Familial hypercholesterolemia (FH) is a common genetic disorder with an estimated prevalence of heterozygous FH (HeFH) between 1 in 200–500 and homozygous FH (HoFH) between 1 in 160,000–300,000. FH can be diagnosed using clinical criteria based on the presence of personal and first-degree family members with high cholesterol levels, premature coronary heart disease (CHD), and tendon xanthomas. The most common mutations observed are in the genes for low-density lipoprotein receptor, apolipoprotein B, and proprotein convertase subtilisin/kexin type 9 (PCSK9). Patients with FH are at 3.5- to 16-fold increased risk of developing CHD. CHD can present before the age of 20 in HoFH and before the age of 55 in HeFH if it is not diagnosed and managed early in life. Moreover, patients with FH with plasma low-density lipoprotein cholesterol (LDL-C) of 4.9 mmol/L and FH mutation are at approximately three-fold greater CHD risk than patients with similarly high LDL-C levels but do not carry the mutation. This can be explained by their cumulative lifelong exposure to high LDL-C due to the genetic defect. Therefore, it is highly important to screen the family (cascade screening) of the individual confirmed to carry the FH mutation using plasma lipid levels and genetic testing, if available. Cascade genetic screening has been shown to be a cost-effective method of diagnosing individuals with FH and starting early lipid-lowering therapies (LLT). Patients with FH should be advised regarding physical activity, diet, and smoking. Potent maximally tolerated statin doses should be started immediately in adults at the time of the diagnosis. For children, the recommended starting age is 8–10 years, usually with a low dose statin which is then up-titrated to a maximum tolerated dose by the age of 18. Statins can reduce LDL-C up to 50% in HeFH and up to 25% in HoFH. Observational studies have shown that starting statins early (before the onset of CHD) can improve patient survival. Despite the wide use of statins in patients with FH, many do not achieve the recommended targets. It has been demonstrated that the addition of other LLTs will help patients achieve their recommended targets. The combination of cholesterol absorption inhibitor, ezetimibe, with a statin can decrease LDL-C by 60–70%. In patients with HoFH, treatment with weekly or biweekly lipoprotein apheresis should be considered, which can acutely reduce LDL-C further by 50–70%. The age threshold for starting lipoprotein apheresis may vary from country to country but is recommended as early as five years in children. Novel therapies have been approved for use as an adjunctive treatment for HoFH. Lomitapide, a microsomal triglyceride transfer protein inhibitor, which is approved for use from 18 years of age, can reduce LDL-C up to 46%. In addition, injectable mipomersen, an antisense RNA therapy is approved in the USA from 12 years old and can reduce LDL-C up to 25%. Monoclonal antibodies to PCSK9 are considered the new horizon in the treatment of FH. In the Rutherford-2 study in HeFH patients on evolocumab, LDL-C was reduced by 61–66% and in the Odyssey FH I and II studies with alirocumab, LDL-C was reduced by 60–68%. Furthermore, the administration of evolocumab every two weeks has been shown to reduce plasma LDL-C by 26.3% from baseline in receptor defective HoFH patients. No randomized clinical trials have been conducted in patients with FH due to ethical reasons, but the cardiovascular disease outcome benefits of LLTs have been extrapolated from non-FH patients.
In summary, FH patients are at a greater risk for CHD and should be diagnosed early and treated intensively to reach very low LDL-C targets using available and optimal LLTs.

REFERENCES


