# Suboptimal consideration and management of potential familial hypercholesterolaemia in patients with suspected premature coronary artery disease

*Yudi M[1,2],* MBBS, *Omera L[1],* MBBS, *McCubbery N[1],* MBBS, *Dick S[1],* MBBS, *Jayasinghe R[1,2],* MBBS, PhD, *Hamilton-Craig I[2],* MBBS, PhD

**INTRODUCTION** Familial hypercholesterolaemia (FH) is caused by an autosomal dominant mutation of the low density lipoprotein (LDL) receptor gene, resulting in high levels of LDL cholesterol and premature coronary artery disease (P-CAD). Studies have shown low detection rates of FH in patients admitted with P-CAD and suboptimal therapy at discharge.
**METHODS** Males aged ≤ 55 years and females aged ≤ 60 years who were admitted with P-CAD to the Gold Coast Hospital during a 12-month period were included in the study. The demographics, cardiovascular risk factors, examination findings, admission and discharge cardiac medications and provisional diagnoses were recorded. Diagnosis of FH was made according to internationally accepted criteria.
**RESULTS** 210 patients were included in the study; 60% were male and 40% female (mean age 48 and 50 years, respectively). Only 96 (46%) patients' fasting lipid levels were documented (LDL-C 2.75 ± 1.0 mmol/L), and FH was considered in three (1%) cases. According to the Dutch Lipid Network criteria, three (1%) patients had probable FH, 50 (24%) had possible FH and 60 (29%) had unlikely FH. Of the 53 patients with probable or possible FH, 12 (23%) were discharged without statin therapy and 13 (25%) on the maximum recommended statin dose.
**CONCLUSION** Our study has found inadequate documentation and screening for FH and suboptimal therapy in patients admitted with P-CAD. We propose a simple screening tool that can be applied to all patients admitted with suspected P-CAD in order to improve the detection rate of FH and its management.

## INTRODUCTION

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder caused by a mutation in the gene that encodes for the low density lipoprotein receptor (LDLR). The associated impairment of function of this receptor results in decreased LDL clearance and thus, elevated plasma levels of total cholesterol and LDL cholesterol (LDL-C). Clinically, this is manifested as tendinous xanthomata and premature coronary artery disease (P-CAD). Heterozygous FH is relatively common, with a reported incidence of 1:500, although it exhibits a milder phenotype than those with the rare (1:10[6]) homozygous disease.[1]

The mutation in FH occurs in the *LDLR* gene. Most geographically based surveys of FH subjects show a large number of mutations segregating in a given population, and to date, over 1,000 variants have been identified. This makes genetic testing an expensive tool for diagnosing FH. A consistent, uniform and widely used clinical definition is required to correctly diagnose and treat the disease. Presently, three FH diagnostic criteria tools are used internationally: the US MedPed Program,[2] the UK Simon Broome Familial Hypercholesterolaemia Register[3] and the Dutch Lipid Clinic Network.[4]

Unfortunately, international and national studies suggest that the majority of families with FH are not diagnosed.[1,5-6] The tragedy of under-diagnosing FH is that patients are not treated with drugs that can successfully lower LDL-C levels and consequently reduce the risk of P-CAD.[7,8] The aims of this retrospective study were to investigate the prevalence of FH in patients admitted to a tertiary hospital with possible P-CAD in a 12-month period and to determine whether these patients were recognised during routine hospital care and treated appropriately.

## METHODS

A retrospective analysis of patients who were admitted to the Cardiology Department of a tertiary hospital in a consecutive 12-month period was undertaken. Patients had to meet two entry criteria to be included in this study. Firstly, they had to be admitted with ischaemic chest pain that required further investigation and management, comprising at least a second troponin I measurement, eight hours after the onset of chest pain. These patients had a provisional diagnosis in the emergency department of acute coronary syndrome, angina, unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) or STEMI. Secondly, the patients had to be aged ≤ 55 years for males and ≤ 60 years for females.

The following data were recorded: basic demographics, cardiovascular risk factor profile, relevant physical examination findings, admission and discharge cardiac medication profile, plasma lipid profile, special blood tests, provisional diagnosis,

[1] Cardiology Department, Gold Coast Hospital, Queensland, Australia, [2] Cardiology Department, Griffith University School of Medicine, Queensland, Australia
**Correspondence**: Dr Matias Yudi, PO Box 1799, Southport BC, Queensland 4215, Australia. matiasyudi@hotmail.com

**Table I. Demographics, risk factor profile and physical examination findings (n = 210).**

| Demographic | No. of patients (%) |
|---|---|
| **Gender** | |
| Male | 126 (60) |
| Female | 84 (40) |
| **Mean age ± SD (yrs)** | |
| Male | 48.0 ± 6.9 |
| Female | 50.0 ± 7.4 |
| **Active smoker** | 101 (48) |
| **Diabetes mellitus** | 27 (13) |
| **Hypercholesterolaemia** | 89 (42) |
| **Hypertension** | 110 (52) |
| **FHx CAD** | 105 (50) |
| **FHx dyslipidaemia** | 8 (4) |
| **Prior MI** | 50 (24) |
| **Waist circumference*** | - |
| **Tendon xanthomata*** | - |
| **Arcus cornealis*** | - |
| **Palpebral xanthamata*** | - |

*Absence or presence of these signs was not recorded.
SD: standard deviation; FH: familial hypercholesterolaemia; FHx: family history; CAD: coronary artery disease; MI: myocardial infarction

**Table II. Lipid profile and other blood tests (n = 96).**

| Profile | Mean value ± SD; normal |
|---|---|
| **Lipid (mmol/L)** | |
| Total cholesterol | 4.89 ± 1.2; < 5.5 |
| LDL cholesterol | 2.75 ± 1.0; 2.0–3.4 |
| HDL cholesterol | 0.99 ± 0.5; 0.9–2.2 |
| Triglyceride concentration | 1.79 ± 0.9; < 2.0 |
| **hs-CRP** | 0 ordered |
| **Apolipoprotein B** | 0 ordered |
| **Apolipoprotein A1** | 0 ordered |
| **Lipoprotein(a)** | 0 ordered |
| **Homocysteine** | 0 ordered |

SD: standard deviation; hs-CRP: high-sensitivity C-reactive protein

**Table III. FH diagnosis according to the Dutch Lipid Clinic Network Criteria.**

| FH diagnosis | No. of patients (%) |
|---|---|
| Definite | 0 (0) |
| Probable | 3 (1.5) |
| Possible | 50 (24) |
| Unlikely | 60 (29) |
| Indeterminate | 97 (46) |

FH: familial hypercholesterolaemia

**Table IV. Demographics and risk factor profile for probable/possible FH (n = 53).**

| Demographic & risk factor | No. of patients (%) |
|---|---|
| **Gender** | |
| Male | 30 (57) |
| Female | 23 (43) |
| **Mean age ± SD (yrs)** | |
| Male | 47.6 ± 6.5 |
| Female | 51.5 ± 5.1 |
| **Active smoker** | 28 (53) |
| **Diabetes mellitus** | 6 (11) |
| **Hypercholesterolaemia** | 27 (51) |
| **Hypertension** | 25 (47) |
| **FHx CAD** | 48 (91) |
| **FHx dyslipidaemia** | 4 (8) |
| **Prior MI** | 16 (30) |

SD: standard deviation; FH: familial hypercholesterolaemia; FHx: family history; CAD: coronary artery disease; MI: myocardial infarction

and whether FH was considered. If particular information was not recorded, it was assumed to be negative. However, the presence or absence of physical findings must be documented. Following the compilation of data, relevant information was applied to the international FH Criteria of the MedPed Program, Simon Broome Familial Hypercholesterolaemia Register and the Dutch Lipid Clinic Network (Appendix).

## RESULTS

Out of the 241 patients who met our criteria, the files of 210 patients were available for review during the two-month auditing period. The demographics, risk factor profile and physical examination findings of the patients are shown in Table I. 60% of the patients were male (mean age 48 years), while 40% were female (mean age 50 years). 50% of the patients had a family history of P-CAD, 4% had a family history of hypercholesterolaemia and 24% had experienced a prior myocardial infarction. The presence or absence of tendon xanthomata, arcus senilis and

palpebral xanthelasmata was not recorded in any of the cases. None of the cases had a recorded waist circumference. The fasting lipid levels of 96 of the 210 patients (46%) were recorded. The mean lipid values are shown in Table II. In all the patients, there was no record of high-sensitivity C-reactive protein values, alipoprotein A1, alipoprotein B100 (apoB-100), lipoprotein(a) or homocysteine levels. The provisional diagnoses were angina in 20% of patients, UA in 32%, NSTEMI in 37% and STEMI in 10%. FH was considered in only three (1%) patients.

On application of international criteria, none of our patients was found to have definite FH. The Simon Broome FH Register diagnostic criteria found seven cases with probable FH and 89 with unlikely FH. Due to the lack of fasting lipid level records, 114 cases were labelled as indeterminate FH. On applying the Dutch Lipid Clinic Network diagnostic criteria (Table III), three (1%) patients were found to have probable FH, 50 (24%) had possible FH and 60 (29%) were unlikely to have FH. Although 114 patients did not have a fasting lipid profile, 17 of these were classified as having possible FH solely based on their personal and family histories of P-CAD. Therefore, 97 (46%) patients were classified with indeterminate FH. The characteristics of the 53 cases with either probable or possible FH according to the Dutch Lipid Clinic Network diagnostic criteria are shown in Table IV. 12 (23%) patients were discharged without lipid-lowering therapy, and only 13 (25%) were discharged on the maximum recommended dose of a statin (atorvastatin 80 mg/day).

**Table V. Possible/probable FH\* patients with lipid medication on discharge (n = 53).**

| | No. of patients (%) |
|---|---|
| **Medication on discharge** | |
| Atorvastatin (mg) | |
| 10 | 1 (2) |
| 20 | 2 (4) |
| 40 | 19 (36) |
| 80 | 13 (25) |
| Simvastatin (mg) | |
| 20 | 2 (4) |
| 40 | 1 (2) |
| Rosuvastatin (mg) | |
| 10 | 2 (4) |
| 20 | 1 (2) |
| **No medication on discharge** | 12 (23) |

\*Based on the 53 cases of possible/probable FH according to the Dutch Lipid Clinic Network Criteria.



**Fig. 1** Graph shows the comparison of FH diagnosis between Gold Coast Hospital and Royal Perth Hospital.
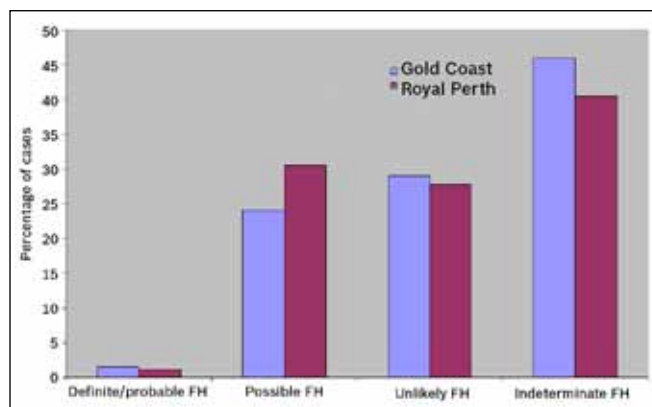
## DISCUSSION

Our study suggests that patients with symptomatic P-CAD admitted to a specialist cardiology department in a tertiary hospital are seldom screened for FH. This is of concern, as patients with FH carry a very high risk of cardiovascular events, which could be reduced by appropriate LDL-lowering therapy with statins and ezetimibe.[9] More specifically, men with FH have an approximately 50% risk of CAD by age 50 years and women have at least a 30% risk of CAD by age 60 years.[10,11]

Inadequate documentation was a major hurdle in attempting to screen for FH. None of the cases documented the presence or absence of characteristic signs of lipid abnormalities, such as tendon xanthomata, arcus senilis and palpebral xanthelasma. Although it does not necessarily suggest that these signs were not noted, it cannot exclude the possibility that they were overlooked. These signs are particularly important in both the Simon Broome and Dutch Lipid Clinic Network criteria. It is even more significant that 114 (54%) patients did not have any documented fasting lipid levels, either during or before admission. This has major implications for further management and prevention of recurrence. It is impossible to completely screen patients for FH with any of the three major criteria without a lipid profile. More importantly, however, one cannot accurately assess the cardiovascular risk profile of these patients, who are already at high risk due to their symptomatic P-CAD.

The finding in this retrospective study is consistent with that of Royal Perth Hospital's FH clinical audit.[12] We compared the percentage of patients with probable, possible, unlikely and indeterminate FH between the two populations, according to the Dutch Lipid Clinic Network criteria (Fig. 1). Our study has shown a high prevalence of a positive family history of P-CAD, which occurred in 91% of patients with probable or possible FH. The entire study initially showed that only 50% of patients had a positive family history of CAD. This finding could provide an important trigger to the clinician to consider FH in patients with P-CAD and a positive family history.

Failure to diagnose FH has implications not only for the individual but can also potentially affect family members. For every index case detected, another 2–4 additional cases may be detected by cascade family screening.[13] This exponentially increases the public health benefit of successful early diagnosis of FH. Furthermore, screening for FH has been shown to be cost-effective.[14,15] Early and effective treatment of FH with lifestyle modification and statin therapy could prevent disease progression and increase life expectancy.[7,8] Unfortunately, out of the 53 patients with possible or probable FH, only 14 (27%) were discharged on the maximum recommended dose of a statin. None of the patients were prescribed combined therapy with statin and ezetimibe, which could result in optimal LDL-C reduction.[9] Of further concern is the finding that 50% of patients were discharged on suboptimal statin therapy and 23% of patients with no statin therapy at all.

Due to the retrospective nature of the analysis, our study has some inherent limitations. It does, however, represent the contemporary clinical practice of a cardiology department in a tertiary institution. Due to inadequate data from the medical records and a lack of a fasting lipid profile for a large proportion of patients, it is likely that the prevalence of possible and probable FH was underestimated. Furthermore, lipid therapy prior to lipid testing could mask baseline lipid levels and result in under-estimation of the diagnosis of FH. It is possible that genetic testing may increase the detection rate of patients with FH. It has been shown, however, that patients with clinical FH may not have a detectable mutation related to the LDLR in up to 50% of cases.[16] More recent studies have suggested that a large proportion of these cases may have gain-of-function mutations in the PCSK9 gene, which increase intracellular degradation of the LDLR.[17] Total gene sequencing of the LDLR and its promoter region is necessary to fully exclude an LDLR mutation causing FH. This has been planned for future studies of our population. Other genes may also be involved, including the LDLR adaptor protein (LDLRAP1), which is responsible for autosomal recessive hypercholesterolaemia, and mutations of the gene coding for apoB-100, which is responsible for familial defective apoB.[16]

Our study clearly portrays the inadequacy of the current practice, which results in underdiagnosis of FH and consequent suboptimal treatment of the disorder. With its highly accelerated
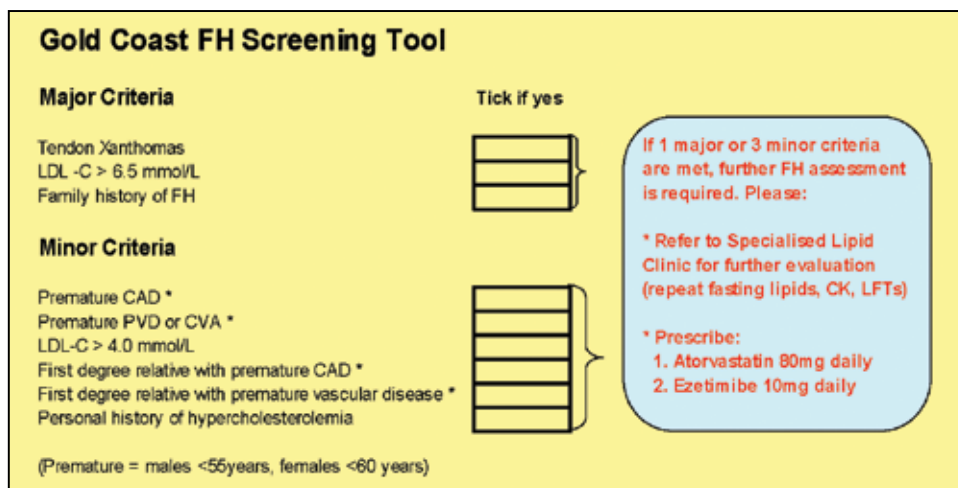
**Fig. 2** Diagram shows the proposed FH screening tool.

atheromatous nature, FH is ignored at the peril of our patients. Thus, we propose a simple screening tool that could be applied to all patients who are admitted with suspected P-CAD. This proposed FH screening tool (Fig. 2) aims to increase awareness and consequently, the diagnostic rate of FH. Patients who meet one of the major criteria or three of the minor criteria are classified as suspected FH. Major criteria include three high-risk characteristics: the presence of tendon xanthomas, LDL-C > 6.5 mmol/L and a family history of FH. Minor criteria include P-CAD, premature peripheral or cerebrovascular disease (P-VD), LDL-C > 4.0 mmol/L, first-degree relative with P-CAD or P-VD and a personal history of hypercholesterolaemia. Suspected FH patients are then referred to a specialised FH clinic for full evaluation of FH based on validated diagnostic criteria. Furthermore, suspected FH patients are commenced on or titrated to atorvastatin 80 mg daily and ezetimibe 10 mg daily. This would ensure optimal treatment from the time FH is first considered.

In conclusion, our retrospective analysis highlights the inadequacy of screening and the consequent under-diagnosis of FH in a major cardiac tertiary institution. A simple screening tool is proposed in order to increase the detection rate of FH index cases. Plans are in place to implement the Gold Coast FH Screening Tool in clinical practice and to assess its efficacy with validation by genetic testing.

## REFERENCES

1. Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis 2003; 168:1-14.
2. Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol 1993; 72:171-6.
3. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991; 303:893-6.
4. Familial hypercholesterolemia: report of a second WHO Consultation. In: World Health Organization: Geneva, Switzerland, 1999.
5. Leren TP. Cascade genetic screening for familial hypercholesterolemia. Clin Genet 2004; 66:483-7.
6. Neil HA, Hammond T, Huxley R, Matthews DR, Humphries SE. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. BMJ 2000; 321:148.
7. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. Atherosclerosis 1999; 142:105-12.
8. Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008; 29:2625-33.
9. Hamilton-Craig I, Kostner K, Colquhoun D, Woodhouse S. Ezetimibe in familial hypercholesterolaemia. Vascular Health Risk Manag 2010; 6:1023-37.
10. Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. Circulation 1974; 49:476-88.
11. Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemic states. Lancet 1969; 2:1380-2.
12. Bates TR, Burnett JR, van Bockxmeer FM, et al. Detection of familial hypercholesterolaemia: a major treatment gap in preventative cardiology. Heart Lung Circ 2008; 17:411-3.
13. Hamilton-Craig I. Case-finding for familial hypercholesterolemia in the Asia-Pacific region. Semin Vasc Med 2004; 4:87-92.
14. Marks D, Thorogood M, Neil HA, Wonderling D, Humphries SE. Comparing costs and benefits over a 10 year period of strategies for familial hypercholesterolaemia screening. J Public Health Med 2003; 25:47-52.
15. Wonderling D, Umans-Eckenhausen MA, Marks D, et al. Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. Semin Vasc Med 2004; 4:97-104.
16. Fahed AC, Safa RM, Haddad FF, et al. Homozygous familial hypercholesterolemia in Lebanon: a genotype/phenotype correlation. Mol Genet Metab 2011; 102:181-8.
17. Duff CJ, Hooper NM. PCSK9: an emerging target for treatment of hypercholesterolemia. Expert Opin Ther Targets 2011; 15:157-68.

## APPENDIX

### THE THREE DIFFERENT FH DIAGNOSTIC CRITERIA

#### 1. MEDPED FH Criteria

| Age (yrs) | 1st degree relative with FH | 2nd degree relative with FH | 3rd degree relative with FH | General Population |
|---|---|---|---|---|
| < 20 | 5.7 | 5.9 | 6.2 | 7.0 |
| 20–29 | 6.2 | 6.5 | 6.7 | 7.5 |
| 30–39 | 7.0 | 7.2 | 7.5 | 8.8 |
| 40+ | 7.5 | 7.8 | 8.0 | 9.3 |

A diagnosis of FH is made if the total cholesterol levels (mmol/L) exceed the cut-off points

#### 2. Simon Broome Criteria

**Criterion**

a. DNA mutation (either LDL-receptor or apoB gene)
b. Tendon xanthomas in patient or first/second degree relative
c. Family history of myocardial infarction in second degree relative aged <50years or in first-degree relative aged <60years
d. Family history of cholesterol >7.5mmol/L in first or second degree relative
e. Total cholesterol >7.5mmol/L (adult) or >6.7mmol/L (age<16 years)
f. LDL-C>4.9 mmol/L (adult) or >4.0mmol/L (age<16 years)

**Diagnosis**
Definite FH:     criterion a. pr criterion b + (e or f)
Probable FH:    criteria c + (e or f), or criteria d + (e or f)

#### 3. Dutch Lipid Clinic Network Diagnostic Criteria

| | Points |
|---|---|
| **Family History** | |
| 1st degree relative with premature CVD  (M<55yrs, F<60yrs) | 1 |
| 1st degree relative with known LDL-C > 95th percentile | 2 |
| 1st degree relative with tendinous xanthomas and/or arcus cornealis | 2 |
| Children < 18 years with LDL-C > 95th percentile | |
| **Personal history of CVD** | |
| Premature CHD (M<55yrs, F<60yrs) | 2 |
| Premature cerebral or peripheral vascular disease (M<55yrs, F<60yrs) | 1 |
| **Physical examination** | |
| Tendinous xanthomas | 6 |
| Arcus senilis in patients <45yrs | 4 |
| **LDL cholesterol level** | |
| ≥8.5 mmol/L | 8 |
| 6.5-8.4 mmol/L | 5 |
| 5.0-6.4 mmol/L | 3 |
| 4.0-4.9 mmol/L | 1 |
| **DNA Analysis** | |
| Functional mutation of LDL-receptor gene identified | 8 |

**Diagnosis**
Definite FH: greater than 8 points
Probable FH: 6 to 8 points
Possible FH: 3 to 5 points