Diagnosis and Management of Dyslipidemia in Family Practice

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Background: Atherosclerotic cardiovascular disease (ASCVD) is a top cause of mortality in the Philippines. A known modifiable risk factor for ASCVD is dyslipidemia. Thus, proper diagnosis and management of dyslipidemia in family practice clinic could significantly decrease the burden of cardiovascular disease in the country.

Objectives: This clinical pathway was developed to guide family and community physicians on the diagnosis and management of dyslipidemia.

Methods: To develop evidence -based recommendations, the authors searched for the latest guidelines of reputable international and local societies. They also searched PubMed using the terms "dyslipidemia", "diagnosis", "therapeutics", "family" and "community medicine". The more rigorous meta-analysis of clinical trials and observational studies were prioritized over low-quality trials in the formulation of the recommendations.

Recommendations: Thorough ASCVD risk assessment for all adults should be done during initial visit in family practice. The physician should review patient's present medication; probe regarding lifestyle habits; conduct complete physical examination; use family assessment tools; and assess risk for ASCVD using calculators or risk factor counting method. For patients ≥ 45 years old and all adult patients regardless of age at increased ASCVD risk the following should be requested: lipid profile, urinary albumin- creatinine ratio/ urinary dipstick test, alanine transaminase (ALT), 12-lead electrocardiography (12-L ECG) and fasting blood sugar (FBS). During subsequent visits, re-assessment of ASCVD risk; checking compliance to non-pharmacologic intervention; and review of medication adherence and adverse effects should be performed. Repeat measurement of lipid profile should be done 6-8 weeks after initiation of statin therapy; 8-12 weeks after dose adjustment; and biannually for patients with controlled lipid levels. For individuals on statin therapy who have already achieved their low-density lipoprotein cholesterol (LDL-C) goal, compute for non- high density lipoprotein cholesterol (non-HDL C). Repeat ALT 6-8 weeks after initiation of statin therapy for those at high risk of statin-induced liver injury. Request creatine kinase (CK) if with development of muscle symptoms while on statin therapy. For primary prevention, start low-moderate intensity statins for following: individuals with diabetes mellitus (DM) Type 2 without ASCVD; individuals with mild-moderate chronic kidney disease (CKD); and individuals without ASCVD aged ≥ 45 years old with LDL -C ≥ 130 mg/dl AND with ≥ 2 risk factors. Start high intensity statins for individuals diagnosed with Familial Hypercholesterolemia. Give high intensity statins as secondary prevention for individuals with established ASCVD. For individuals with ASCVD on maximally tolerated statin therapy not meeting target LDL-C, ezetimibe could be added to their regimen. Low saturated fat diet rich in fruits and vegetable; regular exercise; and smoking cessation should be advised for all adult patients. The physician should also engage other family members to adopt healthy lifestyle. Formation of a community-based lifestyle intervention program to reduce cardiovascular risk should also be supported by the family physician.

Implementation: Adherence to pathway recommendations that are graded as either A-I, A-II or B-I is strongly advised. However, the authors also recommend using sound clinical judgment and patient involvement in the decision making before applying the recommendations.

Introduction

Diseases of the heart and the vascular system are the top causes of mortality in the Philippines. In 2015, these diseases led to almost 200,00 deaths (35.3% of all deaths), causing more deaths among Filipino men (111,403) than women (86,674).[1] Atherosclerosis in the arteries remains as the major underlying pathology of cardiovascular diseases (CVD). In the coronary vessels, atherosclerosis causes myocardial ischemia. In the arteries supplying the brain, it leads to stroke and cerebrovascular ischemia. In the peripheral circulation, it causes claudication in the lower limbs.[2]

A well-established modifiable risk factor for atherosclerosis is dyslipidemia or lipid disorders. Lipid disorders are derangements in plasma lipoproteins and abnormalities in lipid metabolism. Lipoproteins, specifically those containing Apolipoprotein B (ApoB), have an integral role in the development of atherosclerosis. ApoB containing lipoproteins include low density lipoprotein- cholesterol (LDL-C), intermediate density lipoprotein cholesterol (IDL-C), very low-density lipoprotein cholesterol (VLDL-C) and the chylomicrons.[3] The main initiating process to development of atherosclerosis is the entry and retention of ApoB lipoproteins in the subendothelium of the arterial walls. This accumulation of ApoB lipoproteins in the arterial walls which depends on sustained plasma levels of ApoB lipoproteins, will trigger a localized macrophage and t-cell- mediated inflammatory response. This will lead to subsequent steps of atheroma development or plaque formation.[4] LDL-C, the most numerous among the ApoB-containing lipoproteins, has consistently been proven to be associated with risk of ASCVD. Lowering the plasma LDL-C reduces the risk of developing ASCVD and more.[5]

Almost 1 out of 2 Filipinos has increased serum total cholesterol (≥ 200mg/dl) and LDL-C (≥ 130mg/dl) - 47.2% and 47.5%, respectively. According to the 2013 National Nutrition Survey Clinical Health Survey, women are more affected than men with 21.9% of them having LDL-C ≥ 160mg/dl. Disease awareness, treatment and control of dyslipidemia remain poor.[6,7,8]

A multi-center, observational study done among 1868 participants identified as having a need for preventive treatment for ASCVD showed that among 1482 (79.3%) in secondary prevention group, only 67.5% were prescribed with statin and only 18% met the recommended LDL-C goal. Among the 386 (20.7%) into the primary prevention group, only 30.1% received statin therapy and only 10% met the recommended LDL-C goal.[9]

Objectives

This clinical pathway was developed to guide family and community physicians on the diagnosis and management of dyslipidemia. It provides recommendations to the following clinical decisions: 1) clinical history and physical examination; 2) laboratory and ancillary procedures to be requested; 3) pharmacologic interventions; 4) non-pharmacologic interventions; and 5) patient outcomes to expect.

Methods of Development and Implementation

Members of the Philippine Academy of Family Physician (PAFP) Publication Committee reviewed the published medical literature to identify, summarize, and operationalize the evidence in clinical publication on the management of patients with dyslipidemia in family and community practice. The recommendations are time-bound tasks on patient care processes, in terms of history and physical examination, laboratory tests, pharmacologic and non-pharmacologic interventions. The group adopted several strategies in developing the recommendations. The first strategy is emphasizing on evidence-based recommendations as recommended assessments and interventions. The second strategy is recognition of potential variations between-patient and between specific practice settings. The third strategy is the recognition of "stakeholder groups" in family and community practice with careful attention to getting their opinion and support but without sacrificing the objectives of the clinical pathway's implementation. The fourth strategy is emphasis on the commitment to establishment of the goal of improving the effectiveness, efficiency, and quality of patient care in family and community practice.

For the first strategy, the authors searched for the latest guidelines of reputable international and local societies including but not limited to American Heart Association, American College of Cardiology, European Society of Cardiology, European Atherosclerosis Society, Philippine Lipid and Atherosclerosis Society and Philippine Heart Association. They also searched PubMed using the terms "dyslipidemia", "diagnosis", "therapeutics", "family" and "community medicine" Retrieval of articles was focused on the following type of clinical publications: clinical practice guidelines, meta-analysis, randomized controlled trials and clinical trials. The more rigorous meta-analysis of clinical trials and observational studies were prioritized over low-quality trials in the formulation of the recommendations. The evidence for the patient care processes were reviewed and summarized as notes to justify the recommendations. The second strategy was to present the recommendations to the PAFP Research Committee who acted as panel of experts and discussed potential variations in different setting of family practice. As part of the third strategy, the clinical pathway will then be disseminated to the selected PAFP chapters and members and other stakeholders for consensus development. Dissemination will be publication in the Filipino Family Physician Journal, conference presentations (PAFP Annual Convention) and focused group discussions.

As a fourth strategy, the implementation of clinical pathways to be adopted by the PAFP will be quality improvement activities in a form of patient record reviews, audit, and feedback. Audit standards will be the assessment and intervention recommendations in the clinical pathway. Implementation of clinical pathways will be at the practice level and the organizational level. Practice level can be a simple count of family and community medicine practitioners using and applying the clinical pathways. Organizational outcomes can be activities of the PAFP devoted to the promotion, development, dissemination, and implementation of clinical pathways.

Grading of the Recommendations

Chosen members of the PAFP Research Committee met as a panel and graded the recommendations as shown in Table 1. The grading system was a mix of the strength of the reviewed published evidence and the consensus of a panel of experts. In some cases, the published evidence may not be applicable in Philippine family and community

practice setting, so a panel grade based on the consensus of clinical experts was also used. Thus, if the recommendation was based on a published evidence that is a well done randomized controlled trial and the panel of expert voted unanimously for the recommendation, it was given a grade of A-I. If the level of evidence is based on an observational study but the panel still unanimously considered the recommendation, the grade given was A-II and if the level of evidence is just an opinion and the panel still unanimously recommended it, the grade was A-III.

Table 1. Grading of the recommendations.

Panel Grade Level	Evidence Grade Level		
	1	2	3
A	A-I	A-II	A-III
B	B-I	B-II	B-III
C	C-I	C-II	C-III

Panel Grade Levels

A - All the panel members agree that the recommendation should be adopted because it is relevant, applicable and will benefit many patients.

B - Majority of the panel members agree that the recommendation should be adopted because it is relevant, applicable in many areas and will benefit many patients.

C - Panel members were divided that the recommendation should be adopted and is not sure if it will be applicable in many areas or will benefit many patients.

Evidence Grade Levels

I - The best evidence cited to support the recommendation is a well-conducted meta-analysis and randomized controlled trial. The CONSORT standard may be used to evaluate a well-conducted randomized controlled trial.

II - The best evidence cited to support the recommendation is a well-conducted observational study i.e., match control or before and after clinical trial, cohort studies, case control studies and cross-sectional studies. The STROBE statement may be used to evaluate a well-conducted observational study.

III - The best evidence cited to support the recommendation is based on expert opinion or observational study that did not meet the criteria for level II.

In the implementation of the clinical pathways, the PAFP Quality Assurance (QA) committee recommend adherence to guideline recommendations that are graded as either A-I, A-II or B-I. However, the committee also recommend using sound clinical judgment and patient involvement in the decision making before applying the recommendation

Pathway Recommendations

	Pathway Tasks				
Visit	History and Physical Examination	Laboratory	Pharmacologic Intervention	Non-pharmacologic Intervention	Patient Outcomes
First Visit	• Perform thorough ASCVD risk assessment for all adults (Refer to Table 1) (A -I) • Review patient's present medications (A-I) • Probe regarding lifestyle habits (diet, physical activity, smoking) (A-I) • Conduct complete physical examination including the following for assessment of cardiovascular risk (A-I): a. BP measurement b. Waist Circumference/BMI c. Signs of ASCVD • Utilize family assessment tools (A-II) • Assess risk for ASCVD using either calculator (B-I) or risk factor counting method (A-I)	• Request the following for patients ≥ 45 years old and all adult patients regardless of age at increase cardiovascular risk: a. Lipid Profile (B-I) b. Urine albumin-to-creatinine ratio/ Urine protein dipstick test (A-I) c. Alanine Transaminase (ALT) (A-I) d. 12-L-ECG (A-I) e. FBS (A-I) • Request for other laboratory examinations as recommended by pathways/ guidelines appropriate for the patient with co-morbidities such as hypertension, diabetes mellitus (DM) and ASCVD	• No pharmacologic intervention if with no compelling indication (A-I) NOTE: See variation below for pharmacologic treatment.	Patient Interventions • Recommend low saturated fat diet rich in fruits and vegetables (A-I) • Prescribe regular exercise with appropriate frequency and intensity (A-I) • Advise smoking cessation (A-I) Family Intervention • Engage other family members, especially spouses, to also adopt the lifestyle interventions prescribed (A-II) Community-Level Intervention • Promote the formation of a community-based lifestyle intervention program to reduce cardiovascular risk (A-I) Follow-up visit: Within 1- 2 weeks (III-A)	• Awareness of diagnosis and risks (A-II) • Understanding and agreement to diagnostic, pharmacologic and non-pharmacological treatment (A-II)

Pathway Tasks					
Visit	History and Physical Examination	Laboratory	Pharmacologic Intervention	Non-pharmacologic Intervention	Patient Outcomes
Variation			Proceed to second visit table if patient (A-I): • Already has laboratory results • Diagnosed with the following: o ASCVD o Diabetes Mellitus (DM) o Familial Hypercholesterolemia o Moderate-Severe Chronic Kidney disease (CKD)		
Second Visit	• Ask for symptoms pertaining to development of ASCVD (A-I) • Check for compliance to agreed non-pharmacologic intervention (A-I) • Repeat complete physical examination with focus on the following (A-I): o BP measurement o Waist Circumference/BMI o Signs of ASCVD • Review laboratory results (A-I) • Reassess risk for ASCVD using either calculators (B-I) or risk factor counting method (A-I)	• Repeat lipid profile 6-8 weeks after initiation of statin therapy (A-III) • Repeat ALT 6-8 weeks after starting statin therapy for high-risk patients (A-III) • Request CK if with myalgia (A-I)	In the absence of contraindications, start statin for the following: • Give low-moderate intensity statins as primary prevention for the following: o Individuals with DM (A-I) o Individuals with mild to moderate CKD (A-I) o Individuals without ASCVD aged ≥ 45 years old with LDL -C ≥ 130 AND with ≥ 2 risk factors (A-I) or depending on the result of the risk calculator (B-I) • Give high intensity statins for individuals diagnosed with Familial Hypercholesterolemia (A-I) • Give high intensity statins as secondary prevention for individuals with established ASCVD (A-I)	Patient Interventions • Recommend low saturated fat diet rich in fruits and vegetables (A-I) • Prescribe regular exercise with appropriate frequency and intensity (A-I) • Advise smoking cessation (A-I) • Discuss barriers and misperceptions to lifestyle change (A-III) • Explain the dose, frequency, intended effect, possible side effects of medications and importance of medication adherence (A-III) Family Intervention • Engage other family members, especially spouses, to also adopt the lifestyle interventions prescribed (A-II) Community-Level Intervention • Promote the formation of a community-based lifestyle intervention program to reduce cardiovascular risk (A-I) Follow-up visit: • Immediately if with development of muscle symptoms while on statin therapy or if with any adverse event from medication (A-I) • 6-8 weeks after initiation of statin therapy if with no development of adverse event from medication (A-III)	• Adherence to lifestyle change (A-I) • Adherence to diagnostic, pharmacologic and non-pharmacological treatment, and other management plan (A-I) • Awareness of symptoms to watch out for and adverse effect of statins (A-II) • Awareness of goal LDL-C, target BMI and understands the importance of achieving it (A-II)
Variations					

Pathway Tasks					
Visit	History and Physical Examination	Laboratory	Pharmacologic Intervention	Non-pharmacologic Intervention	Patient Outcomes
Continuing Visit	• Ask for symptoms pertaining to development of ASCVD (A-I) • Check for compliance to agreed non-pharmacologic intervention (A-I) • Repeat complete physical examination with focus on the following (A-I): o BP measurement o Waist Circumference/BMI o Signs of ASCVD • Review laboratory results (A-I) • Reassess risk for ASCVD using either calculators (B-I) or risk factor counting method (A-I) • Check for compliance to lipid lowering agent and other medications (A-I) • Check for drug-related adverse effects. For individuals prescribed with statin, ask about statin- induced muscle symptoms (A-I)	• Repeat lipid profile 8-12 weeks after dose adjustment (A-III) • Request CK if with myalgia (A-I) • For individuals on statin therapy who have already achieved their LDL-C goal, compute for non-high-density lipoprotein cholesterol (non-HDL-C). (A-I) • For those patients who already achieved target lipid levels, repeat measurement should be done bi-annually (B-III)	• For individuals already on statin therapy and meeting target LDL-C, continue statin therapy (A-I) • For individuals already on statin therapy but are not meeting target LDL-C, increase dose of statin (A-I) • Dose adjustment of statin should be done for patients with muscle symptoms depending on severity of symptoms and results of laboratory tests. (Refer to Figure 3) (A-I) • For individuals with ASCVD on maximally tolerated statin therapy not meeting target LDL-C add ezetimibe (A-I) • For patients with persistent hypertriglyceridemia ≥ 500 mg/dl despite addressing lifestyle factors and secondary causes of elevated triglycerides, start fibrate therapy (A-I)	Patient Interventions • Recommend low saturated fat diet rich in fruits and vegetables (A-I) • Prescribe regular exercise with appropriate frequency and intensity (A-I) • Advise smoking cessation (A-I) • Discuss barriers and misperceptions to lifestyle change (A-III) • Explain the dose, frequency, intended effect, possible side effects of medications and importance of medication adherence (A-III) Family Intervention • Engage other family members, especially spouses, to also adopt the lifestyle interventions prescribed (A-II) Community-Level Intervention • Promote the formation of a community-based lifestyle intervention program to reduce cardiovascular risk (A-I) Referral • For patients uncontrolled on dual therapy (statin and ezetimibe) and lifestyle modifications, refer patient to specialist (A-III) Follow-up visit: • Immediately if with development of muscle symptoms while on statin therapy or if with any adverse event from medication (A-I) • If with no adverse event from medication: o 8-12 weeks after dose adjustment of statin therapy (A-III) o biannually after patient achieved target lipid levels (B-III)	• Adherence to diagnostic, pharmacologic and non-pharmacological treatment, and other management plan (A-I) • Reduction in LDL-C level and CVD events (A-I) • Improved quality of life (A-I) • Improved patient satisfaction (A-I)
Variations					

Notes On The Recommendations

First Visit

Clinical History and Physical Examination

Most patients with dyslipidemia are asymptomatic and it is often discovered during a routine blood test. It can, however, lead to ASCVD which may manifest with symptoms (i.e., chest pain in coronary artery disease and leg pain when walking in peripheral arterial disease).

History taking is essential in identifying individuals with high risk for ASCVD.[10] Medical conditions that increase a patient's risk of dyslipidemia and/or atherosclerotic cardiovascular disease include abdominal aortic aneurysm, autoimmune or inflammatory disease (e.g., human immunodeficiency virus [HIV] infection or acquired immunodeficiency syndrome [AIDS], lupus, rheumatoid arthritis [RA], periodontal disease, psoriasis), blood coagulation abnormalities, chronic kidney disease, chronic obstructive pulmonary disease (COPD), depression, erectile dysfunction, hypertension, hypertensive diseases of pregnancy or pre-eclampsia, impaired fasting glucose (IFG) or glucose tolerance (IGT), diabetes, hepatitis C, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), overweight or obesity, primary hypercholesterolemia, stress, a history of pancreatitis, and prior cardiovascular or cerebrovascular events.[3,11,12,13,14,15,16,17]

Medications and medication classes have also been reported to cause dyslipidemia.[18] Anabolic steroids, selective estrogen receptor modulators, oral estrogens and progestins, highly active antiretroviral agents such as protease inhibitors for the treatment of HIV, immunosuppressive medications (e.g., cyclosporine, mammalian target of rapamycin [mTOR] kinase inhibitor), glucocorticoids, retinoids, interferon, taxol derivatives, L-asparaginase, cyclophosphamide, atypical antipsychotic agents, beta-blockers and thiazide diuretics are some of the medications noted to negatively affect lipid levels. Bile acid sequestrants, which are used mainly for reduction of cholesterol, may also elevate triglycerides and should be used cautiously in patients with increased triglyceride levels.[12]

Family history would also provide data that would help identify high-risk individuals such as patients whose family members have dyslipidemia, hypertension, premature ASCVD (males < 55 years; females < 65 years.[3,11,12,13,14,15,16,17] These findings, together with the other clinical and laboratory parameters, are among the criteria that will help identify patients with familial hypercholesterolemia, which would warrant aggressive lipid management.

Social history should focus on lifestyle – use of tobacco, alcohol intake, diet and activity. These factors can contribute as secondary causes of dyslipidemia. In developed nations, high carbohydrate diet and sedentary lifestyle leads to dyslipidemia. Dyslipidemia is also caused by high alcohol intake and high saturated fat diet.[12]

The focus of the physical examination are the anthropometric measurements and the cardiovascular system. The height and weight should be determined for the computation of the body mass index [BMI] or the waist circumference should be measured to determine if the patient is obese or overweight. The blood pressure, peripheral and carotid pulses should be determined to check for signs of ASCVD. Advanced evaluation such as cardiac evaluation; vascular bruits; and ankle-brachial index may be conducted. Physical manifestations of dyslipidemia can also be assessed by looking for presence of tendon xanthomas, eruptive xanthomas, , corneal arcus, lipemia retinalis and xanthelasma.[3,10,12,14,17]

With the findings that are obtained during the history taking and physical examination, the individual's risk for ASCVD can be assessed and become the basis of screening and management of dyslipidemia in the patient. The risk factors identified in the different clinical practice guidelines are summarized in Table 1: .[3,11,12,13,14,15,16,17]

Table 1. Risk factors for atherosclerotic cardiovascular disease from various clinical practice guidelines on dyslipidemia.

- Age (40-75 years)
- Sex (Male)
- Race (South Asian ancestry)
- Lack of exercise
- History of smoking or tobacco use
- IFG, IGT
- Elevated HbA1c
- Diabetes
- Hypertension
- Blood coagulation abnormalities
- Chronic Kidney Disease (eGFR 15–59 mL/min/1.73 m^2)
- Chronic Inflammatory Conditions (HIV infection/AIDS, Lupus, Psoriasis, RA)
- COPD
- Depression
- Metabolic syndrome (elevated waist circumference, elevated triglycerides, elevated blood pressure, elevated glucose, and low HDL-C; total of 3 makes the diagnosis)
- Post-menopausal women
- Primary Hypercholesterolemia (LDL-C 160–189 mg/dL; non–HDL-C 190–219 mg/)
- Stress
- History of ASCVD
- History of Premature Menopause (before age 40)
- History of Pre-eclampsia
- Family History of premature ASCVD (males <55 years; females < 65 years)
- Overweight or Obesity
- Reduced ankle–brachial index
- Elevations in apolipoprotein B (may be especially useful if hypertriglyceridemia >2.3 mmol/L [>200 mg/dL] persists)
- High sensitivity C-reactive protein levels of 19.0476 nmol/L (2.0 mg/L) or higher
- LDL-C levels of 4.1 mmol/L (160 mg/dL) or higher
- Lipoprotein(a) levels with elevations above 125 nmol/L (50 mg/dL) (especially useful in those with a family history of premature ASCVD)
- Triglyceride levels persistently elevated above 2.0 mmol/L (175 mg/dL)
- Left ventricular hypertrophy
- Microalbuminuria
- Proteinuria

The four major risk factors remain the same across the different cited guidelines – dyslipidemia, diabetes, hypertension, and tobacco use. The other factors are considered minor or risk enhancers, which may be used to aid the clinician individualize the plan in managing dyslipidemic patients.

Besides the assessment of ASCVD risk, the different guidelines also recommend the use of risk assessment tools or calculators to compute for the 10-year ASCVD risk. The computed 10-year ASCVD risk is used to supplement the identified risk factors to serve as guide as to which type of therapy should be employed to the patient. There are several ASCVD risk assessment tools available, and they are as follows: Framingham Risk Assessment Tool; Multi-Ethnic Study of Atherosclerosis (MESA) 10-year ASCVD (atherosclerotic cardiovascular disease) Risk with Coronary Artery Calcification (CAC) Calculator; Reynolds Risk Score; UK Prospective Diabetes Study (UKPDS) Risk Engine for patients with type 2 diabetes and; American College of Cardiology/American Heart Association pooled-cohort ASCVD Risk Estimator.[12]

However, these risk calculators were not validated for the Filipino population. The 2020 Clinical Practice Guidelines (CPG) for the Management of Dyslipidemia in the Philippines recommended the use Risk Factor Counting as the method in identifying the risk of the Filipino individual for cardiovascular disease. The following are the risk factors to take in consideration: smoker, male, post-menopausal women, family history of premature coronary heart disease (CHD), BMI 25 kg/m^2, hypertension > 140/90 mmHg , proteinuria and left ventricular hypertrophy.[19]

Laboratory

Age for Dyslipidemia Screening

In estimating the ASCVD risk, age is considered as part of the major independent risk factors as noted in the pooled cohort used by the American Heart Association (AHA) Clinical Practice Guideline on Dyslipidemia (2018). The age considered for dyslipidemia screening in US population starts at 40 years old to 75 years old.[20] However, in the local setting, the recommended cut-off age for starting statin for primary prevention is 45 years old for patients with no DM or CKD.[19] This cut-off age is based on epidemiology of dyslipidemia among Filipinos.[17]

In many primary prevention studies, 45 years was also the cut off age for inclusion. Most of these studies also require the presence of at least two risk factors in their participants.[17]

Hence, the authors recommend dyslipidemia screening for all patients ≥45 years old and adult patients with two or more risk factors, regardless of age, but with increased ASCVD risk.

Lipid Profile

Measurement of lipids and lipoproteins are needed to estimate the risk of ASCVD. They are used to guide therapy. Apolipoprotein-B (ApoB) -containing lipoproteins play a central role in the initiation and progression of atherosclerosis. ApoB-containing lipoprotein are VLDL, TG-rich remnant particles, and LDL.[3]

LDL particles are the most abundant of the Apo-B containing lipoproteins. Plasma LDL-C measure the cholesterol carried by LDL particles. Thus, it mirrors the amount of LDL level in the circulation. TG-rich VLDL particles and their remnants carry most of the circulating TGs. Therefore, the plasma TG concentration estimates the levels of circulating ApoB-containing TG-rich lipoprotein.[3]

A study which used two sets of single-nucleotide-polymorphism (SNP) genetic variants for Mendelian randomization analysis of causal factors for coronary artery diseases showed that LDL-C was strongly associated with increased risk for CAD. It also demonstrated that HDL-C was strongly associated with reduced risk for CAD. It was demonstrated that TG is not a causal risk factor for CAD.[21]

Urine Albumin-to-Creatinine Ratio (ACR)/ Urine Protein Dipstick Test

In the Philippine guideline for dyslipidemia (2020), proteinuria was considered as a risk factor for ASCVD.[19] Proteinuria could be assessed by measuring the urine albumin to creatinine ratio or by using urine protein dipstick test. A meta-analysis published in 2011 showed a linear association between log albuminuria and log risk for all-cause mortality without thresholds. Similar findings were demonstrated in studies with dipstick data. The study concluded that in high-risk population, higher albuminuria and lower eGFR and are risk factors for cardiovascular and all-cause mortality independent of each other and of other cardiovascular risk factors.[22] Another similar meta-analysis published in 2015 demonstrated that in the general population there is significant improvement in the determination of cardiovascular outcomes with the addition of eGFR and ACR. Demonstrated improvement was larger with ACR than with eGFR, and more apparent for heart failure and cardiovascular mortality compared to coronary disease and stroke. Smaller improvement was seen when dipstick proteinuria is used. The discrimination improvement with eGFR or ACR was especially apparent for individuals with diabetes or hypertension but remained significant with ACR for cardiovascular mortality and heart failure in those without either of these diseases.[23]

Alanine Transaminase (ALT)

A study published in 2018 revealed that odds ratio for occurrence of liver injury during statin therapy was 1.18 (95% confidence interval (CI): 1.01-1.39).[24] To identify patients where treatment may be contraindicated or may need close follow-up, measurement of ALT as a marker of hepatocellular damage may be done. The European guideline on management of dyslipidemia recommends measurement of ALT before starting statin therapy.[3]

12-Lead Echocardiography (12-L ECG)

Left ventricular hypertrophy (LVH) is a risk factor for ASCVD.17 LVH could be assessed using 12L-ECG. A study published in 2012 showed that independently of other cardiovascular risk factors, participants with ECG LVH had increase probability of experiencing any CVD event before non-CVD death over 15 years of follow up. The study also showed that coronary heart disease/nonfatal myocardial infarction is the most

probable first event among men with ECG LVH was. In contrast, heart failure, followed closely by coronary heart disease/nonfatal myocardial infarction were the most probable events in women.[25]

Fasting Blood Sugar (FBS)

Presence of diabetes mellitus (DM) is an indication for giving statin therapy as primary prevention for cardiovascular disease.[19] Macrovascular complications of DM include cerebrovascular disease, coronary heart disease, arrhythmias and sudden death, cardiomyopathy, and peripheral artery disease. The leading cause of death among patients with DM is cardiovascular disease. Thus, to assess cardiovascular risk, we should screen for diabetes in adults.[26] According to American Diabetes Association guideline in 2021, start of testing is at age 45 for the general population. However, it could be started earlier for adults who are overweight or obese and have one additional risk factor for DM.[27]

Non-Pharmacologic Intervention

Patient- Centered Intervention

Diet and Physical Activity

Several guidelines on management of dyslipidemia emphasized the vital role of healthy diet in lowering LDL-C and decreasing ASCVD risk.[3,19,20] A meta-analysis published in 2012 found that there is a reduction in the risk of cardiovascular events by 14% (Relative Risk (RR) 0.86, 95% CI 0.77-0.96) with the reduction of saturated fat done by reducing and/or modifying dietary fat.[28] Another meta-analysis which focused on Mediterranean diet (consisting mainly of vegetables, fruits, whole grains, and healthy fats) found that an increase in adherence score to the Mediterranean diet by 2 points resulted in 8% lowering of overall mortality (RR 0.92 [0.91-0.93]), a 10% lower risk of CVD (RR 0.90 [0.87-0.92]). The benefit of Mediterranean diet which was characterized by high loadings of olive oil, non-starchy vegetables and cheese was also seen in meta-analysis done in 2019 that showed an inverse association of dyslipidemia and this type of diet (Odds Ratio (OR) 0.53, [0.30-0.95]).[29] A more recent meta-analysis published in 2021 which included 37 guidelines, 108 systematic reviews, and 20 randomized controlled trials (RCTs) found that foods rich in unsaturated fat and contain only small amounts of saturated and trans-fatty acids in addition to plant sterols/stanols and high in soluble fiber caused at least moderate (i.e. 0.20-0.40 mmol/L) reductions in LDL-C.[30]

The 2020 Philippine CPG recommend use of Pinggang Pinoy for Filipinos with dyslipidemia.[19] Pinggang Pinoy is a food guide that demonstrate the advisable amount by food group: Go, Grow and Glow to take for each meal. The plate is divided into the following: ½ consist of Glow foods including fruits and vegetables; 1/6 consist of Grow foods such as meats, eggs, poultry, fish, beans and legumes and 1/3 consists of Go foods like rice, corn, bread, oatmeal, bread, and root crops (see figure below).[31]

Increase physical activity is advocated for decreasing cardiovascular risk by several guidelines on dyslipidemia.[3] For Filipinos, at least 150 minutes of moderate to high-intensity exercise per week is recommended.[19]

Several studies have already proven the benefit of exercise on cardiovascular health. A meta- analysis published in 2015 found that exercise significantly raised absolute and relative cardiorespiratory fitness among adults without cardiovascular disease. People in

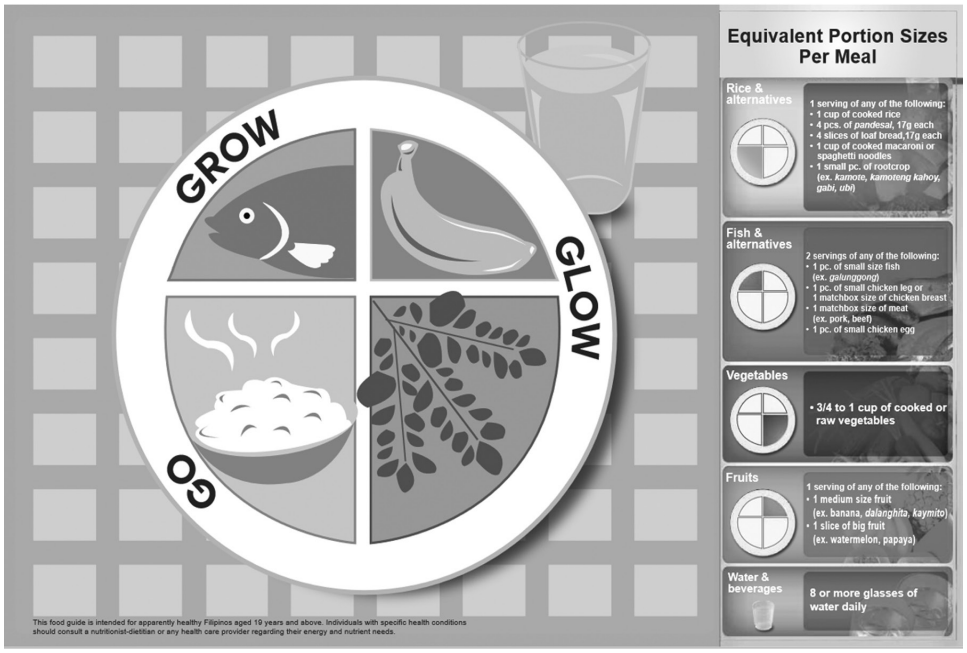

Figure 1. Pinggang Pinoy Food Guide
Image from: Food and Nutrition Research Institute – Department of Health

the exercise intervention had lower triglycerides; higher HDL-C and apolipoprotein A1; and lower fasting insulin and glycosylated hemoglobin A1c.[32] Another study published in 2016 showed that there is lower risk of CVD mortality by 23% (RR 0.77[0.71–0.84]), CVD incidence by 17% (RR 0.83 [0.77– 0.89]), and T2DM incidence by 26% (RR 0.74 [0.72–0.77]) with an increase from being inactive to achieving recommended physical activity level (150 minutes of moderate-intensity aerobic activity per week).[33]

A meta-analysis done for US Preventive Services Task Force showed that the behavioral interventions demonstrated a small, statistically significant between-group mean differences for systolic blood pressure (−1.26mmHg [95%CI, −1.77 to −0.75]), diastolic blood pressure (−0.49mmHg [0.82 to −0.16]), LDL-C (−2.58mg/dL [−4.30 to −0.85], total cholesterol level (−2.85mg/dL [−4.95 to −0.75]), and body mass index (−0.41 [−0.62 to −0.19] at 6 to 12 months among adults with no cardiovascular risk factors. The interventions also showed small-to-modest associations with dietary and physical activity behaviors.[34] A similar but more recent meta-analysis which focused on adults with cardiovascular risk factors showed that there is reduction of cardiovascular events, blood pressure, low-density lipoproteins, and adiposity-related outcomes with the use of the medium- and high-contact multisession behavioral counseling interventions for patients who have hypertension and dyslipidemia.[35]

In patients with dyslipidemia who are overweight or obese, weight reduction of even 5–10% of basal body weight lead to improvement in lipid levels and positively affects the other cardiovascular risk factors.[3]

Smoking Cessation

Smoking cessation is beneficial to decrease cardiovascular disease risk. An individual participant data meta-analysis published in 2006 showed that in men with diabetes, the hazard ratio (HR) comparing current smokers with non-smokers was 1.42 (1.10-1.83) for coronary heart disease, 1.10 (0.88-1.37) for total stroke and 1.15 (0.98-1.35) for total CVD. Similar findings were demonstrated in men without diabetes with the following hazard ratios computed: 1.47 (1.33-1.61) for coronary heart disease, 1.27 (1.16-1.39) for total stroke and 1.35 (1.27-1.44) and for total CVD. Irrespective of diabetes status, smoking cessation was found to lead to a 19% reduction in CVD risk.[36] A meta-analysis published in 2015 showed an increased risk of with cardiovascular mortality (HR 2.07 [95% CI 1.82 to 2.36)]) for current smokers and for former smokers (HR 1.37[1.25 to 1.49]) compared with never smokers among people aged 60 year and older. Among smokers , excess risk is increased with cigarette consumption in a dose-response manner. Among former smoker, excess risk decreases with time since smoking cessation.[37]

A study done in 2019 showed a dose-response relationship between pack-years of smoking and three ASCVD namely peripheral artery disease (PAD), coronary heart disease (CAD) and stroke. The strongest relationship was seen in PAD. Lower risk of the three ASCVD was seen with longer time from smoking cessation. However, significantly increased risk persisted up to 30 years following smoking cessation for PAD and up to 20 years for CHD or stroke.[38]

Family-Focused Intervention

There is limited number of studies focusing on family focused interventions for patients with dyslipidemia. Studies focused mainly on effect of spouses on lifestyle choices of patients. A cohort study published in 2015 showed positive association between individual changes and spousal changes in the sport/exercise and leisure indices. The study demonstrated that the odds that an individual would meet physical activity recommendation is higher if their spouse met these recommendations.[39] A cross-sectional study published in 2018 showed that there is correlation between sedentary behaviors with each other among middle aged and older couples. These correlations were not moderated by attachment to one's spouse. The concordance for physical activity was weaker than that for sedentary behavior.[40] Another cohort study published in 2018 aimed to determine the correlation of ideal cardiovascular health variables among spousal or cohabitating partner. This study found that there was a low prevalence of ideal cardiovascular health. The greatest concordances in achievement of ideal factor status were for the following: non-smoking (26.1%), ideal fruit and vegetable consumption (23.9%), and ideal fasting blood glucose (35.6%). The highest odds of intracouple concordance were for smoking (OR, 3.6; 95% CI, 1.9–6.5), fruit and vegetable consumption (OR 4.8; 95% CI 2.5–9.3) and blood pressure (OR 3.0 [1.2–7.9]). It was also noted that a person had 3-fold higher odds of attaining ≥3 ideal cardiovascular health variables if he or she had a partner who attained ≥3 components (OR 3.0 [1.6–5.6]).[41]

Community-Oriented Intervention

Community-based interventions to reduce cardiovascular risk have been done in the past. One of this is the Complete Health Improvement Program (CHIP). It was formerly known as Coronary Health Improvement Project as it initially only targeted cardiovascular disease. However, because many studies have shown its efficacy in improving other chronic diseases, such as DM Type 2 and even depression, it was renamed in 2012 the Complete Health Improvement Program.[42] The first study on the effectiveness of community- based CHIP was done in Rockford, Illinois. The study's intervention is a 40-hour educational curriculum delivered over a period of 30 days. Before and after intervention, clinical and nutritional assessments were done. This study found that after the intervention, there is significant lowering in total cholesterol, LDL, triglycerides, blood glucose, blood pressure and weight with notably the greatest improvements among those at greatest risk. The authors concluded that well-designed community-based intervention programs can lead to improvement in lifestyle choices and reduction of coronary risk factors.[43] After this study, several other communities adopted CHIP. A study in Canada involving 1003 people enrolled in 27 CHIP interventions hosted in community settings found that after 30 days, there were significant overall reductions in the following parameters: BMI (-3.1%), systolic BP (-7.3%), diastolic BP (-4.3%), total cholesterol (-11.3%), low-density lipoprotein cholesterol (-12.9%), triglycerides ([TG] -8.2%), and FBS (-7.0%).[44] Another study done in Appalachian patients showed that after the CHIP intervention, participants had significant reduction in TC levels, HDL-C, LDL-C, FBG levels, BMI, and systolic blood pressure.[45]

Patient Outcomes

After the initial consultation, the family physician must confirm that the patient understood the disease, risks and agree to the diagnosis and treatment plan. Patients' awareness and understanding is an important surrogate outcome of the effectiveness of health education intervention. This can be measured in a form of patient recall. This is asking the patient to repeat key information he/she learned from the health education advice. This outcome was measured in an observational study within a randomized controlled trial. In the trial patients recalled 43% (alcohol), 52% (diet) to 70% (exercise) of the discussions. This active patient engagement and explicit conversations about the illness and medications are associated with improved treatment information recall.[46] Understanding and adherence to the planned diagnostic and management strategies may also be affected by the patient's trust to their family doctor. This trust rating been measured in some trials on health coaching to patients with DM, hypertension or dyslipidemia.[47]

Second Visit

Clinical History And Physical Examination

On the patient's follow-up visit, evaluate the patient for occurrence of ASCVD from the initial consultation. Check for compliance to medications and the agreed non-therapeutic interventions. Ask for possible drug-related adverse effects. If statin was started during the first visit, ask about statin-induced myopathy. Ask for concomitant intake of gemfibrozil; niacin; cyclosporine; azole antifungals; macrolide antibiotics; HIV protease inhibitors; verapamil and diltiazem; amiodarone and grapefruit juice for these may enhance the myopathy.[13] Review and interpret the laboratory results if there are any and re-assess the patient's ASCVD risk taking the subjective and objective findings.

Laboratory

Repeat Measurement of Lipid-Levels

As mentioned above, lipoproteins are associated with ASCVD risk. They are used to guide therapy and have target levels for different patient groups (see Table 2). The European guideline recommend that for those patients on statin therapy not experiencing muscle symptoms, repeat lipid measurement should be done 4-12 weeks after starting statin therapy or after dose adjustment. However, evidence concerning frequency of monitoring of lipids are limited and the guideline recommendation come from consensus rather than evidence.[3] In this pathway, it is recommended to repeat measurement of lipid profile 6-8 weeks after starting statin therapy.

ALT Level Measurement

Routine monitoring and control of ALT during treatment is not recommended but should be requested if indicated.[3] Frequency of repeat liver enzyme measurement to check for statin-induced liver injury varies across different guidelines. In this pathway, it is recommended to repeat ALT measurement 6-8 weeks after start of therapy for patients at high risk for statin-induced liver injury. A study done in 2018 showed that that Fluvastatin and statin dose over 40 mg/daily significantly increased the risk of hepatic injury with odds ratio of 3.50 (95% CI: 1.07–11.53) and 3.62 (95% CI: 1.52–8.65), respectively. Other patients that may be at high risk for statin-induced liver injury are elderly patients and patients with active liver disease with inflammation.[24]

Table 2. Target lipid levels.

Patient Groups	LDL-C Target	HDL-C Target	Triglyceride Target
Individuals with no clinical ASCVD	<130 mg/dL	>40 mg/dl in Males >50 mg/dl in Females	<150 mg/dl
Individuals with DM	<100 mg/dL		
With ≥1 risk factors / target organ damage	<70 mg/dL		
With ASCVD	<55 mg/dL		
Individuals with clinical ASCVD	<55 mg/dL		
Individuals with FH without ASCVD or without major risk factor / target organ damage	<70 mg/dL		
FH With ASCVD or with ≥1 risk factors / target organ damage	<55 mg/dL		

Table from: Executive Summary of the 2020 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines[17]

Creatine Kinase (CK)

One of the adverse effects of statin therapy is statin-associated muscle symptoms (SAMS). It is described as muscular pain and tenderness without major functional loss.[48] Another adverse effect of therapy with statin is myositis. It is defined as muscle symptoms in association with a substantially high serum creatine kinase (CK) concentration. This adverse effect occurs rarely. CK elevations >10× the upper limit of normal (ULN) occur in 1 per 1000 to 1 per 10 000 people per year, depending on the statin, its dose, and the presence of other risk factors.[49] Patient at risk for myopathy include very elderly with comorbidities, those with previous muscle symptoms and patients receiving interacting drugs.[3]

Routine monitoring of creatinine kinase is not recommended.[3,18] It should be monitored if previous CK was requested for an indication. Check CK immediately in all patients who develops myalgia while on statin therapy.[3]

Pharmacologic Intervention

Statins remain as the major lipid lowering therapy in conjunction with lifestyle interventions.[20] Statins lower cholesterol production in the liver by competitive inhibition of the enzyme HMG-CoA reductase which is needed for cholesterol biosynthesis. Lower levels of cholesterol intracellularly promote increased LDL receptor (LDLR) expression at the hepatocytes' surfaces. Consequently, there will be increased uptake of

LDL from the circulation and reduction of plasma concentrations of LDL- and other Apo B-containing lipoproteins.[3]

Statins are generally safe and well-tolerated. In a statement by the American Heart Association published last 2018 the risk of adverse effects of statins are the following: serious muscle injury (which includes rhabdomyolysis) - <0.1%; serious hepatotoxicity is ≈0.001%; and newly diagnosed diabetes mellitus ≈0.2% per year depending on the underlying risk. There is a possible increased hemorrhagic stroke risk in patients with cerebrovascular disease, but the risk is clearly outweighed by the higher reduction in atherothrombotic stroke risk. There is no conclusive evidence that statins cause cancer, cognitive dysfunction, cataracts, erectile dysfunction, peripheral neuropathy, and tendonitis.[50]

Statin could be subdivided into three categories based on how much they lower LDL-C levels: High-intensity statins lowers LDL-C levels by 50%, moderate-intensity statins by 30% to 49%, and low-intensity statins by <30% (Table 3).[3]

However, it must be noted that there are some racial differences in lipid lowering effects of statins. In some Asian populations, lower doses of statins are needed to achieve the same percentage of lipid lowering compared to the Western population.[51]

The beneficial effects of statins on cardiovascular disease prevention are already well-established.[3,52]

Statins for Patients with Diabetes Mellitus (DM)

Cholesterol Treatment Trialists' Collaborators conducted a meta-analysis in 2008 that was focused on the diabetic population. It showed that statin therapy leads to a reduction in myocardial infarction (MI) or coronary death (RR 0.78; 99 % CI: 0.69–0.87), coronary revascularization (RR 0.75 [0.64–0.88]), and stroke (RR 0.79 [0.67–0.93]). Diabetic patients had similar effects of statin therapy regardless of prior cardiovascular disease (CVD) and other baseline characteristics. The authors concluded that statin should be given to all individuals with DM who have elevated risk of vascular events.53 In 2013, another meta-analysis reported that statins given for DM patients as primary prevention strategy lowered the risk of CVD with pooled odds ratio of 0.757 (95% CI 0.676 -0.847).[54]

A recent randomized controlled trial conducted among Japanese patients who have hypercholesterolemia and diabetic retinopathy in the primary prevention setting showed similar findings with previous primary prevention studies in terms of the relationship between the LDL-C difference and the event reduction rate.[55]

Statins for Patients with Mild to Moderate Chronic Kidney Disease (CKD)

A meta-analysis done in 2014 investigated the effect of statin therapy in patients with mild-moderate CKD. Statin therapy was demonstrated to lead in the reduction of risk of the following: CVD (24% reduction), total mortality (21% reduction), MI (34% reduction), stroke (30% reduction) and cardiovascular mortality (17% reduction). No statistically significant drug-related adverse events were noted in the study.[56]

More recently, a meta-analysis determined the effect of the different statins on cardiovascular complications in patients with chronic kidney disease. The studies included mostly used moderate intensity statins. Pravastatin (40 mg/day) was shown to significantly reduce patient mortality (OR 0.66 [0.46–0.91]) compared to placebo. The following statins showed significant reduction in cardiac events: Atorvastatin 80mg, Fluvastatin 40mg, Lovastatin 20mg, Pravastatin 40mg, and Simvastatin 40mg. Pravastatin showed the best effect at all-cause mortality rate in rank probability. Lovastatin, Fluvastatin, and Pravastatin showed good effects with the 1st, 2nd, and 3rd ranks in cardiac events.[57]

Statins for Patients with Multiple Cardiovascular Risk Factors

There are several meta-analyses done which revealed that statin therapy in patients at increased risk reduces all-cause mortality, major coronary events, major cerebrovascular events, and revascularizations.[58,59,60,61] A meta – analysis study done in 2019 which investigated the effectiveness and safety of statins for primary prevention of CVD showed statistically significant reductions in the risks for following: non-fatal MI (risk ratio [RR] 0.62, 95% CI 0.53-0.72), non-fatal stroke (RR 0.83 [0.75-0.92]),]), unstable angina (RR 0.75 [0.63-0.91]), CVD mortality (RR 0.80 [0.71-0.91]), all-cause mortality (RR 0.89 [0.85-0.93]) and composite major cardiovascular events (RR 0.74 [0.67-0.81]).[62]

Factors to take in consideration in risk assessment for cardiovascular disease in Filipino patients as recommended by the Philippine Heart Association are as follows: male, post-menopausal

Table 3. Classification of statins

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	---	**Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

Boldface type indicates specific statins and doses that were evaluated in RCTs and the Cholesterol Treatment Trialists' 2010 meta-analysis.
†LDL-C lowering that should occur with the dosage listed below each intensity. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.
‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.
§Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

Taken from: 2018 AHA/ACC/AACVPR/AAPA/ ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[20]

women, smoker, family history of premature coronary heart disease, BMI 25 kg/m^2, hypertension > 140/90 mmHg proteinuria and left ventricular hypertrophy.[17]

Statins for Patients with Familial Hypercholesterolemia (FH)

Familial hypercholesterolemia (FH) is an autosomal dominant disorder resulting from mutations in genes that encode proteins needed in the LDL receptor endocytic and recycling pathways. These mutations lead to reduced cellular uptake of LDL leading to higher levels of plasma LDL-C. People with heterozygous FH have 2x higher LDL-C levels compared to general population. Those with homozygous FH have 4x higher LDL-C levels. People with untreated FH has higher risk for premature coronary artery disease (CAD) and stroke. [63] The Dutch Lipid Network criteria could be used to identify individuals with Familial Hypercholesterolemia.[3]

Table 4. Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia.

Criteria	Points
1) Family history	
First-degree relative with known premature (men aged < 55 years; women < 60 years) coronary or vascular disease, or first-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or children aged < 18 years with LDL-C above the 95th percentile	2
2) Clinical history	
Patient with premature (men aged < 55 years; women < 60 years) CAD	2
Patient with premature (men aged < 55 years; women < 60 years) cerebral or peripheral vascular disease	1
3) Physical examination[a]	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C ≥8.5 mmoL/L (≥325 mg/dL)	8
LDL-C 6.5–8.4 mmoL/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmoL/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmoL/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the *LDLR*, *apoB*, or *PCSK9* genes	8
Choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained	
A 'definite' FH diagnosis requires > 8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

CAD = coronary artery disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

[a] Exclusive of each other (i.e. maximum 6 points if both are present).

Taken from: 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk[3]

A systematic review and meta-analysis of epidemiologic studies done in 2015 showed that participants with FH had a lower odd for stroke following the general use of statin therapy (OR 0.251, 95% CI: 0.176-0.358).[63] In addition a cohort done in 2016 showed that giving moderate to high intensity statins to patients with heterozygous FH decreased the risk of CAD and mortality by 44%.[64]

Statins for Patients with Atherosclerotic Vascular Disease (ASCVD)

A meta-analysis done in 2013 found that statins produce significant reduction in all-cause mortality (OR 0.82, 95% CI 0.75–0.90) and major coronary events (OR 0.69 [0.62–0.77]) compared to control in patients with cardiovascular disease.[65] In 2017 another meta-analysis on statins as secondary prevention strategy showed that statins were beneficial in terms of reduction in major vascular events. In terms of types of intervention done in the studies, trials comparing statin vs. no statin had RR 0.77 (95% CI 0.71–0.83) while trials of more-statin vs. less-statin had RR 0.88 (95% CI 0.82–0.93).[66]

A recent randomized controlled study investigated the effect of high-dose vs low-dose statin on the Asian population specifically Japanese patients who have stable CAD. The study compared high-dose Pitavastatin (4mg/day) with low-dose Pitavastatin (1 mg/day.)[67] A composite of nonfatal myocardial infarction, unstable angina requiring emergency hospitalization, nonfatal ischemic stroke, and cardiovascular death is the primary end point of this research. Reduction in this endpoint was found with the use of high-dose Pitavastatin (HR 0.81; 95% CI, 0.69–0.95).[67]

Non-Pharmacologic Intervention

Patient-Intervention

There is only indirect evidence in the effectiveness of patient education in medical adherence to therapy. A meta-analysis published in 2019 which included 18 RCTs demonstrated a low to moderate quality evidence on the improvements of medication adherence with educational interventions. Education interventions benefited participants with DM type 2 but not those with hypertension. No RCTs were found for participants with hyperlipidemia since none fit the eligibility criteria.[68]

Follow-up Visits

As mentioned above, myositis is a rare adverse effect of statins. Thus, it is recommended that patients with muscle symptoms follow-up immediately with their physicians for proper evaluation and management.

For those patients on statin therapy not experiencing muscle symptoms, follow-up could be done at the same time that repeat lipid measurements will be done: 6-8 weeks after starting statin therapy.

Patient Outcomes

After the second consultation, the family physician after providing initial counselling and health education can already measure adherence to the advice on diet and lifestyle. Adherence to the interventions is very important to achieve the expected clinical outcome. Lifestyle and dietary changes are often difficult to follow especially with low-intensity counselling which is often the only feasible method in family practice. However, in a simple clinical trial, measurement of adherence to diet is feasible. Dietary adherence can be evaluated by

using simple questionnaire or checklist. In the trial mentioned, this was associated with decreases in LDL-C levels.[69] Aside from dietary changes, improvement in physical activity can also be measured in the short term. In one clinical trial, the participants exhibited a significant increase in physical activity and a borderline significant decrease in body weight.[70] In general, objectively measured and self-reported changes in diet and physical activity are concordant with intermediate and clinical outcome findings. Lifestyle and dietary changes counselling have been associated with other favorable clinical outcomes like lowering of CVD risks and events. But these findings can be realised during the continuing visits.

If pharmacologic intervention is prescribed during the second visit awareness of the goals of treatment and the side effects must also be assured. The process of checking for the awareness has been described in the patient outcome during the first visit.

Continuing Visit

Laboratory

Non-High-Density Lipoprotein Cholesterol (Non- HDL-C)

Non-HDL-C is a measure of the total cholesterol (TC) carried by all atherogenic ApoB containing lipoproteins. This includes tryglyceride-rich particles in VLDL and their remnants. It could be calculated as: TC – HDL-C.[3] A meta-analysis published in 2012 showed that among statin-treated patients, there is an association between risk of future major cardiovascular events and levels of LDL-C, non-HDL-C, and ApoB. However, the strength of this association was greater for non-HDL-C than for LDL-C and apoB.[71] Another meta-analysis published in the same year demonstrated that non-HDL-C decrease modestly outperformed ApoB decrease for prediction of coronary heart disease (CHD) and CVD.[72]

Non- HDL C could be used as an additional target to decrease cardiovascular risk for statin treated patients who already reached goal LDL-C. Target non-HDL in various guidelines is set at 30 mg/dL above target LDL-C.[19]

Frequency of Lipid Level Measurement

Guidelines differ on frequency of monitoring of lipid levels once target is reached. It may range from 6-12 months.[3] In this pathway, it is recommended to repeat lipid measurement 8-12 weeks after dose adjustment and bi-annually for those already on target lipid levels.

Pharmacologic Intervention

Management of Statin–Induced Elevation of Transaminases and Statin-Associated Muscle Symptoms (SAMS)

Ezetimibe for Individuals with ASCVD on Maximally Tolerated Statin

Ezetimibe prevents intestinal uptake of dietary and biliary cholesterol leading to a reduction in the amount of cholesterol delivered to the liver. This causes the liver to upregulate LDLR expression which leads to higher clearance of LDL from the circulation.[3]

A landmark randomized controlled trial done in 2015 which included 18,144 patients stabilized after acute coronary syndrome demonstrated that significantly more patients given ezetimibe and simvastatin, in comparison with simvastatin alone, met LDL-C and high sensitivity C reactive protein (hs-CRP) targets. It was also shown after multivariable adjustment that reaching these targets was associated with improved outcomes.[73]

A meta-analysis published in 2020 which compared combination ezetimibe and statin vs statin monotherapy on patients with ASCVD demonstrated higher absolute reduction of LDL-C with combination therapy (mean difference – 21.86 mg/dL; 95% CI – 26.56 to – 17.17) after 6 months of treatment or at a timepoint closest to 6 months.[74] Another meta-analysis done in the same year focused on determining the efficacy of statin with ezetimibe therapy as secondary prevention strategy in Asians. Combination therapy showed greater reduction of the following in comparison with control group: LDL-C (weighted mean difference (WMD) – 0.39 mmol/L, 95% CI – 0.73 to – 0.05), triglycerides (WMD - 0.23 mmol/L [– 0.33 to – 0.13]), and total cholesterol (WMD – 0.31 mmol/L, [– 0.45 to – 0.17]). However, the combination therapy had minimal effects on HDL-C and no effect hs-CRP biomarkers in ASCVD.[75]

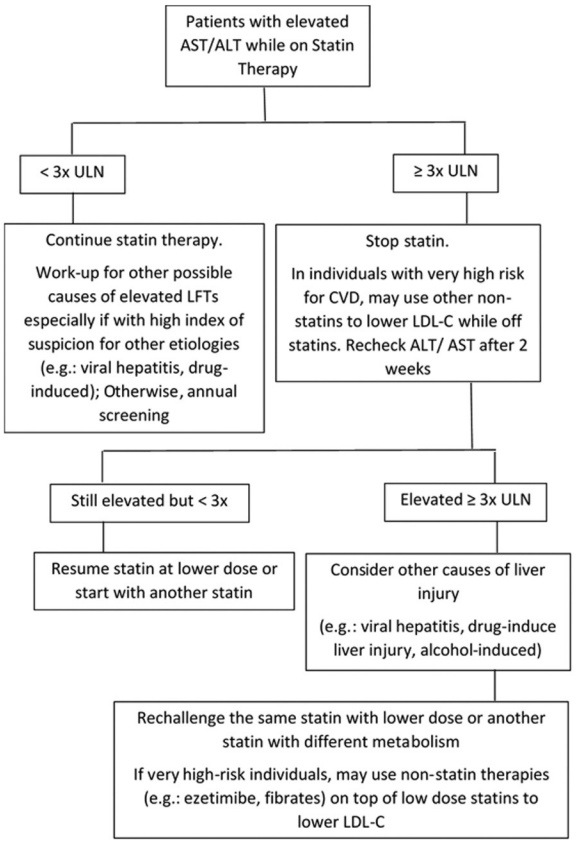

Figure 2. Algorithm for patients who are on statins with elevated liver enzymes
Taken from: 2015 Updated Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines[15]

Statin induced muscle symptoms should be managed as follows:[19]

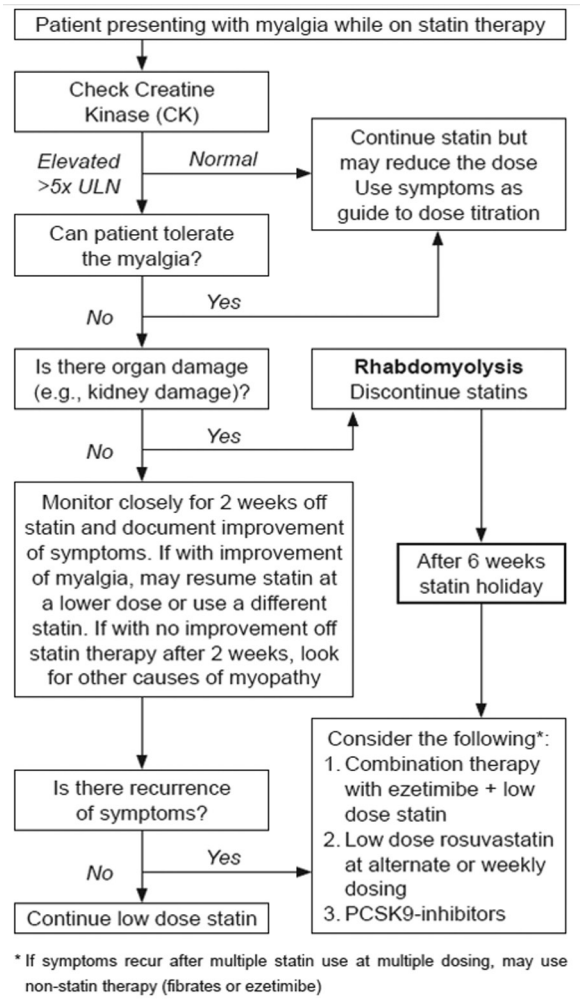

Figure 3. Algorithm for Statin-induced Myopathy
Taken from Executive Summary of the 2020 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines[19]

Management of Persistent Severe Hypertriglyceridemia

Management of hypertriglyceridemia is dependent on the level of triglyceride elevation. Moderate hypertriglyceridemia is diagnosed when fasting or non-fasting triglycerides 175-499 mg/dL (2.0-5.6 mmol/L). Diagnosis of severe hypertriglyceridemia requires a fasting triglycerides ≥ 500 mg/dL (≥5.6 mmol/L). Before considering pharmacologic treatment for hypertriglyceridemia, the following should first be addressed/ treated: lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.[20]

A study published in 2015 showed that among those with severe hypertriglyceridemia who underwent nutritional intervention, there is reduction in triglycerides from median of 961.5 (611.5-1785.3) to 493.0 (337-736.3) mg/dL. Findings were independent of lipid-lowering medication(s) and prior nutrition counseling.[76]

Reduction of cardiovascular events is the primary goal of pharmacotherapy for patients with dyslipidemia. Since studies have demonstrated strong evidence that this reduction is achieved by lowering LDL-cholesterol levels, the first step in the management of patients with hypertriglyceridemia is to attempt to achieve the target LDL cholesterol level. Statins could be used for this purpose.[77] In addition, statins are also known to decreased triglycerides levels. A study done in 2016 using data from VOYAGER meta-analysis which included individuals treated with rosuvastatin, simvastatin and atorvastatin showed that statin therapy results in mean triglyceride reductions of -15.1% to -31.3%.[78]

Most patients with severe hypertriglyceridemia have elevated VLDL and chylomicrons. Patients do not only have elevated risk of ASCVD but also acute pancreatitis. Thus, therapies that target both lipoproteins should be given. Statin therapy could be given. Persistence of severe hypertriglyceridemia even after addressing lifestyle factors and secondary causes of increased levels of triglycerides, fibrate therapy could be initiated to prevent acute pancreatitis. If fibrate therapy is needed in a patient already on statin, it is better to use fenofibrate than gemfibrozil because of lower risk of severe myopathy.[20]

A meta-analysis published in 2014 showed that combination therapy of statin and fibrate provided significantly higher reductions in total cholesterol (Standard difference in means (SE) = 0.430; 95% CI 0.315-0.545), LDL cholesterol (SE = 0.438 [0.321-0.555]) and triglycerides (SE = 0.747 [0.618-0.876]). Combination therapy also leads to significantly higher increase in HDL cholesterol (SE = 0.594 [0.473-0.715]) than treatment with statin alone. In the analysis of safety, statin monotherapy was associated with a significant reduction of the numbers for the following adverse event: liver-related adverse events (RR = 0.396 [0.206-0.760]) kidney-related adverse events (RR = 0.146 [0.075-0.285]) and total adverse events (RR = 0.665; 95% CI 0.539-0.819).[79]

Non-Pharmacologic Intervention

Follow-up Visit:

For those patients on statin therapy not experiencing muscle symptoms, follow-up could be done at the same time that repeat lipid measurements will be done: 8-12 weeks after dose adjustment of statin therapy and biannually for patient who already reached target lipid levels.

Patient Outcomes

Measurement of intermediate and clinical outcomes can be done during the continuing visits. Lifestyle counselling in persons with CVD risk factors lead to reductions in total cholesterol, LDL-C, blood pressure, fasting glucose, diabetes incidence, and weight outcomes. Overall, counselling leads to a reduction in total cholesterol by an average of 4.48 mg/dL (95% CI, 6.36 to 2.59), and LDL cholesterol by 3.43 mg/dL (95% CI, 5.37 to 1.49). Counselling also reduces clinical CVD

Medicines For Dyslipidemia

Table 3. Pharmacologic options for management of dyslipidemia.

HMG-CoA reductase inhibitors/Statins - Lower total cholesterol, LDL, and triglyceride concentrations while increasing HDL concentrations[80]

Drug	Dose	Contraindications, Administration Considerations and Side Effects
Atorvastatin	Usual initial dose: 10-40 once daily Max: 80 mg/day81	Contraindications: active hepatic disease or unexplained persistent elevations in aminotransferase levels, pregnancy, and breastfeeding Administration considerations: • Coadministration of simvastatin and gemfibrozil is contraindicated • Giving some statins in the evening is the recommended (e.g., Fluvastatin, Lovastatin, Pravastatin, and Simvastatin) • Avoidance of grapefruit juice should be done with some statins to decrease CYP3A4 interactions that could lead in higher serum concentrations • Coadministration of CYP3A4 substrate statins (atorvastatin, lovastatin, and simvastatin) with medications that are potent 3A4 inhibitors may lead to increased serum concentrations. Reduction of dose is recommended. • Caution is advised when given with other drugs associated with myopathy • Dose restrictions are recommended with the coadministration of gemfibrozil or other fibrates with statins, and the use of more than one statin is not recommended Side effects: myopathy, rhabdomyolysis (rare), hepatotoxicity (rare), and diabetes mellitus[80]
Fluvastatin	Usual initial dose: 20-40 mg once daily Max: 80 mg/day Dose Adjustments: • Mild-moderate renal impairment: No dosage adjustment needed • Avoid administration of two 40 mg conventional cap at one time82	
Pitavastatin	Usual initial dose: 1-4 mg once daily Dose Adjustments: • Moderate – severe renal impairment and end stage renal disease (ESRD): Initial:1 mg once daily; Max 2 mg once daily • If given with erythromycin or rifampicin, max dose of 1 mg or 2 mg respectively83	
Rosuvastatin	Usual initial dose: 5-10 mg once daily Max: 20 mg once daily; a max of 40 mg once daily may be used only in patients with severe hypercholesterolemia at high CV risk Dose Adjustments: • CrCl 30-60 ml/min: Initially 5 mg once daily; Max of 20 mg once daily • CrCl <30: contraindicated • Those with predisposing factors to myopathy or patients with Asian ancestry: Initially, 5 mg once daily. 40 mg dose is contraindicated.[84]	
Simvastatin	10 – 40 mg once daily Max: 80 mg daily Adjust dose according to patient response at intervals of at least 4 weeks Dose Adjustments: • CrCl<30 ml/min: Initially 5 mg once daily with close monitoring • Patients taking fibrates (except fenofibrate): Max: 10 mg daily • Patients taking amiodarone, amlodipine, ranolazine, verapamil, diltiazem, elbasvir, grazoprevir: Max: 20 mg daily • Patients taking lomitapide: Max: 40 mg daily[85]	

Cholesterol absorption inhibitors - Reduce total cholesterol, LDL, Apo B, and non-HDL[86]

Drug	Dose	Contraindications, Administration Considerations and Side Effects
Ezetimibe	10 mg once daily[87]	Contraindications: Hypersensitivity to any ingredient of the formulation; Concomitant use with an HMG-CoA reductase inhibitor among those with active liver disease or unexplained persistent elevations in serum transaminases, pregnant and breastfeeding patients; moderate to severe hepatic impairment Administration considerations: • If co-administered with bile acid sequestrant: Take it at least 2 hours before or 4 hours after taking bile acid sequestrants Side effects: Headache, runny nose, sore throat, body aches, back pain, chest pain, diarrhea, joint pain, fatigue, weakness, rhabdomyolysis (rare)[86]

Peroxisome proliferator-activated receptor-α (PPAR-α) agonist/Fibrates- Reduce total cholesterol, LDL, triglycerides, and Apo-B. It increases HDL[88]

Drug	1-2 g daily in 2 divided doses	Contraindications, Administration Considerations and Side Effects
Gemfibrozil	Alternate dosing: 900 mg as a single dose in the evening • Should be given 30 mins before meals89 Dose Adjustments: • Mild to moderate (GFR 30-80 mL/min/1.73m2): Initially, 900 mg daily • Severe Renal impairment: Contraindicated	Contraindication: Known hypersensitivity to the drug class, active liver disease, active gall bladder disease, severe renal dysfunction, lactation88,89 Administration considerations: • Gemfibrozil should not be used concomitantly with statin • When fenofibrate is to be used with statin, monitor serum creatinine levels and renal function
Fenofibrate	Standard micronised formulation: • Initially, 67 mg tid or 200 mg once daily. • May reduce to 67 mg bid, or increase to 67 mg 4 times daily, or 267 mg once daily according to response Non-micronised formulation: • Initially 200-300 mg daily given in divided doses • May be adjusted to 200-400 mg daily according to response Improved bioavailability formulation: • 40-160 mg once daily • Should be taken with food90	Side effects: Deranged AST, ALT levels; infrequent elevations in serum CPK (creatinine phosphokinase) levels; increase serum creatinine and homocysteine levels; myopathy, cholelithiasis; venous thrombosis (rare)88

outcomes. In one early good-quality trial, counselling in combination with a protocol to start medication led to reduction in CVD events at 6.6 years compared with usual care (relative risk [RR], 0.71 [95% CI, 0.51 to 0.99]). It also showed improvement on selected QOL measures. Adverse events are not common in counselling interventions.[91] In several meta-analysis on statin treatment, CVD events, CVD risk levels i.e., LDL-C levels and adverse events are often measured and reported.[92] In some trials, quality of life and patient satisfaction are also measured. These should also be monitored as an outcome in the continuing management of dyslipidemia in family practice.

Recommendations For Implementation

Clinic Level

The recommendations for implementation of this clinical pathway are similar to the recommended implementation of the other clinical pathways developed by the PAFP. The committee will disseminate the clinical pathways in a form of lectures and publications. Lectures and publications will also be supplemented by generating evidence of actual practice by family physicians. At the clinic level, self-audit using the recommendations of this clinical pathway as the standard may be done. Passively delivered, complex interventions targeted at identified barriers to change had little effect in changing practice.[93]

Organizational Level

Similarly, at the organizational level the PAFP should create a new model of quality improvement program where self-practice audits are included. Within PAFP chapters, peer group discussions, individual feedback and quality improvement reports are the main components. This model has been shown to improve the care process for urinary problems in one randomized clinical trial. This trial showed that prescribing of first choice appropriate management increased in the intervention group from but remained the same in the control group.[94]

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