Papers that could change practice in cardiovascular research:

23 May 2013 – Rational responses to finding a patient with a high plasma cholesterol

Familial hypercholesterolaemia (FH) is common. About 1in 500 people meet the Simon Broom Diagnostic criteria defined by NICE in 2008, with raised total cholesterol (>7.5mmol/l) and LDL (>4.9mmol/l) and clinical signs of tendon xanthoma. 40% of these people will have identifiable mutations in one of three known genes, 93% of these being in the LDL–receptor, the others being in genes concerned with *APOB*, encoding apolipoprotein B, or *PCSK9* which encodes a protein involved in degradation of the LDL receptor. The other 60% of patients, who have biochemical evidence to support the diagnosis, have no single mutation. A new study from Talmud *et al* reports a study of the cumulative effects of 12 common single nucleotide polymorphisms (SNPs, common genetic variants) which are associated with raised LDL-cholesterol. They examined the genotype of 640 UK patients from three different patient sets and of 3020 normal controls from the Whitehall II study, and subsequently also examined 451 patients from a Belgium clinic who had no identifiable mutations and 273 with recognised mutation.

In mutation negative patients, an assigned numerical score, derived from a summated and weighted score for the 12 SNPs, had a strong association with the LDL-cholesterol concentrations. This suggested a polygenic cause in these patients. In addition the score relating to the SNPs also contributed to the LDL cholesterol level even in the 40% of patients with a dominant mutation, i.e. influencing the phenotype.

FH is treated with statins, and other cholesterol lowering drugs, no matter what its origins. Current advice includes referral for genetic testing and cascade screening of family members. However, the authors of the paper suggest that unless a mutation is found in the proband (the first patient identified in a family), then genetic testing is unlikely to be a useful screen in relatives and it will be more economical to reserve it as a tool study only of those relatives of a patient in whom one of the current three mutations are identified. A high gene score suggests the polygenic form, which should nevertheless be treated aggressively. The same therapeutic approach can be taken with those who have neither a single gene defect nor a high polygene score, and although new dominant single mutations are likely to be rare, study of this group may reveal new monogenic forms of familial FH.

Talmud PJ, Shah S, Whittall R, Futema M, Howard P, Cooper JA, Harrison SC, Li K, Drenos F, Karpe F, Neil HA, Descamps OS, Langenberg C, Lench N, Kivimaki M, Whittaker J, Hingorani AD, Kumari M, Humphries SE. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet. 2013; 381: 1293-1301.

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