Practice Guideline

Synopsis of an integrated guidance for enhancing the care of familial hypercholesterolaemia: an Australian perspective

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ABSTRACT

Introduction: Familial hypercholesterolaemia (FH) is a common, heritable and preventable cause of premature coronary artery disease, with significant potential for positive impact on public health and healthcare savings. New clinical practice recommendations are presented in an abridged guidance to assist practitioners in enhancing the care of all patients with FH.

Main recommendations: Core recommendations are made on the detection, diagnosis, assessment and management of adults, children and adolescents with FH. There is a key role for general practitioners (GPs) working in collaboration with specialists with expertise in lipidology. Advice is given on genetic and cholesterol testing and risk notification of biological relatives undergoing cascade testing for FH; all healthcare professionals should develop skills in genomic medicine. Management is under-pinned by the precepts of risk stratification, adherence to healthy lifestyles, treatment of non-cholesterol risk factors, and appropriate use of low-density lipoprotein (LDL)-cholesterol lowering therapies, including statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Recommendations on service design are provided in the full guidance.

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Potential impact on care of FH: These recommendations need to be utilised using judicious clinical judgement and shared decision making with patients and families. Models of care need to be adapted to both local and regional needs and resources. In Australia new government funded schemes for genetic testing and use of PCSK9 inhibitors, as well as the National Health Genomics Policy Framework, will enable adoption of these recommendations. A broad implementation science strategy is, however, required to ensure that the guidance translates into benefit for all families with FH.

1. Introduction

Familial hypercholesterolaemia (FH) is a common and severe cause of premature coronary atherosclerosis due to variants in genes affecting the clearance of low-density lipoprotein (LDL)-cholesterol. FH is a preventable cause of premature disease and death, with significant potential for positive impact on public health and healthcare savings [1, 2]. However, less than 10% of people with FH have been identified and, of those treated, over 80% do not attain LDL-cholesterol targets [2].

The FH Australasia Network Consensus Group has developed a new guidance to assist clinicians in the care of patients with FH, replacing earlier recommendations [3]. This synopsis provides the key recommendations as actionable statements with their strength of evidence. The full guidance, endorsed by several organisations (see appendix), is available in *Heart, Lung and Circulation* at https://doi.org/10.1016/j.hlc.2020.09.943 [4].

2. Method

A steering committee, selected from board members of the FH Australasia Registry Network [5], appointed a writing group and invited contributions from diverse clinical specialties and health consumers [4]. The protocols followed are detailed elsewhere [4]. Evaluation of the published evidence on the care of FH was based on the GRADE system [4,6]. The totality of evidence, including expert opinion and patient preferences, informed the recommendations.

3. Key evidenced-based recommendations

Recommendations are presented with a class of recommendation (CoR) and level of evidence (LoE). Additional recommendations, including lipoprotein apheresis and organisation of care, are given in the full guidance [4].

Conversion factors in the recommendations are: for cholesterol, from mmol/L to mg/dL multiply mmol/L by 38.67; for triglycerides, from mmol/L to mg/dL multiply mmol/L by 88.57.

3.1. Phenotypic detection of index cases

1. Several strategies should be considered for detecting index cases of FH, including selective, opportunistic and universal screening [1,2,7–10]. *[CoR Moderate; LoE Moderate]*
2. Index cases should be sought by selective screening of adults with premature atherosclerotic cardiovascular disease (ASCVD), primarily coronary artery disease, and a family history of premature ASCVD and/or hypercholesterolaemia [3,7]. *[CoR Strong; LoE High]*
3. Opportunistic screening, based on a plasma LDL-cholesterol level >5.0 mmol/L, should be employed for detecting adults [8]. *[CoR Strong; LoE Moderate]*
4. Universal screening, based on an LDL-cholesterol level >3.5 mmol/L, should be considered before puberty (preferably between 1 and 2 years of age, coinciding with childhood immunisation) to initially detect children with FH [1,9]. *[CoR Moderate; LoE Moderate]*
5. Alerts on laboratory reports on lipid profiles should be employed to enhance case detection [1]. *[CoR Strong; LoE Moderate]*
6. Digital screening of electronic health records should be considered to enable case detection [1]. *[CoR Moderate; LoE Moderate]*

7. The Dutch Lipid Clinic Network (DLCN) criteria (Table 1) should be used to make a phenotypic diagnosis of FH in adults but not in children or adolescents [1,10,11]. *[CoR Strong; LoE High]*
8. Patients with suspected FH should be referred to or discussed with a specialist with expertise in lipidology for further assessment [3,7,8]. *[CoR Strong; LoE Low]*

3.2. Diagnosis and assessment of adults

1. Secondary causes of hypercholesterolaemia should be excluded before making a diagnosis of FH (applies also to children and adolescents) [3,7,10,11]. *[CoR Strong; LoE High]*
2. The diagnosis of FH should be made using both phenotypic (Table 1) and genetic criteria, but when genetic testing is not available the diagnosis should be made phenotypically [3,7]. *[CoR Strong; LoE High]*
3. Genetic testing (a Medicare rebatable item in Australia for index cases with a high phenotypic probability of FH and for close relatives of genetically confirmed index cases) should be used to confirm the diagnosis of FH, especially if cascade testing is planned [3,7,12]. *[CoR Strong; LoE High];*
4. Patients should be risk assessed for the presence of other major ASCVD risk factors, including elevated lipoprotein(a) [Lp(a)] [3,13,14]. *[CoR Strong; LoE Moderate]*
5. Cardiovascular risk prediction equations derived from the general population should not be used in patients with FH [3,13]. *[CoR Strong; LoE Moderate]*
6. Coronary artery calcium score (CACS), computed tomography coronary angiography (CTCA) and carotid ultrasonography may be considered for risk stratifying asymptomatic patients [3,10,11,15,16]. *[CoR Weak; LoE Moderate]*
7. Adults with homozygous FH should be referred to a specialised centre for long-term care [7,17]. *[CoR Strong; LoE High]*

3.3. Diagnosis and assessment of children and adolescents

1. Children suspected of having homozygous FH should be tested as early as possible, at least by 2 years of age [7,10,17]. *[CoR Strong; LoE Moderate]*
2. Testing of children with suspected heterozygous FH using phenotypic and/or genotypic strategies should be considered between the ages of 5 and 10 years [10,18]. *[CoR Moderate; LoE Moderate]*
3. A probable phenotypic diagnosis of FH should be considered in those with [10,18,19]:
   a LDL-cholesterol of >5.0 mmol/L, with a parental history of hypercholesterolaemia or premature ASCVD;
   b LDL-cholesterol of 4.0 to 5.0 mmol/L, with a parental history of hypercholesterolaemia or premature ASCVD; or
   c LDL-cholesterol of >3.5 mmol/L, with a parent carrying a pathogenic or likely pathogenic gene variant. *[CoR Moderate; LoE Moderate]*
4. Children and adolescents with heterozygous FH should be reviewed by a paediatrician with expertise in lipidology [7,10,18,20,21]. *[CoR Strong; LoE Low]*
5. Genetic testing should be offered to diagnose children after a pathogenic or likely pathogenic gene variant has been identified in a parent or first-degree relative [1,3,19]. *[CoR Strong; LoE Moderate]*
6. Children should be risk stratified according to age, other ASCVD risk factors, family history of premature ASCVD and the level of both

Table 1

The Dutch Lipid Clinic Network criteria for making the phenotypic diagnosis of familial hypercholesterolaemia in adult index cases [1–3]. For online use, please access the FH Australasia Network calculator at https://www.athero.org.au/fh/calculator/. These criteria should <u>not</u> be used to diagnose FH in children or adolescents [10].

Criteria*	Score
Section 1: Family history	
First degree relative with known premature coronary and/or vascular disease (men aged <55 years, women aged <60 years)	**1**
OR First degree relative with known LDL-cholesterol above the 95th percentile for age and gender	
First degree relative with tendinous xanthomata and/or arcus cornealis	**2**
OR Children aged <18 years with LDL-cholesterol above the 95th percentile for age and gender	
Section 2: Personal history	
Patients with premature coronary artery disease (men aged <55 years, women aged <60 years)	**2**
Patients with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years)	**1**
Section 3: Physical examination	
Tendinous xanthomata	**6**
Arcus cornealis before 45 years of age	**4**
Section 3: Biochemical results: to convert cholesterol to mg/dL multiply mmol/L below by 38.67	
LDL-cholesterol (mmol/L)†	
LDL-cholesterol ≥8.5	**8**
LDL-cholesterol 6.5–8.4	**5**
LDL-cholesterol 5.0–6.4	**3**
LDL-cholesterol 4.0–4.9	**1**

Diagnosis	Total Score
Definite FH	**>8**
Probable FH	**6–8**
Possible FH	**3–5**
Unlikely FH	**<3**

* Note that only the highest score in each section is chosen to add up to the total score, to a maximum of 18.

† If pre-treatment LDL-cholesterol is not available, use the FH Australasia Network's online calculator (https://www.athero.org.au/fh/calculator/) to derive the LDL-cholesterol by adjusting value for cholesterol-lowering medication.

LDL-cholesterol and Lp(a) at diagnosis [7,10,18,21]. *[CoR Strong; LoE Moderate]*

7 In children and adolescents with heterozygous FH, measurement of carotid intima-medial thickness using carotid ultrasonography may be considered to assess ASCVD risk [1,10,22]. *[CoR Weak; LoE Moderate]*

8 Children and adolescents with homozygous FH should be referred on diagnosis to a specialist paediatric centre for planning of care [7,10,17,21,23]. *[CoR Strong; LoE High]*

3.4. Genetic testing

1. Diagnostic genetic testing and counselling should be offered to all adult index cases with a probable/definite phenotypic diagnosis of FH (Table 1) [1,3,12]. *[CoR Strong; LoE Moderate]*

2. Diagnostic genetic testing in an adult index case may be considered when there is limited information to establish an accurate phenotypic diagnosis of FH [1,3,12,24]. *[CoR Weak; LoE Moderate]*

3. Diagnostic genetic testing of children, as potential index cases, should be considered when parents, or first-degree relatives, are unknown or deceased, or as part of universal screening [1,3,9]. *[CoR Moderate; LoE Moderate]*

4. Genetic testing for FH should be carried out in an accredited laboratory using standardised methods to detect pathogenic and likely pathogenic gene variants causing FH [1,3,12,24]. *[CoR Strong; LoE High]*

5. Variants detected by genetic testing should be classified according to the American College of Medical Genetic and Genomic standards and guidelines, or a comparable classification [24–26]. *[CoR Strong; LoE High]*

6. If a pathogenic, or likely pathogenic, gene variant is not detected, FH should <u>not</u> be excluded, particularly with a highly probable clinical phenotype of FH [3,10,24]. *[CoR Strong; LoE High]*

7. Diagnostic genetic testing of index cases with suspected FH should be requested by a specialist (a requirement of the Medicare Benefits Schedule in Australia) with appropriate skills in the care of patients and families with FH [3,24,27,28]. *[CoR Strong; LoE Low]*

8. All healthcare professionals involved in consenting families for genetic testing should receive education in genomic medicine and have basic skills in genetic counselling [1,3,24,28,29]. *[CoR Strong; LoE Low]*

3.5. Cascade testing and risk notification of families

1. Cascade testing (testing of consenting biological relatives of an individual with FH) should be carried out using both a phenotypic and genotypic strategy (Fig. 1), but if genetic testing is not available a phenotypic strategy should be used [1–3,7,12]. *[CoR Strong; LoE High]*

2. Genetic testing is more cost-effective than phenotypic testing and should be employed to screen family members after a pathogenic, or likely pathogenic, gene variant has been identified in the family [1,12,30]. *[CoR Strong; LoE High]*

3. When genetic testing is not feasible, the diagnosis of FH in close relatives should be made using age- and gender-specific plasma LDL-cholesterol levels (Table 2) [1–3,31]. *[CoR Strong; LoE High]*

4. Risk notification of relatives should be consistent with local legislation and institutional guidelines; risk notification may be indirect (letter provided for notifier to give to relatives) or direct (letter sent to relatives) [1–3,7]. *[CoR Strong; LoE Low]*

5. Pre- and post-test genetic counselling should be offered to at risk family members undergoing cascade testing [1–3,12,19,24]. *[CoR Strong; LoE High]*

6. Cascade testing and risk notification should be co-ordinated by a well-resourced centre, particularly if employing genetic testing [1–3,12,19]. *[CoR Strong; LoE High]*

7. Genetic cascade testing may be undertaken by a GP (as specified by the Medicare Benefits Schedule in Australia) with skills in the care of FH, guided by an appropriate specialist [1–3,8,27,28]. *[CoR Weak; LoE Low]*
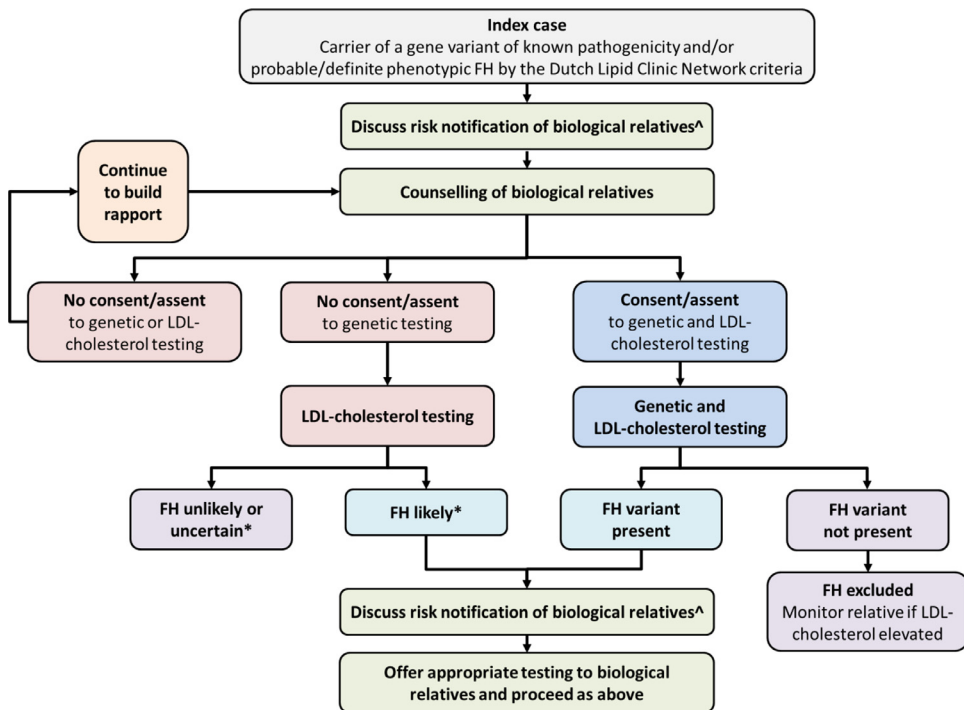
Flowchart (Fig. 1)

Index case
Carrier of a gene variant of known pathogenicity and/or probable/definite phenotypic FH by the Dutch Lipid Clinic Network criteria

Discuss risk notification of biological relatives^

Continue to build rapport

Counselling of biological relatives

No consent/assent to genetic or LDL-cholesterol testing

No consent/assent to genetic testing

Consent/assent to genetic and LDL-cholesterol testing

LDL-cholesterol testing

Genetic and LDL-cholesterol testing

FH unlikely or uncertain*

FH likely*

FH variant present

FH variant not present

FH excluded Monitor relative if LDL-cholesterol elevated

Discuss risk notification of biological relatives^

Offer appropriate testing to biological relatives and proceed as above

Fig. 1. Scheme for cascade testing of biological relatives of an index case with confirmed familial hypercholesterolaemia. Adapted from Watts et al. 2011 [3].
^Consistent with relevant local legislation and institutional guidelines
*According to age- and gender-specific plasma LDL-cholesterol concentrations published by Starr et al. [31].

Table 2
Age-dependent LDL-cholesterol concentrations and thresholds (mmol/L; to convert to mg/dL multiply mmol/L by 38.67) to make a diagnosis of FH during cascade testing in (a) male and (b) female first-degree relatives of an index case. Adapted from Starr et al. [31].

(a) Male

		Age			
0 to 14	15 to 24	25 to 34	35 to 44	45 to 54	55 and older
5.5	5.5	5.5	5.5	5.5	5.5
5.4	5.4	5.4	5.4	5.4	5.4
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

(b) Female

		Age			
0 to 14	15 to 24	25 to 34	35 to 44	45 to 54	55 and older
5.5	5.5	5.5	5.5	5.5	5.5
5.4	5.4	5.4	5.4	5.4	5.4
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

Colour	Likelihood of FH
(Red)	Likely
(Orange)	Uncertain
(Blue)	Unlikely

8. Genetic cascade testing should initially be prioritised for first-degree relatives of a variant carrier and sequentially extended as additional carriers are identified; if first-degree relatives decline testing, testing should be extended to second-degree followed by third-degree relatives (also applies to phenotypic testing alone) (Fig. 1) [1–3,12]. *[CoR Strong; LoE High]*

9. Universal screening of children should be coupled with child-parent (reverse) cascade testing [1,9,20]. *[CoR Strong; LoE Moderate]*

10. All healthcare professionals involved in cascade testing and risk notification of families should receive education in genomic medicine and have basic skills in genetic counselling [3,12,24,28,29]. *[CoR Strong; LoE Low]*

3.6. Management of adults

1. All adult patients with FH should be counselled on lifestyle modifications and non-cholesterol risk factors should be managed according to expert recommendations [1,7,11,32,33]. *[CoR Strong; LoE Moderate]*

2. Care should employ shared decision making and address patients' values and health literacy [1,7,34]. *[CoR Strong; LoE Moderate]*

3. Therapy should initially aim for at least a 50% reduction in LDL-cholesterol [1,11,13,35–37]. *[CoR Strong; LoE Moderate]*

4. The following therapeutic targets should be considered [1,11,13,36–38]:
   a LDL-cholesterol <2.5 mmol/L (absence of ASCVD or other major ASCVD risk factors);
   b LDL-cholesterol <1.8 mmol/L (imaging evidence of ASCVD alone or other major ASCVD risk factors); or
   c LDL-cholesterol <1.4 mmol/L (presence of clinical ASCVD). *[CoR Moderate; LoE Moderate]*

5. Maximally tolerated high potency statins (eg. atorvastatin or rosuvastatin) with or without ezetimibe, and a heart-healthy diet, should initially be employed to achieve the above targets (Fig. 2) [1,2,36,39]. *[CoR Strong; LoE High]*

6. A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor should be employed if the above LDL-cholesterol targets are not achieved with maximally tolerated statins, ezetimibe and diet (Fig. 2) [1,2,11,36,40,41]. *[CoR Strong; LoE High]*

7. Patients with statin intolerance should be managed according to established guidelines and treated with non-statins, including ezetimibe and PCSK9 inhibitors [1,3,36,42]. *[CoR Strong; LoE High]*

8. In FH patients with clinical ASCVD (or diabetes) on maximally tolerated statins and ezetimibe and elevated triglyceride levels (1.5–5.6 mmol/L), use of high-dose omega-3 fatty acids (especially 4 g/day of pure eicosapentaenoic acid ethyl ester) should be considered to further reduce ASCVD risk [1,43]. *[CoR Moderate; LoE Moderate]*

9. Patients with FH should continue cholesterol-lowering drug therapies during acute illness, such as respiratory infections, unless specifically contra-indicated [4,44,45]. *[CoR Strong; LoE Low]*

10. Plasma hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting and dose titrating statin therapy. Hepatic aminotransferases should be monitored regularly and creatine kinase if musculoskeletal symptoms are reported; glucose should be monitored if there is a risk of diabetes (these safety checks also apply to children and adolescents) [1,3,4,7]. *[CoR Strong; LoE Moderate]*

11. All women of child-bearing age with FH should be offered prepregnancy counselling, with individualised advice on contraception, before starting a statin and this should be reinforced annually (applies also to adolescent girls) [1,3,7]. *[CoR Strong; LoE Moderate]*

12. Statins and other systemically absorbed cholesterol lowering drugs should be discontinued 3 months before conception, as well as during pregnancy and breastfeeding [1,3,7]. *[CoR Strong; LoE Moderate]*
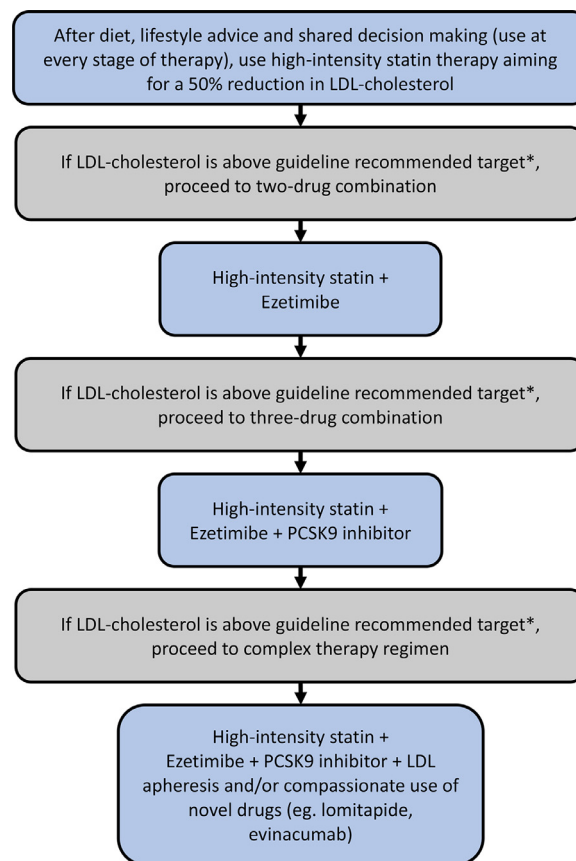

Fig. 2. Sequence of therapy for adults with familial hypercholesterolaemia (FH). Most patients with heterozygous FH can be well controlled with a two- or three- drug combination; statin intolerant patients may be treated with ezetimibe and a PCSK9 inhibitor. Complex therapy regimens will usually apply to patients with homozygous FH [17, 36, 38], which may include children and adolescents. LDL-cholesterol targets are based on primary or secondary prevention settings [1, 4]; patients should be on at least 3 months of therapy and above the targets before proceeding to next step. *For targets, see Management of Adults in text. Adapted from Pang et al. 2020 [2].

13. In women with homozygous FH and clinical ASCVD, use of statins and ezetimibe may be considered after the first trimester [1,5,36]. *[CoR Weak; LoE Moderate]*

14. Although CACS may be useful for initial risk stratification of asymptomatic patients prior to commencing a statin, it should not be used to monitor the efficacy of therapy [1,15,16,46]. *[CoR Strong; LoE Moderate]*

15. In asymptomatic patients with heterozygous FH, carotid ultrasonography and CTCA may be used for monitoring the efficacy of cholesterol-lowering therapy [1,15,22]. *[CoR Weak; LoE Moderate]*

16. In adults with homozygous FH, carotid ultrasonography, CTCA, echocardiography and exercise stress testing should be employed (as clinically indicated) to assess progression of ASCVD and atheromatous involvement of the aortic valve, with the aim of guiding overall management (also applies to children with homozygous FH) [7,15,38]. *[CoR Strong; LoE Moderate]*

3.7. Management of children and adolescents

1. All patients and families with FH should be counselled on lifestyle modifications, and advice to prevent or correct non-cholesterol risk factors (especially smoking) [1,7,10,18,21,33]. *[CoR Strong; LoE Moderate]*

2. Management should be based on shared decision making with parents and offspring, with barriers to treatment adherence addressed [1,7,10,34]. *[CoR Strong; LoE Moderate]*

3. Initiation of statin treatment should be considered at age 8 to 10 years irrespective of gender; LDL-cholesterol targets in children and adolescents need not be as intensive as in adults [1,7,10,18,22]. *[CoR Moderate; LoE Moderate]*

4. Earlier initiation of treatment with statins should be considered in patients with a particularly adverse family history of ASCVD or other major ASCVD risk factors [1,7,10,18,22]. *[CoR Moderate; LoE Moderate]*

5. In children with FH, aged 8 to 10 years on a suitable diet, an LDL-cholesterol treatment target <4.0 mmol/L or a 30–40% reduction in LDL-cholesterol may be considered [1,10,18,21]. *[CoR Weak; LoE Low]*

6. In children with FH older than 10 years on a suitable diet, an LDL-cholesterol treatment target <3.5 mmol/L or a 50% reduction in LDL-cholesterol may be considered [1,10,18,21,22]. *[CoR Weak; LoE Low]*

7. Statin therapy with or without ezetimibe, and a heart-healthy diet with or without plant sterol (or stanol) supplementation, should be employed to achieve the above targets [1,3,7,10,18,21]. *[CoR Strong; LoE High]*

8. Statins licenced for use in this age group (pravastatin, fluvastatin, simvastatin In Australia) should be employed; ezetimibe is also licensed from the age of 10 years and should be used accordingly [2–4]. *[CoR Strong; LoE High]*

9. The use of atorvastatin and rosuvastatin should be considered in heterozygous FH according to clinical indications and shared decision making [1–4]. *[CoR Moderate, LoE High]*

10. The use of maximal doses of high potency statins and ezetimibe should be considered in homozygous FH children as early as possible, preferably by the age of 2 years [1,4,10,21,47]. *[CoR Moderate; LoE Moderate]*

11. Although statins and ezetimibe can be safely used in children, weight, growth, physical and sexual development, and well-being should be monitored [1,3,4,10,18,21,48]. *[CoR Strong; LoE High]*

12. Shared care between a paediatrician and a GP should be considered for managing lower complexity patients [3,4,7,8,10]. *[CoR Moderate; LoE Low]*

13. Management should focus on the nuclear or the immediate family, with at least an annual review of children; non-adherence should be addressed [3,7,10,21]. *[CoR Strong; LoE Low]*

14. Transition of adolescents to young adult services should be considered in advance, with support offered to enable ongoing self-management and shared care into adulthood [3,4,18,48]. *[CoR Moderate; LoE Low]*

15. In children and adolescents with heterozygous FH, carotid ultrasonography may be employed to monitor therapy [1,10,22,49]. *[CoR Weak; LoE Moderate]*

16. In patients with homozygous FH, treatment should commence as soon as possible after diagnosis: the LDL-cholesterol target should be similar to adults, which may require addition of a PCSK9 inhibitor to a statin and ezetimibe, as well as the use of lipoprotein apheresis (Fig. 2) [1,7,10,17,18,23,38]. *[CoR Strong; LoE Moderate]*

4. Conclusion

This guidance is aligned with a recent international call to action on FH [50]. The recommendations need incorporation into healthcare pathways that meet the needs of the population [1, 2]. In Australia, government funded schemes that support appropriate genetic testing and use of PCSK9 monoclonal antibodies will contribute significantly to enhancing the care of patients with FH [2]. The critical barrier that needs to be overcome is translating our guidance into health policy and high-quality care. Implementation research and practice [51,52] must

be embraced as a national health priority to increase the impact of the guidance on improving the care of all people with or at risk of FH. This challenge and recommendation applies globally to all countries aiming to close major gaps in the care of FH [51].

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Disclosures

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Appendix

All tables and figures are reprinted by kind permission of Heart, Lung & Circulation [2,4].

Endorsements

The full guidance [4] has been endorsed by the Australian Atherosclerosis Society, Cardiac Society of Australia and New Zealand, National Heart Foundation (Australia), Australian Cardiovascular Alliance, Human Genetics Society of Australasia, European Atherosclerosis Society, International Atherosclerosis Society, FH Foundation, Heart UK, Asian-Pacific Society of Atherosclerosis and Vascular Disease, National Lipid Association (US) and the American Society of Preventive Cardiology.

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