FH [19,20,66]. The effects of acute illness in lowering LDL-cholesterol should be accounted for and tests repeated if necessary [29,73]. The diagnosis of heterozygous FH is highly likely in children over 2 years of age if the LDL-cholesterol level is greater or equal to 5 mmol/L [68,69], even in the absence of a family history of hyperlipidaemia and premature CHD. Heterozygous FH is also probable at untreated LDL-cholesterol levels between 4 and 5 mmol/L, especially in the setting of a positive family history [68]. Homozygous FH should be considered if the untreated LDL cholesterol level is >13 mmol/L, especially if xanthomata are evident before age 10 years [19,20,32,66,74]. Secondary causes of hypercholesterolemia, including nephrotic syndrome and hypothyroidism, should be excluded before diagnosing FH [19,20,66].

As for adults, a complete CVD risk assessment including determination of blood pressure, body mass index, tobacco use, glucose and lipoprotein(a) should be performed [19,20,66]. The presence of these additional risk factors, or other high risk paediatric conditions, such as diabetes mellitus, Kawasaki disease with giant aneurysms or chronic kidney disease, may be an indication for intensification of lipid lowering treatment [74]. Eliciting a positive family of early CVD, especially amongst first-degree relatives [64,68,69], is important for planning therapy.

Subclinical atherosclerosis imaging, using CIMT and assessment of CAC by CT scanning [53,75], has been used in research settings to determine the presence of early atherosclerosis in children with FH. Its practical value remains to be established, however. There are significant limitations to using subclinical atherosclerosis imaging to monitor treatment in clinical practice [55]. Measurement of CIMT requires special expertise [76]. The recently reported standardized reference intervals for common CIMT [63] excluded children.

There are also no accepted thresholds for defining the presence and progression of atherosclerosis in children by CIMT. CIMT measurements are highly age-dependent and poorly reproducible in young children, making assessment of change difficult [76]. Assessment of CAC is not recommended, since it may be absent in early atherosclerosis due to cholesterol-rich plaques, does not regularly develop until mature adulthood, and repeat CT scans increase the exposure to radiation [55].

5. Cascade screening: risk notification of families

The most cost-effective approach for detecting new cases of FH is family cascade screening of close relatives of a diagnosed index case using a phenotypic or genotypic strategy [5,6,8,77,78]. Diagnostic testing based on a pathogenic mutation is more accurate, however, than using the phenotype alone [79]. If a DNA testing service is not available, cascade screening should be carried out using age-, gender- and country-specific plasma LDL-cholesterol levels alone [71]. Because of higher pre-test probability, clinical diagnostic tools for index cases should not be used for relatives. The drawing of a family pedigree can be valuable in planning the screening process [6,8,33]. Cascade screening should start with first-degree relatives (i.e. parents, siblings, offsprings) and then be extended to second- and third-degree relatives [6,8,33].

5.1. Risk notification

Risk notification underpins cascade screening [6,8,80]. Risk notification informs relatives of their risk of FH, the implications for their health, and the availability of clinical and/or genetic testing. Fundamental ethical precepts regarding autonomy, beneficence and justice must be followed.

5.2. Contacting and informing families

Cascade screening should begin by contacting first- and then second-degree relatives, who then become probands for risk notification of their own relatives [6,8,81]. The index case should discuss family risk notification with the clinician or nurse, who will construct a family pedigree and identify relatives who should be offered testing for FH [6,8,33]. Relatives may be approached either by the index case, the clinical service, or by both [6,8,80]. Dual risk notification may be the best option. Genetic counsellors must be involved when sensitive family issues are identified [6,8,33].

Index cases should be provided with written information which clearly explains the diagnostic testing process and implications, and be encouraged to give this to their relatives [6,8,33]. Information sent to relatives should be written in general language to avoid alarm and concern, while emphasizing the voluntary nature of testing [8,80], and the 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 co-ordinated 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.

5.3. 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, and particularly the family dynamics [8,45,80,83]. A decision to risk notify 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 justifiable [8,84].

6. Genetic testing

FH is a dominantly inherited disorder, affected individuals having a 50% chance of passing the causative mutation to each offspring [1–3]. The majority of cases of FH are due to mutations in the LDL-receptor (LDLR), apolipoprotein B-100 (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 under-studied multiethnic populations [89]. Absence of a pathogenic mutation in the presence of a high LDL-cholesterol gene score may indicate polygenic hypercholesterolaemia, and this may be used to limit further search for novel FH causing mutations [90]. About 95% of the identified mutations are in the LDLR gene, 4–5% 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 DLCNS >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, e.g. The Netherlands [68,69]. Genetic testing of families for FH should be co-ordinated by a specialist service with appropriate education and counselling offered to all individuals [5,6,8,33]. Genetic testing in children can be carried out without invasive venepuncture, 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 MPLA analyses should be carried out 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 non-pathogenic (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 three 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 carried out phenotypically using 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].

7. 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].

7.1. LDL-cholesterol and related lipid targets

Because of lack of clinical trial evidence [97,98], clear therapeutic targets for plasma LDL-cholesterol cannot be categorically defined for FH [6–11,13]. The following is synthesized from various international guidelines [6–13,22,60,51]. In 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 have also been described and are reasonable [8], but not universally ratified [98]. Untreated LDL-cholesterol burden, or life year's exposure, should be considered a major risk factor for driving more intensive and/or earlier therapy [52]. 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 higher risk patients with FH. The LDL-cholesterol of homozygotes should accordingly be reduced as much as possible [8,32,65], noting subsequent recommendations on use of apheresis. Therapeutic targets for apoB and non-HDL-cholesterol have not been defined in FH [8], but with co-existent 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.

7.2. Modification of lifestyle and non-cholesterol risk factors

All patients with FH should be counselled 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 non-fat dairy products, beans, fish and lean meats encouraged [104]. Alcohol intake should be moderated and psychological stress addressed [8,46]. Expert counselling 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 will be culturally dependent. Dietary supplementation with plant sterols or stanols may be employed to incrementally lower plasma LDL-cholesterol [106].

Avoidance and cessation of smoking are 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 counselled on weight loss and aerobic exercise regimens [8,101–103,108]. Prior to initiation of 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 ischaemia [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].

7.3. Pharmacologic therapy

The mainstay of managing FH is therapy with a high potency statin, generally administered at the highest dose tolerated within 6 months of first consultation [6–9,13]. 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 hypertriglyceridaemia, use of fenofibrate or omega-3 fish oils may be advisable [13,100], 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 upregulation 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 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, noting country-specific licencing 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 FH patients adhere to the recommended treatment regimens [8,128,129]. Patients should be counselled on all aspects of their care, including the warning signs of drug related toxicity [128,129].

7.4. 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 two or more medications [8,13,18,120], the risk for adverse events is higher than with monotherapy. Plasma hepatic aminotransferases should be measured prior to initiating a statin [130]. If baseline levels are abnormal, hepatic ultrasonography should be considered. A significant percentage of patients requiring drugs in developed and developing countries 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], noting the recent FDA recommendation that this needs to 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 two occasions within a period of one month. The specific regimen can be re-evaluated and patients rechallenged with a different statin and then drugs re-introduced 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 amongst statins [132,133]. Patients should be counselled about 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 prior to starting therapy, since 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 fat soluble 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 anti-flushing agent, is no longer commercially available, owing to unfavourable 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 (e.g. 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].

7.5. Women: contraception, pregnancy and menopausal hormone therapy

Low oestrogen-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 two options are preferable for those older than 35 years [8]. All women and girls of childbearing age should receive advice on contraception and pre-pregnancy counselling 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 re-assured that the likelihood of foetal complications is low [8,144].

Controlling hypercholesterolaemia 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 hypercholesterolaemia in pregnancy [8,9,121,146], but only modestly lower plasma LDL-cholesterol levels can impair absorption of fat soluble vitamins and gastrointestinal side-effects remain a problem [121,138]; colesevelam is more tolerable than older resins. During breastfeeding, resins could be employed 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 foetus 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 pre-implantation genetic diagnosis [8]. Referral for expert counselling is accordingly recommended [8].

The effect of menopausal hormone therapy (MHT) on risk of CHD in postmenopausal women with FH is unclear. On the basis of data from other populations, MHT 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 oestrogen should be employed.

8. Management of children and adolescents

It is generally agreed that targets for LDL-cholesterol treatment in children need not be as low as adults [8,9,19,20,22,76]. 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 [8,9,19,20,22,76]. Early cholesterol-lowering treatment can substantially alter the natural history of FH [54,67,111–115,149]. Although systematic reviews confirm the safety of currently employed 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 aged 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 with 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 paediatric dietician [74,103]. 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, 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 [8,20,66,67,74,103]. 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 two 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 at 8–10 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 when individualizing drug therapy [152,153]. Children with hozygous FH should be referred to a specialist centre: medications should be initiated at diagnosis, higher potency statins in combination with other agents will be required, and apheresis must be considered [8,19,20,22,62,66,74,154].

Prior to initiating statin therapy, plasma aminotransferases, CK, glucose, and creatinine should be measured [8,19,20,22,66,152,153]. After starting therapy, weight, growth, physical and sexual development should be monitored. Plasma aminotransferases should be monitored routinely, as should glucose and glycated haemoglobin 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 counselled 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 employed 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 paediatric patients with heterozygous FH. Establishing clinical registries is essential for improving the overall care of paediatric patients with FH [154].

9. Lipoprotein apheresis and other invasive therapies

Lipoprotein apheresis (LA) is an extracorporeal treatment that removes apoB-containing lipoproteins from the circulation [65,156, 155]. The removal of LDL by LA improves CHD outcomes, progression of atherosclerosis and aortic fibrosis, endothelial function and coagulation in 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 is a reimbursable indication for LA in Germany, but the evidence supporting the value of apheresis beyond reduction in LDL-cholesterol is questionable [156,158,161,162]. In homozygous children, LA should be considered by age 5 years and no later than 8 years [8,22,157,163]. 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 [8,22,66,156–159]. Untreated heterozygotes typically have plasma LDL-cholesterol from 5 to 13 mmol/L and may be truly non-responders to, or intolerant of, pharmacotherapy [8,22,32,65]. LDL-cholesterol criteria for selecting the above 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 less than 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 [8,22,66,156,159]. Contraindications to apheresis methods employing heparin include haemorrhagic diatheses, resistance to adequate coagulation and hypersensitivity to heparin. LA is efficacious, tolerable and safe for children with severe FH and may be commenced after the age of 5 years [8,156,163,164], or earlier in exceptional circumstances. While lower body weight is a recognized risk factor for complications, successful outcomes have been reported with LA in very young children with homozygous FH [156,164,165]. 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% following a single treatment [157,159]. The FDA approved methods involve the extracorporeal precipitation of apoB-containing lipoprotein with dextran sulphate or heparin [146], while in other countries, alternative systems (immunoadsorption, double cascade filtration or haemoperfusion with direct absorption of lipoproteins units, dextran sulphate 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 to haemodialysis [8]. Therapeutic outcomes and costs can be optimized by collaborating with a specialty experienced in apheresis, such as transfusion medicine [8,170]. 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 a rising 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 centres 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 [8,66,159], 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 contra-indicated with most systems, particularly the dextran sulphate

LDL absorption and haemoperfusion methods, because of bradykinin reactions [8,65,156,157]; side effects (nausea, hypotension, vasovagal episodes, hypocalcaemia, anaemia, 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 [166]. Long-term efficacy of treatment on carotid and aortic valve/root atherosclerosis should be assessed every 2 years in homozygotes using standard imaging methods [8,159,167]. Regular monitoring with exercise electro- or echocardiography and review by a cardiologist is 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 [156,158,168–170], 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 [8,171]; pre-emptive transplantation has been proposed but experience is limited [172]. Coronary artery bypass surgery, aortic valve replacement or a combined heart transplant should be considered according to clinical context prior to liver transplantation [173,174]. Partial ileal bypass should be considered in heterozygous patients who are drug-intolerant [175]. 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 where the above treatments are not available [176]. There may be a future role for gene therapy in treating severe FH [177,178].

10. 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 [169,170], with significant implications also for the treatment of homozygous FH [179]. The long-term efficacy, safety and tolerability of these agents remain to be demonstrated, however. Clinical registries of patients treated with all new therapies are recommended [154].

10.1. PCSK9 inhibition

Proprotein convertase subtilisin-like kexin Type 9 (PCSK9) is a serine protease secreted by hepatocytes that regulates the expression of the LDLR [180]. PCSK9 complexes with the LDLR and is taken up together with the adaptor protein ARH (autosomal recessive hypercholesterolemia) in clathrin coated pits by hepatocytes [180]. 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 [180]. 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 [180]; conversely, dominant gain-of-function mutations lead to a phenotype similar to FH [2,180].

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 [180]. 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 [181] and in patients with primary hypercholesterolaemia with or without statin therapy [182,183]. Similarly, AMG 145 demonstrates a dose–response capacity to reduce plasma LDL-cholesterol 41–66% and has been tested in patients with heterozygous FH [184], as well as in primary hypercholesterolaemia with or without statin therapy [185,186]. AMG 145 can also lower plasma LDL-cholesterol in receptor defective homozygous FH patients [187]. Importantly, PCSK9 Mabs also significantly reduce plasma apoB, total cholesterol, non-HDL-cholesterol, and Lp(a) [180–186]. 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 [169,170, 177]. The long-term efficacy and safety of these agents need to be established In FH.

10.2. Mipomersen

Mipomersen (Kynamro™) is an antisense 20-mer oligonucleotide that binds to a complementary sequence messenger RNA encoding apoB, thereby inhibiting ribosomal translation [188]. By inhibiting the biosynthesis of apoB, hepatic VLDL production and secretion are significantly reduced. Mipomersen consists of a phosphorotioate backbone and 2′-O-(2-methoxyethyl)-modified ends which provide biological stability [188]. Subsequent to subcutaneous injection, Mipomersen is concentrated in the liver where it undergoes catabolism via the action of hepatic endonucleases and exonucleases [188]. 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 [189], and severe hypercholesterolemia with or without CHD [190], respectively. Mipomersen also induces substantial reductions in total cholesterol, apoB, triglycerides, non-HDL-cholesterol, and Lp(a) [127,188–190]. 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 [127,188–190]. These hepatic changes apparently resolve on discontinuing the drug [188]. Mipomersen has orphan drug status and, because of the risk of hepatotoxicity, in the US can only be prescribed through a Risk Evaluation Mitigation Strategy (REMS) programme (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm).

10.3. Lomitapide

Microsomal triglyceride transfer protein (MTP) localizes to the endoplasmic reticulum of hepatocytes and enterocytes and transfers triglycerides into VLDL in the liver and chylomicrons in the intestine [191]. Lomitapide (Juxtapid™) is an oral MTP inhibitor that decreases the hepatic production and secretion of VLDL. Lomitapide is licenced for the treatment of homozygous FH in the US and Europe as an add-on therapy [191]. In a multi-centre study of such patients lomitapide reduced LDL-cholesterol by 50%, 44%, and 38% at 26, 56, and 78 weeks respectively [126]. Lomitapide therapy may also result in significant reductions in other lipids and lipoproteins, including total cholesterol, apoB, triglyceride, non-HDL-cholesterol, and Lp(a) [126,191]. Lomitapide may be hepatotoxic, can elevate plasma aminotransferases, and can increase intrahepatic fat content by approximately 6% after 26 and 78 weeks of therapy [126,191]. Cytochrome P450 3A4 inhibitors increase exposure to lomitapide [191]. 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 co-administration of appropriate supplements is recommended. Because of the risk of hepatotoxicity, lomitapide must also be prescribed in the US through an FDA approved REMS program.

Mipomersen and lomitapide are both FDA approved for homozygous FH. PCSK9 inhibitors are not yet licenced 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 [169,170,181,184] or who are intolerant to statins [192]. All three 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 [169,170], but the efficacy of anacetrapib is currently being tested in a large study of patients with heterozygous FH [169].

11. Organization and development of care

In spite of the recent explosion of interest and research in FH, the care of patients and families remains suboptimal [18,21,25,193–195]. This provides 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, relevant non-government organizations and health networks [8,31,33,99,193,197]. Care pathways for patient flow amongst all health providers, including primary care, should be developed and be specified for local needs [8,31,33,99]. Establishing a national network of clinics managing people with FH is recommended for standardizing care and facilitating research [8,82,193,195]. FH urgently needs a specific International Classification of Diseases (ICD)-10 and/or a Diagnosis-Related Groups (DRG) code to standardize 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 co-ordinated [5,8,31,33,82,198]. Services should be managed by personnel accredited in cardiovascular prevention [8,31,199], and should address all aspects of care, including health-related quality of life [46,200]. Well controlled and low complexity patients could be transitioned to primary care for long-term management, while 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 [8,66,156,159]. Primary care providers have an important role in detecting index cases [8,27], but cascade screening should be co-ordinated centrally within a framework that integrates specialist and primary care [8,27, 31,198]. Education and training of primary care providers in lipid management are important for improving and maintaining the total quality of care [8,33,201]. 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 programme should be employed for remote care [8,202]. Children are best reviewed in a specialist paediatric clinic, with appropriate arrangement made for transitional care [8,18,20,71]; an adult-paediatric clinic may be useful for families [71].

Nurses have a role in co-ordinating screening, as well as in clinical care, medication support, education and training, audit and research, multidisciplinary liaison [8,81,203–205] and working with a family support group [8,31,33]. Dietetic services are highly desirable [8,101–103]. Advice from health and adolescent psychologists [46,84,206] and exercise physiologists [103] may be required. Pharmacists may have a special role in case detection, medication support and research [8,207]. 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 counselling during cascade screening [8,206]. Not all families or patients with FH require genetic counselling, but some exposure and basic training in the principles of genetic counselling are important for managing FH [8,80,206].

FH services should also have close links with laboratory medicine and access to routine and advanced lipid analyses [8,30,31]. DNA testing should only be carried out by accredited laboratories that can screen for mutations in all the major genes of interest [8,80,88]. Adequate patient assessment requires access to cardiac and imaging facilities, including treadmill testing, myocardial perfusion scanning and ultrasonography; close links with cardiology are essential [7,8,55,208]. 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 are 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 health care 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 co-ordination 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, 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 [46,200].

12. 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 judgement 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 [209]. FH requires a specific ICD-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 centres, as well as with health economists, policy makers and government ministers [8,196,202].

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Appendix A. Author contributions and consensus process

International Familial Hypercholesterolaemia Foundation Consensus Group

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International FH Foundation Board Members

RA (Advisor), JD (Chairman), JJPK (Hon. President), ML (Executive Director), PM (Trustee), RDS (Advisor), GFW (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

GFW and DS 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, paediatric management, novel therapies, health economics, regional diversity in management, and models of care. Workshop moderators (GFW, DS, SG, AW, PPT) 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 employed to inform further consensus, as discussed and agreed by group members (AW, JD, ML, PPT, BT, RDS, WGS, GFW) at 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 SG, AW and PPT, with additional comments received from all members of the group. At three teleconferences GFW, SG, AW and PPT discussed and fully concurred on the levels of evidence and gradings for the recommendations, based on previous consensus, published literature and expert opinion. The recommendations were again discussed and agreed with selected group members (AW, PM, FJR, BT, RA, ML) at a workshop at the 81st Congress of the European Atherosclerosis Society (Lyon, 2013), which was also arranged by the International FH Foundation. The writing committee re-examined a pre-final draft of the paper and again reached a full consensus on the recommendations of the guidance. GFW 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.

Appendix B. FH websites and related online resources

- **British Heart Foundation**
  www.bhf.org.uk
  Leading British foundation that provides excellent resources for health professionals and patients, including informative videos on a wide spectrum of conditions and risk factors.
- **FH Australasia Network, Australian Atherosclerosis Society**
  www.athero.org.au/FH
  Website of the FH Australasia Network providing educational material and support for patients and health professionals caring for FH. An integrated model of care for GPs that facilitates screening, diagnosis and referral pathways is included. The FH Network is currently working to create a unique web-based FH Registry that could be linked internationally.
- **FHChol Austria, Austrian FH Patient Organization**
  www.fhchol.at
  Austrian patient support organization that provides support information and education for patients and families on all aspects of the detection and management of FH.
- **FH Guideline Implementation Team Toolkit**
  www.heartuk.org.uk/FHToolkit
  Invaluable resource for implementing the seminal NICE guideline 71 on identification and management of FH.

- **FH Norway, Norwegian FH Patient Organization**
  www.f-h.no
  Norwegian patient support organization that provides support information and education for patients and families on all aspects of the detection and management of FH.
- **FH Support Group of Western Australia**
  www.fhfamilysupportgroup.websyte.com.au
  Website of the first support group in Australia for families with FH; provides relevant information, communication and support services.
- **FH Portugal, Portuguese FH Patient Organization**
  www.fhportugal.pt
  Portuguese patient support organization that provides support information and education for patients and families on all aspects of the detection and management of FH.
- **Foundation for the Identification of Persons with Inherited Hypercholesterolaemia (StoEH)**
  www.stoeh.nl
  Premier organization for case detection in The Netherlands that promotes essential information for patients with FH; to be reviewed in association with general information on CVD (www.hartenvaatgroup.nl); www.jojogenetics provides full guidance on DNA testing for health care providers.
- **German FH Patient Organization**
  www.cholco.org
  German organization that provides support information and education for patients and families with FH, as well as for health professionals and policy makers.
- **HEART UK**
  www.heartuk.org.uk
  Leading UK cholesterol charity that provides extensive resources for health professionals, patients and families on all aspects of the detection and management of FH.
- **Hipercol Brasil**
  www.hipercolesterolemia.com.br
  Website for FH patients and health professionals maintained by the Heart Institute (InCor), University of Sao Paulo Medical School Hospital; provides information about FH in the Portuguese language concerning how to screen and make a clinical and genetic diagnosis of FH in Brazil.
- **Human Genetics Society of Australasia**
  www.hgsa.org.au
  Premier Australasian society that provides educational materials, training, polices, guidelines and position statements on all aspects of human genetics.
- **International FH Foundation**
  www.fh-foundation.org
  Foundation, formed from the merger of MEDPED-International and HEART-EU, that has a vision of a world in which FH is routinely screened for and treated. Provides key support for patients, families, researchers and health professionals.
- **Japan Atherosclerosis Society**
  www.j-athero.org
  Information in Japanese on FH for both patients and general practitioners; to be reviewed in association with website for the patient association www.apheresis.web.fe2.com.
- **Learn Your Lipids, NLA**
  www.learnyourlipids.com
  Information for patients with dyslipidaemia, including FH, provided by the National Lipid Association in the US.
- **Lipids Online, Baylor College of Medicine**
  www.lipidsonline.org
  Established on-line facility, coordinated by Baylor College of Medicine (Houston, Texas, US), providing resources (slides, visual meetings, commentaries) for clinicians, researches and educators on several aspects of dyslipidaemia, atherosclerosis and cardiovascular disease.
- **Make Early Diagnosis Prevent Early Death (MEDPED) FH**
  www.medped.org
  US based website of the original MEDPED Project coordinated by the University of Utah School of Medicine (Salt Lake City, Utah, US), focusing on all aspects of the management of FH, including education of patients and families and the first attempt at establishing a US registry.
- **National Genome Research Institute, National Institutes of Health**
  www.genome.gov/25520184
  General information on FH.
  www.genome.gov/11510372
  Clinical useful tools for evaluating family history.
  www.genome.gov/11510371
  Informative resources on general genetics for all health professionals.
- **National Heart Foundation, Australia**
  www.heartfoundation.org.au
  Leading Australian charity that provides a wealth of resources for health professionals and the community on all aspects of primary and secondary prevention of cardiovascular disease.
- **National Lipid Association (NLA), US**
  www.lipid.org
  US based multidisciplinary specialty society providing education, training, guidelines and position statements on all aspects of the detection and management of dyslipidaemia and related disorders.
- **New Zealand Guidelines Group**
  www.nzgg.org.nz
  New Zealand group of experts that specializes in developing and implementing guidelines for best clinical practice; excellent resources on the assessment and management of all cardiovascular risk factors.
- **The FH Foundation**
  www.thefhfoundation.org
  Patient centred foundation in US dedicated to raising awareness of FH through education, advocacy and research; the first comprehensive national FH Registry was launched in late 2013.
- **Spanish FH Foundation**
  www.colesterolfamiliar.org
  An exemplary foundation providing support and education for patients and families with FH, as well as for health professionals and policy makers; also includes a national registry for research and audit purposes.
- **Preventive Cardiovascular Nurses Association (PCNA)**
  www.pcna.net/patients/familial-hypercholesterolemia
  The US based PCNA provides information on meetings, online education, advocacy and news on cardiovascular risk prevention relevant to FH. A useful patient tear sheet on essentials of FH suitable for people in different countries is available.
- **Public Health Genomics Foundation, UK**
  www.phgfoundation.org
  International foundation that publishes authoritative reports on the role of advances in genomics in health care; has a particularly excellent document on services for inherited cardiovascular conditions.
- **Wales FH Testing Service, Cardiff University**
  www.fhwales.co.uk
  Leading FH service in the UK that provides useful information and resources for clinical practice, including activities of FH Family Forum.

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Cholesterol Absorption Inhibitor Ezetimibe: Risk–Benefits and Role in Treating Dyslipidemias

28

Shizuya Yamashita, Daisaku Masuda and Akifumi Matsuyama

Introduction

Niemann-Pick C1-Like 1 (NPC1L1) is a 13-transmembrane domain cell surface cholesterol-sensing receptor. It is localized on the apical membrane or brush border of small intestines (especially jejunum) and has recently been reported to play an important role in dietary cholesterol absorption and biliary cholesterol reabsorption by enterocytes [1–2]. Genetic inactivation of *NPC1L1* gene decreases cholesterol levels and atherosclerotic lesions in mice with diet-induced hyperlipidemia [3] and in hyperlipidemic apolipoprotein (apo) E-knockout mice fed a Western diet [4]. Ezetimibe, a novel lipid-lowering compound, selectively inhibits intestinal cholesterol absorption by binding to NPC1L1 [5] and inhibiting the internalization of NPC1L1 [6]. NPC1L1 has three large loops that protrude into the extracellular space, several smaller cytoplasmic loops, and a C-terminal cytoplasmic tail [7]. Studies using in vitro ezetimibe-binding assays, demonstrated that ezetimibe directly binds to the second extracellular loop of NPC1L1 [8–9].

Ezetimibe reduces the hepatic influx of cholesterol via chylomicrons (CM) remnants, which enhances the hepatic expression of low-density lipoproteins (LDL) receptor, and thus reducing LDL-cholesterol (LDL-C) levels. Ezetimibe is also reported to reduce the development of atherosclerosis in apoE-knockout mice [10]. Clinically, the administration of ezetimibe has been shown to decrease the fasting levels of total cholesterol and LDL-C in patients with primary hypercholesterolemia [11] and plant sterols (sitosterol and campesterol) in patients with sitosterolemia [12–13]. A meta-analysis demonstrated that a significantly greater percentage reduction in LDL-C levels was achieved in patients treated with ezetimibe–statin combination compared with statin monotherapy [14]. Since ezetimibe is an inhibitor of intestinal cholesterol absorption, the pharmacological effects of ezetimibe have been focused primarily on the metabolism of sterols, including cholesterol, plant sterols, and oxidized cholesterol rather than triglycerides (TG) or TG-rich lipoproteins (TRL).

Ezetimibe has been reported to significantly decrease fasting TG levels in patients with combined hyperlipidemia [15] and those with hypertriglyceridemia (TG≥150 mg/dl); however, its underlying mechanism of action on TRL metabolism has not yet been elucidated. We have recently reported the effects of ezetimibe in patients with

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type IIb hyperlipidemia with a special reference to postprandial TRL and remnant metabolism. We reported that ezetimibe administration could attenuate postprandial hyperlipidemia in oral fat-loading tests [16]. We also evaluated the mechanisms for the attenuation of postprandial hyperlipidemia in mouse models and reported that ezetimibe can reduce the production of CM from the small intestines and decrease the absorption of free fatty acids (FFA) [17].

More recently, ezetimibe has been reported to attenuate nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). This chapter highlights the effects of ezetimibe on postprandial hyperlipidemia, hepatic lipid depositions in NAFLD or NASH, and insulin resistance. The potential and comprehensive mechanisms for the improvement by ezetimibe of these conditions usually associated with metabolic syndrome are presented.

History of Ezetimibe

Although cholesterol was supposed to be absorbed in the small intestine, especially the jejunum, the detailed mechanisms for cholesterol absorption were not understood. From the initial screening of an acyl-CoA to cholesterol acyltransferase 2 (ACAT2) inhibitor, ezetimibe was discovered by Davis HR and colleagues at the Research Institute of Schering-Plough as an inhibitor of cholesterol absorption in the small intestine [18–19]. It was demonstrated that ezetimibe is a potent and selective inhibitor of intestinal cholesterol uptake and absorption in animal models and humans. It was launched into the market before its molecular target was finally identified. Extensive studies were performed to identify the molecular target of ezetimibe. Since ezetimibe was shown localized in the brush border of enterocytes in the jejunum, it was speculated that the target of ezetimibe was localized there. Several candidate genes which are localized in the brush border of the small intestine were investigated, including scavenger receptor class B type I (SR-BI), ATP-binding cassette transporter A1 (ABCA1), and CD36, a transporter of long-chain fatty acids. However, the knockout mice of these genes did not show any changes in the absorption of radio-labeled cholesterol [20]. Thus, it had been very difficult to discover the molecular target of ezetimibe.

Genomic bioinformatics approach was then applied to identify genes involved in the absorption of cholesterol in the small intestine. Altmann et al. [1] hypothesized that intestinal cholesterol transporter should be localized mainly in the luminal surface and brush border of jejunum and possess sequence motifs known to interact with sterols. They generated a complementary deoxyribonucleic acid (cDNA) library of rat intestine, sequenced ~16,500 genes and examined these data in comparison with the database of mice and human genes. They analyzed the sequence database of all transcripts containing transmembrane domains, extracellular signal peptides, N-linked glycosylation sites, and sterol-sensing domain. They finally identified a candidate gene and it was a rat homologue of NPC1L1.

Structure, Function, and Regulation of NPC1L1

NPC1L1 possesses a secretion signal, 13 transmembrane domains, extensive N-linked glycosylation sites located in the extracellular loops, and a sterol-sensing domain. NPC1L1 was shown highly and exclusively expressed in the jejunum of mice. It was localized on the luminal surface of jejunal enterocytes. Altmann et al. [1] generated NPC1L1-knockout mice and showed that cholesterol absorption in these mice was reduced by more than 70%. Furthermore, the low levels of cholesterol absorption in NPC1L1-knockout mice were not affected by administration of ezetimibe. Acute cholesterol absorption was decreased by ~90% in the NPC1L1-knockout mice, which was similar to the inhibition of cholesterol absorption in mice, hamsters, and rats treated with ezetimibe. Thus, NPC1L1 is involved in the uptake and absorption of cholesterol from the lumen of jejunum at the brush border membrane of the enterocytes [21]. The uptake of TG by the intestine and its absorption were not altered in the NPC1L1-knockout mice and animals treated with ezetimibe.

NPC1L1 messenger ribonucleic acid (mRNA) levels in the liver and small intestines are upregulated in animals deprived of cholesterol [22, 23]. Intestinal NPC1L1 mRNA levels are downregulated in cholesterol/cholate-fed mice [24] or ACAT2-deficient and phospholipid transfer protein (PLTP)-deficient mice in which free cholesterol is accumulated [25, 26]. The regulation of NPC1L1 expression by sterol is mediated by the binding of sterol regulatory element-binding protein (SREBP)-2 to 2 sterol regulatory elements within the promoter region of *NPC1L1* gene. Statins are known to increase the expression of intestinal NPC1L1 mRNA [27], leading to an increase in cholesterol absorption. Atorvastatin increased intestinal NPC1L1 mRNA levels by 19%, while it decreased mRNA levels of both ATP-binding cassette transporter G5 (ABCG5) and ATP-binding cassette transporter G8 (ABCG8) by 14% in hyperlipidemic men [27]. These effects were most likely mediated by upregulation of the transcription factors SREBP-2 and hepatocyte nuclear factor-4α (HNF-4α) [27]. Statins that are more potent in lowering LDL-C levels increase NPC1L1 expression in the small intestine more than regular statins [28]. In streptozotocin-induced diabetic rats, and in Zucker diabetic fatty *fa/fa* rats the expression of NPC1L1 in the small intestine and thus cholesterol absorption are enhanced [29]. In mice, the expression of NPC1L1 increases with aging [30]. In humans, 45 single nucleotide polymorphisms (SNPs) of nonsynonymous sequence variants in the NPC1L1 gene have been reported [31, 32]. Some of these SNPs influence the sterol absorption and plasma LDL-C levels [33, 34].

NPC1L1 is abundantly expressed in the small intestine of all species, but not expressed in the liver of mice [1]. In contrast to mice, the expression level of NPC1L1 mRNA is similarly high in the liver of humans, monkeys, pigs, and dogs. NPC1L1 is localized in the bile canalicular membrane in the human liver [35, 36]. Therefore, its function may be the reabsorption of cholesterol excreted into the bile, while ABCG5/G8 excretes cholesterol and phytosterol into bile. Overexpression of NPC1L1 in the transgenic mice liver reduced biliary cholesterol and increased plasma cholesterol level, suggesting that bile canalicular NPC1L1 is involved in the absorption of cholesterol from bile and its reuptake into the hepatocyte [36]. Ezetimibe may also inhibit reabsorption of cholesterol from bile.

Mechanisms of Intestinal Cholesterol Absorption and Chylomicron Synthesis

Plasma TG is mainly found in TRL, including CM, very low density lipoproteins (VLDL), and their remnants. TRL constitute a population of particles of heterogeneous size, origin, and apolipoprotein and lipid content. The cholesterol and plant sterols absorbed from the intestinal lumen via NPC1L1 are esterified by ACAT2, forming cholesteryl esters or plant sterol esters (Fig. 28.1) [37]. These cholesteryl esters are assembled with TG, phospholipids, and apoB-48 by microsomal TG transfer protein (MTP) to form CM, which are secreted into the intestinal lymph [37]. CM enter thoracic lymph, from which they flow into the systemic circulation [37]. CM particles undergo partial hydrolysis predominantly by lipoprotein lipase (LPL) into smaller and denser particles known as CM remnants, which are believed to be more atherogenic than the larger CM [38]. LPL hydrolyses the TG moiety of CM to FFA, and residual particles become CM remnants which are taken up by the liver via remnant receptors.

After the uptake of CM remnants by hepatocytes, VLDL are assembled from endogenous hepatic TG, cholesterol, and apoB-100 and are secreted directly into the blood stream. Thereafter, the TG moiety of VLDL is hydrolyzed to FFA by LPL, becoming VLDL remnants, intermediate-density lipoproteins (IDL). The liver takes up VLDL remnants and LDL via LDL receptors, while these particles are supplying energy and lipids to peripheral tissues. In the postprandial state, the serum levels of CM and CM remnants rise quickly to reflect the increased exogenous lipid supply [39]. The increased hepatic lipid inflow leads to an augmented hepatic production of VLDL.

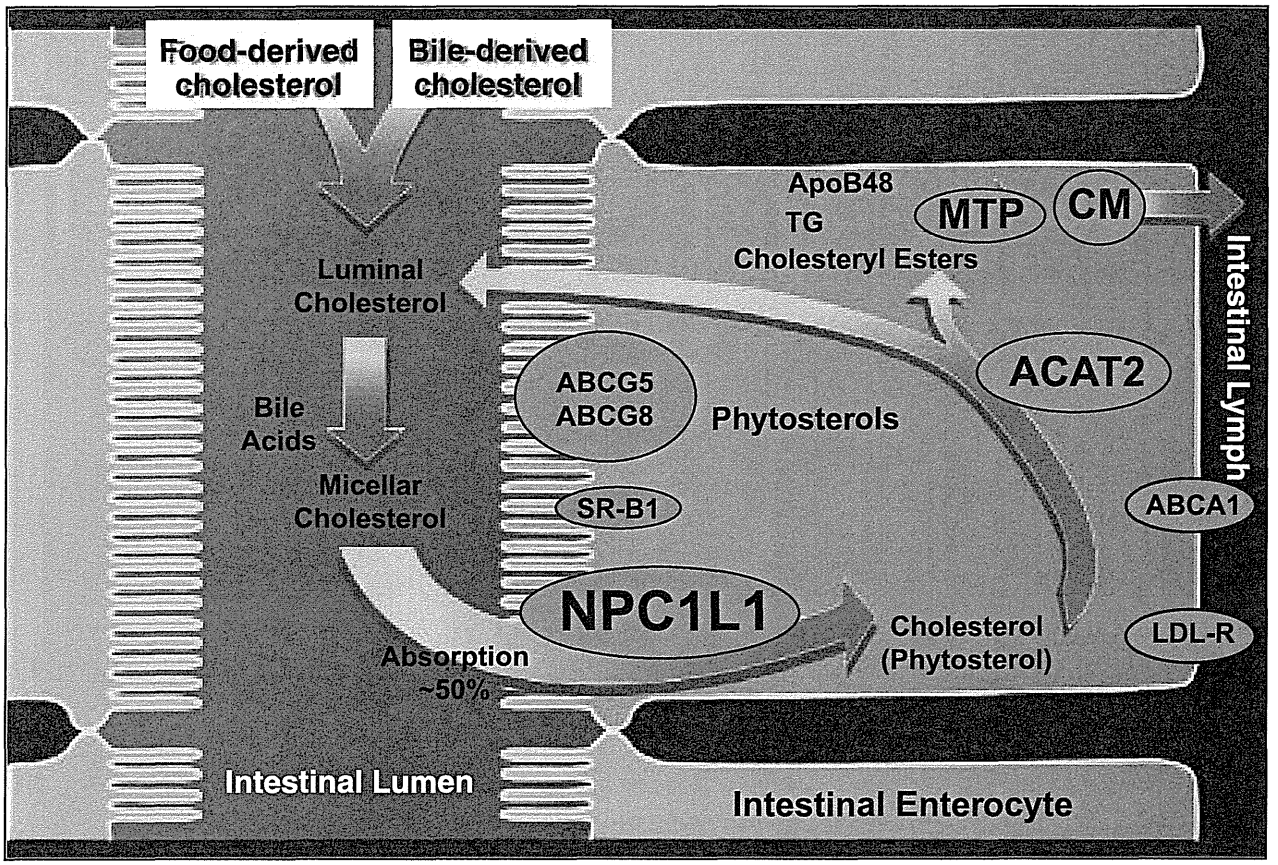

Fig. 28.1 Molecular mechanisms of cholesterol absorption, chylomicron synthesis, and secretion in the small intestines

Absorption, Metabolism, and Pharmacodynamics of Ezetimibe

Ezetimibe (SCH58235; 1-(fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone) was first discovered by utilizing in vivo models of cholesterol absorption [18]. Its chemical structure is illustrated in Fig. 28.2. It was found by the characterization of the active biliary metabolites of its predecessor, SCH48461, and analysis of structure–activity relationship based upon cholesterol feeding of hamsters. Ezetimibe inhibited diet-induced hypercholesterolemia in hamsters and its ED_{50} was 0.04 mg/kg. In rats, ezetimibe inhibited the absorption and appearance of radiolabeled cholesterol into plasma with an ED_{50} of 0.0015 mg/kg [40]. Ezetimibe was also effective in cholesterol-fed rhesus monkeys with an ED_{50} of 0.0005 mg/kg/day [41].

The cholesterol in the lumen of small intestines derives from bile as well as foods. The cholesterol synthesized in the liver is approximately 400 mg/day; however, the food-derived cholesterol intake is 300–500 mg/day and reabsorption of bile-derived cholesterol is two- to fourfold (800–2000 mg/day) more than that from foods. Ezetimibe is a selective inhibitor of cholesterol absorption in the small intestines and does not influence the esterification of ACAT2, hydrolysis of cholesteryl ester by cholesterol esterase (CEase), and the absorption of fatty acids. Ezetimibe does not affect the activity of pancreatic lipase nor the absorption of TG, vitamins A and D, and taurocholic acid in rats. Most importantly, ezetimibe is completely different from resins such as cholestyramine, colestipol, or colestimide since it does not bind bile acids nor inhibit their absorption. Ezetimibe has no significant effect on fat-soluble vitamin levels.

Ezetimibe is rapidly glucuronidated by uridine 5-diphosphate (UDP)-glucuronosyl-transferase in the intestine, after which the glucuronidated ezetimibe is excreted into the bile. Gluc-

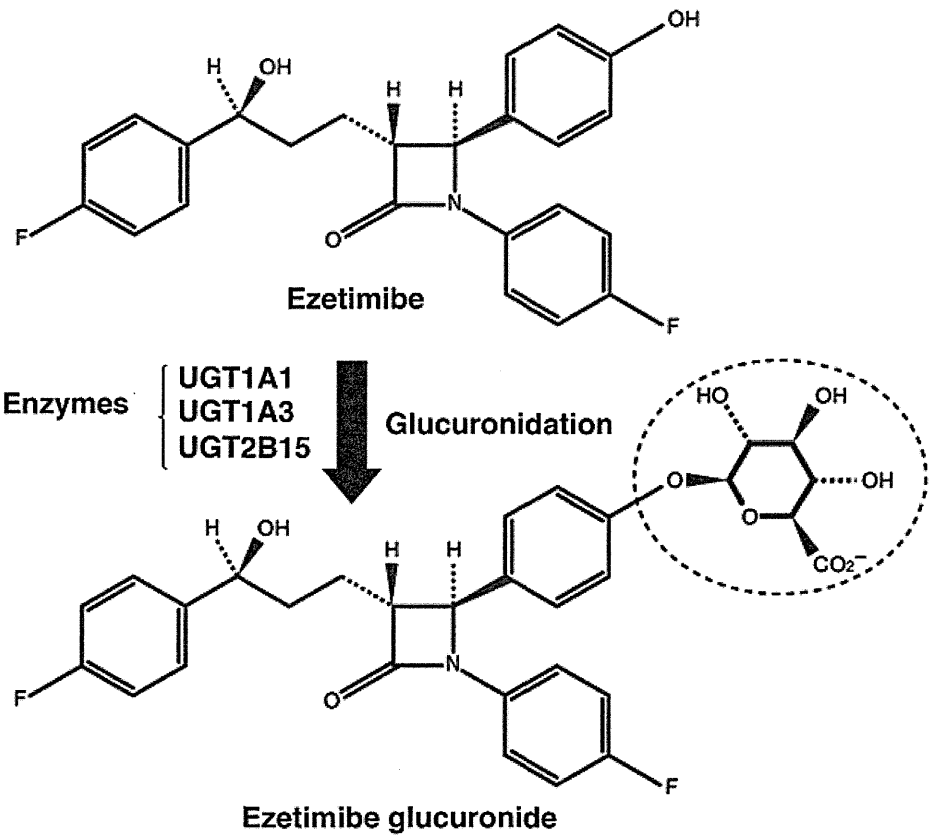

Fig. 28.2 Chemical structure of ezetimibe

uronidated ezetimibe is more potent than original ezetimibe and it is localized in the brush border of enterocytes [40, 42]. In humans, ezetimibe is glucuronidated in the small intestine and the liver and is not metabolized via P450.

Effects of Ezetimibe on Lipid Metabolism and Mechanisms for Its Action

Molecular Mechanisms for Ezetimibe-Induced Inhibition of Cholesterol Absorption

Although ezetimibe was reported to bind NPC1L1 at loop C composed of 61 amino acid residues [43] and block cholesterol absorption, the molecular mechanism of NPC1L1-mediated cholesterol uptake and how ezetimibe inhibits this process were poorly understood. Ge et al. [6] found that cholesterol specifically promotes the internalization of NPC1L1 and that this process requires microfilaments and the clathrin/activator protein (AP2) complex. If the endocytosis of NPC1L1 was blocked, it dramatically decreased cholesterol internalization, suggesting that NPC1L1 may mediate cholesterol uptake via its vesicular endocytosis. Ezetimibe prevents NPC1L1 from incorporating into clathrin-coated vesicles, attenuates cholesterol uptake, and impairs cholesterol influx. Thus, cholesterol is internalized into cells with NPC1L1 through clathrin/AP2-mediated endocytosis and ezetimibe was shown to inhibit cholesterol absorption by blocking the internalization of NPC1L1.

Effects of Ezetimibe on Lipoprotein Metabolism

Ezetimibe Monotherapy

Sudhop et al. [44] examined the effects of placebo or ezetimibe (10 mg/day) for 2 weeks on ra-

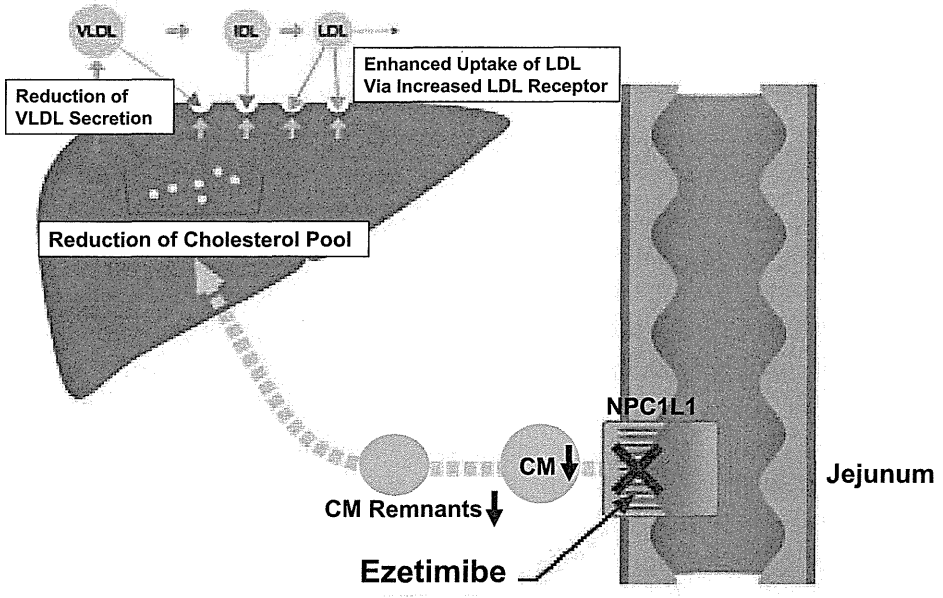

Fig. 28.3 Mechanisms for reduction of serum low-density lipoproteins-cholesterol (LDL-C) levels

diolabeled cholesterol absorption in patients with mild-to-moderate hypercholesterolemia. Ezetimibe reduced total cholesterol by 15%, LDL-C by 20%, campesterol by 48%, and sitosterol by 41%, respectively. Fractional cholesterol absorption rate was reduced by 54% by ezetimibe treatment. Thus, ezetimibe was demonstrated to reduce cholesterol as well as plant sterols in humans. Even in vegetarians, the fractional cholesterol absorption rate was reduced by 58% by ezetimibe treatment and LDL-C levels were also decreased by 17%, although dietary cholesterol intake was less than 30 mg/day, suggesting that ezetimibe inhibits the absorption of both bile-derived and food-derived cholesterol.

In other clinical trials, compared to placebo, ezetimibe (10 mg/day) monotherapy reduced LDL-C levels by 17–22% in hypercholesterolemic patients [45, 46]. In a pooled analysis of 1719 patients with primary hypercholesterolemia, ezetimibe significantly reduced the mean LDL-C levels by 18% (versus a 0.9% increase with placebo) [47]. It also significantly reduced the TG and apoB levels, while it increased HDL-C levels. For Japanese patients, ezetimibe (10 mg/day) was shown to reduce the mean LDL-C level by 18%, but the effect was not enhanced by increasing the dose more than 10 mg/day. Ezetimibe was reported to reduce remnants such as remnant-like particles cholesterol (RLP-C) [16]. It also reduced small dense LDL.

Mechanisms for Reduction of Serum LDL-C Levels (Fig. 28.3)

Ezetimibe inhibits the absorption of cholesterol by inhibiting the internalization of NPC1L1. Thus, the cholesterol content in the CM synthesized in the intestinal epithelium is decreased. The TG moiety of CM is hydrolyzed by the action of LPL, and CM become CM remnants which contain less cholesterol than those without ezetimibe treatment. CM remnants are subsequently taken up by the liver via remnant receptors including LDL receptor-related protein (LRP) and LDL receptor. The flux of exogenous cholesterol into the liver is reduced and the cholesterol pool in the liver is decreased, which causes the upregulation of hepatic LDL receptor. Thus, the uptake and catabolism of LDL by the liver are enhanced, leading to the reduction of serum LDL-C levels. Furthermore, the reduced pool of exogenous cholesterol may attenuate the synthesis and secretion of VLDL from the liver, and thus the metabolized

products of LDL such as IDL and LDL are also reduced. The reduction of hepatic VLDL synthesis and secretion may reduce serum TG levels. Ezetimibe was demonstrated to reduce serum LDL-C levels in patients with homozygous familial hypercholesterolemia (FH) who are deficient in LDL receptors [48, 49]. Therefore, the mechanism of LDL-C reduction in homozygous FH may be partly attributed to the reduction of VLDL synthesis which may lead to the production of IDL and LDL.

Ezetimibe in Combination with Statins and Other Lipid-Lowering Drugs

In clinical practice, doubling the dose of statins reduces LDL-C levels by an additional 6% (6% rule) and may increase side effects such as hepatic dysfunction, myalgia, and rhabdomyolysis. Ezetimibe added to ongoing statin therapy or coadministered with low-dose statins in statin-naive patients was shown to further reduce levels of LDL-C by 5–27%. This combination therapy resulted in favorable effects on several other lipid parameters as well as high-sensitivity C-reactive protein (hsCRP), compared with statins alone in patients with hypercholesterolemia, mixed hyperlipidemia, type 2 diabetes, metabolic syndrome, and older patients during 6–12 weeks of therapy [50]. Moreover, ezetimibe combined with statins increased the attainment of recommended levels of LDL-C, non-HDL-C, and apoB in these patients [51].

When combined with bile acid sequestrants (resins), fenofibrate or niacin, ezetimibe provided significant improvements in LDL-C, TG, total cholesterol, non-HDL-C and apoB, and (variably) HDL-C, compared with the individual component agents alone in patients with hypercholesterolemia and mixed hyperlipidemia (reviewed in ref [52]). Long-term administration of statins may enhance the expression of NPC1L1 in the small intestines and cholesterol absorption, leading to the attenuation of the effects of statins on LDL-C levels. More potent statins are also known to increase the cholesterol absorption more than less potent statins [28]. Therefore, the combination of statins and ezetimibe may be a reasonable strategy [14].

Reduction of Serum TG Levels and Increase of Serum HDL-C Levels by Ezetimibe

Ezetimibe reduces serum TG levels more markedly in hypertriglyceridemic (TG≥150 mg/dl) patients compared with normotriglyceridemic subjects [53]. Moreover, the addition of ezetimibe to statin-treated patients can further reduce serum TG levels. Ezetimibe increases serum HDL-C levels by several percent, and the addition of ezetimibe to statin-treated patients can further increase serum HDL-C levels.

Inhibition of Absorption of Plant Sterols

Ezetimibe was demonstrated to reduce the plasma levels of plant sterols such as sitosterol and campesterol in patients with hypercholesterolemia. It was also shown to reduce the plasma levels of plant sterols as well as serum cholesterol levels in patients with sitosterolemia caused by mutations in ABCG5 or ABCG8 [12, 13]. Both ABCG5 and ABCG8 form a heterodimer and are expressed in the luminal and apical surface of enterocytes and hepatocytes. The function of ABCG5 and ABCG8 is to export plant sterols into the intestinal lumen and the bile. Plant sterol levels were almost undetectable in NPC1L1-knockout mice. The absorption of radiolabeled sitosterol was so much reduced in NPC1L1-knockout mice and wild-type mice treated with ezetimibe. Therefore, NPC1L1 plays an important role as an intestinal transporter for the uptake of both cholesterol and structurally related plant sterols and ezetimibe inhibits the absorption of both cholesterol and plant sterols. Thus, ezetimibe is known as the most appropriate drug for the treatment of sitosterolemia. The long-term administration of ezetimibe was shown to attenuate xanthomas in some patients [54].

Inhibition of Absorption of Oxidized Cholesterol

Staprans et al. [55] examined the effects of ezetimibe in blocking intestinal absorption of oxidized cholesterol in a pilot study. Seven adult subjects were fed a diet containing oxidized cholesterol, α-epoxycholesterol, and 7-keto cholesterol, before and after ezetimibe (10 mg daily for 30 days). Ezetimibe was shown to reduce the serum levels of both cholesterol oxidation products, and this was attributed to the significantly reduced incorporation of oxidized cholesterol into CM and LDL.

Ezetimibe Attenuates Postprandial Hyperlipidemia

Postprandial hyperlipidemia is a very atherogenic state in which CM remnants accumulate in plasma [56]. We investigated the effects of ezetimibe on fasting lipid and lipoprotein profiles as well as postprandial hyperlipidemia [16]. Ezetimibe (10 mg/day) was administered for 2 months in patients with type IIb hyperlipidemia, and it significantly decreased not only fasting serum total cholesterol, LDL-C, and apoB-100 levels but also TG, apoB-48, and remnant lipoprotein cholesterol (RemL-C) levels. High-performance liquid chromatography (HPLC) analysis of serum at fasting state showed that ezetimibe decreased cholesterol and TG levels in the VLDL and LDL size ranges as well as apoB-100 levels, suggesting a decrease in the number of VLDL and LDL particles. After oral fat-loading test, ezetimibe decreased the area under the curve for TG, apoB-48, and RemL-C. Ezetimibe decreased postprandial elevations of cholesterol and TG levels in the CM size range, suggesting that the postprandial production of CM particles was suppressed by ezetimibe. Taken together, ezetimibe improved fasting lipoprotein profiles and postprandial hyperlipidemia by suppressing intestinal CM production in patients with type IIb hyperlipidemia and such treatment may prove to be effective in reducing atherosclerosis. Hiramitsu et al. [57] and Kikuchi et al. [58] also reported the similar effects of ezetimibe on the attenuation of postprandial hyperlipidemia. Yunoki et al. [59] demonstrated that ezetimibe improves postprandial hyperlipidemia and endothelial dysfunction induced postprandially.

Ezetimibe treatment for 3 weeks dramatically reduced postprandial hyperlipidemia in both wild-type mice on a Western diet and CD36-knockout mice, a model of postprandial hyperlipidemia on a normal chow diet [17]. HPLC analysis indicated that the decrease in TG content in CM and CM remnants-sized particles contributed to this suppression. Both TG content and apoB-48 mass in intestinal lymph after oral fat loading were decreased in ezetimibe-treated mice. The mRNA expression of fatty acid transport protein 4 (FATP4), apoB fatty-acid-binding proteins (FABP2), diacylglycerol O-acyltransferase (DGAT) 1, DGAT2, and stearoyl-coA desaturase-1 (SCD1) were reduced after ezetimibe treatment. Intestinal absorption of radiolabeled oleate was significantly reduced by ezetimibe in both animal models, suggesting that the absorption of FFA may be downregulated by the decrease in FATP4 and possibly FABP2 (Fig. 28.4). Taken together, ezetimibe reduces postprandial hyperlipidemia by blocking both the absorption of cholesterol and the intracellular trafficking and metabolism of fatty acids in enterocytes, resulting in the reduction of the formation of apoB-48 necessary for the CM production in the small intestines.

Effects of Ezetimibe on Atherosclerosis in a Variety of Animal Models

The effect of ezetimibe on atherosclerosis was examined in several animal models and reviewed [60]. ApoE-knockout mice develop severe hypercholesterolemia and premature atherosclerosis with features similar to those observed in humans. Techniques ranging from gross visualization of plaques to high-resolution magnetic resonance imaging (MRI) have demonstrated that ezetimibe inhibits atherosclerosis significantly [61]. Scavenger receptor class B type I (SR-BI)/apoE double knockout mice show additional characteristics similar to human coronary heart disease