health consequences of a diagnosis of FH being missed if a person decides not to be tested. Communications should also emphasize the health gains of diagnosis and treatment.[6,8,33] In the absence of a response to the first letter, a second approach by letter or telephone call may be made to the family member.[8]

Family members who consent to being assessed for FH should be offered a standard plasma lipid profile and a genetic test if the family mutation is known and DNA testing available.[6,8,79,81] All individuals with potential FH should be made aware and understand the implications of genetic testing for certain types of insurance cover.[8,82] Systematic cascade screening for FH is best coordinated centrally by a dedicated service that operates closely with primary care and ideally with a patient organization.[6,8,31] Cascade screening should be developed for country-specific and local needs.[8] In less-developed countries, family testing in the home environment at weekends may increase the yield of cascade screening, noting also the opportunity for testing extended family members at the invitation of the index case.

### Risk notification without consent

If the index case does not consent to risk notification of family members, it is important to comprehend the rationale behind this, particularly the family dynamics.[8,45,80,83] A decision to notify individuals of their risk without the consent of the index case should be carefully taken, with attention to the privacy legislation in different countries and localities.[8,84] FH is a potentially lethal condition, and if there are high-risk features in the family, such as a strong history of premature CVD, contacting of relatives without consent could be justified.[8,84]

## Genetic testing

FH is a dominantly inherited disorder, affected individuals having a 50% chance of passing the causative mutation to each offspring.[1–3] Most of cases of FH are caused by mutations in the LDL-receptor (*LDLR*), *apoB*, and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes.[2] A pathogenic mutation in one of these genes is identified in about 70% of phenotypically definite FH and 20% of phenotypically probable/possible FH.[79,85–87] New molecular techniques, such as whole-exome sequencing, can lead to the discovery of novel mutations[88]; this may be particularly applicable to understudied multiethnic populations.[89] Absence of a pathogenic mutation in the presence of a high LDL-cholesterol gene score may indicate polygenic hypercholesterolemia, and this may be used to limit additional search for novel FH causing mutations.[90] Approximately 95% of the identified mutations are in the *LDLR* gene, 4% to 5% in the *apoB* gene and <1% in the *PCSK9* gene.[2,79] Detection of a mutation in a family member allows the definite diagnosis of FH to be made.[2,5,6,8,79] However, failure to detect a mutation does not exclude a diagnosis of FH, particularly if the clinical phenotype is highly suggestive of FH.[6,8] To optimize the use of resources, DNA testing may only be offered to index patients with a Dutch Lipid Clinic Network Score >5 or meeting the Simon Broome possible criteria, especially those with a personal history of early onset (<60 years) CVD or imaging evidence of significant subclinical atherosclerosis.[8,58,85–87]

If a pathogenic mutation is identified in an index case, genetic testing is a cost-effective, accurate, and acceptable approach for detecting new cases.[78,91] Because of ethical issues involved in genetically testing minors,[8,92] it is best to first genetically test a phenotypically affected parent. Children may initially be genetically tested when parents or first-degree relatives are unknown or deceased,[8,19] or with due parental consent, as an acceptable screening practice in certain countries, eg The Netherlands.[68,69] Genetic testing of families for FH should be coordinated by a specialist service with appropriate education and counseling offered to all individuals.[5,6,8,33] Genetic testing in children can be carried out without invasive venipuncture, using a buccal swab or saliva specimen.[8]

Genetic testing for FH has a tier 1 level of evidence that strongly supports its application in clinical practice.[93] Genetic testing for FH should be carried out in an accredited laboratory that will issue timely results to the requesting medical practitioner.[8] A full sequencing strategy that covers point mutations and insertions/deletions should be performed for the LDLR and PCSK9 genes and for relevant parts of exons 26 and 29 of the apoB gene.[85–87,94] Screening for large rearrangements with multiplex ligation probe amplification analyses should be performed in people with a high probability of FH in whom no functional mutations are detected.[95] Accredited laboratories have processes for assessing identified gene mutations or variants and for classifying the variant as clearly pathogenic (a mutation), clearly nonpathogenic (a benign variant), or of uncertain significance (a variant of uncertain significance)[8]; more than 1200 genetic variants in the LDLR have so far been described, but only 79% are recognized to be pathogenic.[96]

The process of screening for genetic mutations, confirming identified genetic variants, assessing pathogenicity, and issuing a formal report should ideally not take longer than 3 months.[8] However, genetic mutations may not be detected in 30% of patients with a definite clinical diagnosis of FH.[79,85–87] In such patients, multiple genetic variants that affect cholesterol metabolism interact to produce a phenocopy of FH,[90] but genetic screening of family members will not be useful. Thus, in a smaller proportion of families, diagnostic testing should be performed phenotypically with LDL cholesterol. Specific reference ranges for patients with high likelihood, low likelihood, and diagnosis uncertain will have to be derived from populations with and without FH in each country.[71] Clinical management of patients should evidently be based on the plasma lipid

phenotype and overall CVD risk status and not on the genetic test result.[6,8,9,61]

## Management of adults

FH is associated with a moderately severe to very severe increase in the lifelong exposure to the atherogenic effects of LDL-cholesterol.[54,67] It warrants aggressive, life-long management from a young age.[19–21,97]

### LDL cholesterol and related lipid targets

Because of lack of evidence from clinical trials,[97,98] clear therapeutic targets for plasma LDL cholesterol cannot be categorically defined for FH.[6–11,13] The following information is synthesized from various international guidelines.[6–13,22,51,60] In patients with heterozygous FH,[6–9] therapy should initially aim for at least a 50% reduction in plasma LDL cholesterol, followed by an LDL cholesterol of <2.5 mmol/L (absence of CHD or other major risk factors) and <1.8 mmol/L (presence of CHD or other major risk factors)[10–12]; three targets for LDL cholesterol according to CV risk stratification also have been described and are reasonable[8] but not universally ratified.[98] Untreated LDL-cholesterol burden, or life-years exposure, should be considered a major risk factor for driving more intensive and/or earlier therapy.[54] However, all recommended targets are difficult to achieve in the majority of FH patients with currently available treatments,[5,8,18] so that the maximal LDL-cholesterol reduction that can be tolerated with therapy is a pragmatic strategy, particularly for greater risk patients with FH. The LDL cholesterol of homozygotes should accordingly be reduced as much as possible,[8,32,65] with subsequent recommendations on use of apheresis noted. Therapeutic targets for apoB and non-HDL cholesterol have not been defined in FH[8] but with coexistent metabolic syndrome or diabetes targets recommended by other expert bodies should be adopted.[12–14,60,99] A therapeutic target for Lp(a) has been specified elsewhere, but the evidence for its use in FH is limited.[49] Other than when investigating symptomatic patients or managing homozygotes,[8] we do not consider that there is a role for cardiovascular imaging in monitoring and guiding therapy.

### Modification of lifestyle and noncholesterol risk factors

All patients with FH should be counseled on lifestyle modifications.[6–14,100] Dietary modification to lower the intake of saturated fat, trans-unsaturated fat, and cholesterol contributes to improvements in the plasma lipid profile.[101–103] A heart-healthy diet should be promoted and regular intake of fruits and vegetables, whole grains, tree nuts, low-fat and nonfat dairy products, beans, and fish and lean meats encouraged.[104] Alcohol intake should be moderated and psychological stress addressed.[8,46] Expert counseling may be indicated.[103] A Mediterranean-type diet supplemented with extra virgin olive oil or nuts may have particular benefits in FH,[105] but its acceptance may be dependent on the patient's cultural background. Dietary supplementation with plant sterols or stanols may be used to incrementally lower plasma LDL cholesterol.[106]

Avoidance and cessation of smoking is mandatory. Smoking cessation can be facilitated with either nicotine replacement products or drugs that modulate the intensity of nicotine withdrawal.[11] Passive smoking should also be discouraged in families. Hypertension should be treated to guideline levels.[107] Patients who are obese and/or insulin resistant should be counseled on weight loss and aerobic exercise regimens.[8,101–103,108] Before initiating an exercise regimen, some patients will warrant stress testing (electro- or echocardiography, nuclear perfusion scanning) to assess myocardial functional capacity and the possibility of silent ischemia.[11,45,109] Diabetes should be treated according to recommended guidelines.[110] Low-dose aspirin should be used in high-risk FH and considered in lower risk patients.[8,11,97]

### Pharmacologic therapy

The mainstay of managing FH is therapy with a high potency statin, generally administered at the greatest dose tolerated within 6 months of first consultation.[6–9,13,51] Statins reduce the risk for cardiovascular events[111–116] and progression of atherosclerosis in FH,[57] and their use is cost-effective.[78,117,118] Adjuvant therapy with ezetimibe, bile acid sequestrants, plant stanols/sterols, and niacin (or its derivatives) may often also be required.[21,119–123] Patients may require 3 or more drugs to achieve adequate LDL-cholesterol reduction, which is particularly important in secondary prevention.[8,18,123] With hypertriglyceridemia, use of fenofibrate or omega-3 fish oils may be advisable,[13,99] and niacin could be considered when plasma LDL-cholesterol and/or Lp(a) are also not at target.[49,122] Probucol is used in Japan, Korea, and China. Probucol is a potent antioxidant and, despite lowering HDL cholesterol, can regress xanthomata and reduce CVD events in FH.[124]

The effectiveness of statins, ezetimibe, and bile acid sequestrants relates to up-regulation of hepatic LDLRs.[41] Given that patients with homozygous FH have a severe or total deficiency in LDLR function, their response to LDL-lowering therapies is usually markedly attenuated.[32] Statins and ezetimibe can lower LDL cholesterol in patients with homozygous FH by potentially decreasing hepatic secretion of apoB,[32,125] but these patients usually require apheresis.[32,65] Homozygous patients with LDLR-null mutations (function <2% of normal) are less responsive to pharmacotherapy and have a worse prognosis than those with LDLR-defective mutations (function 2%–25% of normal).[32] If apheresis is not available, consideration should be given to the addition of lomitapide[126] or mipomersen[127] to further lower LDL cholesterol, and one should note country-specific licensing and use of special access

schemes. Although apparently safe in studies that have facilitated their approval for prescription use, experience with these new agents in clinical practice is very early, and careful attention to guidance from the manufacturers and the regulatory agencies is essential.

It is critical to ensure that all patients with FH follow the recommended treatment regimens.[8,128,129] Patients should be counseled on all aspects of their care, including the warning signs of drug-related toxicity.[128,129]

## Potential medication toxicity

All systemically absorbed cholesterol-lowering therapies can potentially be hepatotoxic and myotoxic,[121,122] although in practice the chances of severe toxicity are extremely low. Given that the majority of patients with FH will be treated with 2 or more medications,[8,13,18,120] the risk for adverse events is greater than with monotherapy. Plasma hepatic aminotransferases should be measured before one initiates a statin.[130] If baseline levels are abnormal, hepatic ultrasonography should be considered. A significant percentage of patients in developed and developing countries who require drugs have insulin resistance and hepatic steatosis. Plasma glucose should particularly be monitored in all patients with impaired fasting glucose,[131] as well as in those with risk factors for type 2 diabetes, including metabolic syndrome. Plasma aminotransferases should be monitored with statins,[8,130] with the recent Food and Drug Administration (FDA) recommendation noted that this need only be undertaken as clinically necessary and not routinely (http://fda.org/Drugs/DrugSafety/ucm293101.htm). Lipid-lowering drugs should be discontinued if plasma aminotransferases increase to 3 times the upper limit of normal on 2 occasions within a period of 1 month. The specific regimen can be re-evaluated and patients rechallenged with a different statin and then drugs reintroduced piecemeal with careful monitoring of plasma aminotransferases. Both mipomersen and lomitapide have FDA black box warnings concerning the potential risk of hepatotoxicity.

Statin-related myalgia is a significant problem in the community setting; it is dose-dependent and varies among statins.[132,133] Patients should be counseled regarding warning signs of myopathy and rhabdomyolysis. Older age, frailty, reduced overall skeletal muscle mass, chronic kidney disease, hypothyroidism, alcoholism, underlying muscle disorders, and drug interactions all increase the risk of myopathy.[133,134] Plasma creatine kinase (CK) levels and a careful physical examination should be performed before the patient begins therapy because there are many causes of myopathy and arthropathy other than statins.[133,134] Similarly, patients reporting musculoskeletal symptoms on statins require careful clinical evaluation, including repeat plasma CK and exceptionally electromyography and referral to a specialist.[133,134] The combination of gemfibrozil with a statin should be particularly avoided,[132–134] the risk of myopathy being significantly lower with fenofibrate.[135,136] Statin myopathy should be managed according to expert recommendations.[60,133,134,137] Ezetimibe is well tolerated and has a statin dose-sparing effect.[119,120] Bile acid sequestrants cause constipation and abdominal discomfort and can impair the absorption of anionic drugs and vitamins; tolerability is greatest with colesevelam.[121,138] In addition to induction of flushing, patients treated with niacin should also be monitored for possible elevations in serum uric acid and glucose and reductions in platelets.[139] Niacin combined with laropiprant, an antiflushing agent, is no longer commercially available because of unfavorable outcomes in a recent trial.[140] Patients should report any new medications prescribed by other health care providers to minimize risk for drug interactions.[121,136] Patients with reduced glomerular filtration rates may require dose adjustment of lipid modifying medications (eg specific statins or fibrates).[121] Statins that are not substantially renally excreted such as atorvastatin and fluvastatin, do not require dose adjustment in chronic kidney disease.[121,130,141]

## Women: contraception, pregnancy, and menopausal hormone therapy

Low estrogen–containing oral agents, intra-uterine devices, and barrier techniques are the preferred methods of contraception for women with FH.[8,22,142,143] The latter 2 methods are preferable for those older than 35 years of age.[8] All women and girls of childbearing age should receive advice on contraception and prepregnancy counseling before starting a statin and this should be reviewed annually.[8,142,144] Statins and other systemically absorbed lipid-regulating drugs should be discontinued 3 months prior to conception and during pregnancy and lactation.[8,142] However, women who become pregnant accidentally while on a statin could be reassured that the likelihood of fetal complications is low.[8,144]

Controlling hypercholesterolemia during pregnancy is particularly important in women with established CHD[8,9,22]; it may also decrease the severity of FH in offspring who inherit the condition.[145] Bile acid sequestrants are the only safe agents to control hypercholesterolemia in pregnancy[8,9,121,146] but only modestly lower plasma LDL-cholesterol levels and gastrointestinal side-effects remain a problem[121,138]; colesevelam is more tolerable than older resins. During breastfeeding, resins could be used to lower LDL cholesterol where indicated.[8,22] More data are required on the outcomes of pregnancy in women with FH and on the effect of statins on the fetus in the first trimester[144]; an appropriate registry of patients is recommended.[8] Pregnant women with heterozygous FH and established CHD, or with homozygous FH, should be considered for apheresis.[8,9,22,65,146]

When one or both members of a couple have FH, several options may enable the couple to avoid having a child affected by FH. These include not conceiving, adoption, using donor gametes, prenatal diagnosis using chorionic

villus sampling or amniocentesis, and preimplantation genetic diagnosis.[8] Referral for expert counseling is accordingly recommended.[8]

The effect of menopausal hormone therapy on risk of CHD in postmenopausal women with FH is unclear. On the basis of data from other populations, menopausal hormone therapy should be avoided in women with FH, except for relief of menopausal symptoms that cannot be controlled with safe natural remedies,[22,147,148] in which case a regimen based on cyclical transdermal estrogen should be employed.

## Management of children and adolescents

It is generally agreed that targets for LDL-cholesterol treatment in children need not be as low as adults.[8,9,19,20,22,66] As in adults, good evidence for an absolute or relative target does not exist in children; international guidelines are consequently not uniform in their recommendations.[8,9,19,20,22,66] Early cholesterol-lowering treatment can substantially alter the natural history of FH.[54,57,111–115,149] Although systematic reviews confirm the safety of currently used statins in children,[150,151] the long-term sequelae of high-intensity statin regimens are unknown. Good long-term data on the safety of statins started early in life are therefore required,[152,153] emphasizing the need to establish a suitable international registry.[154] The plasma LDL-cholesterol targets for children ages 8 to 10 years should be <4.0 mmol/L and for those older than 10 years <3.5 mmol/L.[8,19,20,22,66,67,74,149,152] Boys and girls should be treated to similar targets, but treatment targets could be lowered and therapy intensified in those with a particularly adverse family history of CHD or in the presence of other major cardiovascular risk factors.[8,19,43,44,64,66,74] Therapeutic targets for non-HDL cholesterol, apoB, and Lp(a) have not been clearly defined for children with FH.

Treatment begins with a heart-healthy diet management that is best administered by a pediatric dietician.[74,102] The diet should typically contain <30% of calories from total fat, <7% of calories from saturated fat, and ideally <200 mg of cholesterol/day.[20,74,102] The diet should include nutrient-dense foods with appropriate energy to maintain optimal body weight. Fruits and vegetables, whole grains, low-fat dairy products, beans, and fish and lean meats should be encouraged. Encouraging a Mediterranean diet may be beneficial and particularly acceptable in certain cultures.[105] Dietary supplementation with plant sterols or stanols (sitosterol or sitostanol) may be considered to lower LDL-cholesterol levels.[155] Physical activity should be promoted and active and passive smoking strongly discouraged.[8,20,66,67,74,102] Primordial prevention of the development of risk factors is advised.[8,20,66,67] Additional existing cardiovascular risk factors should be treated according to recommended guidelines.[74,102] FH is not only a disorder that should be diagnosed in a family context but also managed in a similar manner; the entire nuclear family should be strongly encouraged to adopt and support adherence to a lifestyle that addresses all major cardiovascular risk factors.

Drug treatment will be required in a great majority of patients with heterozygous FH and should be initiated in those with plasma LDL-cholesterol levels (measured on 2 occasions) above targets after diet management.[8,19,20,22,66,74] Agents tested in clinical trials and approved for use by regulatory agencies should be used[8,19,20,22,66,67,74]; statin drugs are preferred and should be initiated at low doses.[150,151] Statin treatment with approved medications can be initiated when patients are 8 to 10 years of age and not delayed until 18 years.[8,19,20,22,66,67,74] Children with a particularly adverse family history of CHD and other major risk factors could be considered for earlier treatment with statins[8,19,43,44,66,74,149]; this may be especially important in boys.[1,3,43,44] If goals are not achieved, consideration should be given to the addition of ezetimibe or bile acid sequestrants.[8,19,66,67,152,153] Balancing the need to achieve LDL-cholesterol targets with possible side effects should be considered in individualizing drug therapy.[152,153] Children with homozygous FH should be referred to a specialist center: medications should be initiated at diagnosis, greater potency statins in combination with other agents will be required, and apheresis must be considered.[8,19,20,22,62,66,74,156]

Before statin therapy is initiated, plasma aminotransferases, CK, glucose, and creatinine should be measured.[8,19,20,22,66,152,153] After the patient begins therapy, weight, growth, physical, and sexual development should be monitored. Their plasma aminotransferases should be monitored routinely, as should glucose and glycated hemoglobin if there are co-existent risk factors for diabetes. Plasma CK should be assessed if musculoskeletal symptoms are reported. Statin myopathy should be managed according to adult guidelines.[132–134] Adolescent girls should be counseled to stop statins when contemplating or at risk of pregnancy.[8,142,144]

Paediatric patients with uncomplicated and well-controlled FH could be managed in general practice.[8,20,66] Patients with severely elevated LDL cholesterol, multiple cardiovascular risk factors, complications of pharmacologic therapy, or homozygous FH should be managed by a specialist.[8,20,22,66,74] Family and transitional care clinics are recommended.[8,66] Carotid ultrasonography has been used in research studies,[53,151] but its use and that of other cardiovascular imaging modalities cannot at present be recommended for monitoring therapy in individual pediatric patients with heterozygous FH. Establishing clinical registries is essential for improving the overall care of pediatric patients with FH.[154]

## Lipoprotein apheresis and other invasive therapies

Lipoprotein apheresis (LA) is an extracorporeal treatment that removes apoB-containing lipoproteins from the circulation.[65,156,157] The removal of LDL by LA improves CHD outcomes, progression of atherosclerosis and aortic fibrosis, endothelial function, and coagulation in patients with FH.[146,157,158] LA is an FDA-approved therapy that is

indicated for patients with homozygous (or compound heterozygous) FH or severe heterozygous FH with progressive CHD who are refractory or intolerant to maximal pharmacotherapy.[8,22,146,157–159] By contrast to homozygous FH, the social/patient acceptability and cost-effectiveness of LA for treating refractory heterozygous FH remains unclear and needs further evaluation.[160] Elevation in plasma Lp(a) levels (>0.6 g/L) is a reimbursable indication for LA in Germany, but the evidence supporting the value of apheresis beyond reduction in LDL cholesterol, although compelling, remains questionable.[156,158,161–164] In homozygous children, LA should be considered by age 5 years and no later than 8 years.[8,22,156,165] Untreated patients with a homozygous phenotype typically have plasma LDL cholesterol >13 mmol/L and should be treated with maximally tolerated pharmacotherapy for at least 6 months before considering LA.[8,22,65,156–159] Untreated heterozygotes typically have plasma LDL cholesterol from 5 to 13 mmol/L and may be truly nonresponders to or be intolerant of pharmacotherapy.[8,22,32,65] LDL-cholesterol criteria for selecting the aforementioned patients for apheresis have been recommended elsewhere[8,65,156,157,159] but should be modified according to clinical context; simple criteria are a reduction in LDL-cholesterol of <50% or LDL cholesterol >5 mmol/L on diet and maximally tolerated pharmacotherapy, which should be continued during LA.[8,65]

Different thresholds for LDL cholesterol may be set according to the availability of resources for apheresis. Patients must be psychologically and clinically stable and committed to treatment.[8] Imaging should be carried out at baseline to assess aortic stenosis and aneurysms.[8,22,65,156,159] Contraindications to apheresis methods that use heparin include hemorrhagic diatheses, resistance to adequate coagulation, and hypersensitivity to heparin. LA is efficacious, tolerable, and safe in the treatment of severe FH and may be commenced in children older than of 5 years of age,[8,156,165,166] or earlier in exceptional circumstances. Although lower body weight is a recognized risk factor for complications, successful outcomes have been reported with LA in very young children with homozygous FH.[156,166,167] Women with severe FH may be successfully treated during pregnancy.[8,22,159]

There are several LA methods that are selective for LDL and all acutely lower plasma LDL cholesterol and Lp(a) levels by 50% to 70% after a single treatment.[157,159] The FDA-approved methods involve the extracorporeal precipitation of apoB-containing lipoprotein with dextran sulfate or heparin,[146] whereas in other countries, alternative systems (immunoadsorption, double cascade filtration or hemoperfusion with direct absorption of lipoproteins, dextran sulfate or polyacrylate) are available.[65,156,157,159] Plasma exchange may be used but is not selective for LDL. The choice of method will depend on local expertise and resources.[157,159] A major barrier is the cost of treatment, which is comparable with hemodialysis.[8] Therapeutic outcomes and costs can be optimized by collaborating with a specialty experienced in apheresis, such as transfusion medicine.[8,159] The cost-effectiveness of treating homozygous FH with LA appears to be greater than for heterozygous FH, questioning whether present health care systems could meet an increasing demand for LA posed by refractory heterozygous FH patients.[160] In developing countries, creative approaches, such as corporate support and public donations, should be adopted to support the funding of LA. There is a need for an extended international network of treatment centers and registry of patients on LA.[154,156,161]

The frequency of LA should be adjusted to achieve a time-average plasma LDL-cholesterol concentration between therapy of <6.5 mmol/L and <2.5 mmol/L for homozygotes and heterozygotes,[8,65,159] respectively; a mean reduction of 65% in LDL-cholesterol relative to no treatment is a simple target. This will usually require an acute reduction of ≥70% in LDL cholesterol and weekly or fortnightly treatments; weekly treatments may be required in very severe homozygous FH.[156–159] Statins should be continued to slow post-exchange rebound in LDL cholesterol.[8,65,159] Angiotensin-converting enzyme inhibitors are contraindicated with most systems, particularly the dextran sulfate LDL absorption and hemoperfusion methods because of bradykinin reactions[8,65,156,157]; side effects (nausea, hypotension, vasovagal episodes, hypocalcemia, anemia, sepsis) are not uncommon but are rarely serious.

Patients who are intolerant of a particular method of LA should be tested on an alternative method, including plasma exchange if required.[8,65,157] Because of the demands of treatment, psychological status and quality of life should be addressed[8]; recent data suggesting that lower quality of life may relate specifically to the severity of CVD.[168] Long-term efficacy of treatment on carotid and aortic valve/root atherosclerosis should be assessed every 2 years in homozygotes using standard imaging methods.[8,159,169] Regular monitoring with exercise electro- or echocardiography and review by a cardiologist are recommended.

Lomitapide should be considered as an adjunctive treatment to further lower LDL cholesterol in adults with homozygous FH on LA,[126,156,158] as well as in children and adolescents with homozygous FH (under special access or compassionate use schemes) on LA with rapidly progressive atherosclerosis. By contrast to lomitapide, experience with use of mipomersen has not yet been reported in homozygous FH patients on LA. In those who cannot tolerate lomitapide, mipomersen should be accordingly considered.[127,156,158] Novel LDL cholesterol–lowering therapies may reduce the need for or the frequency of LA in severe FH,[156,158,170–172] but this needs to be demonstrated.

Orthotopic liver transplantation should also be considered in younger homozygous patients when LA is not available, or cannot be tolerated, and LDL cholesterol cannot be adequately controlled with intensive pharmacotherapy[8,173]; pre-emptive transplantation has been proposed but experience is limited.[174] Coronary artery bypass

surgery, aortic valve replacement, or a combined heart transplantation should be considered according to clinical context before liver transplantation.[175,176] Partial ileal bypass should be considered in heterozygous patients who are drug-intolerant.[177] Portacaval shunting can theoretically decrease the hepatic secretion of LDL in homozygous FH, but LDL-cholesterol reduction is variable and the procedure carries a high risk of encephalopathy; it could exceptionally be considered to treat severe homozygotes in countries when the aforementioned treatments are not available.[178] There may be a future role for gene therapy in treating severe FH.[179,180]

## Emerging therapies

Many patients with FH cannot attain optimal and sustained reductions in plasma levels of LDL cholesterol.[18,32] This has prompted the development of highly innovative therapies that can provide substantive reductions in LDL-cholesterol additional to standard therapies,[171,172] with significant implications also for the treatment of homozygous FH[181]; however, the long-term efficacy, safety, and tolerability of these agents remain to be demonstrated. Clinical registries of patients treated with all new therapies are recommended.[154]

### PCSK9 inhibition

PCSK9 is a serine protease secreted by hepatocytes that regulates the expression of the LDLR.[182] PCSK9 complexes with the LDLR and is taken up together with the adaptor protein autosomal-recessive hypercholesterolemia in clathrin-coated pits by hepatocytes.[182] PCSK9 either prevents the recycling of LDLR to the hepatocyte cell surface from the endosomal compartment or chaperones the LDLR to the lysosome for degradation.[182] Loss-of-function genetic variants in PCSK9 enhance hepatic LDL receptor activity, with significant lifelong reductions in plasma LDL cholesterol and reduced risk of CHD[182]; conversely, dominant gain-of-function mutations lead to a phenotype similar to FH.[2,182]

Therapeutic human monoclonal antibodies (mAbs) against PCSK9 increase both the residence time of LDLR on the cell surface and receptor density, leading to augmented clearance of LDL-cholesterol from the circulation.[182] REGN727/SAR236553 demonstrates a dose-response capacity to reduce serum levels of LDL-cholesterol (40%–72%) in patients with heterozygous FH receiving statin therapy with or without ezetimibe[183] and in patients with primary hypercholesterolemia with or without statin therapy.[184,185] Similarly, AMG 145 demonstrates a dose-response capacity to reduce plasma LDL-cholesterol 41% to 66% and has been tested in patients with heterozygous FH,[186] as well as in primary hypercholesterolemia with or without statin therapy.[187,188] AMG 145 can also lower plasma LDL cholesterol in receptor-defective homozygous FH patients.[189] Importantly, PCSK9 mAbs also significantly reduce plasma apoB, total cholesterol, non-HDL cholesterol, and Lp(a).[182–188] These mAbs are in phase 3 trials and are not yet approved for use but clearly hold great promise either as monotherapy or adjuvant therapy in the management of FH.[171,172,182] The long-term efficacy and safety of these agents needs to be established In FH.

### Mipomersen

Mipomersen (Kynamro; Genzyme, Cambridge, MA) is an antisense 20-mer oligonucleotide that binds to a complementary sequence messenger RNA encoding apoB, thereby inhibiting ribosomal translation.[190] By inhibiting the biosynthesis of apoB, hepatic very-low-density lipoprotein (VLDL) production and secretion are significantly reduced. Mipomersen consists of a phosphorotioate backbone and 2′-*O*-(2-methoxyethyl)-modified ends, which provide biological stability.[190] Subsequent to subcutaneous injection, mipomersen is concentrated in the liver, where it undergoes catabolism via the action of hepatic endonucleases and exonucleases.[190] Mipomersen is FDA approved for use in patients with homozygous FH. Mipomersen has been shown to reduce serum LDL cholesterol by approximately 25%, 28%, and 36% in patients with homozygous FH,[127] heterozygous FH,[191] and severe hypercholesterolemia with or without CHD,[192] respectively. Mipomersen also induces substantial reductions in total cholesterol, apoB, triglycerides, non-HDL cholesterol, and Lp(a).[127,190–192] In addition to frequent injection site reactions and short-lived fatigue and myalgia, mipomersen can induce hepatic steatosis (assessed by magnetic resonance imaging) in 16% of patients, as well as elevations in plasma aminotransferases in 8% of patients.[127,190–192] These hepatic changes apparently resolve on discontinuing the drug.[190] Mipomersen has orphan drug status and, because of the risk of hepatotoxicity, can only be prescribed in the United States through a Risk Evaluation Mitigation Strategy program (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm).

### Lomitapide

Microsomal triglyceride transfer protein localizes to the endoplasmic reticulum of hepatocytes and enterocytes and transfers triglycerides into VLDL in the liver and chylomicrons in the intestine.[193] Lomitapide (Juxtapid; Aegerion Pharmaceuticals, Cambridge, MA) is an oral microsomal triglyceride transfer protein inhibitor that decreases the hepatic production and secretion of VLDL. Lomitapide is licensed for the treatment of homozygous FH in the United States and Europe as an add-on therapy.[193] In a multicenter study of such patients, lomitapide reduced LDL cholesterol by 50%, 44%, and 38% at 26, 56, and 78 weeks,

respectively.[126] The use of lomitapide may also result in significant reductions in other lipids and lipoproteins, including total cholesterol, apoB, triglyceride, non-HDL cholesterol, and Lp(a), although its effects on elevated Lp(a) may not be sustained in the long term.[126,193] Lomitapide may be hepatotoxic, can elevate plasma aminotransferases, and can increase intrahepatic fat content by approximately 6% after 26 and 78 weeks of therapy.[126,193] Cytochrome P450 3A4 inhibitors increase exposure to lomitapide.[193] It can induce gastrointestinal symptoms related to reduced small intestine absorption of fat so that dietary fat restriction is frequently required to control such symptoms. Lomitapide may reduce the absorption of fat-soluble vitamins and essential fatty acids, so coadministration of appropriate supplements is recommended. Because of the risk of hepatotoxicity, in the United States, lomitapide must also be prescribed through an FDA-approved Risk Evaluation Mitigation Strategy program.

Mipomersen and lomitapide are both FDA approved for the treatment of patients with homozygous FH. PCSK9 inhibitors are not yet licensed for use in FH, but clinical trial data suggest that they may have broad applications for patients with heterozygous FH who are not at LDL-cholesterol targets on maximal statin therapy[171,172,183,186] or who are intolerant to statins.[194] All 3 classes of agents may reduce the need for LA and other radical therapies for severe FH. The results of trials of cholesteryl ester transfer protein inhibitors have been universally disappointing to date,[171,172] but the efficacy of anacetrapib is currently being tested in a large study of patients with heterozygous FH.[171]

## Organization and development of care

Despite the recent explosion of interest and research in FH, the care of patients and families remains suboptimal,[18,21,25,195–197] which creates an important mandate to standardize and improve service delivery at all levels. The development and implementation of initiatives and strategies to improve the care of FH requires a close collaboration between health care systems, patient support groups, and related nongovernment organizations and health networks.[8,31,33,98,198,199] Care pathways for patient flow among all health providers, including primary care, should be developed and be specified for local needs.[8,31,33,98] Establishing a national network of clinics managing people with FH is recommended for standardizing care and facilitating research.[8,81,196,197] FH urgently needs a specific *International Classification of Diseases*, Revision 10 and/or a Diagnosis-Related Groups code to standardize the assessment of quality outcomes and organizational performance, as well as to facilitate research, health care financing, and reimbursement strategies.

Models of care for FH should be multidisciplinary[8,31,33] and, in principle, centrally coordinated.[5,8,31,33,81,200] Services should be managed by personnel accredited in cardiovascular prevention[8,31,201] and should address all aspects of care, including health-related quality of life.[46,202] Well-controlled and low-complexity patients could be transitioned to primary care for long-term management, whereas high-complexity patients should be followed-up by a service with special expertise in lipid management.[8,31,33] Review intervals will vary according to clinical context. Patients with severe FH on apheresis require careful lifetime follow-up by specialist services.[8,65,156,159] Primary care providers have an important role in detecting index cases,[8,27] but cascade screening should be coordinated centrally within a framework that integrates specialist and primary care.[8,27,31,200] Education and training of primary care providers in lipid management is important for improving and maintaining the total quality of care.[8,33,203] A structured review should be offered at least annually to all patients.[8,33] This is particularly important for low complexity patients who may be more at risk of loss to follow-up; the process could be centrally monitored via a registry.[154] A telehealth program should be employed for remote care.[8,204] Children are best reviewed in a specialist pediatric clinic, with appropriate arrangement made for transitional care[8,18,20,66]; an adult-pediatric clinic may be useful for families.[66]

Nurses have a role in coordinating screening, as well as in clinical care, medication support, education and training, audit and research, multidisciplinary liaison[8,81,205–207] and working with a family support group.[8,31,33] Dietetic services are highly desirable.[8,100–102] Advice from health and adolescent psychologists[46,83,208] and exercise physiologists[103] may be required. Pharmacists may have a special role in case detection, medication support and research.[8,209] A multidisciplinary approach should be adopted to address the quality of life of FH patients on various treatment modalities.

Links with clinical genetics are important for special counseling during cascade screening.[8,208] Not all families or patients with FH require genetic counseling, but some exposure and basic training in the principles of genetic counseling is important for managing FH.[8,79,208]

FH services should also have close links with laboratory medicine and access to routine and advanced lipid analyses.[8,30,31] There may be a particularly useful role for community laboratory in alerting healthcare providers about FH when plasma LDL-cholesterol levels are significantly elevated.[30] DNA testing should only be carried out by accredited laboratories that can screen for mutations in all the major genes of interest.[8,79,87] Adequate patient assessment requires access to cardiac and imaging facilities, including treadmill testing, myocardial perfusion scanning and ultrasonography; close links with cardiology are essential.[7,8,55,210] Collaboration with a transfusion medicine or dialysis unit is important for managing apheresis.[8,156,157,159]

A specialized database for storing clinical and family data and information technology support systems is essential for effective provision of services.[8,30,31] Computerized programs should be capable of pedigree drawing, workflow management, production of template letters, archiving data, clinical audits and research. An international database with information on mutations recognized as causing FH[96] is

available, but should be developed for those countries or healthcare systems adopting DNA testing.[85–87]

A well-designed and comprehensive clinical registry provides invaluable information for research and audit, as well for improving the quality of care.[26,154] A registry can facilitate the coordination of cascade screening at a local, community and national level, increasing also the cost-efficiency of DNA testing where a mutation has been previously identified and registered in a family.[154] Hybrid enrolment options, including patient enrolment, may enhance the identification of FH. Every effort should be made to establish an active association for patients and families via a support group.[8,30,31] This forum can provide a useful network for facilitating mutual support and education, establishing an effective advocacy group and interacting with health policy makers, and developing a national registry of affected families. All models of care must address the perspectives and requirements of patients and families.[46,202]

## Conclusion: into the future

This international guidance is derived from knowledge of best contemporary practice, and aims to achieve the best outcomes for patients with FH by providing a standard of practice that will hopefully remove variability and inequalities in the care of FH worldwide. The recommendations cannot, however, meet universal needs for the care of FH. They therefore need to be complemented by judicious clinical judgment and adjusted for country-specific and local health care needs and resources. Clinical trials in people with FH are needed to close evidence gaps. Research agendas should be broad but also specific to national and local needs. Research should ideally be conducted by clinical networks and integrated into a quality cycle to improve the development of models of care.[211] FH requires a specific *International Classification of Diseases*, Revision 10 classification code as a matter of priority. Future developments in the health care of FH need to evolve within the framework of the Chronic Care Model,[23] and hence in a positive policy environment. This will entail establishing effective partnerships with a wide spectrum of stakeholders, including patient support groups, public participants, heart foundations and related non-government organizations, universities and academic centers, as well as with health economists, policy makers, and government ministers.[8,198,199]

## Author contributions and consensus process

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### International FH Foundation board members

R.A. (Advisor), J.D. (Chairman), J.J.P.K. (Hon. President), M.L. (Executive Director), P.M. (Trustee), R.D.S. (Advisor), G.F.W. (Trustee). The International FH Foundation, a UK-based, not-for-profit charity, was commissioned with the major aim of improving the care of FH worldwide. An international board of patients, clinicians, and other skilled representatives has set new targets to address strategic priorities, which through continually improving communications between clinicians with interests in FH, aims to establish and support new country foundations, campaigning, consensus, research, education, patient registries, and family practitioner engagement projects.

### Process

G.F.W. and D.S. arranged a series of workshops and discussions at the International Atherosclerosis Society (Sydney 2012) that involved 16 members of the group and addressed evidence for treatment, screening and DNA testing, pediatric management, novel therapies, health economics, regional diversity in management, and models of care. Workshop moderators (G.F.W., D.S., S.G., A.W., P.P.T.) identified and collated consensus-based on published research, clinical experience, common themes, expert opinion, and other international guidelines on FH. To gauge wider international opinion, a brief questionnaire on potentially contentious issues in FH (screening options, DNA testing, risk stratification, testing and treatment of children, use of imaging, and therapeutic targets) was completed by all members of the group and a group of 26 international experts. The majority view was used to inform additional consensus, as discussed and agreed by group members (A.W., J.D., M.L., P.P.T., B.T., R.D.S., W.G.S., G.F.W.) at a satellite workshops arranged by the International FH Foundation at the 80th Congress of the European Atherosclerosis Society (Milan, 2012) and the World Congress of Clinical Lipidology (Budapest, 2012). GFW produced a first copy of the recommendations and manuscript, which was subsequently extended and revised by S.G., A.W., and P.P.T., with additional comments received from all members of group. At 3 teleconferences G.F.W., S.G., A.W., and P.P.T. discussed and fully concurred on the levels of evidence and gradings for the

recommendations on the basis of previous consensus, published literature, and expert opinion. The recommendations were again discussed and agreed with selected group members (A.W., P.M., F.J.R., B.T., R.A., M.L.) at a workshop at the 81st Congress of the European Atherosclerosis Society (Lyon, 2013), also arranged by the International FH Foundation. The writing committee re-examined a pre-final draft of the paper and again reached full consensus on the recommendations of the guidance. G.F.W. then prepared a final draft of the paper. All members approved the final document before submission. The recommendations and documents were also reviewed and fully endorsed by the National Lipid Association in August 2013.

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