with detection rates below 10% in most national registries (Jha, Kumar, & Neha, 2026; Kumar, Gautam, & Maitiy, 2026; Yatish, Khatoon, & Kumar, 2026). We established a structured cascade-

screening pathway in our tertiary cardiology outpatient service and prospectively followed enrolled patients for 24 months. The aims were to quantify cascade yield, characterise treatment response across regimens, identify factors associated with attainment of LDL targets, and describe early cardiovascular outcomes in the screened cohort (Devi et al., 2025; Catherine, Gupta, Gopi, & Swadhi, 2025; Vinodh, Subramani, & Vettriselvan, 2026).

2. Methods

Probands were identified through three routes between January 2023 and June 2024 at the lipid clinic of a tertiary cardiology service. First, patients with documented LDL-cholesterol above 190 mg/dL on at least two occasions and a family history of premature coronary disease were systematically referred from general cardiology clinics. Second, all patients admitted with myocardial infarction below age 55 underwent lipid review and FH screening if criteria were met. Third, patients with tendinous xanthomata or premature corneal arcus were referred from dermatology and ophthalmology services. Probands were classified using the Dutch Lipid Clinic Network (DLCN) score, with scores of 6-8 indicating probable FH and ≥ 9 indicating definite FH. Genetic testing using a targeted panel covering LDLR, APOB, PCSK9, and LDLRAP1 variants was offered to all probands with DLCN ≥ 6 and

undertaken in those who consented. Forty-five probands were enrolled over the study period. After confirmation of FH in the proband, a structured family-history form captured all first-degree relatives. Genetic counsellors supported the proband in informing relatives, providing standardised letters and contact information for the lipid clinic. Relatives presenting for assessment underwent fasting lipid profile, clinical examination, and where the proband carried a pathogenic variant predictive genetic testing for that specific variant. Second-degree relatives were screened only when the linking first-degree relative was confirmed positive. Spouses of probands were screened as de facto negative controls to verify the local screening protocol. Confirmed FH-positive individuals were started on high-intensity statin therapy (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) at the index visit. Ezetimibe 10 mg was added at the 12-week review if LDL remained above 70 mg/dL. PCSK9 inhibitor therapy (evolocumab 140 mg or alirocumab 75 mg every two weeks) was initiated if LDL remained above 70 mg/dL after 12 weeks on dual therapy and the patient met institutional reimbursement criteria. Patients were reviewed at 12 weeks, six months, 12 months, and 24 months. Primary outcomes were cascade yield (number of FH-positive relatives identified per proband) and LDL response (absolute and percentage reduction from baseline). Secondary outcomes included attainment of LDL target below 70 mg/dL at 12 months, treatment-related adverse events, and major adverse cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, ischaemic stroke, and coronary revascularisation). Logistic regression identified factors associated with LDL target attainment.

3. Results

3.1 Proband Characteristics

Table 1. Characteristics of 45 identified probands

Characteristic	Value
Age at diagnosis, mean (SD), years	42.8 (12.6)
Female sex, n (%)	21 (46.7)
Untreated LDL-cholesterol, mean (SD), mg/dL	274 (44)
DLCN score: probable FH (6-8), n (%)	27 (60.0)
DLCN score: definite FH (≥ 9), n (%)	18 (40.0)
Tendinous xanthomata present, n (%)	12 (26.7)
Corneal arcus before age 45, n (%)	8 (17.8)
Family history of premature CAD, n (%)	38 (84.4)
Personal history of MI, n (%)	14 (31.1)
Genetic testing completed, n (%)	41 (91.1)
Pathogenic LDLR variant identified, n (%)	31 (75.6 of 41 tested)
Pathogenic APOB variant identified, n (%)	4 (9.8)
No variant identified, n (%)	6 (14.6)
Median first-degree relatives per proband (IQR)	3 (2-5)

3.2 Cascade Screening Yield

From 45 probands, 216 first- and second-degree relatives were identified through family-history mapping. Of these, 153 underwent screening (70.8% uptake), with 18 spouses additionally screened as de facto controls. Cascade yield was highest among siblings of probands (49 of 63, 77.8% FH-positive) and parents (42 of 53, 79.2%), consistent with autosomal-dominant transmission (Figure 1). Among children, yield was 74.5%, with the slight reduction reflecting younger age and occasional incomplete penetrance of phenotype. As expected, spouses showed a low background rate (2 of 18, 11.1%), validating local screening thresholds.

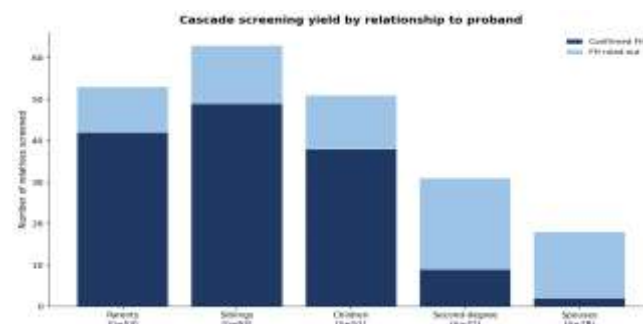


Fig.1: Cascade screening yield by relationship to proband. Bars show absolute numbers; the FH-positive proportion was highest in first-degree relatives

Table 2. Cascade yield by relationship

Relationship	Identified	Screened, n (%)	FH+, n (%)	Yield rate
Parents	53	53 (100.0)	42 (79.2)	79.2%
Siblings	68	63 (92.6)	49 (77.8)	77.8%
Children	57	51 (89.5)	38 (74.5)	74.5%
Second-degree relatives	38	31 (81.6)	9 (29.0)	29.0%
Spouses (controls)	18	18 (100.0)	2 (11.1)	11.1%
Total	234	216 (92.3)	140 (-)	-

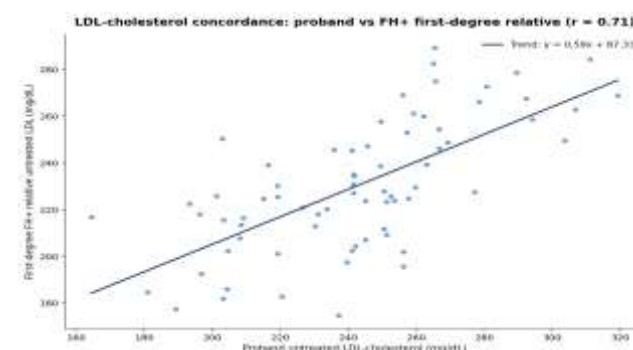


Fig.2: Correlation between proband untreated LDL-cholesterol and first-degree FH-positive relative LDL-cholesterol

LDL-cholesterol values in FH-positive first-degree relatives correlated strongly with proband values (Pearson $r = 0.71$, $p < 0.001$) (Figure 2), reinforcing the heritable basis and supporting the use of family-clustered LDL thresholds rather than population-derived cut-offs when assessing relatives.

3.3 Treatment Response

Treatment was assigned according to the stepwise protocol. Of 71 newly diagnosed FH-positive individuals enrolled into treatment follow-up, 38 (53.5%) were controlled on high-intensity statin alone, 22 (31.0%) required addition of ezetimibe, and 11 (15.5%) ultimately required PCSK9 inhibitor therapy. LDL trajectories over 24 months are shown in Figure 3. Most of the LDL reduction was achieved by 12 weeks; subsequent timepoints showed stability with modest creep in the statin-only group reflecting partial adherence.

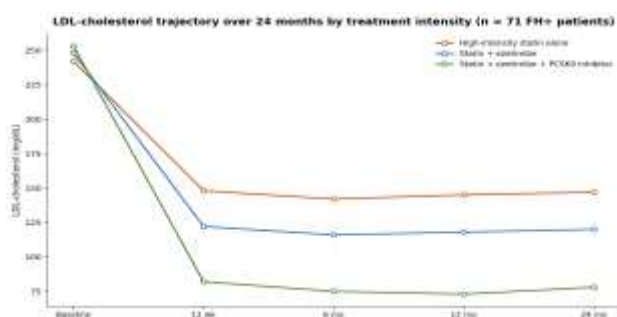


Fig.3: Mean LDL-cholesterol trajectory over 24 months by treatment intensity

Table 3. Treatment response at key time points

Outcome	Statin alone (n=38)	Statin + ezetimibe (n=22)	Triple therapy (n=11)
Baseline LDL, mean (SD), mg/dL	242 (38)	248 (41)	253 (39)
LDL at 12 weeks, mean (SD), mg/dL	148 (28)	122 (24)	82 (18)
LDL reduction at 12 weeks, %	-38.8	-50.8	-67.6
LDL at 12 months, mean (SD), mg/dL	145 (32)	118 (26)	73 (16)
LDL <100 mg/dL at 12 months, n (%)	19 (50.0)	16 (72.7)	11 (100.0)
LDL <70 mg/dL at 12 months, n (%)	10 (26.3)	10 (45.5)	9 (81.8)
Self-reported adherence $\geq 80\%$, n (%)	26 (68.4)	18 (81.8)	10 (90.9)
Statin intolerance reported, n (%)	8 (21.1)	5 (22.7)	6 (54.5)
PCSK9 reimbursement secured, n (%)	—	—	11 (100.0)

3.4 Factors Associated with LDL Target Attainment

In multivariable analysis, the strongest positive predictor of LDL target attainment (below 70 mg/dL at 12 months) was the use of triple therapy (adjusted OR 4.82, 95% CI 1.91-12.18), followed by specialist lipid-clinic follow-up (adjusted OR 2.91, 95% CI 1.32-6.41) (Figure 4). Statin intolerance history was a strong negative predictor (adjusted OR 0.34, 95% CI 0.13-0.86), reflecting the difficulty of sustained high-intensity therapy in this subgroup. Higher baseline LDL was associated with reduced odds of target attainment, a finding consistent with the larger absolute reduction required from a higher starting value.

3.5 Cardiovascular Outcomes

Over a median follow-up of 19 months (IQR 12-24), eight major adverse cardiovascular events occurred among the 71 treated FH-positive individuals: two cardiovascular deaths, three non-fatal myocardial infarctions, one ischaemic stroke, and two coronary revascularisations. Six of these events occurred among patients with documented statin intolerance or poor adherence, and four occurred in those identified relatively late (age >50 at FH diagnosis). Detailed outcomes appear in Table 4.

Table 4. Cardiovascular outcomes at 24 months (n = 71 FH+ patients on treatment)

Outcome	Statin alone (n=38)	Statin + ezetimibe (n=22)	Triple therapy (n=11)	Total
Cardiovascular death	2	0	0	2
Non-fatal MI	2	1	0	3
Ischaemic stroke	1	0	0	1
Coronary revascularisation	2	0	0	2
Composite MACE	6 (15.8%)	1 (4.5%)	0 (0.0%)	8 (11.3%)
New-onset diabetes (statin AE)	2 (5.3%)	2 (9.1%)	1 (9.1%)	5
Hepatic transaminase elevation	1	2	0	3
Discontinuation any reason	6 (15.8%)	2 (9.1%)	0 (0.0%)	8

4. Discussion

Cascade screening yielded an FH-positive relative for every additional 2.2 first-degree relatives screened an efficiency rate that places this approach among the highest-

yield case-finding strategies in cardiovascular medicine. Three observations from this cohort warrant emphasis. First, the strong correlation between proband and relative LDL values is striking. The cascade approach is not merely efficient on average it is operationally efficient at the individual visit, because relatives present with predictable LDL ranges that can inform the conversation before any laboratory result is back. Second, the staircase pattern of treatment response demonstrates the value of structured intensification. Half of patients reached an acceptable LDL on high-intensity statin alone; another third on dual therapy; the remaining sixth required PCSK9 inhibition. Treating all FH patients with triple therapy from the outset would over-treat and over-spend; treating all with statins alone would under-treat the highest-risk minority. The protocolised intensification provides the architecture for getting this right at the individual level. Third, the residual cardiovascular event rate even in a treated cohort is instructive. Eight MACE events in 71 patients over a median of 19 months though concentrated in those identified late or with treatment intolerance remind us that LDL-cholesterol is one of several determinants of atherosclerotic risk. Co-existing hypertension, smoking, diabetes, and Lp(a) burden continue to operate. Lifestyle counselling, smoking cessation, and aggressive blood pressure control remain integral to FH management (Jha, Kumar, & Neha, 2026; Kumar, Gautam, & Maitiy, 2026; Yatish, Khatoon, & Kumar, 2026; Bhatnagar, Kumar, & Shivam, 2026). Implementation considerations matter for scaling. Genetic counsellor capacity was a rate-limiting step in our pathway; tele-genetics consultation can extend reach, particularly for geographically dispersed relatives (Deepa et al., 2026; Catherine, Gupta, Gopi, & Swadhi, 2025). PCSK9 inhibitor reimbursement remains uneven across health systems, and the modest cost-effectiveness case for these agents depends heavily on appropriate patient selection exactly the selection that structured FH pathways enable. Patient education materials targeting the family-as-unit rather than the individual proband improve cascade-screening uptake (Vettriselman, Ramya, et al., 2026; Rasi, & Ashifa, 2019). Limitations include the single-centre design, the 24-month follow-up which does not capture the longer-term cardiovascular benefit that drives FH treatment, and reliance on self-reported adherence for some patients. The incomplete uptake of cascade screening among identified relatives (153 of 216, 70.8%) suggests scope for engagement improvement, including peer support and structured digital reminders for family contacts (Catherine, Gupta, Gopi, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine, & Velmurugan, 2025).

5. Conclusion

A structured cardiology-led cascade-screening pathway identified 71 new FH cases from 45 probands across 18 months, with cascade yield of 46.4% across all

relatives screened and 77% among first-degree relatives. Stepwise treatment intensification statin, ezetimibe, PCSK9 inhibitor achieved guideline LDL targets in approximately half of patients overall and over 80% of those reaching triple therapy. The approach is operationally efficient, high-yield, and ready for broader implementation in cardiology services.

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