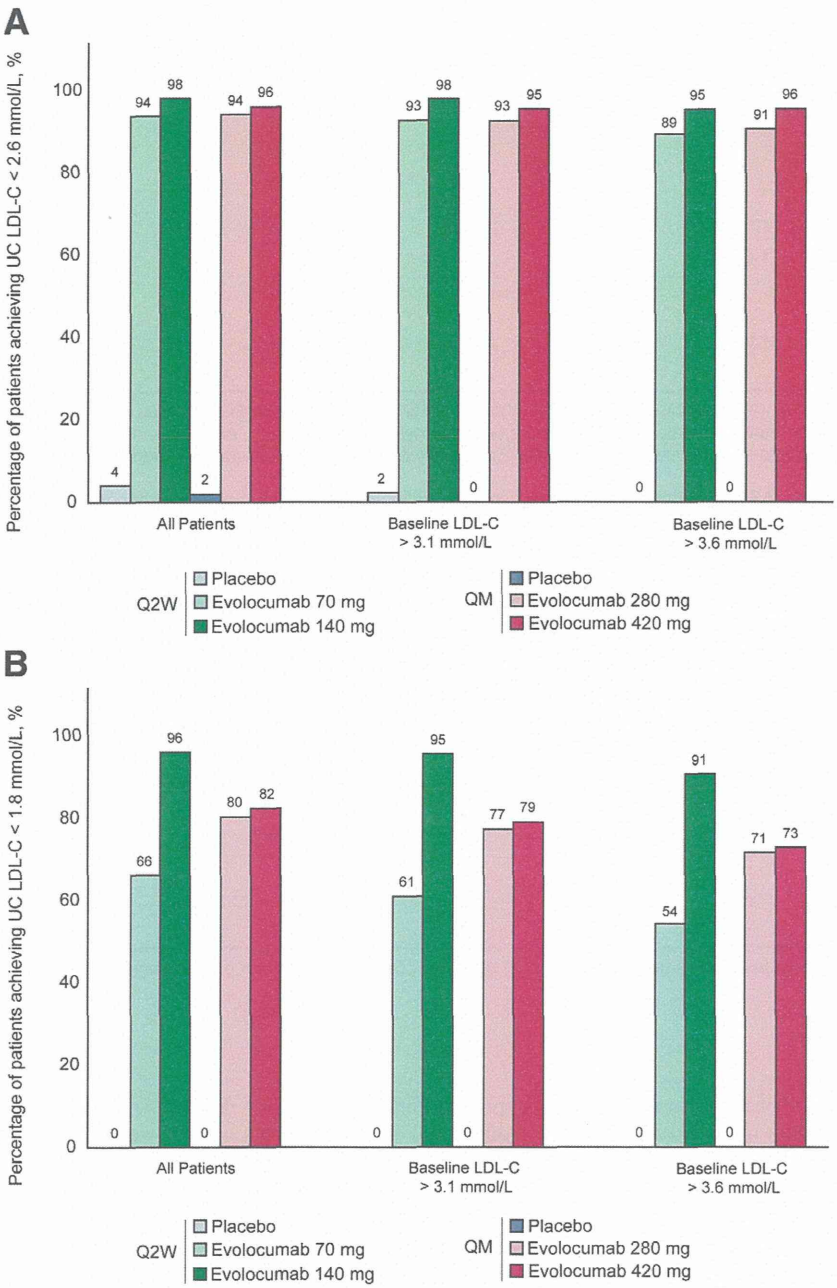

Figure 4. Frequency of attaining week-12 LDL-C targets measured by ultracentrifugation and stratified by baseline LDL-C. Percentage of patients reaching (**A**) LDL-C <2.6 mmol/l or (**B**) LDL-C <1.8 mmol/L. Percentages are based on the number of patients within each subgroup. LDL-C, low-density lipoprotein cholesterol.

tein B (ApoB), lipoprotein a (Lp[a]), the ApoB:ApoA1 ratio, and the TC:HDL-C ratio, and in all but the evolocumab 70 mg Q2W group for HDL-C and ApoA1 at week 12 (**Table 2**, **Table S2**). Favorable changes were also seen in other lipids for the mean of weeks 10 and 12 (**Table S3**).

The majority (94% to 98%) of patients in the evolocumab treatment groups achieved the most stringent JAS-recommended LDL-C goal of <2.6 mmol/L[12] at week 12. Goal achievement was highest in the 140 mg Q2W and 420 mg QM groups (98% and 96%, respectively, vs. 3% placebo; **Figure 4A**). The majority of evolocumab-treated patients also achieved LDL-C levels <1.8 mmol/L (**Figure 4B**).

Although more AEs were reported in evolocumab-treated (51%) vs. placebo-treated (38%) patients (**Table 3**), most were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 (mild or moderate),[23] and no imbalances in AEs were observed with respect to dose or dose frequency. Nasopharyngitis was the most frequent AE; 4 (2%) patients in the evolocumab treatment group reported serious AEs (**Table 3**), none of which was considered related to the study drug. These AEs were carcinoid tumor of the cecum with a pre-randomization history of anal bleeding (drug was withdrawn); fracture of left clavicle, ribs, and ankle (dose was altered or withheld); prostate cancer (dose was unchanged); and worsening of arteriosclerosis (dose was unchanged). In total, 4 evolocumab-treated patients discontinued treatment because of any AE,

Table 3. Incidence of Adverse Events in Patients

n (%)	Placebo Q2W (n=52)	Evolocumab 70 mg Q2W (n=49)	Evolocumab 140 mg Q2W (n=52)	Placebo QM (n=50)	Evolocumab 280 mg QM (n=51)	Evolocumab 420 mg QM (n=53)
All treatment-emergency AEs[a]	18 (34.6)	24 (49.0)	28 (53.8)	21 (42.0)	21 (41.2)	31 (58.5)
Leading to drug discontinuation	0	1 (2.0)	1 (1.9)	0	0	2 (3.8)
Serious AEs[b]	0	0	1 (1.9)	0	1 (2.0)	2 (3.8)
Leading to drug discontinuation	0	0	0	0	0	1 (1.9)
Potential injection-site reactions[c]	1 (1.9)	1 (2.0)	2 (3.8)	0	0	1 (1.9)
Binding antibodies detected[d]	1 (1.9)	0	0	0	0	0
AST or ALT >3x ULN	0	1 (2.0)	0	0	0	0
CK >5x ULN	0	0	0	1 (2.0)	1 (2.0)	0
Positively adjudicated cardiovascular events[e]	1 (1.9)	0	0	1 (2.0)	0	0
All-cause mortality	0	0	0	0	0	0

All percentages are based on n. [a]The most common treatment-emergency AE for both the placebo and evolocumab group was nasopharyngitis. [b]Serious AEs: fracture, carcinoid tumor of the cecum, prostate cancer, and arteriosclerosis. [c]Pain, bruising, erythema, hemorrhage, or pruritus at injection site. [d]No neutralizing antibodies to evolocumab detected. [e]The 2 positively adjudicated cardiovascular events were percutaneous coronary revascularizations.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ULN, upper limit of normal. Other abbreviations as in Table 1.

Table 4. Adverse Events [n (%)] Stratified by Lowest Post-Baseline LDL-C Score

n (%)	LDL-C <0.65 mmol/l		LDL-C <1.04 mmol/l		LDL-C ≥1.04 mmol/l	
	Placebo[a] (n=0)	Evolocumab (n=90)	Placebo[a] (n=0)	Evolocumab (n=157)	Placebo (n=102)	Evolocumab (n=48)
Treatment-emergency AEs	NA	49 (54.4)	NA	79 (50.3)	39 (38.2)	25 (52.1)
Serious AEs	NA	1 (1.1)	NA	3 (1.9)	0 (0.0)	1 (2.1)
Myalgia	NA	2 (2.2)	NA	3 (1.9)	1 (1.0)	1 (2.1)
CK >5xULN	NA	0 (0.0)	NA	1 (0.6)	1 (1.0)	0 (0.0)
CK >10xULN	NA	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)
AST or ALT >3xULN	NA	0 (0.0)	NA	0 (0.0)	0 (0.0)	1 (2.1)
Total bilirubin >2xULN	NA	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)
Positively-adjudicated cardiovascular events	NA	0 (0.0)	NA	0 (0.0)	2 (2.0)	0 (0)

All percentages based on n. LDL-C categories are based on patient's lowest, post-baseline LDL-C. [a]No placebo patients achieved these 2 post-baseline LDL-C levels.
Abbreviations as in Tables 1,3.

only 1 of which was serious (carcinoid tumor of the cecum with pre-randomization history of anal bleeding; not considered treatment related). Incidences of positively adjudicated cardiovascular events and elevations in creatine kinase (CK) and aminotransferases were comparable between placebo- and evolocumab-treated patients (Table 3). Binding antibodies to evolocumab were not detected in any evolocumab-treated patients (Table 3). Incidences of AEs, serious AEs, myalgia, and positively adjudicated cardiovascular events, as well as CK and aminotransferase elevations, were comparable between placebo-treated and evolocumab-treated patients irrespective of lowest post-baseline LDL-C (Table 4).

Discussion

Results from YUKAWA suggest that evolocumab dosed Q2W or QM yields significant reductions in LDL-C and other lipids (Table 2). Congruent with global evolocumab phase 2 results,[16–18,20] the greatest and most sustained LDL-C reductions were seen in the highest dose groups (140 mg Q2W and 420 mg QM; Table 2, Table S2). As mentioned before, time-averaged reductions in LDL-C can be estimated using the mean of weeks 10 and 12. When comparing the mean reduction at weeks 10 and 12 between the 140 mg Q2W and 420 mg QM groups, results were also similar (Table S3). Favorable changes were seen in additional lipid parameters at both week 12 and the mean of weeks 10 and 12, with the 140 mg Q2W and 420 mg QM doses resulting in the greatest changes. Most (94–98%) of the YUKAWA patients on evolocumab Q2W or QM achieved the JAS-recommended lipid target of <2.6 mmol/L.[12] In this study, the mean (SD) baseline LDL-C was 3.7 (0.5) mmol/L, with no patients having an LDL-C <2.6 mmol/L. At 12 weeks, up to 98% of patients receiving evolocumab achieved an LDL-C <2.6 mmol/L (Figure 4).

Because of the less potent and lower doses of statins used in Japan, fewer patients in YUKAWA were on high-intensity statin therapy compared with the LAPLACE-TIMI-57[17] or RUTHERFORD[18] global phase 2 studies, in which evolocumab was administered with a background of statin therapy (Table 1). Compared with LAPLACE-TIMI 57, the prevalence of diabetes, hypertension, and smoking were higher in YUKAWA.[17] Despite these differences, and consistent with results of the evolocumab phase 1b study performed in Japanese patients,[24] changes in LDL-C and other lipid parameters in the YUKAWA patients were comparable to those seen in the other evolocumab phase 2 studies at week 12.[17,18] Additionally, reductions in LDL-C did not appear to be significantly affected by factors such as age, weight, baseline lipid concentrations, or

CV risk factors (Figure 2).

Although AEs were more frequent in patients receiving evolocumab vs. placebo, the majority were CTCAE grade 1 or 2 (mild or moderate), and showed no appreciable relationship to dose or dose frequency. Serious AEs were infrequent (2% evolocumab vs. 0% placebo), and none was considered to be treatment related. In addition, elevations in CK (0.5% evolocumab; 1.0% placebo) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT; 0.5% evolocumab, 0% placebo) were rare. As evolocumab is a monoclonal antibody, patients were actively monitored for hypersensitivity- and immunogenicity-related side effects, such as injection-site reactions and antidrug antibodies:[25] 4 patients in the evolocumab group reported potential injection-site reactions, and none of the evolocumab-treated patients was found to have antidrug antibodies (binding or neutralizing). One patient in the placebo group was reported to have a positive evolocumab-binding antibody titer at the week 12 visit. This finding likely reflects non-specific evolocumab-binding antibodies that were detected by a highly sensitive assay. This case was not associated with any reported AE or alteration in patient treatment.

Intracerebral hemorrhage and cognitive impairment have been reported as potential causes of concern in the context of lipid reduction with statins.[26,27] A recent longer term study of evolocumab in approximately 1,100 subjects did not identify a difference in the incidence of either hemorrhagic stroke or cognitive impairment between the evolocumab (plus standard of care) arm vs. standard of care alone, irrespective of achieved LDL-C.[28] Similarly, in YUKAWA, there were no reported cases of hemorrhagic stroke or cognitive impairment over the study period. Rates of other AEs, serious AEs, myalgia, and CK and AST/ALT elevations were comparable between patients who achieved low (<1.04 mmol/L) or very low (<0.65 mmol/L) LDL-C levels. These results suggest that evolocumab can be used effectively and safely to reduce LDL-C in Japanese patients. As YUKAWA was a 12-week study, the long-term safety of achieving low and very low LDL-C will be better understood once longer term data are available for Japanese patients.

Current guidelines for lipid management recommend targeting either specific LDL-C concentrations (<2.6 mmol/L or <1.8 mmol/L),[29–31] or a percentage reduction in LDL-C (≥50%) for high-risk patients.[32] However, patients receiving statin therapy may not be able to achieve these goals,[33–35] and patient risk for CVD could be lowered with additional LDL-C reduction using other therapies.[30,31,33] In this study, the baseline LDL-C for high-risk patients was 3.7 mmol/L, despite stable use of background statin therapy. After 12 weeks of treatment with evolocumab, patients showed LDL-C reductions of up to 69%, and most (up to 96%) of the evolocumab-treated patients achieved LDL-C levels <1.8 mmol/L. Stable LDL-C reductions of the magnitude described here have not been seen with other classes of non-statin therapies.[36,37]

Close to half of high-risk Japanese patients are not at recommended LDL-C levels.[11,12] Thus, long-term use of evolocumab is poised to become an important treatment option for patients at high cardiovascular risk and/or unable to achieve their lipid goal. The YUKAWA study results suggest that novel, antibody-based therapies such as evolocumab may be used effectively and safely to reduce LDL-C in Japanese patients. Results from a large, ongoing cardiovascular outcomes trial will help elucidate whether the additional LDL-C lowering seen with evolocumab is associated with a reduction in cardiovascular events.[38]

Conclusions

Evolocumab Q2W or QM in combination with background statin therapy demonstrated robust efficacy and was well tolerated in a 12-week study in high-cardiovascular-risk Japanese patients with hypercholesterolemia. The greatest LDL-C reductions from baseline were observed with the 140 mg Q2W and 420 mg QM dosages. These findings support the continued investigation of evolocumab treatment in Japanese patients in a similarly designed phase 3 study currently underway (NCT01953328).

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Supplementary Files

Supplementary File 1

Inclusion/Exclusion criteria

Supplementary File 2

Table S1. Baseline lipid-lowering therapy

Table S2. Efficacy at 12 weeks

Table S3. Efficacy: mean of weeks 10 and 12

Please find supplementary file(s);
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Impact of the Integrated Guidance on the Care of Familial Hypercholesterolaemia

Watts G.F. *et al.* recently reported the Integrated Guidance on the Care of Familial Hypercholesterolaemia issued by the International FH Foundation[1]. On behalf of the Asia-Pacific Society of Atherosclerosis and Vascular Biology (APSAVD), we herein describe our perspective regarding the care of FH. In this summary, the authors described the guidelines for the detection, diagnosis, assessment and management of familial hypercholesterolemia (FH) in adults and children, which were determined following the discussions held at seminars and workshops at the 16th International Symposium on Atherosclerosis in Sydney in 2012. The recommended treatment is based on risk stratification, the management of non-cholesterol risk factors and the administration of safe and effective treatment to lower the LDL-cholesterol level. In addition to treatment with lipid-lowering medications, such as statins, ezetimibe, resin, fibrates and probucol, the authors described emerging therapies for FH, including mipomersen, lomitapide and anti-PCSK9 antibodies. These guidelines should have a significant impact on the management of FH in the Asia-Pacific region, as awareness of the clinical importance of FH remains very low in many countries, despite the fact that more than half of the world's population lives in this region. In the Asia-Pacific region, Japan and Australia are the only countries with published guidelines in English for the diagnosis and management of FH[2, 3], and only a few countries have published such guidelines in their mother language. FH is an autosomal dominant disease caused by the presence of abnormal LDL receptors or LDL receptor-related genes that is characterized by the triad of hyper-LDL-cholesterolemia, premature coronary artery disease (CAD) and tendon/cutaneous xanthoma. In our Japanese guidelines, we revised our diagnostic criteria for heterozygous FH, as indicated in **Table 1**, in a somewhat similar fashion to Simon Broome's criteria, although we determined the cutoff value for the LDL-cholesterol level based on the results of our multicenter study[4]. Considering that FH by itself is a very high-risk condition for CAD and that untreated patients are likely to develop CAD, such as myocardial infarction and angina pectoris, at a young age[3], providing an early diagnosis and appropriate treatment is mandatory for preventing premature death. Additionally, heterozygous FH is detected in one in 137 to 500 individuals and is one of the most frequently encountered genetic diseases in general practice[5]. Therefore, according to these guidelines, it is important to encourage the training of specialists of FH in each country and educate general practitioners regarding the diagnosis and treatment of FH. We hope that these guidelines will help to spread knowledge regarding the clinical implications of FH throughout the Asia-Pacific region and identify gaps in care, including collaborative efforts to enhance detection (especially in children), the introduction of effective early treatment, the development of country-specific models of care and the establishment of family support groups, relevant research agendas and funding mechanisms by the government and other organizations.

Table 1. Diagnostic Criteria for Heterozygous FH in Adults (Aged 15 Years or Older)[2]

1. Hyper-LDL-cholesterolemia (untreated LDL-C of ≥ 180 mg/dL)
2. Tendon xanthoma (tendon xanthoma on the backs of hands, elbows, knees, etc. or Achilles tendon hypertrophy) or xanthoma tuberosum
3. Family history of FH or premature CAD (within the second-degree relatives)

- Diagnosis should be made after excluding secondary hyperlipidemia
- If a patient meets two or three of the above-mentioned criteria, the condition should be diagnosed as FH. In the case of suspected FH, diagnosis by genetic testing is desirable.
- Xanthoma palpebrarum is not included in xanthoma tuberosum.
- Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is ≥ 9 mm on soft X-ray imaging.
- An LDL-C of ≥ 250 mg/dL strongly suggests FH.
- If a patient is already receiving drug therapy, the lipid level that led to treatment should be used as the reference for diagnosis.
- Premature CAD is defined as CAD in men aged < 55 years or women aged < 65 years.
- If FH is diagnosed, it is preferable to also examine the patient's family members.

Conflicts of Interest

H. Arai: research grants from Otsuka Pharmaceuticals. Ltd and Daiichi Sankyo Co. Ltd.; YA. Ding: None.; S. Yamashita: MSD K.K., Bayer Yakuhin Ltd., Kowa Pharmaceutical Co., Ltd., Skylight Biotech Inc., Astellas Pharma Inc., Shionogi & Co., Ltd., Otsuka Pharmaceuticals Co., Ltd., Kissei Pharmaceuticals Co., Ltd.

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Executive Summary

Integrated Guidance on the Care of Familial Hypercholesterolaemia from the International FH Foundation: Executive Summary

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Familial hypercholesterolaemia (FH) is a dominantly inherited disorder present from birth that markedly elevates plasma low-density lipoprotein (LDL) cholesterol and causes premature coronary heart disease. There are at least 20 million people with FH worldwide, but the majority remains undetected and current treatment is often suboptimal.
To address this major gap in coronary prevention we present, from an international perspective, consensus-based guidance on the care of FH. The guidance was generated from seminars and workshops held at an international symposium. The recommendations focus on the detection, diagnosis, assessment and management of FH in adults and children, and set guidelines for clinical purposes. They also refer to best practice for cascade screening and risk notifying and testing families for FH, including use of genetic testing. Guidance on treatment is based on risk stratification, management of non-cholesterol risk factors and safe and effective use of LDL lowering therapies. Recommendations are given on lipoprotein apheresis. The use of emerging therapies for FH is also foreshadowed.
This international guidance acknowledges evidence gaps, but aims to make the best use of contemporary practice and technology to achieve the best outcomes for the care of FH. It should accordingly be employed to inform clinical judgment and be adjusted for country-specific and local healthcare needs and resources.

Key words: Familial hypercholesterolaemia, International guidance, Adults, Children, Screening, Diagnosis, Assessment, Treatment, Models of care

Endorsement

The recommendations contained in this document have been fully endorsed by The National Lipid Association, 6816 Southpoint Parkway (Suite 1000), Jacksonville, FL3316, US.

Conversion Factor

mg/dL cholesterol = mmol/L × 38.7

Levels of Evidence and Grades of Recommendation

Levels of Evidence

1 = systematic review/meta-analysis/at least one randomised control trial/good quality diagnostic tests.

2 = good quality clinical or observational studies.

3 = expert opinion or clinical experience/argument from first principles.

(The evidence for therapeutic interventions was considered principally in respect of effects on plasma LDL-cholesterol concentrations, but where available was also based on data on subclinical atherosclerosis or cardiovascular outcomes.)

Grades of Recommendation

A = can be trusted to guide practice.

B = can be trusted to guide practice in most situations.

C = can be used to guide practice, but care should be taken in application.

Summary of Recommendations

1. Detection of Index Cases: Screening and Phenotypic Diagnosis

1.1 Targeted, opportunistic and universal screening strategies should be employed to detect index cases [**2B**].

1.2 Index cases should be sought by targeted screening of adults with premature cardiovascular disease (CVD), primarily coronary heart disease (CHD) and a personal and/or family history of hypercholesterolaemia. [**1A**]

1.3 Opportunistic screening of adults and children in primary care, based on age- and gender-specific plasma LDL-cholesterol levels, should be routinely adopted. [**2B**]

1.4 Universal screening based on age- and gender- specific plasma LDL-cholesterol levels should be considered prior to age 20 years and ideally before puberty. [**2C**]

1.5 In adults, country-specific clinical tools, such as the Dutch Lipid Clinic Network, Simon Broome, MED-PED or Japanese FH criteria, may be used to make a phenotypic diagnosis. [**1A**]

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1.6 The effect of acute illness and concurrent use of statins in lowering plasma LDL-cholesterol must be considered: testing for FH should not be carried out during acute illness; LDL-cholesterol level should be appropriately adjusted in people on statins, particularly if a reliable pre-treatment value is not available [**2A**]

1.7 All patients with suspected FH should be referred to a clinic specialising in lipidology and/or metabolic disorders for further assessment, if such a service is available. [**3A**]

2. Diagnosis and Assessment of Adults

2.1 Secondary causes of hypercholesterolaemia should first be excluded. [**1A**]

2.2 The most reliable diagnosis of FH can be made using both phenotypic (see 1.5 above and 4.8 below) criteria and genetic testing, but when genetic testing is not available the diagnosis can be made phenotypically. [**1A**]

2.3 DNA testing increases the accuracy of detecting FH and, if resources permit, should be considered to confirm the diagnosis, especially if cascade screening is planned; a fully accredited laboratory should be used. [**1A**]

2.4 Although FH is a life-time coronary risk equivalent, patients should be assessed for additional major cardiovascular risk factors, including lipoprotein(a) [Lp(a)], the level of hypercholesterolaemia at diagnosis and the prematurity of the family (especially first-degree relatives) or personal history of CVD. Framingham or other cardiovascular risk equations should not be used. [**2A**]

2.5 The presence of additional cardiovascular risk factors should guide the intensity of medical management. [**2A**]

2.6 Cardiovascular imaging (eg. cardiac computed tomography and carotid ultrasonography) may be useful for assessing asymptomatic patients, but its value is not fully established. [**2C**]

3. Diagnosis and Assessment of Children and Adolescents

3.1 Secondary causes of hypercholesterolaemia should first be excluded. [**1A**]

3.2 With the exceptions noted in 3.3, children should be genetically tested for FH only after a pathogenic variant (mutation) has been identified in a parent or first degree relative. [**1A**]

3.3 Children may initially be genetically tested for FH when parents or first degree relatives are unknown or deceased, or as an accepted screening practice in certain countries, such as the Netherlands [**3B**]

3.4 Age-, gender- and country -specific plasma LDL-cholesterol concentration thresholds should be used to make the phenotypic diagnosis; because of biological variation, two fasting LDL-cholesterol values are recommended. [**1B**]

3.5 A plasma LDL-cholesterol of 5.0 mmol/L or above indicates high probability of FH in the absence of a positive parental history of hypercholesterolaemia or premature CHD; an LDL-cholesterol of 4.0 mmol/L or above indicates high probability of FH in the presence of a positive parental history of hypercholesterolaemia or premature CHD [**1B**]

3.6 Patients should be risk stratified according to age, presence of other cardiovascular risk factors, family history of early onset CVD (especially in first-degree relatives) and the level of LDL-cholesterol at diagnosis. [**2A**]

3.7 The presence of additional cardiovascular risk factors, and hence risk stratification, should guide the intensity of medical management. [**3A**]

3.8 Carotid ultrasonography may be employed to assess risk, but its value is not fully established; it should only be carried out in centres with specific expertise. [**2C**]

3.9 Cardiac CT should not be used routinely to assess patients with heterozygous FH. [**3A**]

4. Cascade Screening: Testing and Risk Notification of Families

4.1 Notification of relatives at risk of FH should generally not be carried out without the consent of the index case. [**3A**]

4.2 Relatives should only be directly notified of their risk without consent of the index case if there is specific legislative provision for breach of confidentiality in the relevant jurisdiction. [**3C**]

4.3 A proactive approach that respects the principles of privacy, justice and autonomy is required. [**3A**]

4.4 Pre-testing counselling should be offered to at risk family members of an index case prior to any form of testing. [**1A**]

4.5 Systematic cascade screening should ideally be co-ordinated by a dedicated centre and should not be carried out in primary care without central co-ordination, particularly if employing DNA testing. [**1B**]

4.6 Cascade screening of families should be carried out using both a phenotypic and genotypic strategy, but if DNA testing is not available a phenotypic strategy alone should be used [**1A**]

4.7 Cascade screening should initially be carried out as a priority in first-degree relatives and then extended to second- and third-degree relatives. [**1A**]

4.8 In the absence of genetic testing, the diagno-

sis of FH should be made in close relatives using age- , gender- and country- specific plasma LDL-cholesterol levels. Diagnostic clinical tools for index cases, such as the Dutch Lipid Clinic Network and Simon Broome criteria, should not be employed to make the diagnosis of FH in relatives [**1A**]

4.9 DNA testing makes cascade screening more cost-effective and should be employed to screen family members after the mutation is identified in the index case. [**1A**]

4.10 Children with xanthomata or other physical findings of homozygous FH, or at risk of homozygous FH should be screened as early as possible and definitely by 2 years of age. [**2A**]

4.11 Children with suspected heterozygous FH should be screened between the ages of 5 and 10 years; age at screening should be similar in boys and girls. [**2B**]

5. Genetic Testing

5.1 Genetic testing for FH should ideally be offered to all 'index cases' who have a phenotypic diagnosis of FH. [**3A**]

5.2 When the phenotypic diagnosis of FH is unlikely (e.g. by Dutch Lipid Clinic Network Criteria), genetic testing of the 'index case' need not be carried out. [**1C**]

5.3 Genetic testing for FH must be carried out in an accredited laboratory using standardised methods that target specific mutations and/or by exon-by-exon sequencing. [**1A**]

5.4 If genetic testing detects a variant, its significance as a pathogenic mutation, a previously reported variant of uncertain significance, a novel variant of uncertain significance or a benign (normal) variant needs to be assessed and recorded. [**1A**]

5.5 If genetic testing does not detect a variant, FH due to undetected mutations or mutations in untested genes cannot be excluded, particularly if the clinical phenotype is strongly suggestive of FH. [**1A**]

6. Management of Adults

6.1 All adult patients with FH must receive advice on lifestyle modifications and advice to correct all non-cholesterol risk factors should be provided according to expert recommendations. [**2A**]

6.2 Therapy should ideally aim for at least a 50% reduction in plasma LDL-cholesterol, followed by an LDL-cholesterol <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). [**2C**]

6.3 Achieving these targets will require a fat-modified, heart-healthy diet and statin therapy with or without ezetimibe. [**1A**]

6.4 Drug combinations including bile acid sequestrants, niacin, probucol or fibrates, may be required with more intensive strategies to further reduce LDL-cholesterol. [**1B**]

6.5 Plasma levels of hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting drug therapy. All patients on statins should have hepatic aminotransferases monitored; creatine kinase should be measured when musculoskeletal symptoms are reported; glucose should be monitored when there are risk factors for diabetes. [**2A**]

6.6 All women of child-bearing age should receive pre-pregnancy counselling, with appropriate advice on contraception, before starting a statin and this should be reinforced at annual review. [**2A**]

6.7 Statins and other systemically absorbed lipid regulating drugs should be discontinued 3 months before planned conception, as well as during pregnancy and breast feeding. [**2A**]

6.8 Although carotid ultrasonography has been used in clinical trials, its role in monitoring therapy as part of the clinical care for FH has not been established and it should therefore not be used at present for this purpose. [**3C**]

6.9 Lomitapide and Mipomersen should be considered as adjunctive treatments to diet and cholesterol lowering drugs in adults with homozygous FH to further reduce plasma LDL-cholesterol, particularly if lipoprotein apheresis is not available. [**1C**]

6.10 Well controlled and low complexity patients should be followed-up in primary care, whereas higher complexity patients will need regular review by a specialist, with the option of shared care. Review intervals should vary according to clinical context. Opportunities should be created for integrating the primary and specialist care of FH. [**3B**]

7. Management of Children and Adolescents

7.1 Patients must receive advice on lifestyle modifications and on correcting non-cholesterol risk factors; primordial prevention (counselling to inhibit the development of risk factors) is particularly important. [**2A**]

7.2 To lower elevated plasma LDL-cholesterol in this age group generally requires a fat-modified, heart-healthy diet and a statin, with the possible addition of ezetimibe or a bile acid sequestrant. [**1A**]

7.3 All patients should be treated with diet, with statins considered at age 8 to 10 years and ideally started before age of 18 years; plasma LDL-cholesterol targets in this age group need not be as intense as for