Dyslipidemia Guidelines 2015

2015 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines - Executive Summary

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The Philippine Heart Association, the Philippine Lipid and Atherosclerosis Society, and the Philippine Society of Endocrinology, Diabetes, and Metabolism, collaborated to develop the 2015 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines (2015 CPG). These guidelines are meant to update the 2005 Clinical Practice Guidelines on the Management of Dyslipidemia in the Philippines (2005 CPG). A panel of experts in the fields of dyslipidemia, cardiology, endocrinology and epidemiology were assembled to comprise the technical research committee (TRC) tasked to review available clinical evidence on dyslipidemia management. The main objective for this document is to develop clinical guidelines in the management of Filipino patients who are diagnosed with elevated cholesterol. This may influence standards and national policies for optimal patient care and cardiovascular health.

The physician may employ the recommendations confidently in caring for most patients; however, this CPG is meant to define practices that meet the needs of patients in most circumstances. The ultimate decision must be made by the Filipino physician and patient together, and should not be a replacement for clinical judgment.

SCOPE OF THE GUIDELINES

The scope of this CPG includes current statistics on the prevalence of dyslipidemia in our setting, recommendations on screening and monitoring using lipid profile determination, identification of groups at risk for cardiovascular (CV) events which will be targeted for prevention and treatment, and recommendations for the treatment of dyslipidemia for the prevention of CV events and mortality in Filipinos.

METHODS

The TRC initially reviewed the recommendations in the 2005 CPG and proposed clinical questions to be answered by the 2015 CPG. In order to update the 2005 CPG, the current guideline generally used the same methods as the earlier document. The TRC specified the population, intervention and outcomes for each clinical question, and defined the criteria for eligible studies.

Table 1. Clinical Questions

Clinical Questions	
CQ1	Among patients diagnosed to have dyslipidemia, regardless of their present morbid condition or risk profile, should lifestyle modifications (i.e., smoking cessation, weight management, regular physical activity and adequate blood pressure monitoring and control) be advised to reduce overall CV risk?
CQ2	Among non-diabetics without ASCVD but with multiple risk factors, should statin therapy be given?
CQ3	Among diabetic patients without ASCVD, should statins be recommended?
CQ4	Among diabetic patients without ASCVD, should fibrates be recommended as an alternative to statin therapy?
CQ5	Among patients with established ASCVD, should statins be given?
CQ6	Among individuals with ASCVD, should fibrates be given as an alternative to statins?
CQ7	Among patients with acute coronary syndrome (ACS), should statin therapy be given?
CQ8	Among patients with established ASCVD or diabetes, should lipid profile determination be done? Among patients without ASCVD but with multiple risk factors, should lipid profile determination be done?
CQ9	Among patients with ASCVD, should omega-fatty acids be given as an alternative to statin treatment?

CLINICAL QUESTIONS

The TRC developed an initial set of questions based on their expertise and from the 2005 CPG. From the initial document, nine (9) clinical questions (CQs) were prioritized and were used to provide the guidelines for the 2015 CPG.

CLINICAL OUTCOMES

Various clinical outcomes were rated and ranked using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) categories of importance. The clinical outcomes were rated numerically on a 1-to-9 scale following the GRADE categories, where a score of 7-9 is critical; 4-6 important; and 1-3, of limited importance. According to GRADE, ranking outcomes by their relative importance can help to focus attention on those outcomes that are considered most important and help to resolve or clarify disagreements.

The TRC designated the following outcomes to be **CRITICAL** with a score of 9:

- Total mortality
- Cardiovascular deaths;
- Fatal and non-fatal myocardial infarction and
- Stroke or cerebrovascular disease

Cardiovascular events was ranked as **CRITICAL** with a Score of 7. Coronary revascularization was assigned to be an **IMPORTANT** outcome with a GRADE PRO Score of 6. Additional important outcomes were added when deemed necessary for the particular clinical scenario (e.g., angina in ACS).

Table 2. Criteria for recommendation

Quality of Evidence	Outcome	NNT	Recommendation
High	Critical	Low	Strongly Recommend
Moderate	Critical	Low	Recommend
Moderate	Important	Low	May Recommend
Low	Critical or important	High or not significant	Do not recommend

With regards to the recommendation on the use of lipid profile determination, draft recommendations were formulated so as to facilitate the implementation of the therapeutic interventions (e.g., lifestyle modification, statins, and non-statins) recommended in these 2015 CPG.

CPG CQs and Recommendations

For the 2015 CPG, we have nine clinical questions but only six statements. There were issues on clinical questions on non-statin therapies (CQs 4, 6 and 9) so no statements were made. The TRC and the voting panel decided to provide a section on the use of non-statin therapy despite the lack of clinical data.

Clinical Question 1

CQ1. Among patients diagnosed to have dyslipidemia, regardless of their present morbid condition or risk profile, should lifestyle modification (i.e., smoking cessation, weight management, regular physical activity and adequate blood pressure monitoring and control) be advised to reduce overall CV risk?

The importance of lifestyle modifications, such as proper diet and exercise, has been repeatedly emphasized and been given increasing attention because of their relation to cardiovascular disease. The TRC recommends that lifestyle modification be advised to patients diagnosed with dyslipidemia regardless of their risk profile. Specific recommendations for this clinical question are on diet, exercise and smoking. Recommendations on adequate blood pressure control and weight loss are already documented in the guidelines of the Philippine Society of Hypertension (PSH) and Philippine Association in the Study of Overweight and Obesity (PASOO), respectively.

Statement 1.1 Diet

For individuals at any level of cardiovascular risk, especially those with established atherosclerotic cardiovascular disease (ASCVD), a low-fat, low-cholesterol diet, rich in fruits and vegetables, is **RECOMMENDED**.

Simple Dietary Plan for Fat Modification

In 2014, the FNRI released a simpler version of the food pyramid, which they termed as “Pinggang Pinoy” or “Pinoy Plate”. It used a science-based approach with the best scientific evidence and compliments and supplements the food pyramid of the FNRI. It serves as a reminder to Filipinos on how to fill up their plates properly. A nine-inch plate is advised, and distributing foods proportionally among the food groups provides approximately 1,200 to 1,500 calories per day. It is advised that half of the plate is composed of green leafy vegetables and one serving of fruit per meal. For fruits, 4 to 6 servings are encouraged per day.

PINGGANG PINOY™

Healthy food plate for Filipino adults

Figure 1. Pinggang Pinoy

Statement 1.2 Smoking Cessation

For individuals at any level of cardiovascular risk, cigarette smoking cessation is **STRONGLY RECOMMENDED**.

Statement 1.3. Exercise

For individuals at any level of cardiovascular risk, adequate exercise is **RECOMMENDED**.

Clinical Question 2

CQ 2. Among non-diabetics without ASCVD but with multiple risk factors, should statin therapy be given?

This clinical question aims to give guidance to the use of cholesterol-lowering treatment for primary prevention in patients with several cardiovascular risk factors. These risk factors were identified based on the clinical trials reviewed for the CPG.

Statement 2

For non-diabetic individuals aged ≥ 45 years with LDL-C ≥ 130 mg/dL AND ≥ 2 risk factors*, without atherosclerotic cardiovascular disease, statins are **RECOMMENDED** for the prevention of cardiovascular events.

**Risk factors are: male sex, postmenopausal women, smoker, hypertension, BMI > 25 kg/m², family history of premature CHD, microalbuminuria, proteinuria, and left ventricular hypertrophy.*

**Patients who fulfill the criteria for the diagnosis of familial hypercholesterolemia (see statement 8 on screening and lipid monitoring for familial hypercholesterolemia) should be initiated therapy for aggressive LDL-C lowering*

Clinical Question 3

CQ 3. Among diabetic individuals without ASCVD, should statins be recommended?

Statement 3

For diabetic individuals without evidence of atherosclerosis (ASCVD), statins are **RECOMMENDED** for primary prevention of cardiovascular events.

Clinical Question 4

CQ 4. Among diabetic individuals without ASCVD, should fibrates be recommended as an alternative to statin therapy?

Statement 4

See section on non-statin therapy.

Clinical Question 5

CQ 5. Among patients with established ASCVD, should statins be given?

Statement 5

For patients with established atherosclerotic cardiovascular disease (ASCVD), statin therapy is **RECOMMENDED**.

This updated guideline recommends that high-intensity statin therapy be used in secondary prevention of patients diagnosed with ASCVD. It should be emphasized that the definition of statin treatment intensity (Table 3) rests on the degree of LDL-C reduction, and less on the drug dose used.

Table 3. Statin treatment intensity

Treatment intensity	% LDL-C reduction	Drug regimen
Low intensity	20% - 30%	Fluvastatin 20-40 mg Pravastatin 5-40 mg Simvastatin 10 mg
Moderate intensity	31% - 50%	Atorvastatin 10-20 mg Fluvastatin 80 mg Rosuvastatin 5 mg Simvastatin 20-40 mg
High intensity	>50%	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

Statin Treatment Goal

In general, the 2015 CPG recommends a **30% or greater reduction in LDL-C** for appropriate treatment goal with statin therapy, as trials on moderate- vs high-intensity statin therapy have shown a dosedependent response in terms of benefit in the reduction of adverse outcomes. However, for purposes in clinical practice, a **treatment goal LDL-C level of < 70 mg/dL** may be recommended, as adapted by some international guidelines.

Clinical Question 6

CQ6. Among patients with ASCVD, should fibrates be given as an alternative to statins?

Statement 6

See section on non-statin therapy.

Clinical Question 7

CQ7. Among patients with acute coronary syndrome (ACS), should statin therapy be given?

Statement 7

For individuals with acute coronary syndrome, early high-intensity statin therapy is **RECOMMENDED** and should be continued when already on statin therapy.

Clinical Questions 8

CQ8. Among patients with established ASCVD or diabetes, should lipid profile determination be done?

Among patients without ASCVD but with multiple risk factors, should lipid profile determination be done?

Statements 8

For individuals with evidence of ACSVD or diabetes, the use of the lipid profile is **RECOMMENDED** for monitoring of treatment response since ALL patients with ASCVD should be on lipid-lowering therapy.

For individuals without evidence of ASCVD but aged > 45 years AND with 2 or more risk factors*, the use of lipid profile for screening is **RECOMMENDED**.

For individuals on lipid-lowering therapy, the use of lipid profile for monitoring of treatment response is **RECOMMENDED**.

* Risk factors are: male, postmenopausal women, smoker, hypertension, BMI > 25 kg/m², family history of premature CHD**, microalbuminuria, proteinuria, and left ventricular hypertrophy.

Screening of Familial Hypercholesterolemia

Patients who fulfill the criteria for the diagnosis of familial hypercholesterolemia (Table 4) should be initiated therapy for aggressive LDL-C lowering

Table 4. Dutch Lipid Network criteria on the diagnosis of heterozygous familial hypercholesterolemia⁹⁴

CRITERIA	POINTS
Family history	
First-degree relative with known premature* coronary and vascular disease, OR First-degree relative with known LDL-C level above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C level above the 95th percentile	2
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C ≥ 330 mg/dL (≥8.5)	8
LDL-C 250 – 329 mg/dL (6.5–8.4)	5
LDL-C 190 – 249 mg/dL (5.0–6.4)	3
LDL-C 155 – 189 mg/dL (4.0–4.9)	1
DNA analysis	
Functional mutation in the LDLR, apo B or PCSK9 gene	8
DIAGNOSIS (diagnosis is based on the total number of points obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6-8
Possible Familial Hypercholesterolemia	3-5
Unlikely Familial Hypercholesterolemia	<3

* Premature: < 55 years in men; < 60 years in women
LDL-C; low density lipoprotein cholesterol; FH, familial hypercholesterolemia; LDLR, low density lipoprotein receptor; Apo B, apolipoprotein B; PCSK9, proprotein convertase subtilisin/kexin type 9.

Due to the high cardiovascular risk of these patients from prolonged exposure to elevated LDL-C levels very early on in life, the lipid profile should be carried out initially as screening, even younger than age 45 years, in patients with high index of suspicion (patients with elevated LDL-C levels > 190 mg/dL, significant personal or family history of premature cardiovascular disease) then subsequently for monitoring treatment response since ALL patients with FH should be on aggressive LDL-C lowering therapy.

Lipid determination in secondary prevention

Since treatment is recommended among patients with ASCVD with or without diabetes, regardless of lipid levels, lipid profile determination is not necessary for screening but for monitoring therapeutic response since ALL patients should already be on treatment. The role of the lipid profile lies in its ability to determine the percent reduction or the level of LDL achieved after six weeks of treatment to 3-6 months thereafter. The time to achieve target levels based on the trials ranged from 1 to 8 years.

Lipid monitoring in diabetics in primary prevention

If the repeat levels are still below the desired reductions or LDL-C level, intensification of lifestyle modification and pharmacologic therapy is warranted. Statins can then be increased to the maximal dose tolerated.

Lipid determination in primary prevention

For individuals without evidence of ASCVD who are ≥ 45 years old and with 2 or more risk factors, the use of lipid profile for screening is recommended. Moreover, lipid profile determination is also needed to monitor treatment response. In the trials on primary prevention, the average reduction of TC and LDL-C was 20% and 29% respectively with a minimum duration of 1 year (range: 1.9 to 5 years) for benefit to be achieved. Lipid profile determination was done after 3 months of treatment and yearly thereafter. Lastly, based on the trials, monitoring of lipid profile after 3 months of treatment is also recommended to determine achievement of treatment goals.

To guide clinicians, Figure 2 outlines a proposed algorithm for the screening and treatment of patients.

Figure 2. Screening and treatment algorithm for the management of dyslipidemia

Legend:

* Risk factors: male, smoker, hypertension $> 140/90$ mmHg, BMI 25 kg/m^2 , family history of premature coronary heart disease, proteinuria, left ventricular hypertrophy and post menopausal women

** The guideline recommends high intensity dose of statins to reach target

** Treatment goal is to reduce LDL-C by $>30\%$, or $< 70 \text{ mg/dl}$

Note: If the patient is suspected or considered to have Familial Hypercholesterolemia (FH) based on the Dutch Lipid Network score, lipid profile is used for screening and monitoring of effect of treatment.

Monitoring for adverse drug reactions

Long-term treatment of dyslipidemia may bring about concerns for adverse drug reactions such as myalgias, myopathies and elevations of liver function tests.

Baseline measurement of hepatic transaminase levels (alanine and aspartate aminotransferase) should be performed before initiation of statin therapy in patients at risk for developing liver injury. Serial liver function test monitoring in asymptomatic individuals are not recommended. However, should testing reveal elevations in transaminase levels during the course of statin therapy, the recommended course of action is outlined in Figure 3.

Figure 3. Algorithm for patients who are on Statins with Elevated Liver Enzymes

Legend:

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal

Statin-induced Myopathy

Statin myopathies are classified as either myalgias, myopathies, myositis, or rhabdomyolysis (Table 5). In patients at risk for development of statin myopathies, baseline creatine phosphokinase and subsequent monitoring should only be performed when symptoms are present.

Table 5. Classification of statin myopathies

	Myalgia	Myopathy	Myositis	Rhabdomyolysis
ACC/AHA NHLBI	Focal or diffuse muscle aches or weakness with normal CK	Any disease of muscle	Muscle pain with CK elevation	Severe muscle damage with damage to another organ (i.e., kidney) and CK $> 10 \times \text{ULN}$
NLA		Myalgia with CK $> 10 \times \text{ULN}$		
US FDA				CK $> 50 \times \text{ULN}$ + organ damage

ACC/AHA, American College of Cardiology/American Heart Association; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; FDA, Food and Drug Administration; CK, creatine kinase; ULN, upper limit of normal.

The TRC recommends a localized management algorithm for statin-treated patients with muscle symptoms (Figure 4).

Figure 4. Algorithm for Statin-induced Myopathy

*If symptoms recur after multiple statin use at multiple dosing, may use non-statin therapy (fibrates or ezetimibe)

Clinical Question 9

Among patients with ASCVD, should omega-fatty acids be given as an alternative to statin treatment?

Statement 9

See Section on Non-statin therapy

Non-statin Therapy

For diabetic and non-diabetic individuals with or without evidence of ASCVD, the use of fibrates and poly-unsaturated fatty acids (PUFA) or omega 3 fatty acids are **NOT RECOMMENDED** as alternative to statins for the secondary prevention of cardiovascular events.

The use of fibrates may be considered among patients with a high baseline TG > 204 mg/dl and low HDL-C < 34 mg/dl once LDL-C has been reached on a maximally dosed statin.

Combination Therapy

The TRC and the voting panel are in agreement that combination therapy of a non-statin therapy (eg: omega 3 FA, ezetimibe, fibrates) and a statin allows for a greater degree of LDL-C reduction and results in achievement of goal attainment for primary and secondary prevention.

However, there are no clinical trials to date supporting the use of more ideal combination therapies. Recommendations regarding combination of fenofibrate/statin and ezetimibe/statin may be recommended only in patients who may benefit from the combination treatment.

CONCLUSION

Six clinical statements were made by the TRC and the recommendations revolve around the holistic management of dyslipidemia. Lifestyle modification should be recommended to all patients regardless of their CVD risk. High intensity statins are recommended to lower LDL-C by > 30% or < 70 mg/dl in the primary and secondary prevention of ASCVD, both for diabetic and non-diabetic patients. The simplified algorithm was provided to serve as a quick reference in the management of clinicians.

The updated 2015 CPG is designed to be a guide for clinicians in managing dyslipidemia for the Filipino patient. This, however, should not replace sound clinical judgment by doctors and the ultimate decision for treatment should involve both clinician and the patient.