Heartbeat: improved diagnosis of familial hypercholesterolaemia

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Familial hypercholesterolaemia (FH) is the most common autosomal dominant genetic condition, affecting about 1 in 250 people, caused by a pathogenic variant in one of several genes involved in lipoprotein cholesterol catabolism. Treatment of elevated serum low-density lipoprotein cholesterol in people with FH substantially reduces the risk of ischaemic heart disease and cardiovascular mortality. Yet, the vast majority of FH cases are undiagnosed and, thus, untreated. Diagnosis is challenging because patients typically are asymptomatic, may not know their family history, are unaware of the seriousness of the diagnosis and may not even be seeing a physician regularly. In addition, the phenotypic diagnosis requires more than just serum cholesterol levels.

In this issue of *Heart*, Carvalho and colleagues[1] demonstrated the feasibility of the FH Case Ascertainment Tool (FAMCAT) for identifying patients likely to have FH in a cohort of 777 128 primary care patients in London. The FAMCAT score is based on systematic screening of routine primary care records for cholesterol measurements, age, triglycerides, family history, diabetes, kidney disease and current use of lipid-lowering drugs (figure 1). The use of FAMCAT to identify patients likely to have FH could ensure more accurate and rapid diagnosis (and subsequent treatment) for this group of patients at high risk of cardiovascular disease.

A different approach to detection of FH was used by Brett and colleagues[2] in a cohort of 232, 139 Australian general practice patients. Using a pragmatic two-step approach, they first identified those at higher risk of FH using the TARB-Ex electronic screening tool. Then, in the 1843 (0.8%) of patients identified electronically by TARB-Ex, clinical assessment by the physician was used to confirm a high FH risk the based on the phenotypic Dutch Lipid Clinic Network Criteria score. In a subset of 77 patients with FH, subsequent intensification of lipid-lowering therapy led to a further reduction in serum cholesterol levels .

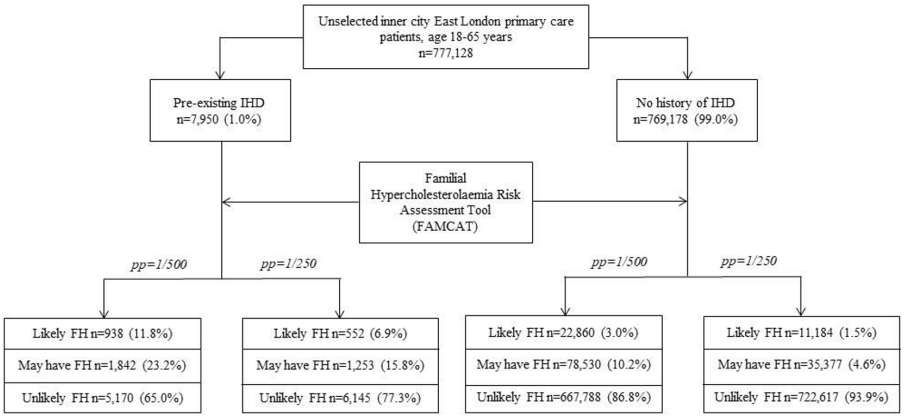

Figure 1 Risk of familial hypercholesterolaemia (FH) in inner East London calculated using FAMCAT algorithm, assuming population prevalence of 1 in 500 and 1 in 250. IHD, ischaemic heart disease; PP, population prevalence.

In an editorial, Qureshi and Patel[3] summarise methods using the electronic health record (EHR) for improved diagnosis of FH (figure 2) and point out that the EHR approach often is limited by inadequate or missing data about family history, physical signs and other information. Cholesterol levels, while not diagnostic in isolation, are essential for the diagnosis but may not have been measured in many asymptomatic individuals. They conclude: 'Ultimately, successfully identifying the thousands of people with FH in the UK and abroad will require a system-wide approach from opportunistic identification at routine health encounters, systematic case finding in primary care, screening people at the time of a premature CVD event to child–parent screening and cascade testing.'

Also, in this issue of *Heart*, Schwerzmann and colleague[4] report clinical outcomes in 105 patients adult congenital heart disease (ACHD) with COVID-19 infections. Overall, 5 patients died and 13 had a complication disease course. Clinical features associated with a complicated disease course were similar to the general population including older age, the presence of two or more comorbidities, and obesity (figure 3). In addition, those with a complicated disease course were more likely to have cyanotic heart disease such as unrepaired cyanotic defects are Eisenmenger syndrome, compared with ACHD patients with an uncomplicated COVID-19 course (OR 60, 95% CI 7.6 to 474).

Yuan and Oechslin comment in an editorial[5] that 'Contrary to our previous conceptualisation of risk, anatomical complexity does not appear to predict

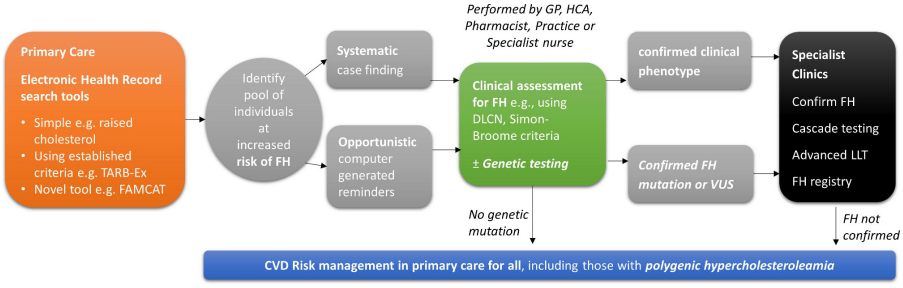

Figure 2 Pathway to identification of FH from primary care. CVD, cardiovascular disease; DLCN, Dutch Lipid Clinic Network; FAMCAT, FH Case Ascertainment Tool; FH, familial hypercholesterolaemia; GP, general practitioner; HCA, healthcare assistant; LLT, lipid-lowering treatment; VUS, variant of unknown significance.

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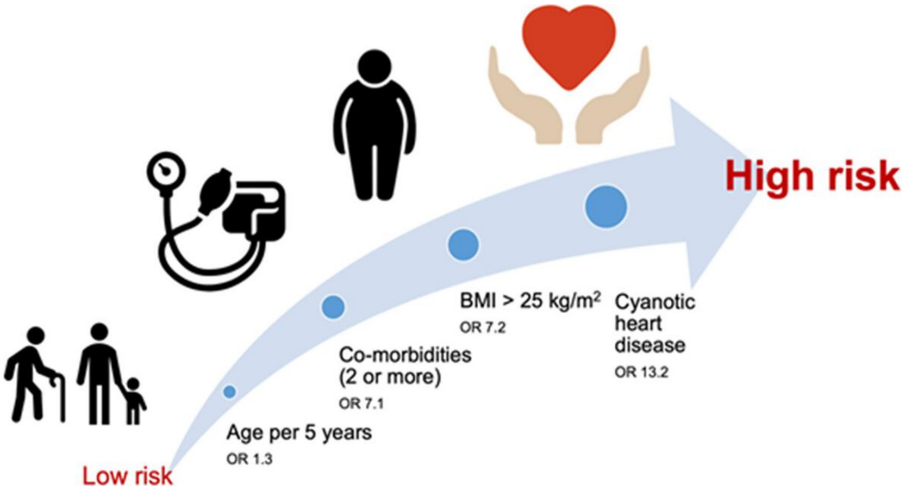

Figure 3 Univariable significant COVID-19 risk factors in patients with adult congenital heart disease and the corresponding ORs. We propose to stratify patients based on age, number of comorbidities, weight and presence of a high-risk cardiac lesion (cyanotic heart disease). BMI, body mass index.

severe infection or death. Rather, patient-specific risk factors similar to those in the non-CHD cohort remain important, while strong CHD-specific risk factors for severe illness or death after COVID-19 infection were cyanotic heart disease and physiological stage. These results help us to tailor patient recommendations but require further confirmation in large international, multicentre studies that are sufficiently powered to answer our remaining questions.'

A meta-analysis by Imazio and colleagues[6] supports the efficacy of anti-interleukin-1 agents, such as anakinra and rilonacept, for prevention of recurrent episodes of pericarditis in patients with corticosteroid-dependent and colchicine-resistant recurrent pericarditis. Anthony and Collier[7] remind us that recurrent pericarditis complicates 15%–30% of index cases of pericarditis; the clinical consequences, in addition to pain, can be serious including recurrent effusions, tamponade physiology and constrictive pericarditis; and there is little data on effective therapies (figure 4).[8] They conclude 'Inhibition of the IL-1 pathway may represent a paradigm shift in the treatment of patients with recurrent pericarditis despite standard therapy. However, larger RCT data are required for further validation of the efficacy and safety of these novel medications in the treatment of recurrent pericarditis.'

The *Education in Heart* article in this issue provides a quick overview of cardio-oncology for the general cardiologist. Cardio-oncology is defined as 'the treatment and prevention of cardiovascular disease in cancer patients both during oncology treatment and afterwards.'[9]

A basic understanding of cardio-oncology now is considered core knowledge for every cardiologist, given the demographic overlap in the prevalence of cardiovascular disease and cancer, in addition to the potential cardiotoxic effects of cancer treatments. The information and practical advice in this review article are a concise resource for busy practitioners.

Our short *Cardiology in Focus* article[10] provides a brief overview of cost-effectiveness methodology, with a short list of references for those who wish to dive deeper into this topic.

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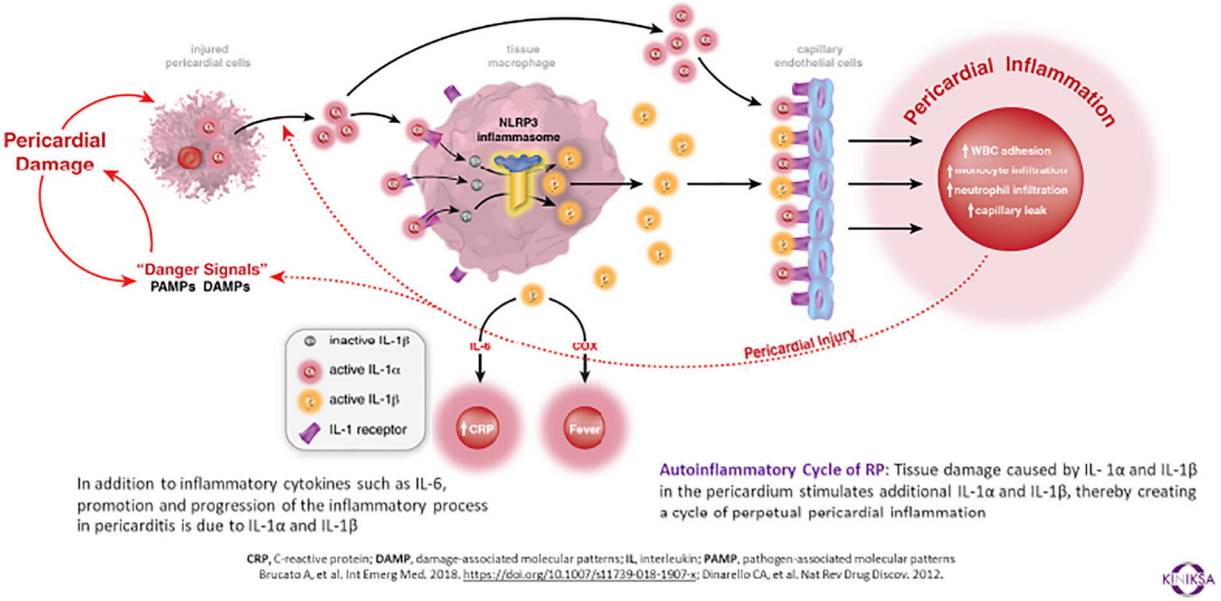

Figure 4 Interleukin-1 alpha and beta in pericardial inflammation. Adapted from Klein *et al*.[8]

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