Familial hypercholesterolaemia: underdiagnosed and undertreated

Alan Rees*

Department of Medicine, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, UK

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This editorial refers to ‘Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study’* by A. Neil et al., on page 2625

Autosomal dominant familial hypercholesterolaemia (FH) is the most common inherited disorder known to cause premature coronary heart disease in people of European descent. The estimated prevalence of FH is 1 in 500, and heterozygous FH carries a high risk of premature coronary disease if left untreated (>50% risk in men by the age of 50 and >30% in women by 60 years). However, the condition is underdiagnosed and it is estimated that <20% of index cases are ascertained. With the notable exception of The Netherlands, there is generally a complete lack of organization in European countries to ensure the delivery of systematic care such as an established cascade screening programme and a genetic register for FH.

Although the phenotypic presentation of FH is relatively homogeneous [high levels of low-density lipoprotein (LDL) cholesterol, premature atherosclerosis ± tendon xanthomata], the genotype is heterogeneous, with >1000 mutations described at the LDL receptor locus as well as the Apo B-3500 mutation in the LDL receptor ligand Apo B. More recently, missense mutations at the protease proprotein convertase subtilisin/kexin type 9 (PCSK9) gene—a protein involved in regulating hepatic LDL receptor expression—have been described and shown to result in an identical FH phenotype with dominant inheritance. With recent technical improvements in fast-throughput mutational analysis techniques, such as DNA microarray, a gene mutation causing FH may be found in up to 90% of cases, depending on which testing strategy is used. Thus, DNA mutational analysis in patients with ‘possible’ or ‘probable’ FH is now feasible and may help resolve the diagnostic ambiguities as to whether a patient has true autosomal dominant FH or polygenic hypercholesterolaemia.

The recent publication of the National Institute for Health and Clinical Excellence (NICE)’s most recent guidelines and evidence review for familial hypercholesterolaemia: identification and management of adults and children with familial hypercholesterolaemia is most welcome, together with a summary in the BMJ. In essence, the NICE guidance gives detailed advice on the diagnosis of FH in adults and advocates making the diagnosis using the Simon Broome criteria: a combination of a family history of coronary heart disease (at age <60 years in a first-degree relative or <50 years in a second-degree relative), clinical examination (specifically tendon xanthomata), and a total cholesterol concentration >7.5 mmol/l or LDL cholesterol >4.9 mmol/l. The guidelines also state that all patients with a clinical diagnosis of FH should be offered a DNA diagnostic test and referral for family ‘cascade’ testing of the proband’s pedigree in order to identify relatives affected. Cascade testing is most effective using a combination of genotype and LDL cholesterol concentration but should be carried out with LDL cholesterol alone if a genetic mutation is not found. The recommendations also advise clinicians to consider prescribing a high intensity statin to achieve a recommended reduction in LDL cholesterol of >50% from baseline (i.e. LDL cholesterol concentration before treatment). For children found to have FH, the guidelines suggest starting statins at age 10 years. This is based on a review of randomized trials of childhood statin treatment which found no adverse effects on growth or development over the short term (median duration on treatment was 27 weeks). The American Academy of Pediatrics supports the use of statin treatment for children as young as 8 years with a family history of early heart disease and an LDL cholesterol level of >4.1 mmol/l, although there is no clear evidence base for this particular threshold.

Before effective treatment with statins became available, mortality from coronary disease was increased nearly 100-fold in young adults aged 20–39 years and ~4-fold for patients aged 40–59 years. As no randomized placebo-controlled trials of statin therapy have been conducted in FH cohorts (for ethical reasons), clinical management of patients with FH is largely based on extrapolation from cholesterol-lowering trials conducted...
in patients with polygenic hypercholesterolaemia, from evidence utilizing carotid intimal medial thickness in FH as a surrogate outcome, and from a small number of prospective observational studies. One such prospective observational study is the Simon Broome register of FH which is a register of patients with heterozygous FH recruited from 21 lipid clinics in Britain. Early results from the register suggested that the prognosis for the heterozygous autosomal condition had improved since the introduction and widespread use of statins. Neil et al. have published the most recent report describing and extending previous reports from the Simon Broome register. Clinical data from a large cohort of 3382 heterozygous patients followed-up for up to 26 years until the end of 2006 are described. This has allowed the authors to examine more informatively changes in mortality compared with the general population both before and after the routine use of statins.

They report a statistically significant reduction in coronary mortality of about one-third subsequent to the widespread use of statins. Primary prevention resulted in a halving of risk for fatal coronary events (from a 2-fold excess to none), with a smaller reduction of nearly 25% in patients with established disease. Women benefited more than men, in both primary and secondary prevention. This data set also confirms a previous report that in patients with known coronary disease at registration, all-cause mortality was significantly lower than in the general population, mainly due to a reduction of more than a third in the risk of fatal cancer.

There are clearly limitations to this study, which are acknowledged by the authors. Undoubtedly, some patients with polygenic hypercholesterolaemia may have been misclassified as having FH. Moreover, although statin treatment has been used routinely only after 1991, some patients may have been prescribed statins earlier although the majority will have received other forms of treatment such as bile acid sequestrants, fibrates, and possibly nicotinic acid. The results are therefore likely to underestimate the maximum potential benefits of widespread statin treatment.

**Clinical implications**

The benefits of early ascertainment, diagnosis, and treatment are mainly in primary prevention. Moreover, these data support a cascade screening policy to include diagnosis in childhood. It is children with FH who have the highest rate of underdiagnosis.

Implicit in this report is that more intensive treatment may be needed in those with established coronary heart disease and that adherence to lifestyle advice and/or statin treatment in a well-motivated cohort of patients has major benefits, particularly in the reduction in mortality from cancer. It is likely that the prevalence of obesity, diabetes, and smoking in this cohort is less than in the general population due to the aforementioned adherence to lifestyle advice, but statin therapy may also have potential anticancer properties.

The timely publication of both the NICE guidelines on FH in the UK and the encouraging data included in the study of Neil et al. mandates all clinicians to coordinate clinical services to ensure the delivery of systematic care for patients with FH and to establish a family cascade testing programme and a genetic register for the condition.

**Conflict of interest:** none declared.

**References**