Adherence to pharmacotherapy: sine qua non for reducing cumulative risk of premature coronary disease in familial hypercholesterolemia

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Purpose of review
Familial hypercholesterolemia (FH) is a dominant and highly penetrant monogenic disorder present from birth that markedly elevates plasma low-density lipoprotein (LDL)-cholesterol concentration and, if untreated, leads to atherosclerotic cardiovascular disease (ASCVD). The risk of ASCVD can be substantially reduced with lipid-lowering treatment (LLT). However, adherence to LLT remains a major challenge in FH patients and an under-recognized issue. We review several barriers to treatment adherence and implementation strategies for improving adherence in patients with FH.

Recent findings
Barriers that negatively affect patient adherence to treatment include the misunderstanding of perceived and actual risk of FH and the benefits of LLT, inadequate knowledge, lack of standardization of treatment, insufficient monitoring of LDL-cholesterol level, and inequalities in healthcare resources. Education of patients, carers and healthcare providers, guideline-directed treatment goals, regular monitoring, medication regimen simplification and greater access to established and new drugs are crucial enablers for improving adherence to treatment. However, given FH is present from birth, strategies for life-long adherence from childhood or young adulthood is critically important and requires further study. To be effective, strategies should be multifaceted, targeted and patient-centred involving a multidisciplinary-team with support from family, communities and peer groups.

Summary
FH confers a significant risk for ASCVD from a young age. Achieving better medication adherence is foundational for improving clinical outcomes and reducing the burden of atherosclerosis over a lifetime. Identification of key barriers and enablers are critical for implementing better adherence to treatment across the life-course of patients with FH.

Keywords
cardiovascular disease, familial hypercholesterolemia, lipid-lowering therapy, medication adherence, nonadherence, statins

INTRODUCTION

Familial hypercholesterolemia (FH) is a common autosomal co-dominant and highly penetrant disorder, characterized by elevated levels of low-density lipoprotein (LDL)-cholesterol [1,2▪▪]. The risk of atherosclerotic cardiovascular disease (ASCVD) can be substantially reduced with lifestyle modification and pharmacological treatments, including high-intensity statins, ezetimibe and more recently proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors [3,4]. However, adherence to lipid-lowering treatment (LLT) remains a major challenge in FH patients, particularly with the need for lifelong adherence in patients who remain asymptomatic. We review several barriers to pharmacological treatment and propose implementation strategies for improving adherence in patients with FH. Readers should also refer to more general reviews on this topic [5,6,7▪▪].

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Curr Opin Endocrinol Diabetes Obes 2024, 31:22–30
DOI:10.1097/MED.0000000000000842

KEY POINTS

- Familial hypercholesterolemia (FH) confers a very high risk for atherosclerotic cardiovascular disease (ASCVD) with a significant burden on public health from lifetime exposure to LDL-cholesterol if untreated. Poor adherence to lipid-lowering treatment (LLT) is a major challenge for achieving guideline treatment goals in FH.
- Misunderstanding of perceived and actual risk of FH and the benefits of LLT, inadequate knowledge, lack of standardization of treatment, insufficient monitoring of LDL-cholesterol level and inequalities in healthcare resources have negative impacts on adherence to LLT in FH.
- Implementation strategies to improve adherence should be patient-centred, country-specific and contextualised to a given healthcare system, including support from family, community and peer groups, patient and healthcare provider education, lifestyle and behavioural interventions, potent combination therapy, simple treatment and long-acting regimens, subsidies for essential therapies, regular patient followed up and monitoring of treatment.

REVIEW CRITERIA

A search for original and review articles was performed in the PubMed database using the following key terms: 'cardiovascular disease', 'barriers', 'enablers', 'FH', 'LDL-cholesterol', 'lipid-lowering therapy', 'medication adherence', 'primary hypercholesterolemia' and 'statins' either alone or in combination. All articles selected were in the English language, full-text articles, with no restriction applied to the date of publication.

LIPID-LOWERING TREATMENT: BENEFITS AND GOALS IN FAMILIAL HYPERCHOLESTEROLEMIA

Composite evidence strongly supports that earlier lifestyle management and robust cholesterol-lowering therapy can maximally lower lifetime exposure to LDL-cholesterol and lead to a greater reduction in risk of ASCVD in FH [1,2▪▪,8▪,9,10▪]. Observational studies confirm that reductions in LDL-cholesterol lower the risk of coronary events in younger [11] and older patients with FH [12]. In the CHARON study, rosuvastatin treatment for 2 years resulted in significantly less progression of carotid intima-media thickness in children with heterozygous FH compared with their untreated unaffected sibling [13]. In a long-term follow-up study, children commenced on low-to-moderate intensity statin had a 1% incidence of ASCVD events compared with 26% in their affected parents who were treated with statins later in life [11]. These findings strongly support the early use of LLT in FH.

Current guidelines recommend a relative reduction in plasma LDL-cholesterol of more than 50% in all patients with FH, followed by an absolute goal of less than 55 mg/dl (<1.4 mmol/l) and less than 70 mg/dl (<1.8 mmol/l) for adult FH patients with and without ASCVD, respectively [2▪▪,3]. In children with heterozygous FH, an LDL-cholesterol goal of less than 135 mg/dl (<3.5 mmol/l) or approximately 50% reduction is considered in patients with no additional risk factors for ASCVD, whilst an LDL-cholesterol goal of less than 2.5 mmol/l is recommended in those with additional risk factors for ASCVD [2▪▪,14▪]. However, more than 80% of FH patients treated with conventional LLT (mostly statins and/or ezetimibe) do not achieve recommended LDL-cholesterol goals. For example, the Spanish (SAFEHEART) registry showed that more than 95% of adult FH patients with ASCVD receiving LLT failed to achieve guideline recommended LDL-cholesterol targets [15] and less than half of the children (<18 years) with FH attained treatment goals [16]. In another study from Norway, only 43% of 302 FH children achieved an LDL-cholesterol treatment goal of less than 135 mg/dl (≤3.5 mmol/l) [17]. Data from the European Atherosclerosis Society (EAS) Familial Hypercholesterolaemia Studies Collaboration (FHSC) global registry showed that only 2.7% of FH patients achieved LDL-cholesterol levels less than 70 mg/dl [18▪]. Other studies have also demonstrated low rates of LDL-cholesterol goal attainment in FH [19,20,21▪]. Likewise, more than 50% of FH patients fail to attain recommended LDL-cholesterol goals even when additionally treated with PCSK9 inhibitors [22▪]. Poor patient adherence to LLT is the major contributor to the lack of LDL-cholesterol goal attainment [2▪▪,8▪].

ADHERENCE TO LIPID-LOWERING TREATMENT

Medication adherence is defined by the WHO as 'the degree to which the patient's behaviour corresponds with the agreed recommendations from a healthcare provider' [23▪▪] and is reported in terms of the percentage of prescribed doses taken for the defined period of time. Medication persistence is a parameter measured in units of time, and represents the time from initiation to discontinuation of therapy. Nonadherence to medication can be primary or secondary. Primary medication nonadherence occurs when the patient does not initiate the medication or an appropriate alternative within an

acceptable period after it was newly prescribed by their doctor. Secondary nonadherence measures prescription refills among patients who previously filled their first prescriptions [24]. Poor-adherence can be intentional (e.g. a self-decision to not follow the prescriber's instruction) or nonintentional (e.g. forgetting to take the medication) that negatively affects the efficacy and costs of therapies, especially in chronic conditions that entail long-term duration of treatments, such as in FH. In Australia, nonadherence to LLT costs at least $6 billion AUD per year [25]. Statins are a core treatment for FH and ASCVD, and poor adherence to statin therapy or discontinuation may diminish treatment benefit for the prevention of ASCVD in FH. Numerous studies have reported high rates of nonadherence to statin therapy in the real-world setting [5,26]. The magnitude and impact of poor adherence is higher in developing countries, given the disparities in health resources and inequalities in access to healthcare [5]. However, there are limited data on statin adherence in people with FH. In a study of FH patients prescribed a statin, poor adherence to statins was reported by 11% of patients [27]. Similar findings were reported in children with FH showing 22% nonadherence to statin treatment [28]. In a long-term follow-up study of children and young adults with FH treated with statins, 30% had poor adherence to cholesterol-lowering treatment [29▪]. In a study of young FH patients (<40 years), adherence (expressed as mean medication possession ratio, that is, the ratio of the number of days covered by the drug divided by the length of the observation period) was found to be 69%, with only 47% of patients showing persistent use of statins (i.e. continuous drug coverage without gaps ≥60 days) [30]. Likewise, nonadherence to PCSK9 inhibitors or treatment discontinuation were reported in 20–30% of high-risk patients [31–34]. However, a recent report from the SAFEHEART study showed a high persistence with long-term PCSK9 inhibitor treatment, with only 4% of FH patients discontinuing treatment after a median follow up of 3.7 years [22▪]. As discussed later, discrepant findings on nonadherence to PCSK9 inhibitors may be reflected by differences in patient and healthcare system related factors that bear on out-of-pocket medication costs.

FACTORS AFFECTING TREATMENT ADHERENCE IN FAMILIAL HYPERCHOLESTEROLEMIA

Adherence to long-term pharmacotherapies is a complex behavioural process that encompasses five different dimensions: socioeconomic, patient, medical condition, therapy, healthcare provider (HCP) and healthcare system factors [23▪▪]. As discussed below, the level of medication adherence is largely dependent on the characteristics, awareness, knowledge, attitudes, beliefs, perceptions (risk and treatment) and expectations of the patient [35]. Figure 1 depicts the possible factors that may affect adherence to LLT in patients with FH.

Demographic and socioeconomic-related factors

Age is consistently and inversely associated with adherence to LLT in FH [27,29▪,36]. In a study of 321 Dutch FH patients above age 18 years who were treated with a statin by a specialised team in an outpatient clinic, younger FH patients (≤35 years) were 10 times less adherent to medications (defined as use of the prescribed medication for <90% of the time) than older FH patients (>50 years) [27]. FH is a silent disease and young FH patients may not perceive an immediate need for LLT because they are asymptomatic. A fear of perceived lifestyle change and prioritization of other life commitments (family and career obligation) over self-management of FH may contribute to a lower adherence level among some young FH patients. It is noteworthy that individuals with FH who started statin therapy at very young age demonstrated excellent adherence, with 80% persisting to take LLT [28,37]. This suggests that early customization to LLT improves long-term adherence in patients with FH. Social and health inequalities due to sex (men vs. women), race/ethnicity (white vs. nonwhite), socioeconomic status (low vs. income countries), health literacy and education levels, mental health issues, employment status and living conditions all bear on adherence to LLT in FH [26,32]. Results from 3167 adult FH patients enrolled in the U.S. CASCADE-FH registry found that women were less likely than men to receive statin treatment and achieve LDL-cholesterol goals [38]. The study also found that Asians and blacks were less likely to achieve targets for LDL-cholesterol [38]. This observation suggests that sex and ancestry contribute to undertreatment of FH patients, but whether this relates to poor adherence remains unclear.

FH-related factors

Poor adherence is also influenced by several features of FH, such as the severity of the disease and the risk of ASCVD. A relatively low plasma concentration of untreated total cholesterol and absence of a history of ASCVD was reported as strong predictors of poor adherence in FH patients [27,36]. Patients with an

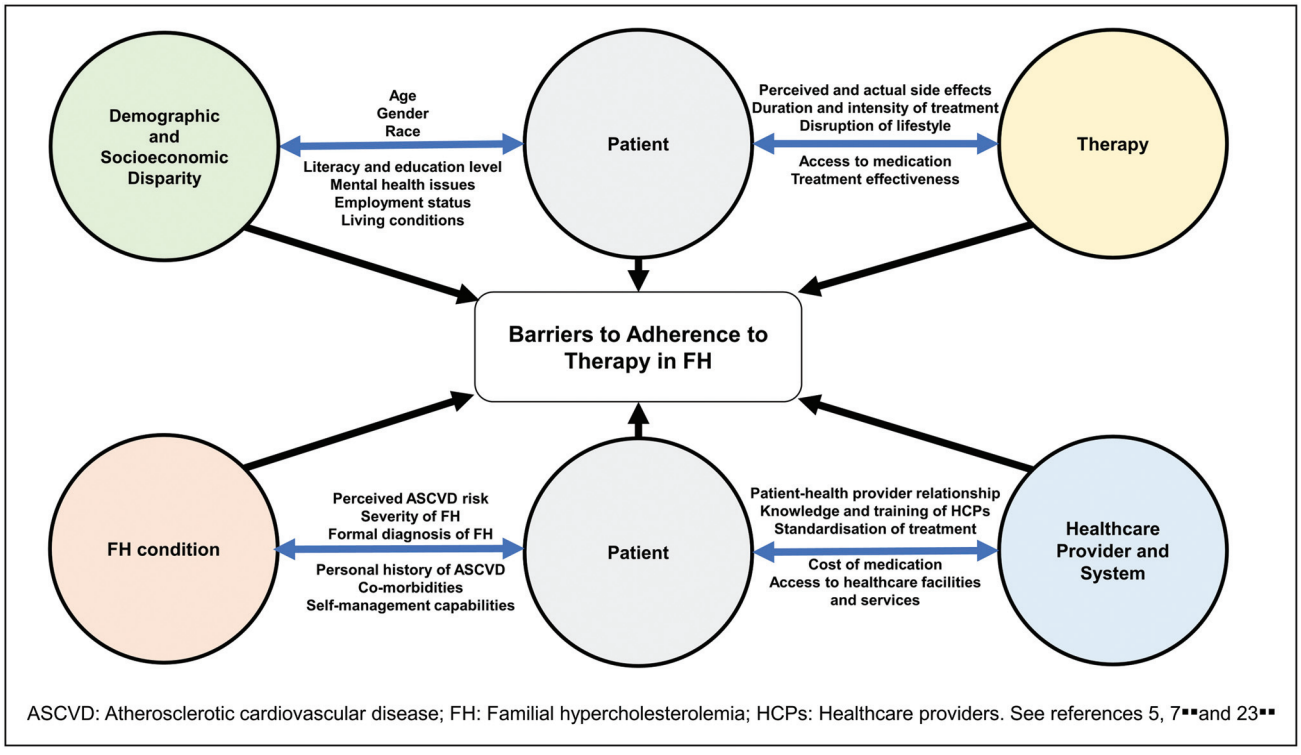

FIGURE 1. Factors that can influence medication adherence according to five dimensions: demographic and socioeconomic, patient, FH condition, therapy, healthcare provider and system factors.

untreated baseline cholesterol less than 8 mmol/l were four times more nonadherent than patients with an untreated cholesterol more than 10 mmol/l. In contrast, a personal history of ASCVD was, as expected, associated with better adherence [30]. This observation suggests that many FH patients lack motivation to manage their condition because perceived risk is lower than actual risk of ASCVD. Poor adherence to LLT in FH was associated with high plasma concentration of treated total cholesterol [27], a likely consequence of not adhering to cholesterol-lowering therapy. Loss of motivation may contribute to nonadherence and poor response to LLT in FH patients. Choice of therapeutic regimen is important: a regimen of a combination of a high-potency statin, ezetimibe and PCSK9 inhibitor therapy may be the best first-line treatment for FH patients with severe hypercholesterolemia or homozygous FH [2▪▪].

Disbelief in the diagnosis of FH also has a negative impact on adherence to LLT in FH. In a study of individuals and families with FH involving interview and focus groups, some FH patients reported their willingness to begin treatment if they better understood and accepted the nature of the diagnosis of FH [39]. The presence of other cardiovascular co-morbidities, such as hypertension, obesity and/or diabetes, may have paradoxical effect on adherence and nonadherence to LLT. Patients with comorbidities are more likely to adhere to medication because they perceive risk of ASCVD as very high. By contrast, multiple and complex drug regimens (polypharmacy) can lead to poor adherence, particularly among elderly patients. The effect of cardiovascular co-morbidities on medication adherence remains to be investigated in FH patients [26].

Therapy-related factors

Adherence to LLT is also influenced by therapy-related factors. One of the major reasons for poor adherence to LLT or discontinuation is the actual or perceived side-effects of LLT [40]. Up to 20% of FH patients were not prescribed statin therapy mostly because of partial or complete intolerance to statin-associated muscle side effects [41]. However, muscle symptoms may be merely associated with a nocebo effect among patients receiving statin treatment [42]. Use of ezetimibe may cause gastrointestinal discomfort and dizziness [43]. PCSK9 inhibitors are most commonly associated with local injection site reaction, influenza-like symptoms, nasopharyngitis and back pain [44]. Patients newer to statins are more likely to be less adherent compared with long-term users of these drugs [27]. High-intensity

statins have also been reported to increase perceived risk of side effects, leading to a lower adherence to LLT in FH patients [36]. Likewise, a shorter duration of statin prescription (e.g. a 30-day prescription) was associated with an increased probability of poor adherence compared with a 90-day prescription in patients with FH [36], intuitively due to a higher risk of running out of medication. Adherence is also affected by other therapy-related factors, including type of LLT (such as low vs. high-intensity statins), complexity of treatment regimen, and frequency of prescription.

Healthcare provider and system-related factors

The healthcare team and system-related factors also bear on treatment adherence. Lack of knowledge, training and skills of HCPs may not allow them to provide patients with adequate and/or correct knowledge of FH and treatment advice (options, effectiveness, side effects, need for lifelong adherence to reduce ASCVD risk) [45▪]. As a result, FH patients may not perceive their ASCVD risk as a threat to health or the benefits of treatment. Clinical inertia is also a major issue. This is defined as LLTs not being prescribed and intensified according to current guidelines. In a Canadian study of patients with FH and/or CVD, the proportion of patients receiving statin was lower among FH compared with patients with CVD [46]. This may be partly due to HCPs' perception of a lack of evidence to support some treatment regimens [45▪]. Lack of standardization or persistence in monitoring treatment (e.g. regular follow-up for assessing attainment of guideline recommended LDL-cholesterol goals) may also discourage FH patients from adhering to LLT [47]. A heavy clinical caseload is also a barrier for HCPs doing longer consultations, as required for motivational counselling and shared decision making [45▪]. These barriers suggest that inadequate healthcare resources for training HCPs, monitoring patients' treatment and providing adequate consultation time increases the risk of nonadherence in FH.

Another barrier to adherence is the out-of-pocket cost of the medication to the patient. While statin and/or ezetimibe are widely available at low or no cost, newer options, such as PCSK9 inhibitors (alirocumab and evolocumab), remain currently expensive. High cost of treatment (self-payment or co-payment costs) was associated with poor adherence to and persistence with PCSK9 inhibitors [32,48]. In a study of more than 45 000 patients who were newly prescribed PCSK9 inhibitors, higher out-of-pocket costs was associated with a higher likelihood of stopping treatment [48]. These findings highlight the importance of government support or subsidy to improve adherence to essential drugs for treating FH.

Taken together, poor adherence is a multifactorial problem that affects FH patients' behaviour and capacity to adhere to treatment. Hence, LLT should be tailored to the needs of the individual FH patient in order to improve and maintain an adequate level of adherence and achieve maximum effectiveness. As discussed below, the development of effective implementation strategies is required to improve treatment adherence in FH.

ENABLERS AND SOLUTIONS TO IMPROVE ADHERENCE TO TREATMENT IN FAMILIAL HYPERCHOLESTEROLEMIA

Improved adherence to LLT can maximize health outcomes for patients with FH [2▪▪]. Treatment adherence should fundamentally be patient-centred using shared-decision making principles, where the HCPs and FH patients (and their families) work and participate together to make treatment decisions that align with a patient's needs, goals, preferences and values [2▪▪]. This requires a tailored, personalized treatment plan that considers all the possible enablers and barriers to adherence for each FH patient. Several enablers or facilitators can play significant roles in improving treatment adherence in FH (Table 1).

Patient-level

Skills in the care of FH and use of resources (e.g. decision support tools) are effective in motivating patients to integrate treatment into their daily lives [45▪]. Education plays a critical role ensuring that patients and their families have a good awareness and understanding of FH, ASCVD risk, treatment options and side effects. In a recent systematic review, educational interventions, from the use of information leaflets to family centred and/or peer group support, were effective in improving treatment adherence in FH [49▪]. Visualizing carotid intima media wall (thickness and plaque formation) or coronary calcium using cardiovascular imaging modalities has also been used to improve adherence to statin and clinical outcomes in high-risk patients [50–52]. A formal genetic diagnosis of FH can empower patients to engage actively with their treatment regimens [53]. A positive family influence can also improve treatment adherence, particularly among children or adolescents. For example, having other family members following similar LLT has been suggested to enable treatment

adherence [53]. As discussed earlier, commencement of LLT from a young age can improve long-term adherence [27], but this requires childhood screening for FH and parental responsibility to care for their child's treatment [14▪,53]. Long-term adherence to LLT in affected children or adolescents is unlikely to be successful unless parents perceive that FH presents a substantial risk to their affected children and parents understanding the benefits of treatment [53]. Peer support groups can offer empirical knowledge and real-world experience about FH to share with patients that can enhance their confidence and self-management abilities [45▪].

Table 1. Generic factors influencing adherence to medication and potential solutions in patients with chronic disorders, such as familial hypercholesterolemia

Level	Issues	Solutions/Strategies
Patients	Lack of awareness and knowledge of FH (e.g. cardiovascular risk and early treatment)	Education about FH and ASCVD risk
		Screening of children for FH with parental support
	Uncertainty about FH diagnosis	Formal FH diagnosis
	Scepticism about treatment (e.g. adverse effects, overdose and effectiveness)	Education about LLT (e.g. treatment options, side effects and effectiveness)
	Experience of care and treatment gaps	Shared decision-making with healthcare providers
		Treat with guideline recommended goals
		Regular follow-up visits and treatment monitoring
		Access to new medication
		Pharmacist and skilled nurse counselling
	Forgetting medication	Use of telephone, mobile apps/text messages, e-mail and calendar reminders
		Family support (e.g. reminder/follow-up)
		Pharmacist support (e.g. medications dispensed in time-specific packs)
Healthcare providers	Lack of awareness and knowledge of FH (e.g. cardiovascular risk and early treatment)	Education about FH and cardiovascular disease
	Uncertainty about FH diagnosis	Well defined FH diagnostic criteria
	Lack of sufficient evidence and knowledge of effective treatment	Education about lipid-lowering treatment (e.g. treatment options, side effect and effectiveness)
	Difficulties convincing patients about medication adherence (e.g. insufficient consultation time or lack of skill)	Shared decision-making with patients
		Training in adherence management
		Expanding the healthcare team members (e.g. pharmacist and skilled nurse)
Healthcare system	Lack of awareness and knowledge of FH (patients, their family and the general public)	Development of online or mobile tools and resources (e.g. cardiovascular risk estimator, diagnostic application and education video)
	Complexity of treatment regimen	Use of fixed dose combination regimen (e.g. polypills)
		Less frequent drug administration
	Short supply of medication	Longer duration prescriptions
	Limited access to new medication (e.g. availability and high cost)	Government subsidy (free or co-payment)
	Inadequate patient care	Shared decision-making with patients and/or family
		Regular follow-up visits and treatment monitoring
		Expanding the healthcare team members to share clinical management of the patient (e.g. pharmacist and skilled nurse)

Healthcare provider level

Educational and training initiatives targeted at HCPs can enhance awareness and knowledge of the care of FH and is crucial for improving adherence to treatment. HCPs also need to be specifically trained in adherence management (such as behavioural counselling); shared strategies involving pharmacists and nurses in general practice can promote adherence to treatment [2▪▪]. HCPs should manage FH patients by following guideline-directed treatment recommendations [5]. A definite genetic diagnosis for FH may also motivate HCPs following guideline-recommended treatments [53].

Healthcare system level

Multiple interventions for improving adherence to treatment should be used. Technology reminder interventions, such as the use of telephones, mobile phone text messages, apps for mobile devices, e-mail, calendar remainders and/or alarms, can help to minimize nonadherence due to forgetful behaviour [2▪▪]. Development of online or mobile device tools and resources, such as ASCVD risk estimators, FH diagnostic applications and educational videos, can motivate adherence to treatment. Increasing government subsidy for treatments can reduce the cost of treatments (free or co-payment) and ensure affordability of established and new drugs [48]. Increased healthcare visits with more follow-up and routine treatment monitoring (e.g. lipid blood tests) are also key elements to meet patient needs and expectations [47]. Expanding the healthcare team role can also reinforce treatment adherence [2▪▪]. For example, pharmacists can provide standardised education, regular follow-up and support whilst nurses or psychologists can offer motivational counselling to FH patients [2▪▪,25]. The healthcare system should provide adequate resources for simplifying complex medication regimens. For example, streamlining treatment dosing regimens with use of fixed dose combination therapy (e.g. polypills), longer-duration prescriptions or less frequent drug administration. For example, inclisiran is the most advanced siRNA-treatment targeting hepatic PCSK9 that has been demonstrated to provide sustained reductions in LDL-cholesterol [54▪▪]. Twice-yearly dosing with inclisiran is likely to increase convenience for patients and improve treatment adherence [55].

Taken together, a systematic and integrated approach is required at the level of patients, HCPs and system, as well as government, in order to implement effective strategies to improve treatment adherence. The recent International Atherosclerosis Society (IAS) guideline recommends several implementation strategies on the treatment of patients with FH (Table 2) [2▪▪].

FUTURE DIRECTIONS

Given the complexity of medication adherence as an interplay of socioeconomic, patient, medical condition, therapy, HCP and system factors [23▪▪], predicting nonadherence at the individual patient level is difficult. The determinants of nonadherence in FH will depend on the healthcare landscape, and will vary from country to country. Therefore, future intervention trials and implementation strategies must be tailored to the local determinants, and it is most likely that multifaceted interventions will be required; from tailored solutions addressing the patient's own adherence barriers to population-level strategies to facilitate adherence on a larger scale.

CONCLUSION

FH confers a very high risk for ASCVD with a significant burden on public health from lifetime exposure to LDL-cholesterol if untreated. While expert guidelines have identified different implementation strategies for preventing ASCVD in FH, poor adherence to medication remains a real challenge for achieving treatment goals. Lack of standardized definitions for measuring medication adherence needs to be addressed using reliable, objective and biochemical approaches. The misunderstanding of perceived and actual risk of FH, acute risk and benefits of LLT, knowledge and standardization of treatment or monitoring, and availability of healthcare resources are known to affect patient adherence to treatment in FH. Hence, implementation strategies to improve adherence should be patient-centred, country-specific and contextualised to a given healthcare system, involving a multidisciplinary-team based approach with support from family, community and peer groups. Family-based strategies involving children, adolescents, parents and possibly grandparents may be most rewarding but remains untested. Patient and HCP education, use of cardiovascular imaging as a motivating tool, lifestyle and behavioural interventions, potent combination therapy (e.g. a combination of statin, ezetimibe and PCSK9 inhibitors), simple treatment and long-acting regimens (e.g. inclisiran), subsidies for essential therapies, regular patient follow-up and monitoring of treatment are all crucial for improving treatment adherence. However, these multifactorial interventions for addressing adherence can be expensive and their cost-effectiveness requires assessment in the context of well designed clinical trials.

Table 2. Selected implementation strategies from the International Atherosclerosis Society guidance [2▪▪] for addressing medication nonadherence in patients with familial hypercholesterolaemia

Clinical recommendations
1. Development of a personalized treatment plan for all patients using shared decision-making, considering age, additional risk factors for cardiovascular disease, psychological and socioeconomic factors, barriers to adherence, and personal and family values and preference. Design of personalized treatment plans for children and adolescents should include discussions with parents.
2. Engagement of a patient-centred and family-centred discussion using shared decision-making to decide treatment options, covering risk stratification, expected cardiovascular risk-reduction benefit, potential adverse effects and drug interactions, socioeconomic factors, and personal and family values and preferences.
3. Development of a behavioural counselling approach at subsequent review (e.g. 5A model: assess, advise, agree, assist and arrange) to address and promote adherence to medications and other treatments.
4. Identification of multifactorial barriers related to patient, clinician, drug, healthcare system, psychological and socioeconomic factors in adult FH patients with strategies to address these barriers using appropriate resources by all healthcare providers; medical care should include a more holistic approach for meeting the emotional, psychological and self-management needs of patients.
5. Initiation of maximally tolerated high-potency statins (e.g. atorvastatin, rosuvastatin or pitavastatin) with or without ezetimibe and/or bempedoic acid (if available), and a fat-modified, heart-healthy diet in most adult FH patients; the combination of a high-potency statin, ezetimibe and PCSK9-target therapy should be used in extremely high-risk FH. The initiation medication of choice in children with FH should be a statin that is approved in the relevant country for use in paediatric patients.
6. Identification of patients who are not receiving guideline-directed medical therapy followed by initiation of corresponding treatment using multifaceted strategies.
7. Measurements of plasma level of hepatic aminotransferase (ALT), creatine kinase (CK), glucose (or HbA1c) and creatinine before starting statin therapy.
8. Adoption of multiple interventions for improving adherence to medication with appropriate resources, including provision of free or subsidised medication of established and new drugs, telephone, mobile text messages, E-Mail and calendar reminders, use of single-pill combination drug therapies, expanded role of allied healthcare providers (e.g. simplified dosing by pharmacists and motivational counselling by skill nurses and pharmacists), comprehensive multidisciplinary education programs, patient tools for improving knowledge and understanding of medication and self-care, decision support aids to empower patients and improve the patient-provider relationship, and clinical decision support system-based interventions to improve the quality and safety of prescribing.
9. Use of imaging of cardiovascular disease (e.g. carotid ultrasonography and CT coronary angiography for the detection of plaques and stenosis) to monitor the effectiveness of cholesterol-lowering treatment in asymptomatic FH patients

Acknowledgements

None.

Financial support and sponsorship

No relevant financial support concerning the article.

Conflicts of interest

G.F.W. declares received financial support for advisory boards, lecturing activities and research grants from Amgen, Arrowhead, Esperion, Novartis and Sanofi.

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