

## The Protocol for the Development of Iranian Clinical Practice Guideline on Dyslipidemia

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### Original Article

#### Abstract

**INTRODUCTION:** The prevention and control of dyslipidemia, as an important risk factor for cardiovascular diseases (CVDs), is a priority for the healthcare system to reduce the burden of these diseases. The purpose of this protocol is to outline the key steps of the first Iranian Dyslipidemia Clinical Practice Guideline development, which can be used by other researchers as a guide to design a standard, comprehensive, evidence-based, and local context-based guideline.

**METHOD:** This guideline will be developed and reported according to the format of the World Health Organization (WHO) Handbook for Guideline Development. All members of the guideline development team will sign the declaration-of-competing-interests (DOI) forms. The development of the authors' guideline will be supported by five groups: the steering committee (SC), the Guideline Developing Group (GDG), the systematic review (evidence synthesis) group, and the external review group. The authors will also establish a patient advisory group to inform guideline development by patients' values and preferences. The SC and GDG will determine the scope of the guideline and will design PICO questions. The systematic review group will systematically search Embase, PubMed, Scopus, Web of Sciences, Cochrane Library, and Google Scholar from inception. The systematic review group will assess the risk of bias and create evidence summaries using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. The recommendations of this guideline will be divided into strong recommendations and weak or conditional recommendations or suggestions.

**CONCLUSION:** This clinical practice guideline will provide clinicians and healthcare professionals with new evidence-based recommendations for the diagnosis, management, and treatment of dyslipidemia in children and adults.

**Keywords:** Dyslipidemias, Practice guidelines, GRADE Approach, Recommendations, Suggestion

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#### Introduction

Dyslipidemia is a disorder of lipoprotein metabolism that results in elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides, or high-density lipoprotein (HDL-C) cholesterol. Although dyslipidemia covers a wide range of fat disorders,

the increase in TC and LDL-C has attracted the most attention due to their important role in the development of atherosclerosis<sup>1,2</sup>.

Plasma lipid levels vary from person to person in different communities due to genetic and lifestyle differences, including diverse dietary behaviors and physical activity. The results of a systematic review showed that the prevalence

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of hypercholesterolemia was 42% and the prevalence of high levels of LDL-C was 36% in Iranian adults <sup>1,2</sup>. A national survey in Iran showed that the prevalence of dyslipidemia in Iranian children and adolescents (in terms of hypertriglyceridemia) was 47.5% <sup>2</sup>.

On the other hand, a significant increase in the risk factors for coronary heart disease (CHD) in children and adolescents, especially in developing countries, indicates that this group of the population is at risk of early CHD in the near future <sup>3,4</sup>. Unfortunately, growing evidence shows an association between childhood dyslipidemia and atherosclerosis and its consequences in adulthood. It has been reported that 40-55% of children with dyslipidemia develop dyslipidemia in adulthood <sup>5</sup>. Prevention and control of cardiovascular disease (CVD) risk factors, including dyslipidemia, from an early age may be considered as a preliminary measure in primary or secondary prevention and as a priority for the healthcare system to reduce the burden of CVDs <sup>2</sup>. Given the proven role of dyslipidemia in causing cardiovascular events, especially CHD and stroke, its control is crucial and it requires up-to-date and evidence-based clinical practice guidelines <sup>6,7</sup>.

Most physicians in Iran follow the guidelines of other countries for the diagnosis, management, and treatment of dyslipidemia. Due to differences in determinants of dyslipidemia, funding priorities, available infrastructure resources, health service delivery, insurance and coverage of health services, health priorities, health workforce type, availability of medications and diagnostic tools, burden of disease, and patient value and preferences, Clinical Practice Guidelines (CPGs) need to be contextualized and evidence should be applicable to the local context.

Customizing a CPG to a particular context may improve acceptance and adherence <sup>8</sup>. For successful implementation of a CPG, local policy-makers, clinicians, managers, funders, and end users, including patients and local health providers, need to accept the recommendations <sup>7,9,10</sup>.

The Ministry of Health and Medical Education (MHME) initiated the development of

the clinical practice guideline for the comprehensive care of persons with dyslipidemia to address local issues and target the local context of healthcare.

### *Scope*

The objective of this clinical practice guideline is to provide updated and new evidence-based recommendations for the diagnosis, management, and treatment of dyslipidemia in children and adults to clinicians, other healthcare professionals and stakeholders, and individuals with dyslipidemia and their caregivers.

## **Materials and Methods**

### *Development of dyslipidemia Guideline protocol*

In developing this guideline, the steering committee will follow the format of the Ministry of Health and Medical Education (MHME) in Iran for Guideline Development <sup>11</sup>. The format of the MHME is based on the World Health Organization (WHO) Handbook for Guideline Development <sup>12</sup> and its report items are derived from the Reporting Items for Practice Guidelines in Healthcare (RIGHT) <sup>13</sup>.

### *Guideline development team*

The development of our guideline was supported by five groups:

### *Steering Committee (SC)*

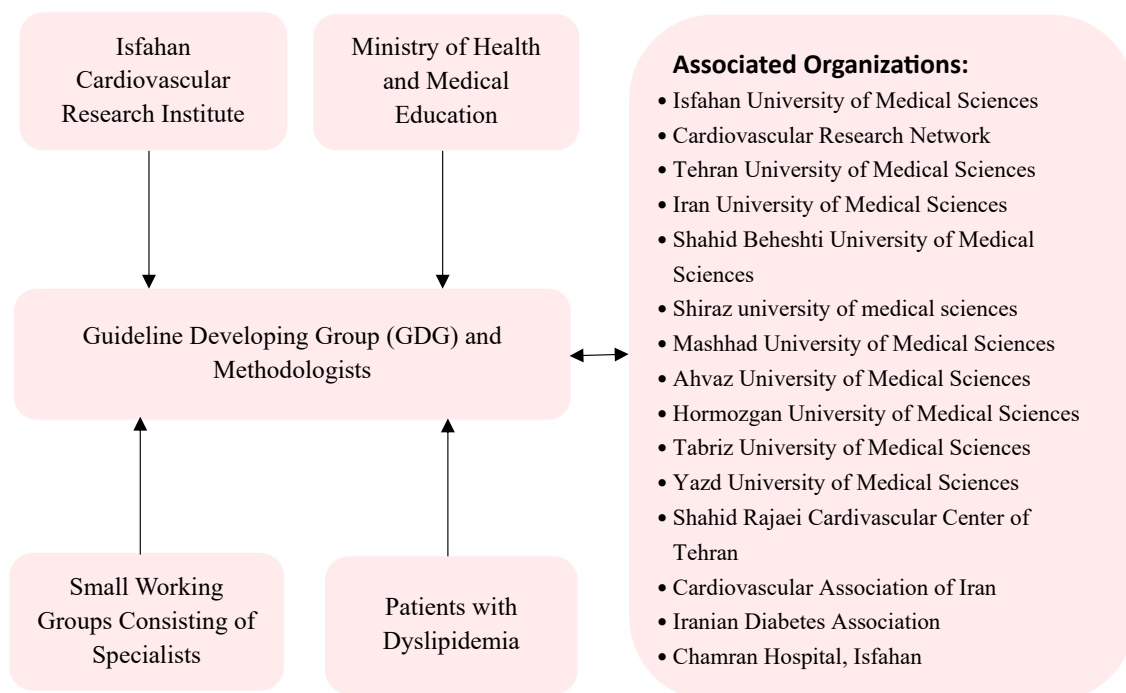
The five-member steering committee, representing the MHME of Iran and the Internal Medicine Society, along with a clinician with extensive methodological training (NSZ) and two associates from the Isfahan Cardiovascular Research Center (SHSH, FB), set the main policies and will oversee all aspects of guideline development. The steering committee will also nominate potential members of the Guideline Developing Group (GDG), Systematic Review Group (SRG), and External Review Group (ERG), organize and set up guidance sessions, and monitor the timing of the development and finalization of the guideline.

### *Guideline Developing Group (GDG)*

The Guideline Development Group will

consist of experts from all over the country (MHME, medical universities, related scientific associations, and research centers) and patient representatives (Figure 1). To ensure that guideline development is informed by the necessary expertise in the management of dyslipidemia, experts will be invited from the fields of cardiology, internal medicine, endocrinology, nephrology, neurology, pediatrics, nutrition, epidemiology, pharmacology, and clinical pharmacy. GDG members have a clear

understanding of the context of health services in Iran in order to correctly identify resources, facilities, and constraints and develop a new guideline, based on the latest available evidence. Two methodologists with sufficient expertise in developing guidelines will supervise the guideline development process. They will assist members of the GDG in designing PICO questions, oversee evidence synthesis, achieve consensus, and facilitate the development of recommendations.



**Figure 1.** Stakeholders and Participating Organizations in Developing Dyslipidemia Guidelines

#### *Systematic Review Group (SRG)*

This group is responsible for evidence synthesis and conducting systematic reviews or other literature searches. The evidence synthesis team will create evidence summaries using the GRADE system to provide a clear description of the certainty of evidence.

#### *External Review Group (ERG)*

This group consists of interested specialists, stakeholders, and experts related to dyslipidemia, as well as experts who are familiar with the structure of the healthcare system. This

group is selected by the steering committee based on specialty and experience. Geographical and gender differences are taken into account. External evaluation team members will review the various stages of the guideline development process. They will review the scope, PICO questions, and draft of recommendations. They will also be consulted about turning the results of the systematic review into recommendations and selecting important outcomes for decision making, and will review and comment on the completed draft guideline based on the AGREE checklist. This group may dis-

agree with or criticize the results based on scientific or philosophical differences. Although it may not be possible to reach an agreement with this group, it is important to pay attention to their criticisms and opinions (14).

#### *Patient Advisory Group*

Patient and consumer participation is a key part of the guideline development process that is effective in identifying priority problems, determining the effectiveness of changes, evaluating the benefits and harms, and assessing the feasibility and acceptability of interventions (15). To ensure the guideline development is informed by patients, the authors will set up a patient advisory group with seven patients with various types of dyslipidemia and some of their family members to determine the needs, values, and preferences of patients with dyslipidemia.

#### *Consumer and Stakeholders*

This guideline will be used by all those involved in the diagnosis, treatment, and management of dyslipidemia in adults and children. This includes cardiologists, endocrinologists, neurologists, pediatricians, nephrologists, gynecologists, general practitioners, nurses, healthcare providers, and health workers, patients with dyslipidemia, and their families.

#### *Scope of Clinical Questions and Outcomes*

The authors will determine the scope of the dyslipidemia guideline by surveying and consulting with MHME and GDG. This guideline will provide recommendations for the diagnosis, management, and treatment of dyslipidemia in children and adults. After identifying priority areas (diagnosis, management, and treatment), members of GDG will identify problems in the areas that need to be addressed. The GDG will identify the required method for diagnosing and monitoring dyslipidemia, and the risk assessment of CVD in children and adults. Furthermore, GDG will recommend effective pharmacological and non-pharmacological interventions in the treatment of dyslipidemia. To manage dyslipidemia, LDL-C and TG thresholds for starting

treatment, treatment goals, and how to follow up patients in adults and children will be noticed. The steering committee provides the list of proposed patient-important outcomes and asks the GDG members to rate the importance of the outcome on a 1-9 scale (7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance). Then the average score will be calculated for each outcome, which indicates its relative importance (16).

#### *Developing PICO questions*

After determining the scope of the guideline, the members of the GDG will send their clinical questions in the areas of diagnosis, management, and treatment of dyslipidemia to the SC. The SC reviewed prior guidelines (17-22) and summarized all prior recommendations and presented them to GDG. A small working group of GDG members will prepare preliminary PICO clinical questions, after eliminating duplicates and irrelevant questions and merging similar questions. The SC will hold a meeting with GDG, and GDG will discuss and reach consensus on the final set of clinical questions.

#### *Identifying the Evidence*

In the first stage, members of the SRG will conduct a search to find a systematic review for each PICO question. The purpose of this step is to find a systematic review and meta-analysis that may answer the PICO question, eliminating the need to conduct a de novo systematic literature review. For this purpose, the SRG will systematically search Embase, PubMed, Scopus, Web of Sciences, Cochrane Library, and Google Scholar. If a systematic review addressed the PICO questions, the reference list, as well as papers that cite the systematic review, will also be reviewed. If the search for eligible systematic reviews was performed over 2 years ago, the SRG will update the search. If the search did not yield any relevant systematic review that addresses the PICO questions, the SRG will develop specific search strategies for the above-mentioned databases and systematically search the literature for original studies from the inception of each database. The SRG will also search for gray literature and unpub-

lished papers in the ProQuest database. Relevant papers and documents, in English and Farsi languages, will be reviewed and evaluated if they meet the inclusion criteria.

### *Evaluating the evidence*

Pairs of reviewers will independently assess the risk of bias of each study using tools developed by the Cochrane group for each type of study (23-26). Disagreements will be resolved through discussion. The SRG will use the approach suggested by the GRADE (Grading of

Recommendations Assessment, Development, and Evaluation) Working Group for rating the certainty (quality) of evidence as high, moderate, low, or very low. The SRG will create an evidence profile using the GRADE system to provide a clear description of benefits and harms, along with the rating of certainty of evidence for each PICO question on an outcome basis (Table 1). The GDG will use these summaries as a basis for discussing and formulating its recommendations (27).

**Table 1.** Evidence profile for overall findings

| Certainty assessment |              |              |               |              |             |                  | № of patients |              | Effect            |                   | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|------------------|---------------|--------------|-------------------|-------------------|-----------|------------|
| № of studies         | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Intervention  | no treatment | Relative (95% CI) | Absolute (95% CI) |           |            |
| Outcome1             |              |              |               |              |             |                  |               |              |                   |                   |           |            |
|                      |              |              |               |              |             |                  |               |              |                   |                   |           |            |
| Outcome2             |              |              |               |              |             |                  |               |              |                   |                   |           |            |
|                      |              |              |               |              |             |                  |               |              |                   |                   |           |            |
| Outcome3             |              |              |               |              |             |                  |               |              |                   |                   |           |            |
|                      |              |              |               |              |             |                  |               |              |                   |                   |           |            |

### *Value and Preferences*

The authors will set up discussion sessions with the patient advisory group to determine the needs, values, and preferences of patients with dyslipidemia. This endeavor will be held before designing PICO questions and patients' opinions will be used in developing PICO questions and the patient advisory group will approve the outcomes. Patients' values and preferences will also be used in the recommendations developing stage.

### *Preparing Evidence to Decision (EtD) Table*

The SRG will prepare EtD tables to help the GDG develop guidelines and move from evidence to recommendations. The EtD tables include an evidence profile, desirable and undesirable anticipated effects, patients' values and

preferences, resources, cost (cost-effectiveness), acceptability by key stakeholders, health equity, and feasibility of implementing the recommendations according to different levels of providing health services in Iran.

### *Developing recommendations*

The GDG will have some online video conference meetings to review relevant evidence for each recommendation and vote for recommendations as strong or weak.

### *Strength of recommendations*

The strength of recommendations indicates the degree to which the GDG is confident that the desirable effects of the recommendations (e.g., beneficial health outcomes) outweigh the



undesirable effects (e.g., side effects).(28). The recommendations of this guideline will be divided into two groups:

#### *Strong recommendation*

A strong recommendation states that all or almost all fully informed patients will choose the recommended course of action.

#### *Weak or conditional recommendation (Suggestion)*

A weak recommendation implies that not all informed patients will be best served by the recommended course of action. There is a need to consider more carefully than usual the individual patient's values and preferences.

#### *Terminology*

Dyslipidemia is described as an increase in the plasma concentration of lipids (triglycerides (TG), total cholesterol (TC) and their blood transport lipoproteins; HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol) (29).

### Discussion

This article is about the protocol of developing the first Iranian clinical practice guideline for the diagnosis and management of dyslipidemia in adults and children. Management of dyslipidemia, as one of the main risk factors of CVD, is one of the important priorities of the healthcare system of any country. Considering that the levels of plasma lipids in different societies vary according to genetics and lifestyle habits, preparing recommendations and suggestions according to the social, economic, political, and cultural conditions of Iran and also based on the values and preferences of patients, available resources, cost of diagnostic and treatment services in the country, and the infrastructure of the healthcare system is crucial.

Recognizing the gap in the management of dyslipidemia is an important challenge from an operational point of view. Therefore, when developing a guideline, a suitable strategy should be considered to involve the people of the executive system and patients, along with scientific and academic individuals.

Recognizing the strengths and weaknesses of the current process of controlling and treating dyslipidemia and identifying better methods to provide care and treatment for patients with dyslipidemia is one of the most important priorities of the dyslipidemia guideline. Identifying these issues will be one of the challenges of the designed protocol.

### Strength and limitations

The proposed guideline has several strengths. First, the GDG will represent all groups of stakeholders involved in the diagnosis, management, and treatment of dyslipidemia. Second, the authors will have a patient advisory group to explore patients' values and preferences, and the patient advisory group will approve the outcomes. Third, the authors will use the GRADE approach to assess the certainty of evidence and formulate recommendations in a systematic and transparent manner.

A potential limitation is the lack - or very limited - research evidence to develop clinical expert guidance and answer some PICO questions. Another challenge in this regard is evidence synthesis and literature review. Getting help from experts and research institutions and getting the cooperation of Cochrane can be effective solutions.

### Conclusions

Based on previous experiences and the latest methodological developments, the authors have improved the CPG development methods as described in this protocol. This will result in an enhanced quality CPG which is expected to be widely implemented.

### Dissemination and implementation

Dissemination includes making guidelines available, advertising their availability, and distributing them widely. The instructions will be published through the MHME and will be communicated to medical universities. They will also be posted on the website of the MHME and other related websites (such as the

websites of medical sciences universities and scientific associations), and an article about them will also be published in one of the scientific journals.

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### Conflicts of interest

The process of identifying and managing conflicts of interest for all groups involved in the development of guidelines, including GDG, systematic review group, external review group and external partners, will be done by the steering committee. The members of each group, at the beginning of their formation, will declare their interests and affiliations of any kind (financial, labor, research, consulting, intellectual) of conflict of interest in a specific and written manner. After reviewing the DOI of members, if any conflict of interest was identified, the cases will be managed by the steering committee and possible actions such as removal from group participation or restriction on participation in discussions or restriction on voting on the recommendation are taken.

Ethics approval and consent to participate: The study is being conducted in compliance with the principles of Declaration of Helsinki. This study is approved by the Ethics Committee of Isfahan University of Medical Sciences with proprietary ID, IR.MUI.REC.1399.006. Informed consent will be obtained from all subjects and/or their legal guardian(s).

**Consent for publication:** Not applicable

**Availability of data and materials:** Not applicable

plicable

**Competing interests:** The authors declare that they have no competing interests.

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