INTERNATIONAL ATHEROSCLEROSIS SOCIETY

International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia

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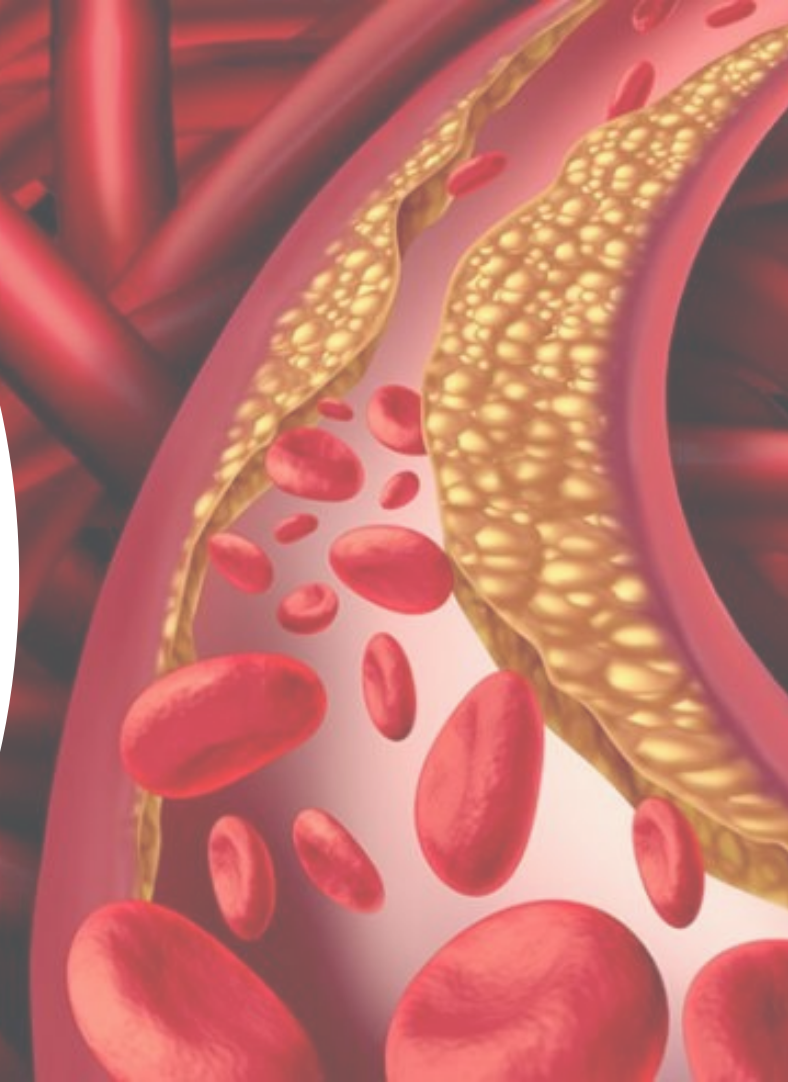

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International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia (doi.org/10.1038/s41569-023-00892-0)

Author contributions

- Gerald F. Watts, Samuel S. Gidding, Robert A. Hegele, Frederick J. Raal, Amy C. Sturm, Laney K. Jones, Mitchell N. Sarkies, Jing Pang and Gilbert R. Thompson **researched data.**
- All the authors **contributed to discussion of content**.
- Gerald F. Watts, Samuel S. Gidding, Robert A. Hegele, Laney K. Jones, Frederick J. Raal, Mitchell N. Sarkies, Amy C. Sturm and Gilbert R. Thompson **wrote first and final drafts of the manuscript**.
- All the authors **reviewed/edited the manuscript** before submission.

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Introduction

Introduction

- Familial hypercholesterolaemia (FH) is a co-dominant and highly penetrant monogenic disorder that markedly elevates LDL-cholesterol concentration from birth and, if untreated, leads to premature atherosclerotic cardiovascular disease (ASCVD).
- FH is a tier 1 genomic condition i.e. a preventable cause of premature disease and death owing to ischaemic heart disease, with substantial effects on public health.
- The public health importance of FH is highlighted by an overall phenotypic frequency in the population of 1 in 311. FH may affect up to 35 million people worldwide, but only 10% are currently diagnosed, and >80% of those treated do not achieve LDL-cholesterol goals.

International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia (doi.org/10.1038/s41569-023-00892-0)

Introduction

- The unmet needs in the care of FH have prompted several clinical practice guidelines, international collaborations and global calls to action. Implementation of guideline recommendations is generally overlooked.
- Implementation science offers the best approach for translating clinical recommendations into routine practice by overcoming barriers to and leveraging enablers of improved care, aiming to maximize benefit for the population at risk.
- We have promoted this methodology to develop implementation strategies to increase the impact of clinical recommendations on the care of FH.

International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia (doi.org/10.1038/s41569-023-00892-0)

Introduction

- This evidence-informed guidance provides a systematic compendium of clinical recommendations, informed by best contemporary evidence, for the detection and management of patients with FH.

- The recommendations are supplemented with general and specific implementation strategies to optimize the deployment in models of care.

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Methodology

Methodology

- Development of the guidance was led by the International Expert Working Group (IEWG), selected by the board of the International Atherosclerosis Society (IAS) for having diverse expertise in FH.
- The IEWG defined the scope and focus of the task, developed the evidence evaluation process, appointed a writing committee and sought stakeholder involvement.
- The development of the clinical guidance was based on previous guidelines that had used evidence-informed recommendations and scored highly based in the Appraisal of Guidelines for Research Evaluation II instrument.

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Design of the Guidance

- The guidance was divided into aspects of **detection, management and implementation.**
    - **Detection** covered screening, diagnosis, genetic testing and counselling.
    - **Management** covered risk stratification, treatment of adults and children with heterozygous FH (HeFH) or homozygous FH (HoFH), management of FH during pregnancy and use of lipoprotein apheresis.
    - The detection and management sections included preambles, clinical recommendations and **implementation recommendations**.

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Design of the Guidance

- **Clinical recommendations** were given Classes of Recommendation (1 = strong, 2 = moderate and 3 = weak) and corresponding Levels of Evidence (A = high, B = moderate and C = low).

- **Implementation recommendations** were developed by consensus, based on relevant published works, and were guided by a framework provided by the Expert Recommendations for Implementing Change (ERIC).

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Part I: Clinical Recommendations

Classes of Recommendations

Strong recommendation: There is high certainty based on the evidence that the net benefit is substantial; *can be trusted to guide practice; Wording: should be performed*	**Strong = 1**
Moderate recommendation: There is moderate certainty based on the evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate; *can be trusted to guide practice in most situations; Wording: should be considered*	**Moderate = 2**
Weak recommendation: There is at least moderate certainty based on the evidence that there is a small net benefit; *can be trusted to guide practice, but care should be taken in its application; Wording: may be considered*	**Weak = 3**

This system was based on the American Heart Association/American College of Cardiology[1] and the National Lipid Association[2] cholesterol guidelines.

[1]Stone, N. J. *et al.* 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* **129**, S1-S45, doi:10.1161/01.cir.0000437738.63853.7a (2014).

[2]Jacobson, T. A. *et al.* National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. *J. Clin. Lipidol.* **9**, 129-169 (2015).

Levels of Evidence

Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect *Bases: Randomised-controlled trials/meta-analyses/systematic reviews/good quality diagnostic studies*	**High = A**
Moderately certain about the estimate of effect; further research may have an impact on our confidence in the estimate of effect and may change the estimate *Bases: Good quality clinical or observational studies*	**Moderate = B**
Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate *Bases: Expert opinion based on clinical experience or argument from first principles*	**Low = C**

This system was based on the American Heart Association/American College of Cardiology[1] and the National Lipid Association[2] cholesterol guidelines, and adapted from the original GRADE system of evidence rating[3].

[3]Guyatt, G. H. *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924-926, doi:10.1136/bmj.39489.470347.AD (2008).

Detection – Screening for FH

Screening for FH

Clinical Recommendations	Class	Level
1. Multiple screening strategies (for example, selective, opportunistic and/or universal) should ideally be used to detect index cases with FH.	1	B
2. Age-specific, sex-specific and country-specific LDL-cholesterol concentrations (estimated in plasma or serum) above the corresponding 95th percentiles for the population should preferably be used to screen for index cases with FH.	1	B
3. Selective screening should be used to detect index cases among adults with premature ASCVD, mainly coronary artery disease, and a family history of premature ASCVD and/or hypercholesterolaemia.	1	A

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Screening for FH

Clinical Recommendations	Class	Level
4. Opportunistic screening, such as an LDL-cholesterol concentration >4.9 mmol/l (≥190 mg/dl), should be used to detect cases in the community.	1	B
5. Universal screening using age-specific and sex-specific criteria for LDL-cholesterol concentration should be considered initially to detect children and adolescents with FH, after which the diagnosis should be formally confirmed and reverse cascade testing offered to parents, as indicated.	2	B
6. Cascade testing should be offered to all close relatives of an index case with definite FH and be carried out using phenotypic and genetic methods; if genetic testing is not feasible, LDL-cholesterol testing (based on appropriate age-specific and gender-specific thresholds) should be used.	1	A

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Screening for FH

Clinical Recommendations	Class	Level
7. Genome-based population screening of adults may be considered for wider and more accurate detection of FH, but requires careful implementation.	3	C
8. After initial detection of potential index cases, the diagnosis of FH should be formally confirmed using country-specific (or internationally accepted) phenotypic criteria and ideally with genetic testing.	1	A
9. Children with suspected HoFH (for example, with physical stigmata), or at risk of FH (both parents known to have FH), should be tested as early as possible (at the newborn stage or by 2 years of age), with measurement of LDL-cholesterol concentrations, followed by genetic confirmation.	1	B

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Screening for FH

Clinical Recommendations	Class	Level
10. Screening of children at risk of HeFH should be considered using LDL-cholesterol concentrations at or after the age of 5 years, or as early as 2 years in those with a strong family history of premature ASCVD, with confirmation of the diagnosis genetically, as indicated.	2	B
11. Non-fasting samples may be considered when screening for FH; the Friedewald equation should be used with caution owing to the confounding effect of hypertriglyceridaemia on the estimation of LDL-cholesterol concentration.	3	B

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Screening for FH

Clinical Recommendations	Class	Level
12. Patients with hypertriglyceridaemia > 4.5 mmol/l (>400 mg/dl), in whom FH is strongly suspected, should be re-screened for FH with a 12-h fasting sample and LDL-cholesterol concentration measured using a direct assay.	1	A
13. In the absence of a direct assay for LDL-cholesterol concentration, the probability of FH should be reconsidered in patients with very severe hypertriglyceridaemia after therapeutic lowering of triglyceride concentrations to <4.5 mmol/l (<400 mg/dl), or by calculating LDL-cholesterol using a novel equation (e.g. Martin-Hopkins or Sampson), if triglycerides are between 4.5 mmol/l and 10.0 mmol/l (400–850 mg/dl).	2	C

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Screening for FH

Clinical Recommendations	Class	Level
14. The effects of cholesterol-lowering medications and acute illness should be accounted for when phenotypically screening for FH; LDL-cholesterol concentrations should be adjusted for the use of statins, ezetimibe, PCSK9 inhibitors and other therapies, particularly if a reliable pretreatment value is unavailable; if the diagnosis of FH is in doubt, LDL-cholesterol measurement should be repeated after full recovery from acute illness.	1	B

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Detection – Diagnosis of FH

Diagnosis of FH

Clinical Recommendations	Class	Level
1. A diagnosis of HeFH or HoFH should be made, whenever possible, using genetic testing that identifies pathogenic variants (such as in LDLR, APOB, PCSK9 or LDLRAP1) that impair the LDL-receptor pathway; such testing is particularly important when phenotypic features are less obvious, such as in children, and for planning long-term care and cascade testing of family members. Conversely, if the phenotype strongly suggests FH and a pathogenic or likely pathogenic variant is not detected, FH should not be excluded.	1	A

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Diagnosis of FH

Clinical Recommendations	Class	Level
2. If genetic testing is not feasible, a clinical diagnosis of FH in adults should be made using country-specific or recognized phenotypic criteria (such as the Dutch Lipid Clinic Network, Simon Broome criteria, MED-PED, AHA, Canadian or Japanese criteria) for index cases.	1	A
3. A phenotypic diagnosis of FH in adults and children requires exclusion of, or correction for, secondary causes of high LDL-cholesterol concentrations; in the absence of an untreated value, LDL-cholesterol concentration should be adjusted for concurrent use of cholesterol-lowering medication; LDL-cholesterol concentrations should ideally be measured after fasting and on two occasions.	1	A

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Diagnosis of FH

Clinical Recommendations	Class	Level
4. Use of imaging-based detection of subclinical Achilles tendon xanthomas may be considered to increase the specificity and accuracy of the phenotypic diagnosis of FH in adults.	3	B
5. A clinical diagnosis of FH in children and adolescents should be considered as highly probable in the presence of an untreated LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on at least two occasions (fasting lipid profile, >2 weeks but <3 months apart), and a parental history of high LDL-cholesterol levels, premature ASCVD or a positive genetic test for FH.	2	B

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Diagnosis of FH

Clinical Recommendations	Class	Level
6. After exclusion of secondary causes of high LDL-cholesterol levels, a clinical diagnosis of FH in children and adolescents should be considered as probable in the presence of an untreated: (a) LDL-cholesterol concentration > 4.9 mmol/l (>190 mg/dl; recorded on at least two occasions), even in the absence of a parental history of high LDL-cholesterol concentrations or premature ASCVD; (b) LDL-cholesterol concentration > 4.0 mmol/l (>160 mg/dl; recorded on at least two occasions), with a parental history of high LDL-cholesterol concentrations or premature ASCVD; (c) LDL-cholesterol concentration > 3.5 mmol/l (>135 mg/dl; recorded on at least two occasions), with a parent having a pathogenic gene variant for FH; (d) LDL-cholesterol concentration (recorded on at least two occasions) exceeding a country specific LDL-cholesterol threshold (lower than the above) and a parental history of elevated LDL-cholesterol concentrations or premature ASCVD.	2	B

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Diagnosis of FH

Clinical Recommendations	Class	Level
7. Phenotypic criteria developed for making a diagnosis of HeFH in adult index cases (such as the Dutch Lipid Clinic Network criteria) should not be used in children or adolescents, or when undertaking cascade testing.	1	A

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Diagnosis of FH

Clinical Recommendations	Class	Level
8. After excluding secondary causes of high LDL-cholesterol levels, a clinical diagnosis of HoFH (that is, phenotypic HoFH) should be made in children and adults with an untreated LDL-cholesterol concentration > 10 mmol/l (>400 mg/dl; recorded on two occasions) in the presence of:	1	C
(a) physical stigmata (tendon or cutaneous xanthomas, arcus cornealis) before the age of 10 years and/or (b) untreated LDL-cholesterol concentrations consistent with HeFH in both parents; in the absence of genetic testing and a clear history of FH in both parents, sitosterolaemia and hypercholestanolaemia (cerebrotendinous xanthomatosis) should also be excluded.		

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Diagnosis of FH

Clinical Recommendations	Class	Level
9. If cascade testing in the family is recommended, the diagnosis of FH in the proband or index case should ideally be confirmed genetically.	1	A
10. The diagnosis of FH during phenotypic cascade testing should be made using age-specific, sex-specific and country-specific LDL-cholesterol concentrations, ideally measured after fasting and on two occasions.	1	A

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Detection – Genetic Testing and Counselling

Genetic Testing and Counselling

Clinical Recommendations	Class	Level
1. Genetic testing for FH should be offered to all individuals in whom there is a strong suspicion of FH based on clinical and/or family history (for example, phenotypic HoFH, definite or highly probable phenotypic HeFH in an adult, child or adolescent).	1	B
2. Genetic testing should be considered in individuals with a probable phenotypic diagnosis of HeFH.	2	B
3. Genetic testing may be considered in individuals with a phenotypic diagnosis of possible HeFH, especially when there is incomplete information to establish a diagnosis and the genetic result affects clinical management.	3	C

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Genetic Testing and Counselling

Clinical Recommendations	Class	Level
4. Genetic testing for FH should be carried out using an accredited method in a certified laboratory, using targeted next-generation sequencing of all exons and exon–intron boundaries *of LDLR, APOB, PCSK9 and LDLRAP1,* and the exons in *APOB* that encode the LDLR ligand-binding region, as well as analysis for deletions and duplications in *LDLR.*	1	A
5. Variants detected by genetic testing should be classified and reported according to contemporary standardized guidelines, for example, those of the ACMG, AMP or ClinGen FH Variant Curation Expert Panel.	1	A

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Genetic Testing and Counselling

Clinical Recommendations	Class	Level
6. If a pathogenic or likely pathogenic variant is not detected, FH should not be excluded, particularly if the clinical phenotype is strongly suggestive of FH, because the condition may result from undetected genetic variants.	1	A
7. Genetic counselling should be offered, before and after genetic testing, to all individuals suspected of having FH.	1	B
8. Genetic counselling should at a minimum include obtaining a three-generation family medical history, risk assessment, family-based care, enabling of cascade testing, anticipatory guidance and psychological assessment.	1	A

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Genetic Testing and Counselling

Clinical Recommendations	Class	Level
9. Preconception counselling should be offered to all couples, especially if both partners/parents are known, or suspected, to have FH.	1	B
10. Prenatal or pre-implantation genetic testing should be offered if both partners/parents are known to have FH, counselling being particularly important in parents with HeFH who have previously had a child with HoFH.	1	C
11. Polygenic scores for hypercholesterolaemia may be useful but are not yet fully standardized, so that they should be used with caution when assessing the differential diagnosis of FH in clinical practice.	3	B

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Genetic Testing and Counselling

Clinical Recommendations	Class	Level
12. Cascade genetic testing is highly cost-effective and should be used after a disease-causing variant has been identified in the proband or index case.	1	A
13. Pre-test and post-test genetic counselling should be offered to all at-risk relatives as an integral component of cascade testing.	1	A
14. Cascade testing should be undertaken using both phenotypic and genotypic approaches; if genetic testing is not available, a phenotypic approach (that is, a plasma or serum lipid profile, including the LDL-cholesterol concentration) should be used.	1	A

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Genetic Testing and Counselling

Clinical Recommendations	Class	Level
15. Cascade genetic testing for the specific variant (variants) identified in the proband (that is, known familial variant testing) should initially be offered to all first-degree relatives; if first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to at-risk second-degree and then third-degree relatives, with sequential extension to the entire family until all at-risk individuals have been offered testing.	1	A
16. At-risk children should be offered cascade genetic testing at the earliest opportunity (and more than once if not pursued at the first offer) if an FH-causing variant has been identified in a parent or other first-degree relative.	1	A

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Genetic Testing and Counselling

Clinical Recommendations	Class	Level
17. When genetic testing is not feasible, the diagnosis of FH in at-risk relatives should be made phenotypically using age-specific, sex-specific and country-specific LDL-cholesterol concentrations; clinical tools for diagnosing FH probands (such as the Dutch Lipid Clinic Network criteria and Simon Broome criteria) are not valid for this purpose. Phenotypic cascade testing should initially be offered to all first-degree relatives. If first-degree relatives are unavailable, or decline testing, phenotypic testing should next be offered to second-degree and then third-degree relatives, with sequential extension to the entire family until all at-risk individuals have been offered testing.	1	A

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Genetic Testing and Counselling

Clinical Recommendations	Class	Level
18. 'Reverse' cascade testing (from child to parents) should be offered to parents after a child is identified as a proband with FH, such as after making a diagnosis following a clinical presentation or via a universal or newborn screening programme.	1	B

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Management – Risk Stratification

Risk Stratification

Clinical Recommendations	Class	Level
1. Routine assessment and stratification of the risk of ASCVD in all patients with FH should be used to develop effective personalized treatment plans and guide overall management, aiming to maximize reduction in the risk of cardiovascular events and improve quality of life.	1	B
2. All patients with FH, including children and adolescents, should be assessed for the presence of heart-healthy behaviours and non-cholesterol risk factors (that is, age, sex, smoking, hypertension, diabetes, obesity and mental health conditions) to stratify the risk of ASCVD.	1	B
3. The use of coronary artery disease polygenic risk scores may be considered for stratifying the risk of ASCVD in patients with HeFH, but their value in patient care remains to be established.	3	B

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Risk Stratification

Clinical Recommendations	Class	Level
4. Additional factors particularly relevant to FH that should be assessed to stratify risk include plasma or serum concentrations of LDL-cholesterol and lipoprotein(a) at diagnosis, LDL-cholesterol life-years, family history of premature ASCVD (especially in first-degree relatives), tendon xanthomas (detected clinically or with imaging) and a positive genetic test result if available.	1	A
5. Female-specific factors (such as reproductive history, duration off statin therapy owing to pregnancy and breast feeding, and age at menopause) should be considered when assessing the risk of ASCVD in women with FH.	2	B

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Risk Stratification

Clinical Recommendations	Class	Level
6. Use of FH-specific cardiovascular risk calculators (such as the SAFEHEART risk equation and the FH Risk Score) should be considered to assess the risk of ASCVD in adult patients with an established diagnosis of HeFH.	2	B
7. Cardiovascular risk calculators developed for the general population (such as the Framingham Risk Score, Pooled Cohort Equation, SCORE-2 or QRISK-3) should not be used in patients with FH.	1	B
8. In asymptomatic adult patients with HeFH, CACS, CT coronary angiography and carotid ultrasonography may be considered to document the presence and extent of atherosclerotic plaque burden and to guide risk assessment, the timing of initial evaluation being dependent on clinical context and indications.	3	B

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Risk Stratification

Clinical Recommendations	Class	Level
9. Use of FH-specific cardiovascular risk calculators combined with CACS should be considered to risk stratify adult patients with FH treated with Statins.	2	B
10. In children and adolescents with HeFH, measurement of carotid intima–media thickness with ultrasonography should not be routinely considered for assessing the risk of ASCVD in clinical practice, because extensive technical expertise is required and clinical value is not established.	2	B
11. In children and adolescents with HeFH, CACS, CT coronary angiography and current FH risk calculators (such as the SAFEHEART risk equation or FH Risk Score) should not be used to assess ASCVD risk.	1	C

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Risk Stratification

Clinical Recommendations	Class	Level
12. In all patients with HoFH, CT coronary angiography (or cardiac catheterization), carotid ultrasonography (or more advanced methods), echocardiography and exercise stress testing should be offered, at initial diagnosis and as clinically indicated (for example, because of cardiac symptoms or a high plaque burden at diagnosis), to assess coronary atherosclerosis (particularly high-risk coronary ostial disease), carotid plaques, atheromatous involvement of the aortic valve (or root), aortic stenosis and inducible myocardial ischaemia, respectively, with the aim of guiding overall management, including the intensity of the cholesterol-lowering therapy.	1	B

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Management – Treatment of Adults with HeFH

Treatment of Adults with HeFH

Clinical Recommendations	Class	Level
1. All patients should be offered advice on cardiovascular risk factors (including smoking, hypertension, obesity, metabolic syndrome and diabetes mellitus) and counselled on lifestyle modifications (a fat-modified, heart-healthy diet, regular physical exercise, reduction in psychological stress, moderation in alcohol intake and sleep hygiene).	1	B
2. In patients whose treatment is stable, non-fasting lipid profiles should be used to monitor treatment, but when making decisions on changing treatment, a fasting LDL-cholesterol concentration should be used, especially in patients with concomitant hypertriglyceridaemia.	1	B

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Treatment of Adults with HeFH

Clinical Recommendations	Class	Level
3. After approximately 50% reduction in LDL-cholesterol concentration, the following treatment goals should be considered according to the level of ASCVD risk:	2	B
(a) LDL-cholesterol concentration < 2.5 mmol/l (<100 mg/dl) in the absence of ASCVD or other major ASCVD risk factors; (b) LDL-cholesterol concentration <1.8 mmol/l (<70 mg/dl) with imaging evidence of ASCVD alone or other major ASCVD risk factors and (c) LDL-cholesterol concentration <1.4 mmol/l (<55 mg/dl) with clinical ASCVD.		

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Treatment of Adults with HeFH

Clinical Recommendations	Class	Level
4. In patients with a recurrent ASCVD event within 2 years while taking maximally tolerated statin treatment, a lower LDL-cholesterol goal of <1.0 mmol/l (<40 mg/dl) may be considered.	3	C
5. Use of secondary treatment goals based on non-HDL-cholesterol and apolipoprotein B levels may be considered, particularly in patients with hypertriglyceridaemia.	3	C
6. Maximally tolerated high-potency statins (such as atorvastatin, rosuvastatin or pitavastatin) with or without ezetimibe and/or bempedoic acid (if available), and a fat-modified, heart-healthy diet should initially be used in most patients (for exception, see recommendation 9) to achieve LDL-cholesterol goals.	1	A

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Treatment of Adults with HeFH

Clinical Recommendations	Class	Level
7. If LDL-cholesterol goals are not achieved, plant sterols (stanols) or bile acid sequestrants (such as colesevelam) may be considered as adjunctive therapies.	3	B
8. PCSK9-targeted therapy (monoclonal antibodies or a small interfering RNA (inclisiran)) should be added if LDL-cholesterol goals are not achieved with diet, maximally tolerated statins, ezetimibe, bempedoic acid and other adjunctive therapies.	1	A
9. In patients with extremely high-risk HeFH (for example, after myocardial infarction or those with multivessel coronary atherosclerosis or polyvascular disease), the combination of a high-potency statin, ezetimibe and PCSK9-targeted therapy should be considered as first-line treatment.	2	B

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Treatment of Adults with HeFH

Clinical Recommendations	Class	Level
10. Plasma levels of hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting drug therapy. Plasma levels of hepatic aminotransferases should be monitored in patients taking statins (particularly with an increased risk of hepatoxicity related to a history of liver disease, excess alcohol or adverse drug interactions), and plasma levels of creatine kinase should be measured if musculoskeletal symptoms are reported; plasma levels of glucose or HbA1c should be monitored if there are risk factors for diabetes.	1	B

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Treatment of Adults with HeFH

Clinical Recommendations	Class	Level
11. Provided there are no bleeding contraindications, low-dose aspirin may be considered as a primary prevention measure in asymptomatic patients at higher risk of ASCVD (those with a marked elevation of lipoprotein(a) concentration, diabetes or adverse findings on cardiovascular imaging).	3	C
12. Cholesterol-lowering drug therapies and other anti-ASCVD treatments should be continued and optimized during acute illness (such as respiratory infections, including COVID-19), unless their use is specifically contraindicated, as with potential adverse drug interactions and abnormal liver function.	1	B

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Treatment of Adults with HeFH

Clinical Recommendations	Class	Level
13. Patients with cardiovascular sequelae of COVID-19 should be investigated, assessed and managed according to contemporary expert guidelines.	1	B
14. All adult patients, especially those with ASCVD, aged >65 years or at an increased risk of exposure, should be offered SARS-CoV-2, influenza, pneumococcal and other related vaccines as a preventive measure against respiratory infections and acute ASCVD events, in accordance with country-specific health policy.	1	C
15. Although CACS is useful in the initial risk assessment in asymptomatic patients before starting cholesterol-lowering medication, CACS should not be used to monitor the effectiveness of cholesterol-lowering treatment.	1	B

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Treatment of Adults with HeFH

Clinical Recommendations	Class	Level
16. In asymptomatic patients, imaging of ASCVD (for example, carotid ultrasonography and CT coronary angiography for the detection of plaques and stenoses) may be considered for monitoring the effectiveness of cholesterol-lowering treatment.	3	B

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Management – Treatment of Children and Adolescents with HeFH

Treatment of Children & Adolescents

Clinical Recommendations	Class	Level
1. At diagnosis, all patients should be offered counselling on following a heart-healthy, low saturated fat (<10% of total calories), high-fibre diet and correcting all other behavioural risk factors for ASCVD, particularly smoking, lack of exercise, obesity and psychological stress.	1	B
2. Pharmacological treatment should be offered at age 8–10 years with an LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on two occasions with a fasting lipid profile.	1	B
3. Pharmacological treatment should be considered for those aged 8–10 years with an LDL-cholesterol concentration >4.0 mmol/l (>160 mg/dl), recorded on two occasions with a fasting lipid profile, in the presence of multiple ASCVD risk factors or family history of premature ASCVD.	2	B

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Treatment of Children & Adolescents

Clinical Recommendations	Class	Level
4. Initiation of pharmacological treatment at age <8 years may also be considered with an LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on two occasions.	3	B
5. An LDL-cholesterol goal of <3.5 mmol/l (<135 mg/dl) or approximately 50% reduction may be considered in patients with no additional risk factors for ASCVD (for example, diabetes, hypertension, elevated lipoprotein(a) concentration or parental history of ASCVD in the second or third decade of life); non-fasting blood samples may be used to monitor LDL-cholesterol levels in those receiving stable therapy.	3	C
6. An LDL-cholesterol goal of <2.5 mmol/l (<100 mg/dl) may be considered in patients with additional risk factors for ASCVD.	3	C

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Treatment of Children & Adolescents

Clinical Recommendations	Class	Level
7. To achieve LDL-cholesterol treatment goals, the initial medication of choice should be a statin that is approved in the relevant country (or jurisdiction) for use in paediatric patients.	1	A
8. Other medications that should be considered, in addition to the maximal tolerated and safe dose of a statin, are ezetimibe and bile acid sequestrants.	2	B
9. Use of a PCSK9 inhibitor may be considered according to clinical indications and regulatory approvals, with the caveat of limited evidence of long-term safety in children and adolescents.	3	B
10. Plasma levels of liver enzymes, creatine kinase, glucose and creatinine should be measured before starting statin therapy; plasma levels of liver and muscle enzymes and glucose should be monitored as in adults.	1	B

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Treatment of Children & Adolescents

Clinical Recommendations	Class	Level
11. Growth and adherence to lifestyle management and LDL-cholesterol-lowering medication should be monitored annually or as clinically indicated.	1	A
12. Adolescent girls should be offered advice on the basis of current recommendations regarding contraception and the use of lipid-lowering medications in pregnancy.	1	B

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Management – Treatment of Patients with HoFH

Treatment of Patients with HoFH

Clinical Recommendations	Class	Level
1. Treatment of patients with HoFH should begin at diagnosis and ideally by the age of 2 years, with counselling on heart-healthy lifestyles, psychological support for the family and LDL-cholesterol-lowering medications.	1	B
2. The following treatment goals should be considered:	2	B
(a) LDL-cholesterol concentration <2.5 mmol/l (<100 mg/dl) in the absence of ASCVD or other major risk factors for ASCVD; (b) LDL-cholesterol concentration <1.8 mmol/l (<70 mg/dl) with imaging evidence of ASCVD alone or additional major risk factors for ASCVD; (c) (c) LDL-cholesterol concentration <1.4 mmol/l (<55 mg/dl) with a previous ASCVD event; fasting and non-fasting blood measurements of LDL-cholesterol concentrations could be used as recommended for patients with HeFH.		

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Treatment of Patients with HoFH

Clinical Recommendations	Class	Level
3. To achieve LDL-cholesterol goals, all currently approved medications (such as high-potency statin, ezetimibe and colesevelam) should be used; medications should be used sequentially, starting with a statin with rapid up-titration to maximally tolerated and approved doses, followed within 8 weeks by the addition of ezetimibe and possibly colesevelam if tolerated.	1	B
4. A PCSK9 inhibitor should be added within a further 8 weeks in patients without biallelic LDLR null mutations and continued only after demonstration of an acceptable response (≥15% additional reduction in LDL-cholesterol concentration).	1	B

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Treatment of Patients with HoFH

Clinical Recommendations	Class	Level
5. In the highest-risk patients (for example, those with symptomatic ASCVD or multivessel coronary atherosclerosis), the combination of a high-potency statin, ezetimibe and PCSK9-targeted therapy should be strongly considered as first-line treatment.	2	B
6. Lipoprotein apheresis should be offered, if feasible, at the age of 3 years (and no later than 8 years) when LDL-cholesterol goals are not achieved with a maximally tolerated regimen of cholesterol-lowering medications.	1	A

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Treatment of Patients with HoFH

Clinical Recommendations	Class	Level
7. In patients with markedly elevated LDL-cholesterol concentrations when receiving conventional therapy or with rapidly progressive ASCVD, the use of lomitapide (a microsomal triglyceride transfer protein inhibitor) or evinacumab (an angiopoietin-related protein 3 inhibitor) should be considered, adjunctive to diet and conventional drugs, to lower the LDL-cholesterol concentration further, especially if lipoprotein apheresis is not available or feasible.	2	B
8. In patients with rapidly progressive ASCVD, the use of evinacumab may be considered, adjunctive to diet, conventional cholesterol-lowering drugs and lomitapide, to lower the LDL-cholesterol concentration further, especially if lipoprotein apheresis is not available or feasible.	3	C

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Treatment of Patients with HoFH

Clinical Recommendations	Class	Level
9. CT coronary angiography, carotid ultrasonography, echocardiography (including measurement of aortic valve gradients) and exercise stress testing should be used, as clinically indicated, to assess the severity and progression of ASCVD, aortic valve (or root) atheromatous involvement and inducible myocardial ischaemia, as well as to guide overall management and the intensity of LDL-cholesterol lowering treatment.	1	B

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Treatment of Patients with HoFH

Clinical Recommendations	Class	Level
10. Recommendations made for the management of HeFH should be followed concerning control of behavioural and non-cholesterol cardiovascular risk factors, blood sampling to monitor cholesterol-lowering therapy, use of aspirin, treatment of FH during acute illness, use of vaccinations (including for SARS-CoV-2), treatment of cardiovascular sequelae of COVID-19, blood testing protocol for monitoring drug safety and potential toxicities, assessment of growth in children and pre-pregnancy counselling of adolescent girls.	1	*

**Refer to levels of evidence for patients with HeFH pertaining to each of the items listed in this recommendation.*

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Treatment of Patients with HoFH

Clinical Recommendations	Class	Level
11. Liver transplantation should be considered in patients with HoFH and rapidly progressive ASCVD who do not attain guideline-recommended LDL-cholesterol goals when receiving all available treatment, including lipoprotein apheresis (or who cannot tolerate lipoprotein apheresis or do not have access to suitable lipoprotein apheresis services), and are considered psychologically suitable for this treatment; combined liver and heart transplantation from a single donor should also be considered in the most severely affected patients.	2	B

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Treatment of Patients with HoFH

Clinical Recommendations	Class	Level
12. Liver transplantation may be considered in patients with HoFH and minimal or stable ASCVD who do not attain an LDL-cholesterol goal of <10 mmol/l (<400 mg/dl) when receiving all available LDL-cholesterol-lowering treatments; this situation will typically apply to children and young adults with severe biallelic null variants in *LDLR*.	3	C

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Management – Treatment of FH During Pregnancy

Treatment of FH During Pregnancy

Clinical Recommendations	Class	Level
1. All women with FH who are of child-bearing age, including adolescents, should be educated about the risks of pregnancy; advice on safer and preferred methods of contraception, with minimal cardiovascular risk, and the importance of contraception should be reinforced to prevent unplanned pregnancy.	1	B
2. Reinforcement and optimization of heart-healthy behaviours, including diet, physical activity and psychological well-being, should be prioritized before, during and after pregnancy and breastfeeding.	1	B

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Treatment of FH During Pregnancy

Clinical Recommendations	Class	Level
3. Pre-pregnancy counselling should be offered to all women before starting a statin, ezetimibe, PCSK9 inhibitor or other lipid-modifying therapies, and this advice should be reinforced as clinically indicated.	1	B
4. Assessment of ASCVD using imaging (for example, CT angiography for coronary artery disease or echocardiography for aortic stenosis) should be offered to women with HoFH or high-risk HeFH before a planned pregnancy.	1	B
5. Given that LDL-cholesterol and triglyceride concentrations increase during pregnancy, assessment of plasma lipids and lipoprotein levels should not routinely be considered, unless the results will be used to change management, as in women with HoFH.	2	B

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Treatment of FH During Pregnancy

Clinical Recommendations	Class	Level
6. Bile acid sequestrants should be considered to treat hypercholesterolaemia, ideally 3 months before a planned pregnancy, as well as during pregnancy and lactation; routine monitoring for malabsorption of fat-soluble vitamins (particularly vitamin K with an international normalized ratio) and folate should also be considered	2	B
7. Statins and other systemically absorbed cholesterol-lowering drugs should ideally be discontinued 3 months before planned conception and during pregnancy and lactation. If a woman with FH becomes pregnant while taking a statin, ezetimibe, a PCSK9 inhibitor or other lipid-modifying therapies, this treatment should be stopped, and she should be reassured that this therapy is unlikely to harm the foetus	1	B

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Treatment of FH During Pregnancy

Clinical Recommendations	Class	Level
8. In women with HoFH and clinical ASCVD, the continued use of statin therapy should be considered; use of statins, ezetimibe, PCSK9 monoclonal antibodies or other lipid-modifying therapies should particularly be considered after the first trimester, especially if the LDL-cholesterol goal is not achieved and lipoprotein apheresis is not available or feasible.	2	B
9. Lipoprotein apheresis should be continued or initiated during pregnancy in women with HoFH, especially in those with established ASCVD and in whom LDL-cholesterol levels are not at guideline-recommended goal; similar advice applies to women with severe HeFH, including those with a lipoprotein(a) concentration ≥ 125 nmol/l (≥60 mg/dl).	1	B

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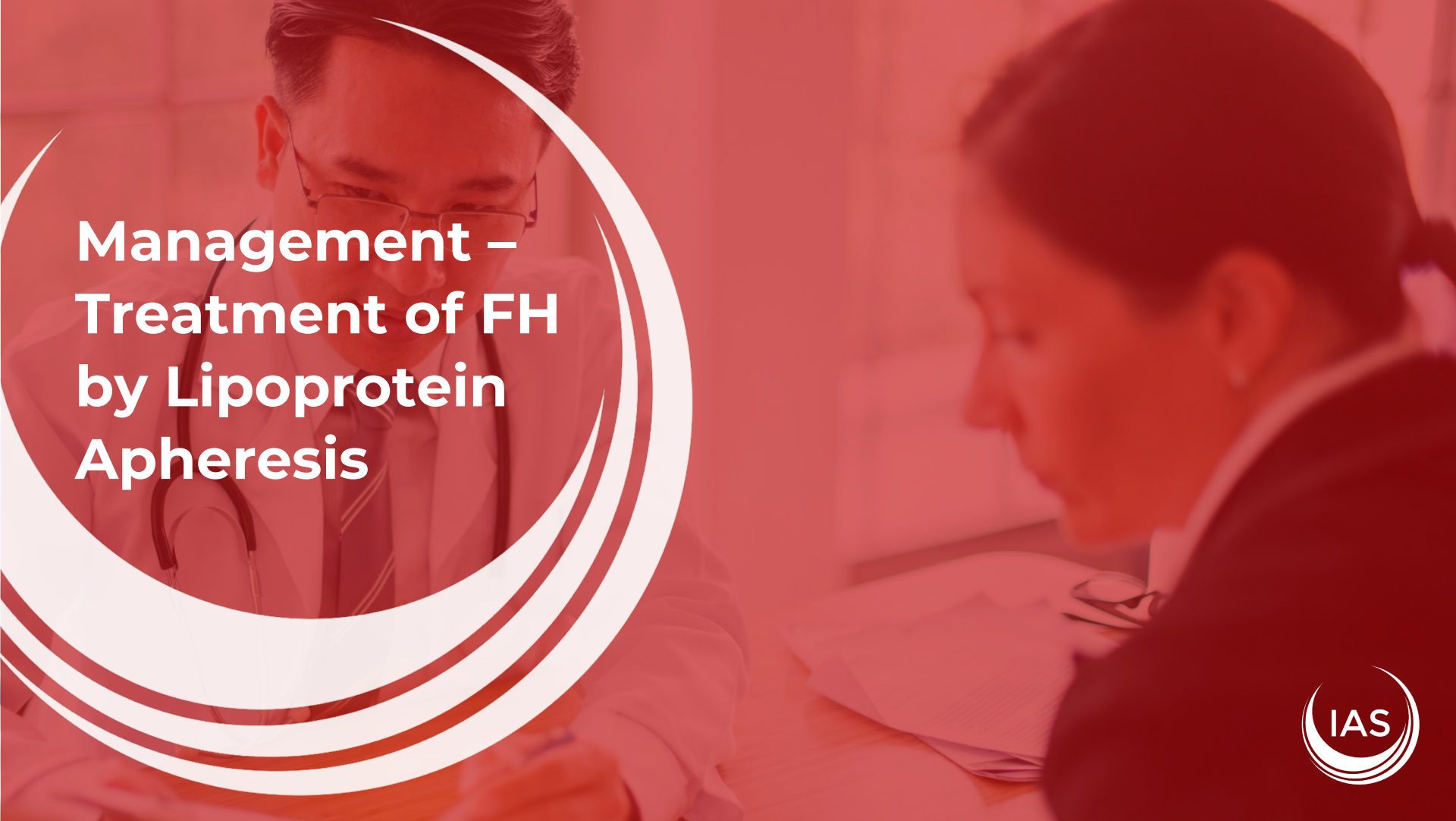
Management – Treatment of FH by Lipoprotein Apheresis



Lipoprotein Apheresis

Clinical Recommendations	Class	Level
1. Lipoprotein apheresis should be undertaken, if feasible, in children (aged ≥3 years and <8 years) and adults with HoFH who do not achieve guideline-recommended LDL-cholesterol goals, despite maximally tolerated, combination drug therapy.	1	A
2. Lipoprotein apheresis should be undertaken in adults with phenotypic HeFH and progressive ASCVD who do not achieve LDL-cholesterol goals despite combined treatment with a high-potency statin, ezetimibe and a PCSK9 inhibitor, especially those with a lipoprotein(a) concentration ≥125 nmol/l (≥60 mg/dl).	1	B

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Lipoprotein Apheresis

Clinical Recommendations	Class	Level
3. Vascular access for lipoprotein apheresis should initially be via peripheral veins, but an arteriovenous fistula may be needed if peripheral venous access becomes impossible, which may be particularly relevant to children. Central venous catheters are not recommended except in an emergency or as a temporary measure.	1	B
4. Onefold to twofold plasma volumes (body weight in kg × 0.045 l) or blood volumes [plasma volume/(1 − haematocrit)] should be treated weekly or fortnightly in a specialized setting (a lipid clinic, nephrology unit or blood transfusion centre). Plasma exchange requires a smaller extracorporeal blood volume than lipoprotein apheresis and is recommended as an alternative in children with a body weight <30 kg.	1	A

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Lipoprotein Apheresis

Clinical Recommendations	Class	Level
5. All diet and drug therapy to lower LDL-cholesterol concentrations should be continued during treatment with lipoprotein apheresis, and comprehensive psychosocial support should be offered to all patients receiving lipoprotein apheresis.	1	A
6. Routine full blood counts should be monitored regularly, and iron supplementation initiated if iron-deficiency anaemia develops in patients with FH receiving long-term lipoprotein apheresis.	1	A
7. Angiotensin-converting enzyme inhibitors should not be used in patients undergoing lipoprotein apheresis based on apolipoprotein B adsorption, and angiotensin-receptor blocking agents should be substituted.	1	A

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Lipoprotein Apheresis

Clinical Recommendations	Class	Level
8. Patients receiving anticoagulants, such as warfarin, will require dose adjustment or discontinuation several days before an apheresis procedure that uses intravenous heparin, but antiplatelet therapy should be maintained. Direct oral anticoagulants (such as apixaban, dabigatran or rivaroxaban) need only be stopped on the day of apheresis because of their shorter half-life.	1	B

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Lipoprotein Apheresis

Clinical Recommendations	Class	Level
9. The cholesterol-lowering efficacy of lipoprotein apheresis should be monitored by measuring acute reductions in LDL-cholesterol and lipoprotein(a) concentrations (ideally 65–70%) and by calculating the interval mean (C_{mean}) between consecutive procedures, using the Kroon formula: $C_{mean} = C_{min} + k(C_{max} – C_{min})$, for which C_{max} is the pre-procedure value and C_{min} is the post-procedure value. Values for k are 0.65 for LDL-cholesterol in patients with HoFH and 0.71 for LDL-cholesterol in patients with HeFH receiving statin therapy and undergoing lipoprotein apheresis at fortnightly intervals. Comparison of interval means with the recommended LDL-cholesterol goals for patients with HoFH should be used to adjust the volume of blood or plasma to be treated and/or the frequency of lipoprotein apheresis procedures as necessary.	1	B

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Lipoprotein Apheresis

Clinical Recommendations	Class	Level
10. Because the rate of rebound of plasma lipoprotein(a) levels after lipoprotein apheresis is similar to that of plasma LDL-cholesterol levels in patients with HeFH, a value for k of 0.71 in the Kroon formula should be considered appropriate when estimating the interval (intercycle) mean concentration of lipoprotein(a); this value may be used to adjust the lipoprotein apheresis regimen to achieve a therapeutic goal of <90 nmol/l (<43 mg/dl) in patients with elevated lipoprotein(a) concentrations.	2	B

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Lipoprotein Apheresis

Clinical Recommendations	Class	Level
11. In children and adults with HoFH and aortic root or coronary artery disease, the effect of lipoprotein apheresis on disease progression should be monitored at least annually by echocardiography or coronary angiography, respectively. The latter procedure is also applicable to patients with HeFH with coronary disease and should be performed as and when indicated.	1	B
12. Adjunctive therapy with a PCSK9 inhibitor, either evolocumab or alirocumab, should be attempted in all patients with FH before starting or while receiving lipoprotein apheresis. These therapies will be effective mainly in patients with HeFH and often may replace lipoprotein apheresis. Injected therapeutic agents should be administered soon after, but not immediately before, a lipoprotein apheresis procedure.	1	B

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Lipoprotein Apheresis

Clinical Recommendations	Class	Level
13. Adjunctive therapy with lomitapide or evinacumab should be considered in patients with HoFH, particularly in those with progressive ASCVD, who do not reach guideline-recommended LDL-cholesterol goals while receiving lipoprotein apheresis combined with statin, ezetimibe and a PCSK9 inhibitor. This adjunctive therapy increases LDL-cholesterol lowering and may reduce the frequency of lipoprotein apheresis and, if tolerated, sometimes replaces it.	2	B
14. When lomitapide or evinacumab is first selected in preference to lipoprotein apheresis, adjunctive use of lipoprotein apheresis should be considered in all patients with HoFH who do not reach guideline-recommended LDL-cholesterol goals.	2	B

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Part II: Implementation Recommendations

Implementation Science and Process

Selection of Implementation Recommendations
1. Define the evidence-based practice or intervention.
2. Choose an implementation theory, model or framework.
3. Assess determinants, barriers, enablers and context in respect of the practice or intervention.
4. Select implementation strategies.
5. Select options for assessing the outcomes of implementation.

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Implementation Recommendations

- Implementation recommendations were developed by consensus, based on relevant published works, and were guided by a framework provided by the Expert Recommendations for Implementing Change (ERIC)

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Expert Recommendations for Implementing Change

Use evaluative and iterative strategies	• Assess for readiness and identify barriers and facilitators • Audit and provide feedback • Purposefully reexamine the implementation
Adapt and tailor to context	• Tailor strategies • Promote adaptability • Use data experts
Train and educate stakeholders	• Conduct ongoing training • Distribute educational material • Use train-the-trainer techniques
Engage consumers	• Increase demand • Use mass media • Involve patients/consumers and family members
Change infrastructure	• Mandate change • Change record systems • Change physical structure and equipment

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Powell, B. J. *et al.* A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. *Implement. Sci.* **10**, 21, doi:10.1186/s13012-015-0209-1 (2015).

Expert Recommendations for Implementing Change

Provide interactive assistance	• Facilitation • Provide local technical assistance • Provide clinical supervision
Develop stakeholder interrelationships	• Identify and prepare champions • Organize clinician implementation team meetings • Identify early adopters
Support clinicians	• Remind clinicians • Revise professional roles • Facilitate relay of clinical data to providers
Utilize financial strategies	• Alter incentive/allowance structures • Access new funding • Fund and contract for the clinical innovation

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Implementation of Screening for FH

Screening for FH

Implementation Recommendations - General Screening
1. Detection and diagnosis of index cases in the community should ideally use an integrated, patient-centred approach, underpinned by a multidisciplinary strategy involving community and paediatric physicians, obstetric physicians and gynaecologists, nurses and counsellors.
2. Screening and detection strategies should ideally be centrally coordinated, enabling testing by all designated requestors, such as specialist practitioners and genetic counsellors, and linked to a clinical quality registry, particularly when undertaking cascade testing of family members.
3. In countries or regions with limited resources, a skilled healthcare professional may lead and coordinate screening and diagnostic strategies, preferably in consultation with a specialist centre and with appropriate training in the care of FH.

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Screening for FH

Implementation Recommendations - General Screening
4. Digital technologies should be used to search electronic health records to enable systematic detection of index cases, particularly in the community care setting.
5. All health-care professionals involved in screening and documentation of the outcome of testing for FH should be adequately trained and fully aware of the local guidance on data protection; this training is particularly important in cascade testing of family members.

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Screening for FH

Implementation Recommendations - Opportunistic Screening

6. Opportunistic detection of FH with LDL-cholesterol testing should be performed by dermatologists (for example, on a lipid profile before commencing isotretinoin), rheumatologists and orthopaedic surgeons (for example, for patients having Achilles xanthomas and tenosynovitis), ophthalmologists and optometrists (for example, for patients having premature arcus cornealis, xanthelasma palpebrarum or planar xanthomas), occupational physicians (for example, workplace wellness programmes) and pharmacists (for example, point-of-care testing with a history that is suggestive of FH).

7. Alerts and interpretive comments on laboratory reports of standard lipid profiles should be used to enable case detection, emphasizing the need to make a formal diagnosis and referral for further assessment of FH.

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Screening for FH

Implementation Recommendations - Universal Screening
8. Universal screening for FH should be integrated into routine population health surveillance strategies (for example, health checks in adults and community health screening programmes) and prevention procedures (for example, immunization in children).
9. Genetic testing may be considered, if feasible and potentially implementable, for population screening for FH, provided that testing also includes other actionable Centers for Disease Control Tier 1 genetic conditions; the programme should also be equitable, cost-effective and integrated into a well-structured, risk-reduction model of care for FH.
10. Patient support and professional organizations should strongly advocate for health policy to implement universal screening of FH in paediatric populations; this screening is particularly relevant to the early detection of HoFH.

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Implementation of Making a Diagnosis of FH

Diagnosis of FH

Implementation Recommendations

1. Cost-effective pathways for making a diagnosis of FH, including referrals to specialists, should be seamlessly integrated with all screening strategies for FH.

2. The diagnosis of FH in children and adolescents should ideally be made by a paediatrician with training and expertise in lipidology, and with attention to assessing the psychological effect of the diagnosis on the family and need to follow regulations on child protection (safeguarding); in those who have difficulty fasting, a non-fasting blood sample may be considered to make a clinical diagnosis.

3. All patients diagnosed with HoFH should be referred to a specialist centre for further physical and psychological assessment and careful planning of care.

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Diagnosis of FH

Implementation Recommendations
4. Whenever possible, all index patients with a phenotypic diagnosis of FH should be offered genetic testing, especially if cascade testing is planned.
5. All health-care professionals involved in making a diagnosis of FH should be aware of the local guidance on data protection.

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Implementation of Genetic Testing and Counselling

Genetic Testing and Counselling

Implementation Recommendations

1. Eligible patients should be referred to a specialized clinic or centre that offers genetic testing and supporting services; direct-to-consumer genetic tests are not recommended or appropriate for clinical use in making a diagnosis of FH.

2. A standardized process for obtaining informed consent for genetic testing should be used, ensuring:

a. Informed consent considers literacy and level of comprehension and sociocultural and psychological background of the patient, includes a lay explanation of risk, addresses the possible impact of either a positive or negative result and allows the patient to withdraw consent.
b. Modifications to the process for paediatric patients, specifying appropriate assent be given by a custodial parent or guardian.

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Genetic Testing and Counselling

Implementation Recommendations

3. Sample collection, testing, analyses and reporting of findings should use a standardized process, as follows:

a. Standardize collection procedures for blood and/or saliva samples.
b. Carry out testing using a centralized service in a fully accredited laboratory.
c. Apply validated bioinformatics to interpret results of genetic testing and establish a process to manage variants of uncertain significance.
d. Use a standardized reporting format, with the option of providing both a hard and an electronic copy of results to the patient.

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Genetic Testing and Counselling

Implementation Recommendations

4. Return of genetic test results to patients should follow a standardized process, as follows:

a. First assess overall literacy and understanding and then clarify objectives and expectations before discussing results with the patient.
b. Tailor disclosure of results to the level of comprehension of the patient.
c. Gauge patient attitudes towards benefits and threats, consider sociocultural and psychological factors and recognize their intentions for the future.
d. Communicate in everyday, jargon-free language and provide written and/or pictorial information according to the level of comprehension of the individual.
e. Restrict reporting of variants in general to those with clear pathogenic or likely pathogenic impact; refrain from reporting results based on benign variants or common polymorphisms.
f. Variants of uncertain significance may be reported, conditional on communication of the result and its implications to the patient being undertaken by a genetic counsellor, or a clinician with expertise in genetics.

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Genetic Testing and Counselling

Implementation Recommendations

5. Follow-up and re-assessment of genetic test results should involve the following:

a. Establish a process for patient follow-up regarding questions or concerns that may arise at a later time.
b. Assess subsequent changes in attitudes, behaviour and adherence to treatment advice of patients.
c. Carry out regular performance audits to improve the quality of genetic services.
d. Re-interpret genetic findings regularly, as a collaboration between the issuing laboratory and a clinician with expertise in genetics, accounting for new phenotypic findings in the patient and family and for evolving research knowledge.

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Genetic Testing and Counselling

Implementation Recommendations

6. Diagnostic genetic testing of index cases with suspected FH should be requested by a specialist clinician skilled in counselling, genomic medicine and the care of patients and families with FH. Where indicated (for example, rural centres and remote regions), diagnostic genetic testing of index cases may be requested by a general practitioner guided closely by a specialist clinician.

7. Referral to a professional genetic counselling service should be considered, whenever feasible, to optimize the counselling process for all patients and families at risk of FH.

8. Genetic test results (positive, negative or indeterminate) should be disclosed by an appropriate health-care provider, such as a skilled and experienced clinician, including a family doctor, or certified genetic counsellor.

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Genetic Testing and Counselling

Implementation Recommendations

9. Simple and pragmatic tools for counselling, consenting and disclosure of genetic information should be developed and tested to support health-care professionals in providing genetic testing.

10. Cascade testing of family members should be based on shared decision-making and a fully informed consenting process; results should be communicated in a timely manner, with appropriate risk communication and counselling offered.

11. Cascade testing should ideally be centrally coordinated by a well-resourced, dedicated centre. Cascade testing may be undertaken by a general practitioner with skills in the care of patients and families with FH, under the guidance of an appropriate specialist. The organization of cascade testing may vary according to differences in health policies across and within countries at national, state and regional levels.

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Genetic Testing and Counselling

Implementation Recommendations
12. Direct notification of at-risk relatives regarding their risk of FH should generally be undertaken (or pursued) only with authorization from the proband or index case.
13. Probands and index cases with FH should be offered tools and resources by their health-care providers to assist them in communication about the risk of FH with their relatives.
14. Digital technologies (such as chatbots and social media) should be used, with due consideration to safety and privacy issues, to increase the reach, adoption and effectiveness of family communication about FH and cascade testing of families.
15. Novel family communication tools and programmes (such as technology including secure web portals, chatbots and direct contact by a clinician) should be tested for acceptability, feasibility and effectiveness before implementation.

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Genetic Testing and Counselling

Implementation Recommendations

16. The process of risk notification of at-risk relatives should comply with local legislation and institutional guidelines; risk notification may be indirect (such as providing a family letter for the notifier to share with relatives) or direct (such as the clinical service directly contacting relatives after receiving consent or authorization from the proband or index case).

17. At-risk relatives should be notified directly without authorization from the proband or index case only if there is specific legislative provision for breach of confidentiality; this legislative provision may vary between countries.

Implementation of Risk Stratification

Risk Stratification

Implementation Recommendations
1. Risk assessment and stratification strategies should be used to triage patients for referral to other services involved in the multidisciplinary care of FH (such as apheresis; general practice support; specialty care in paediatrics, cardiology or diabetes and nicotine cessation programmes).
2. Clear and salient information in written, diagrammatic and electronic format that recognizes cultural, psychological, language and health literacy barriers should be designed and used, together with shared decision-making, to communicate the outcome of risk assessment and stratification, with the aim of developing personalized treatment plans; recognition of patient-reported experience measures and provision of psychosocial and social support are particularly important.

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Risk Stratification

Implementation Recommendations
3. Digital health technologies and decision support systems should be used to facilitate all risk assessment strategies (such as the use of FH risk equations or ASCVD imaging) and the corresponding capabilities and capacity of the workforce caring for patients; telehealth services with adequate facilities should be used to support the risk assessment of patients in rural and remote regions.
4. All registries should include comprehensive, high-quality data on ASCVD risk, including assessments using validated risk equations and cardiovascular imaging, linked to patient outcomes and used to improve the cost–effectiveness of models of care for FH.

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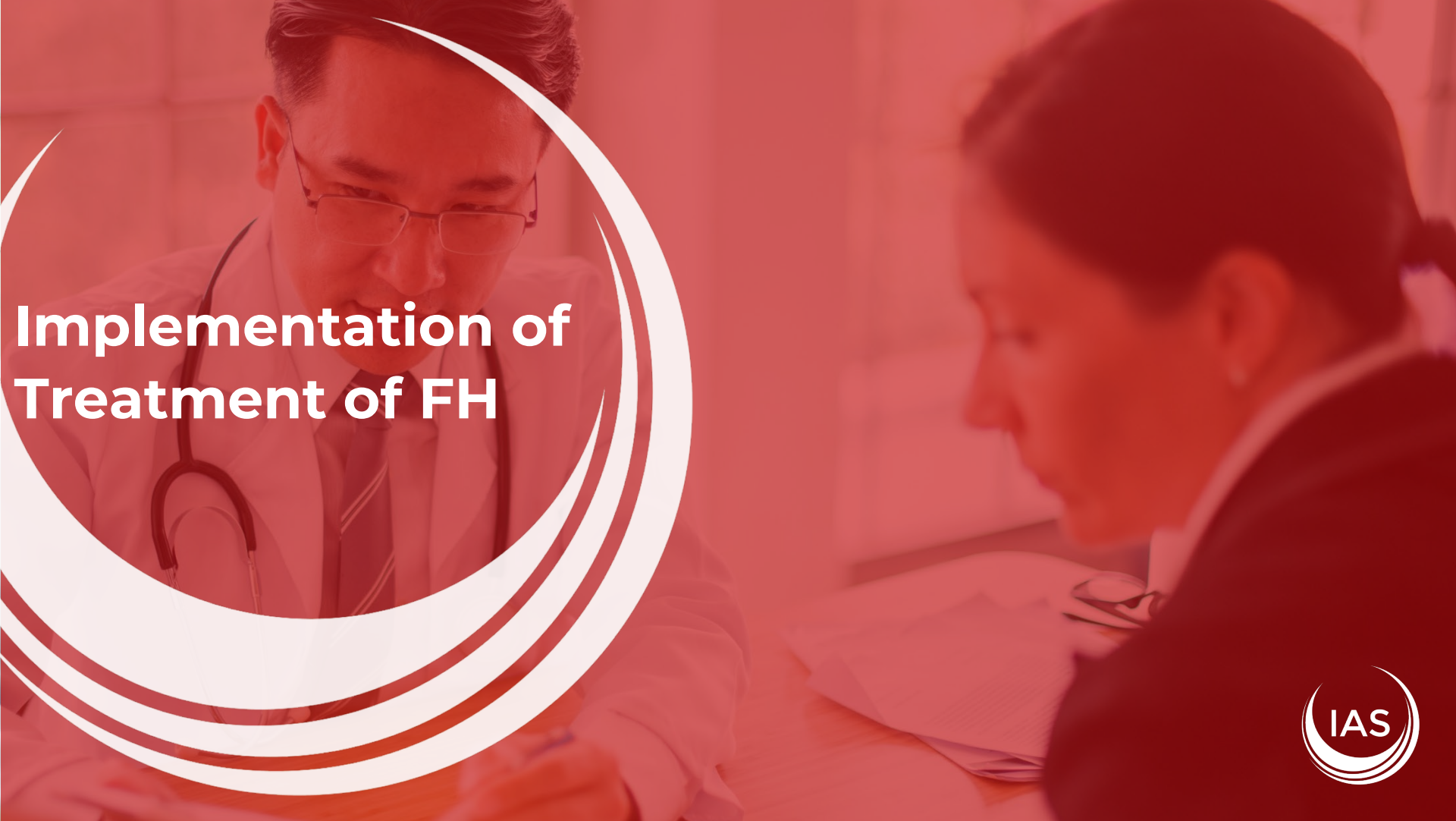
Implementation of Treatment of FH



Treatment of Patients with FH

Implementation Recommendations
1. A personalized treatment plan should be developed for all patients using shared decision-making, considering age, additional risk factors for ASCVD, psychological and sociocultural factors, economic status, barriers to adherence, and personal and family values and preferences.
2. Clear and salient information (in written, diagrammatic and electronic format) that addresses age-related, sociocultural, psychological, language and health literacy barriers should be designed and used to develop personalized treatment plans.
3. Personalized treatment plans for children and adolescents should be designed on the basis of shared decision-making with parents and, in the case of adolescents, using a developmentally appropriate approach.

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Treatment of Patients with FH

Implementation Recommendations
4. Care pathways should be clearly defined between general practice and paediatric centres: well-controlled and lower-complexity patients should be managed in general practice; less well-controlled (such as those who are not achieving LDL-cholesterol goals or who have several cardiovascular risk factors) and higher-complexity patients (such as those with HoFH) should be managed in specialist centres, with the option of shared care with general practice.
5. Children and adolescents with HoFH should ideally be managed by a multidisciplinary team in centres with paediatric expertise in lipidology, cardiology and apheresis.
6. Management of children and adolescents should ideally focus on the nuclear or immediate family, with (at a minimum) annual reviews in general practice and/or paediatric services to assess well-being, mental health issues, the safety of medication and adherence to therapy.

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Treatment of Patients with FH

Implementation Recommendations

7. Transition of care of adolescents to adult services should be planned well in advance, and support should be given to facilitate and sustain self-management and involvement in shared management into adulthood.

8. Before prescribing medication and other interventions in children or adolescents with FH, clinicians should engage in a patient-centred and family-centred discussion that uses shared decision-making and covers risk stratification, expected ASCVD risk-reduction benefit, potential adverse effects and drug interactions, sociocultural and economic factors, and values and preferences. At subsequent reviews, clinicians should use, as clinically indicated, a behavioural counselling approach (such as the 5A model of assess, advise, agree, assist and arrange) to address and promote adherence to medication and other treatments.

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Treatment of Patients with FH

Implementation Recommendations
9. Multifactorial barriers (for example, those related to patients, clinicians, drugs, health-care systems and sociocultural, psychological and financial circumstances) to medication adherence in adult patients with FH should be systematically identified and addressed using appropriate resources by all health service providers; this approach should extend beyond medical care to include a more holistic approach for meeting the emotional, psychological and self-management needs of patients.
10. Clinicians, health systems and health-care plans should identify patients who are not receiving guideline-directed medical therapy and facilitate the initiation of corresponding treatment using multifaceted strategies.

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Treatment of Patients with FH

Implementation Recommendations

11. Multiple interventions for improving adherence to medication should be used, with appropriate resources, for managing patients with FH; these interventions should include provision of free or subsidized medication, thereby ensuring affordability of established drugs and special access to new drugs; telephone, mobile text, e-mail and calendar reminders; use of single-pill combination drug therapies; expanded role of allied health-care provider interventions, such as simplified dosing by pharmacists and motivational counselling by skilled nurses and pharmacists, and comprehensive multidisciplinary education programmes; patient tools for improving knowledge and understanding of medication and self-care; decision support aids to empower patients and improve the patient-provider relationship; clinical decision support system-based interventions to improve the quality and safety of prescribing; and financial incentives and rewards for treatment goals attained. These strategies should be used in addition to adaptive, complex interventions shown to be effective in the care of other chronic conditions.

Treatment of Patients with FH

Implementation Recommendations

12. Iterative strategies, based on key performance indicators (such as adherence to treatment guidelines, attainment of therapeutic goals and patient-reported outcomes and experience measures, notably quality of life in patients with HoFH), should be used regularly or as clinically indicated. These approaches should ideally be part of an audit cycle every 12 months and aim to improve the reach, effectiveness, adoption, implementation and sustainability of service delivery. Multifaceted strategies should be used to improve implementation of treatments.

13. Services for FH should host regular multidisciplinary case discussions, provide local guidance on the best standards of treatment and develop strategies for implementing these recommendations.

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Treatment of Patients with FH

Implementation Recommendations

14. Paediatric and adult services for FH should participate in a national and international network of FH clinical centres to share educational, clinical and research experience and develop a comprehensive and high-quality registry of patients. Real-world registry data from these collaborations should be regularly used to assess the safety and effectiveness of conventional and new drug therapies, to advocate for policy change to close treatment gaps, to educate registrants and health-care providers, and to provide a resource of potential participants for clinical trials of new interventions.

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Treatment of Patients with FH

Implementation Recommendations

15. Multidisciplinary preoperative and postoperative care, with shared decision-making (involving patients and close relatives), should be prioritized in all management plans for patients with severe HoFH undergoing liver transplantation; as a fundamental principle of quality health care, this radical treatment should be undertaken only in highly experienced paediatric or adult liver transplantation centres.

16. The long-term cardiovascular and lipid outcomes and the complications of liver transplantation, as well as patient-reported outcome measures (including mental health issues), should be audited regularly and recorded in a dedicated registry, and this should be used to promote the best standard of care across all centres.

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Treatment of Patients with FH

Implementation Recommendations

17. The principles underpinning the concept of rare genetic (or intractable) diseases should be used to seek government funding for comprehensive care of all patients with HoFH, which may include developing a dedicated, specialist centre, as well as special access schemes for new therapies for all patients with HoFH.

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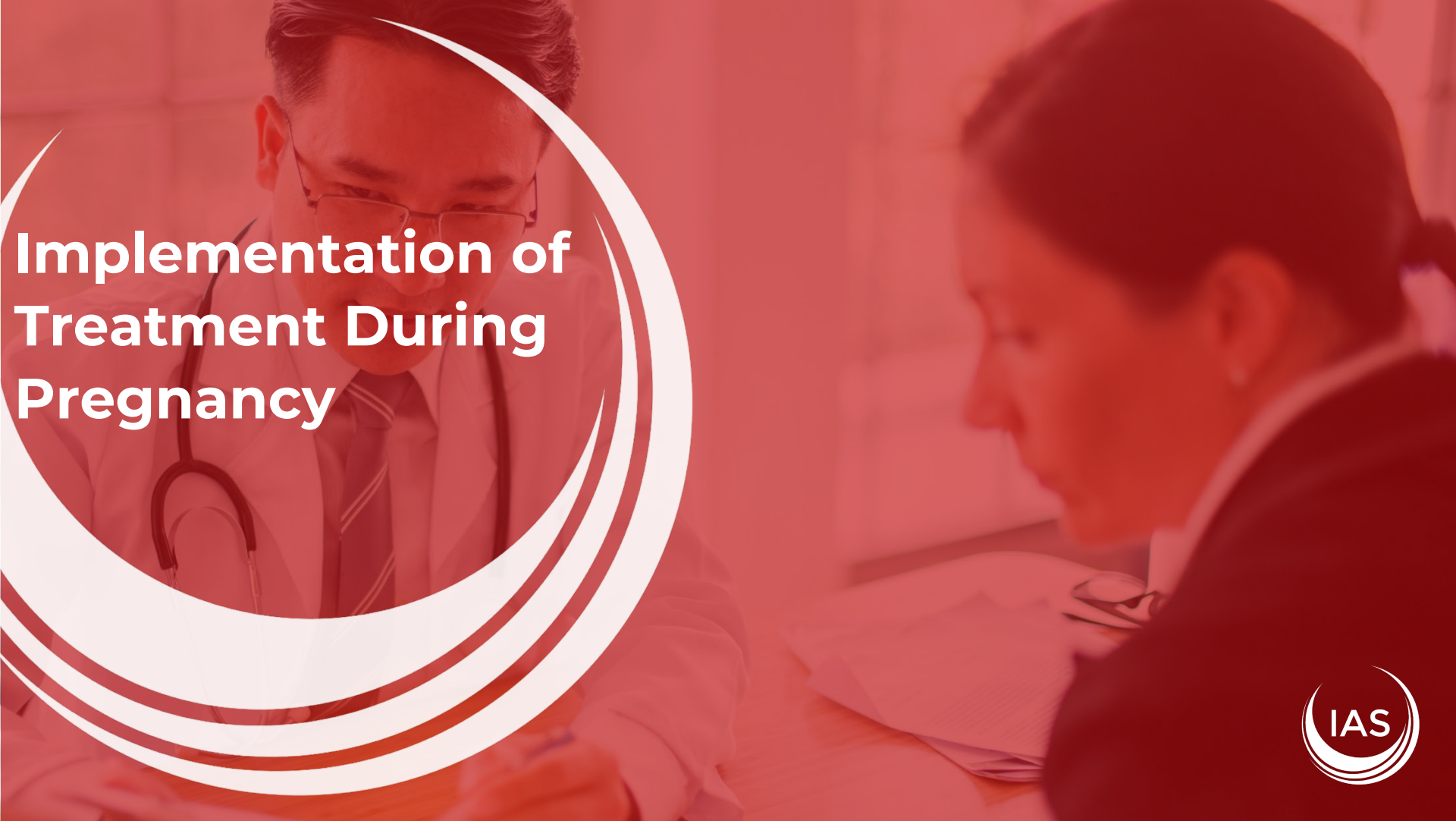

Implementation of Treatment During Pregnancy

Treatment of FH During Pregnancy

Implementation Recommendations

1. The care of pregnant women with FH should be designed to meet the needs of local, regional and remote communities; services should be multidisciplinary, involve the general practitioner of the patient, and ideally be coordinated by a clinician with expertise in FH and obstetric medicine.

2. All women with FH who are planning a pregnancy should ideally be referred for further advice to a specialist centre that provides a dedicated multidisciplinary service and holistic care. Such a service should include care of medical conditions (such as depression, hypertension and gestational diabetes) and counselling (such as psychological and mental health issues) and take account of sociocultural background and preferences and values of patients.

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Treatment of FH During Pregnancy

Implementation Recommendations
3. Clear and relevant information (in written, diagrammatic, pictorial and electronic formats) that addresses sociocultural, language and health literacy barriers should be designed and offered to women during pregnancy-related counselling sessions. This information should include shared decision-making, choice of contraception, importance of heart-healthy behaviours, risks of pregnancy, drug safety and teratogenicity, risk of ASCVD from cessation of drug therapy, and care during lactation.
4. Iterative strategies should be used, based on key performance clinical indicators, such as maternal-reported outcome and experience measures, fetal outcomes and quality of life of patients to improve the implementation of care.

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Treatment of FH During Pregnancy

Implementation Recommendations
5. Existing clinical resources (such as obstetric and gynaecological medicine, lipidology, dietetics, nursing, mental health care, family planning, genetic counselling, imaging facilities, cardiology and diabetes services) should be adapted to provide an integrated model of care for women with FH planning and undergoing pregnancy.
6. A clinical quality registry of pregnant women with FH, linked to patient-reported and experience measures, should be used to improve pregnancy and family care.

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Implementation of Lipoprotein Apheresis

Lipoprotein Apheresis

Implementation Recommendations
1. All patients being considered for lipoprotein apheresis should be assessed for physical and psychological suitability for treatment by a specialist with training in lipidology and experience in apheresis, supported by other specialists where indicated.
2. If lipoprotein apheresis is not available or feasible (for example, because of a lack of resources or in children with HoFH who have a small blood volume), the use of therapeutic plasma exchange (which is more widely available) should be considered as an alternative.
3. Facilities and resources for apheresis services should be regularly reviewed and cost analyses submitted to the relevant organization to obtain adequate financial support for the service.

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Lipoprotein Apheresis

Implementation Recommendations
4. Apheresis services should be designed to meet local needs and be centralized in a dedicated unit, headed by a director who should be the lead of a multidisciplinary team of accredited personnel.
5. Existing clinical infrastructure (for example, haemodialysis, transfusion medicine and vascular surgery services) should be adapted to improve the availability of lipoprotein apheresis and to increase the quality of the service.
6. Given the varied expertise required to provide a quality apheresis service, a coalition of specialties (including lipidology, cardiology, vascular surgery, paediatrics, mental health care, nephrology, transfusion medicine, pharmacy and nursing) should be established; this coalition should hold regular multidisciplinary case meetings, plan implementation strategies for improving service delivery and develop local guidance on the best evidence-based standard of care.

Lipoprotein Apheresis

Implementation Recommendations
7. Key performance indicators, such as the efficacy, tolerability and safety of lipoprotein apheresis, as well as the effect on patient-reported outcomes and experiences (including quality of life) should be reviewed as clinically indicated and as part of a regular audit cycle every 12 months.
8. Apheresis units should participate in a national or international network of similar centres to share educational, clinical and research experience and to establish and consolidate a comprehensive clinical quality registry of patients receiving treatment.

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General Strategies for Implementation of Care

Implementation of Care

General Implementation Recommendations
1. The design and implementation of health services for FH should deliver quality care that is patient-centred, safe, effective, efficient, equitable, well led and integrated, and sustainably resourced.
2. Care and support processes for FH should be widely based on evidence from public health and prevention and precision medicine; these should be adapted to local, regional and national needs, guided by contextual barriers and facilitators, and subjected to regular evaluation.
3. Implementation of improvements in the detection and care of FH should be underpinned by an integrated national cholesterol awareness campaign targeted at young people, high-risk individuals and all health-care professionals.

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Implementation of Care

General Implementation Recommendations

4. National and regional centres with expertise in lipidology, genetics and ASCVD prevention should be established to accept referrals and give advice, as indicated. All patients with suspected FH should be referred to, or discussed with, a relevant specialist to plan further management and care; a key priority is to establish specialized centres for managing patients with severe FH or HoFH.

5. General practice and primary care should be actively involved in the care of all individuals and families with FH and provide support for screening, diagnosing, managing cholesterol-lowering therapy and addressing comorbidities; regular review and evaluation of health and patient-reported outcomes data are essential.

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Implementation of Care

General Implementation Recommendations
6. A multidisciplinary team with expertise in caring for individuals with FH should partner with primary care and include representation from appropriate specialty disciplines, including mental health care.
7. Models of care should ideally consider the entire family as a patient unit. Appropriate strategies for paediatric patients to transition to adult care should be used.
8. Individuals with FH should be active participants in their care and work with their primary care and multidisciplinary team to discuss care pathways.
9. Patient-reported outcome and experience measures form the bedrock of value-based health care and should accordingly be used to improve implementation practice across the continuum of care for FH.

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Implementation of Care

General Implementation Recommendations
10. The implementation of all clinical recommendations for FH should account, as a priority, for the access to and the acceptability of health services for patients and families of diverse ancestries, including minority groups.
11. Health services should partner with academic and professional organizations and foundations to improve teaching, training and research.
12. When planning and designing treatment protocols across the continuum of care for FH, service providers should seek the collaboration of another clinical centre that provides excellence of care and arrange for relevant staff to visit and train there.

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Implementation of Care

General Implementation Recommendations

13. All health professionals involved in the care of individuals with FH, including those at the primary care level, should have appropriate accreditation, in addition to ongoing education, training and skills in lipidology, cardiovascular disease prevention, family communication, interpretation of test results, local guidance on data protection, and genomic medicine. Clinical practice guidelines for managing FH should be simplified to improve accessibility and use by all health-care professionals.

14. Digital technologies (telehealth, adherence applications and decision support systems in electronic health records) that target both patients and clinicians should be developed to improve the precision, accuracy and communication of the detection and management of FH.

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Implementation of Care

General Implementation Recommendations

15. Awareness, advocacy and educational campaigns including social media, website banner advertisements, billboards and/or celebrity endorsements should be conducted to increase public awareness of FH and the importance of genetic testing.

16. Advocacy and peer groups of patients, family members and other stakeholders should be established to support patients with FH and their care, particularly across different sociocultural communities, levels of health literacy and economic circumstances; advocacy for patients with HoFH is crucial for ensuring that health policy addresses all aspects of the care of this most severe form of FH.

17. Sustainable financing and sharing of existing resources should be used, enabled by key opinion leaders and stakeholder organizations, to deliver an impactful and cost-effective clinical service.

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Implementation of Care

General Implementation Recommendations
18. The national coding systems for FH should be used in primary and specialist care to improve the precision of data acquisition and linkage and their use for audit, research and development of health policy.
19. A national registry for FH should be established and used for linking patient outcomes, raising awareness, improving advocacy efforts and iteratively auditing key performance indicators, and for international collaborations for improving care.
20. Comprehensive research strategies and programmes, based on the core principles of implementation science, should be developed for evaluating and improving all models of care for FH. This process should focus on the acceptability, adoption, appropriateness, cost, feasibility, fidelity and sustainability of all interventions.

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Core Implementation Strategies

Screening for FH

Core Implementation Strategies

- Integrate screening strategies (selective, opportunistic and universal).
- Use a patient-centred and multidisciplinary approach, including general practice.
- Use digital technologies and search of electronic health records.
- Deploy alerts and comments on high LDL-cholesterol levels in laboratory reports.
- Train and upskill all health-care providers on screening methods.
- Identify referral pathways for expert evaluation, offering of genetic testing and risk-reduction treatment.
- Develop health-care policy and funding for integrated screening strategies.

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Genetic Testing and Counselling

Core Implementation Strategies

- Establish a centre for coordinating cascade testing and a peer-support group.
- Use standardized processes for consenting, testing and reporting of results.
- Ensure the genetic test requestor is skilled in counselling, genomics and FH.
- Use digital tools and practical resources to facilitate counselling and risk communication.
- Align testing processes with local legislation on privacy and data protection.
- Use shared decision-making and decision support tools to enable testing.
- Integrate with other screening strategies and link to local or national registry.

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Treatment of FH

Core Implementation Strategies

- Use risk-reduction strategies to triage patients and use cost effective therapies and resources.
- Establish networks of clinical centres to share experience and education; upskill all health-care providers.
- Use iterative strategies and key performance indicators to optimize risk-reduction pathways.
- Define multidisciplinary care pathways, transitional services for adolescents and dedicated services for family planning and women during pregnancy.

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Treatment of FH

Core Implementation Strategies

- Develop personalized treatment plans using shared decision making, with culturally appropriate clear information.
- Identify patients not receiving guideline-directed therapy and facilitate treatment using multifaceted strategies; use advocacy and peer support.
- Use multiple and evidence-informed interventions to improve adherence to medication.

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Lipoprotein Apheresis

Core Implementation Strategies

- Establish a centralized apheresis unit staffed by accredited personnel; use advocacy and peer-support groups.
- Assess suitability for treatment by a specialist; offer plasma exchange if lipoprotein apheresis is not available.
- Adapt existing infrastructure to widen the clinical availability of apheresis; meet local and regional needs of care.
- Establish regular multidisciplinary meetings involving a coalition of specialties that contribute to service delivery.

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Lipoprotein Apheresis

Core Implementation Strategies

- Use apheresis-specific key performance indicators and patient outcome and experience measures to iteratively improve services.
- Participate in networks to share educational, clinical and research experiences; establish a comprehensive clinical quality registry of patients.

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Implementation of Care

Core General Implementation Strategies

- Adapt and integrate models of care to local, regional and national needs; develop referral centres of expertise.
- Integrate general practitioners with multidisciplinary teams; train and accredit health-care providers in essential skills.
- Use shared decision-making for management and patient reported outcome and experience measures to improve services.
- Promote academic–service partnerships, share existing resources and ensure sustainable funding.

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Implementation of Care

Core General Implementation Strategies

- Establish a national cholesterol awareness campaign; use advocacy and peer-support groups to improve care.
- Use digital health technologies, registries and national coding systems to improve care.
- Promote implementation science; develop integrated healthcare systems and health policy.

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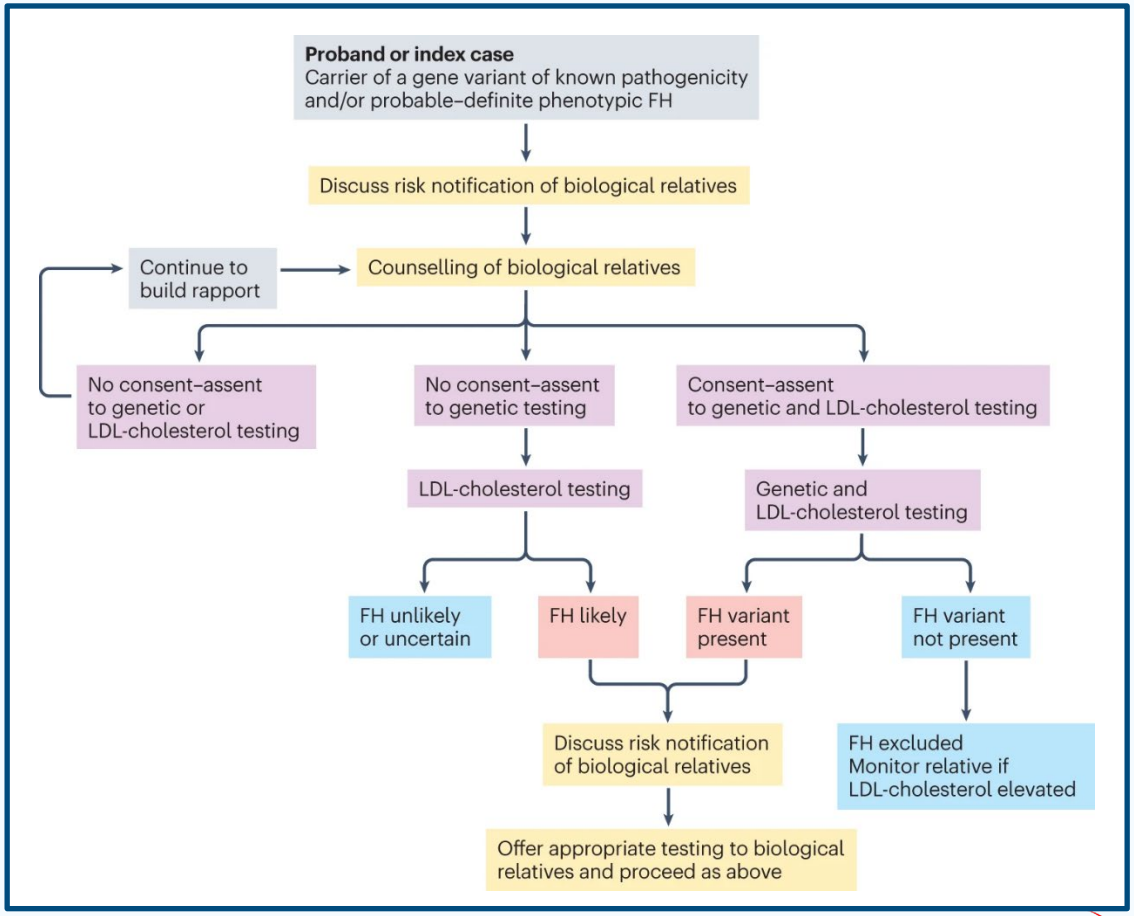
Figures

Algorithm for cascade testing family members for FH



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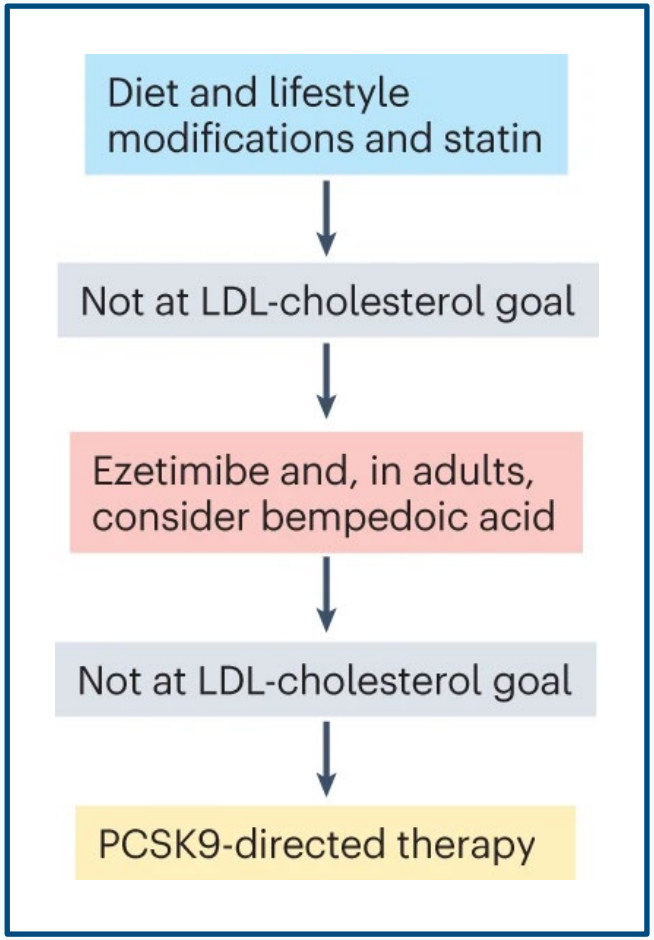
Treatment algorithm for patients with heterozygous FH



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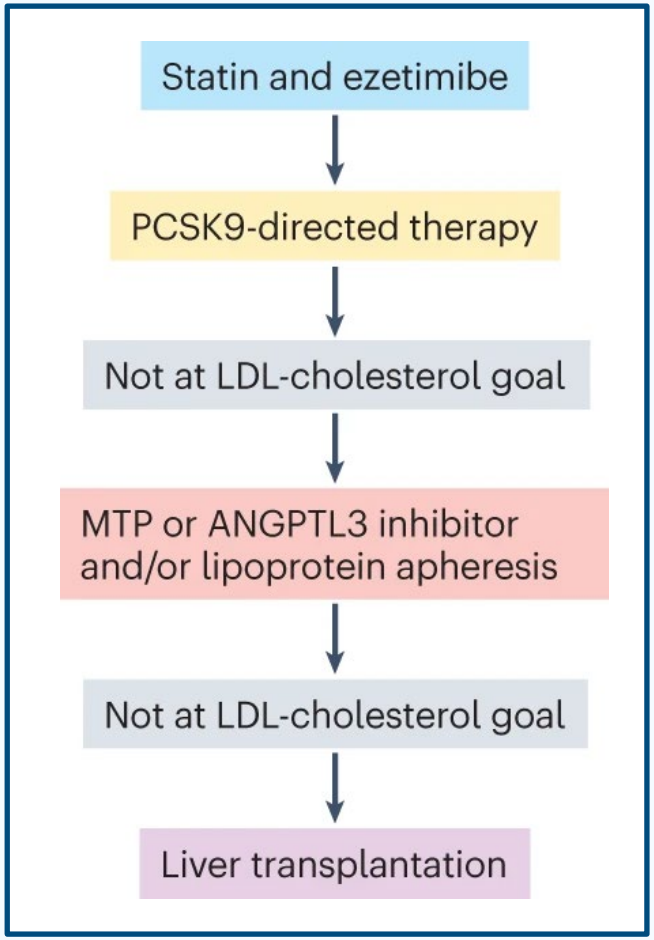
Treatment algorithm for patients with homozygous FH



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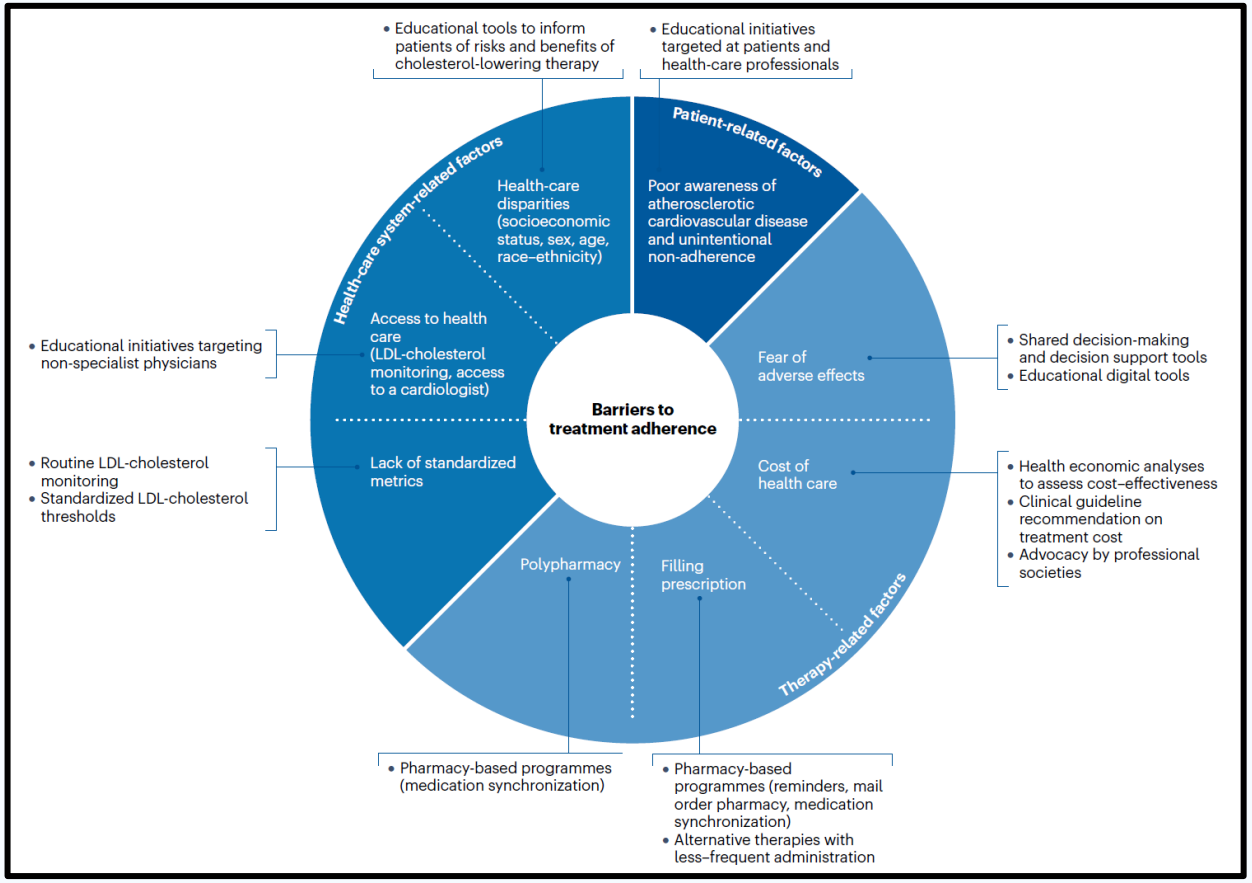
Barriers to treatment adherence, with some solutions



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Conclusions

Conclusions

- This guidance provides comprehensive recommendations for best clinical care for the greatest number of people with FH worldwide.
- The recommendations inform both broad and narrow areas of practice across the continuum of care.
- Strong recommendations, mostly informed by high-quality evidence and by common sense, should be followed as best practice, whereas the weaker recommendations are optional and provide a basis for further research.
- Because of economic, political, cultural and social differences among countries, the recommendations made may not be universally applicable or adopted.

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Conclusions

- Exponential growth in knowledge on the diagnosis of and therapies for FH has set a precedence for countries to aspire to developing high-quality, integrated healthcare systems for FH.
- A challenge for health-care organizations is adapting to the demands of the complexities of changes required.
- Implementation science provides the best approach to address this challenge and was accordingly in the guidance.

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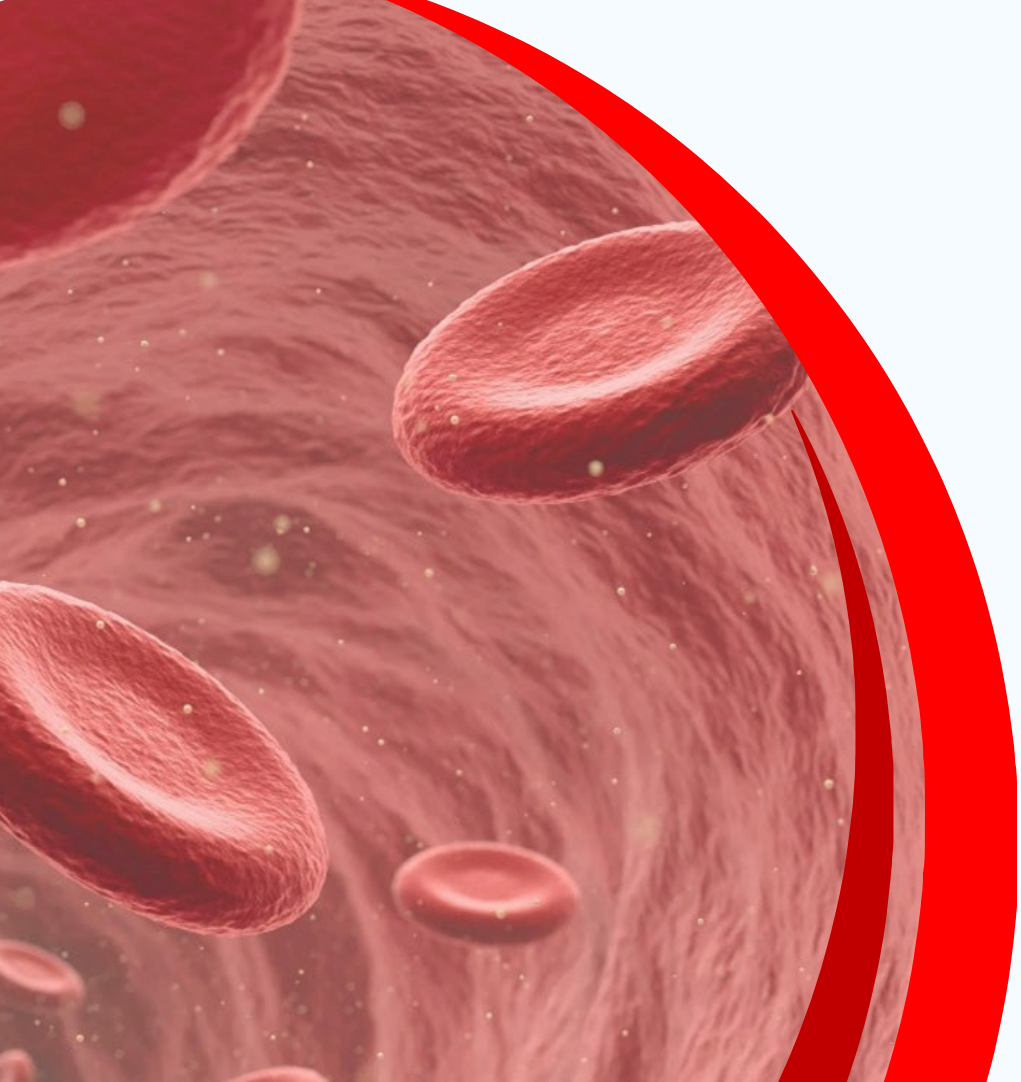
Conclusions

- Evaluating implementation practice, including patient-reported outcomes and experiences, is an ongoing challenge for evolving models of care.
- Beyond observational investigations, future implementation research on FH should involve interventional studies.
- Researchers should make special efforts to include people from diverse socioeconomic strata, ancestries and geographical location.
- The development of integrated systems for improving health outcomes in FH remains a global challenge for implementation practice.

International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia (doi.org/10.1038/s41569-023-00892-0)



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

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