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THE INCLEN TRUST
Research and Training for Improving Equity, Efficiency and Quality in Health Care

PHILIPPINE HEART ASSOCIATION, INC. • PHILIPPINE COLLEGE OF CARDIOLOGY

The Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines

EXECUTIVE SUMMARY

The recommendations contained in this document are intended to GUIDE practitioners in the detection and management of adult patients with dyslipidemia. In no way should the recommendations be regarded as absolute rules, since nuances and peculiarities in individual cases or particular communities may entail differences in the specific approach. The recommendations should supplement, not replace, sound clinical judgment on a case-to-case basis.

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The following organizations are represented:

Voting panel:

- PHA-Council on Preventive Cardiology, Council on Coronary Artery Disease, and Council on Hypertension
- Philippine Society of Hypertension
- Manila Doctors Hospital
- Philippine Lipid Society
- Philippine Diabetes Association
- Philippine College of Physicians
- Philippine Academy of Family Physicians
- Food and Nutrition Research Institute - Department of Science and Technology
- Department of Health - Republic of the Philippines
- Nutritionists-Dietitians Association of the Philippines
- Institute for Studies on Diabetes Foundation, Inc.
- Philippine Medical Association
- Philippine Hospital Association
- Las Piñas District Hospital
- Philippine Society of Endocrinology and Metabolism

Nonvoting panel:

- Philippine Health Insurance Corporation
- Past Presidents and the Directors of the PHA, and the offices of the PHA President, the PHA Vice President and the PHA Treasurer

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Contents

The applicability of foreign dyslipidemia clinical practice guidelines (CPGs) to the Philippine setting is impaired by differences in epidemiological, socioeconomic and cultural factors that may affect the overall benefit of specific preventive, diagnostic and therapeutic interventions. To address the need for relevant and appropriate dyslipidemia CPGs for Philippine clinical practice, a panel representing several professional societies, government agencies, healthcare institutions and other stakeholders came together through the initiative of the Philippine Heart Association and the support of the International Clinical Epidemiology Network (INCLEN). Using the INCLEN CPG Development Cycle known as "Knowledge Management Plus", the panel appraised relevant literature on dyslipidemia to formulate consensus recommendations. Importantly, the appraisal focused on the applicability of literature to the Philippine population to ensure that recommendations are useful to local practice. To address existing health inequities and ensure applicability to disadvantaged sectors of society, crude costs of interventions were also considered. To prevent vested interests from influencing the formulation of the CPGs, financial support from private corporations during the development process was avoided. Furthermore, issues regarding conflicts of interests involving members of the technical research committee, as well as the panel, were addressed. Hence, the resulting document is a comprehensive, appropriate, balanced and unbiased set of evidence-based guidelines for the management of dyslipidemia in the Philippines.

The Clinical Practice Guidelines (CPGs) for the Management of Dyslipidemia in the Philippines presents evidence-based recommendations for the management of cardiovascular disease (CVD) risk and dyslipidemia. The full document, outlined by the executive summary, contains the complete guidelines deemed relevant for Filipinos.

The CPGs considered lifestyle and diet modification as integral components of CVD risk management. In addition, the present CPGs proposed strategies for primary and secondary prevention of dyslipidemia. The guidelines also defined indications for screening and pharmacotherapy, as well as the target lipid levels. All recommendations, presented in statements, were formulated after meticulous appraisal of literature and consideration of costs, resulting in CPGs that are valid and applicable to the Philippine setting.

Statements

The Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines

Executive Summary

The burden of cardiovascular disease (CVD) in the Philippines is rising. In 1999, the cause-specific mortality rate for cardiac and vascular disease were 78.4 and 58.4 deaths/100,000 population, respectively.[1] The following year (2000), these figures rose to 79.1 (16.5% of total deaths) and 63.2 deaths/100,000 population (13.2%). In 2001, hypertension (408.7 cases/100,000 population) ranked as the 5th leading cause of morbidity while heart disease ranked 7th (60.4 cases/100,000 population).

The prevalence of established risk factors for coronary artery disease (CAD) are also on the rise (Table 1).[2,3] More importantly, from 1998 to 2003, the prevalence of high cholesterol doubled, which was observed regardless of whether the cut-off level was >200 or >240 mg/dL. Hence, by 2003, almost a third of Filipinos had low-density lipoprotein (LDL) levels >130 mg/dL, while 11.7% had LDL >160 mg/dL.[3] More than half had low levels of high-density lipoprotein (HDL) (i.e., <40 mg/dL). In patients with type 2 diabetes, which is considered a coronary disease equivalent, the approximate prevalence of dyslipidemia are as follows: 60% to 75% (based on high total cholesterol), 50% to 60% (low HDL), 70% (high LDL), and 40% to 50% (hypertriglyceridemia).[4,5]

Developing national clinical practice guidelines (CPGs)

Strategies are needed to improve dyslipidemia management, given the rising burden of dyslipidemia as a risk factor for CVD. One of these strategies is the development of appropriate clinical practice guidelines (CPGs) to improve decision-making and clinical performance. Although foreign CPGs may be adopted in the local setting, these may not be appropriate, as suitable strategies for prevention may differ between countries because of demographic,

Table 1. Prevalence of risk factors for CAD[2,3]

Risk factors	1998 (%)	2003 (%)
Current smoker (age ≥20)		
Male	53.9	56.3
Female	12.6	12.1
Hypertension	17.2	17.4
Diabetes mellitus		
FBS (>125 mg/dL)	3.9	3.4
History of diabetes	—	4.6
High total cholesterol		
>200 mg/dL	15.9	28.0
>240 mg/dL	4.0	8.5
High LDL		
>130 mg/dL	23.8	31.5
>160 mg/dL	8.1	11.7
Low HDL	65.4*	54.2**
Obesity (BMI >25)	20.2	23.9

*<35 mg/dL in 1998; **<40 mg/dL in 2003; BMI, body mass index.

epidemiological, cultural, social, medical and economic reasons.[6] Risk-factor treatment thresholds and goals may also differ, as well as medical therapies.

The adoption of foreign practice guidelines may be particularly problematic in the Philippine setting, where both the state and its citizens have very limited health resources. Four out of five Filipinos live below the poverty line.[7] In 2003, the average Filipino spent only USD 14.73 for medicine, comprising only 1.9% of total family expenditure.[8,9] The Philippines' per capita pharmaceutical consumption is one of the lowest among the Asian countries.[8]

Whereas the World Health Organization recommends that governments spend at least 5% of their gross national product on health, the national health expenditure of the Philippines has decreased from 3.4% in 1997 to only 3.1% in 2001.[9] In the face of the national government's inability to provide adequate health care, patients have to pay out-of-pocket for health care services. This being the case, patient care based on foreign guidelines may be too expensive for Filipino patients.

In 1996, CPGs for dyslipidemia management were developed in the Philippines.[10] After careful appraisal, these CPGs were found to have several shortcomings.[10,11] The 1996 CPGs were made on the assumption that everyone can afford tests and treatment. Certain medications as well as monitoring of adverse events were not considered. Lastly, no formal process was done to quantify the importance of different outcomes.

To formulate national dyslipidemia CPGs that are more appropriate for Filipinos, the Philippine Heart Association (PHA)-Council on Preventive Cardiology spearheaded the development of the Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines. This was accomplished through the cooperation of partner organizations and the technical and sole financial support of the International Clinical Epidemiology Network (INCLEN). The objective of this endeavor is to develop valid and applicable dyslipidemia CPGs for Filipinos, with special consideration for existing health inequities.

I. Methodology: the KM+ process

Literature review and appraisal

The Philippine CPGs on Dyslipidemia were developed using the INCLEN Guideline Development Cycle, referred to as Knowledge Management Plus (KM+).[11] Using KM+, literature was appraised for validity as well as applicability to the target population, which in this case are Filipinos, including those who are disadvantaged. The quality of evidence was graded as high, moderate, low or very low.

Applicability appraisal is particularly important for this set of guidelines because most large-scale trials were conducted on Western populations, which significantly differ from that of the Philippines. This may affect the manner by which the results of these trials are interpreted and applied in the local setting. Demographic and epidemiological differences may alter the burden of illness, as well as the magnitude and impact of risk exposure. Cultural and social differences may also affect risk exposure (especially since CVD is largely related to lifestyle practices), perceptions of illness and approaches to intervention. Differences in medical and economic resources

INCLEN Guideline Development Cycle Knowledge Management Plus (KM+)[11]

The Philippine CPGs on Dyslipidemia were patterned after the INCLEN Guideline Development Cycle (Knowledge Management Plus [KM+]), which is as follows:

1.a Identification of the topic
1.b Organization of the panel members
1.c Appraisal of the previous guidelines
1.d Identification of the research questions

2. Literature search and retrieval of studies
3. Validity appraisal of literature
4. Appraisal of literature in terms of applicability
5. Preparation of evidence-based summaries
6. Preparation of balance sheets for interventions
7. Developing judgments by consensus
8. Presentation of the guidelines in a public forum
9. Plan for guideline implementation; disseminate guidelines
10. Monitor guideline implementation and impact

may limit the extent by which diagnostic and therapeutic recommendations may be carried out and complied with. Hence, profound population differences may markedly impair the usefulness of foreign studies in formulating appropriate guideline recommendations for the Philippine setting.

Evaluation of treatment benefit

After appraisal, the outcomes of studies were graded according to their relative importance, with the critical ones (graded 7 to 9) given primary consideration. For these CPGs, the following seven outcomes were considered as critical: total mortality, CV mortality, myocardial infarction (MI) (fatal and nonfatal), stroke (fatal and nonfatal), CV events, revascularization and serious adverse events.

Balance sheets of benefits and harm were prepared from data in literature, following the KM+ process. They included treatment- and control-event rates,

relative risks (RR*) and numbers-needed-to-treat (NNT†) for each outcome. Whenever possible, local event rates were predicted by ratio and proportion using the ratio of local prevalence rates to the rates observed in the country where the study was conducted. The balance of benefits and harm were then determined and classified as follows:

- Net benefits (the intervention clearly does more good than harm);
- Trade-offs (there are important trade-offs between benefits and harm);
- Uncertain net benefits (it is not clear whether the intervention does more good than harm); or
- No net benefits (the intervention clearly does not do more good than harm).

Formulation of recommendations

Crude cost-benefit analyses were conducted after the benefit of intervention was described by review and appraisal. Costs were computed on the basis of the local cost of the drug/intervention, the mean duration of therapy and the number of patients needed to undergo treatment to achieve the magnitude of outcome benefits indicated by the trial (i.e., NNT). A balance of net benefits and costs was then made to determine if incremental health benefits are worth the costs. Following the KM+ process, recommendations were then formulated based on the extent to which one can be confident that adherence will do more good than harm. The recommendations are as follows:

- Do it;
- Probably do it;
- No recommendation;
- Probably don't do it; or
- Don't do it.

When recommendations on certain patient subsets and therapeutic approaches require thresholds for laboratory parameters (e.g., lipid levels), these levels were set at one standard deviation (SD) from baseline levels of the respective studies. The choice to use either the upper one-SD boundary or the lower one-SD boundary was based on the parameter (i.e., total cholesterol vs LDL vs HDL) and the relative magnitude of benefit of the specific treatment compared with alternative therapies and non-treatment. For treatments which will produce benefits that are profoundly greater than those of alternative treatments or non-treatment, treating more patients was deemed desirable. Hence, cut-offs that will include more patients were chosen accordingly. Lastly, as these CPGs are intended to assist decision-making, cut-off values were harmonized when possible, especially when values for the same parameter but different indications approximate each other. This is to improve physicians' recall of these values.

Other important features

The Philippine CPGs on Dyslipidemia were specifically designed to suit Philippine clinical practice by taking into consideration the Philippines' demographic, socioeconomic and health situation. The scientific evidence used has been critically appraised for its relevance and applicability to clinical practice in the country. Therefore, the recommendations in these CPGs are, for the most part, relevant to Filipinos and primarily pertain to them.

Furthermore, these CPGs deal with equity issues and considered the disadvantaged groups in Philippine society, particularly those who live below the annual poverty threshold of PHP 12,267.00 (as of 2003), cannot afford laboratory examinations and drug therapy, have limited or no access to health care, or are undernourished (BMI <18.5).

To ensure that the CPGs are unbiased and that the interests of Filipinos, especially the disadvantaged, remain foremost, members of the Technical Research Committee (TRC) took efforts to systematically resolve issues concerning conflicts of interest. They voluntarily disclosed affiliations and, in some cases, divested themselves of assets to avoid actual, potential or perceived conflicts of interest. These included memberships in advisory boards and speakers' bureaus of pharmaceutical companies; research management; ownership of stocks or equipment in hospitals; involvement in clinical trial review and research; and travel, sports, leisure and convention sponsorship. Some members voluntarily excluded themselves from specific steps in the guideline development cycle that were deemed sensitive to

***RR** – the ratio of the incidence rate for persons exposed to a factor to the incidence rate for those not exposed

†NNT – number of patients who must be treated with an intervention for a specific period of time to prevent one bad outcome, or result in one good outcome

conflicts of interest. Panelists were encouraged but not required to disclose or give up ownership, affiliations or activities which may constitute conflicts of interest, or exclude themselves from steps of the guideline development process.

With these unique features, the resulting document contains groundbreaking evidence-based guidelines that are balanced, unbiased, appropriate and useful for local practice and relevant to all sectors of Philippine society.

II. Guideline recommendations on total CVD risk management for the general population

Statement 1

To reduce overall CV risk, all patients, regardless of their present morbid condition or risk profile, should be advised on the need for the following:

- **Smoking cessation;**
- **Weight management;**
- **Regular physical activity; and**
- **Adequate blood pressure monitoring and control.**

Public health measures are highly cost-effective and become increasingly relevant considering that the distinction between asymptomatic high-risk individuals and those with established atherosclerosis is artificial: majority of high-risk individuals are also likely to have advanced subclinical atherosclerosis.[6] Hence, the distinction between primary and secondary prevention is also artificial. The prevention of CVD at a population and individual level, ranging from those with clinically evident CVD to those who are asymptomatic and/or at high risk, is a continuum with significant overlap. Preventive interventions applicable to both patients with or without clinically evident disease include general modifiable-risk management and lifestyle modification. Lifestyle interventions are implementable worldwide regardless of the impact of economic factors, unlike pharmacological, interventional and laboratory testing strategies.[12]

Table 2. Weight classification (by BMI) in adult Asians[24]

Classification	BMI (kg/m²)	Risk of comorbidities
Underweight	<18.5	Low*
Normal	18.5-22.9	Average
Overweight (at risk)	23-24.9	Increased
Obese I	25-29.9	Moderate
Obese II	>30	Severe

*But increased risk of other clinical problems

Lifestyle

Interventions in relation to smoking cessation, healthy food choices, weight control and physical activity are essential elements of preventive cardiology and overall CVD risk reduction.

Smoking. Cigarette smoking increases CVD risk in both men and women in a dose-dependent manner.[13] It approximately doubles coronary heart disease (CHD) risk, which may further increase with the number of cigarettes smoked. Conversely, smoking cessation in primary prevention settings substantially reduces cardiac risk within months after quitting.[14-17] Hence, smoking cessation is consistently included in CVD risk management. For significant CV risk reduction, the goal is complete smoking cessation and avoidance of passive smoking. The physician's advice is the crucial first step.

Weight management. Adiposity is associated with CVD, as well as stroke and numerous other comorbid conditions.[12,18,19] It is also associated with higher all-cause mortality, largely because of an increase in CVD mortality.[20,21] In addition, people who are overweight or obese have a high burden of other CHD risk factors, including dyslipidemia.[22,23] Meanwhile, reducing weight reduces blood pressure, plasma LDL and triglyceride levels, increases HDL levels and decreases glucose intolerance.[6]

Although BMI is the most widely used measure of adiposity (Table 2), abdominal obesity is more strongly correlated with CV risk.[5,12,24] The goals and approaches to abdominal obesity vary with geographic region. Abdominal obesity may be

Table 3. Comorbidities risk according to BMI and waist circumference in adult Asians[24]

Classification	BMI (kg/m²)	Risk of comorbidities	
		Waist circumference	
		<90 cm (men) <80 cm (women)	≥90 cm (men) ≥80 cm (women)
Underweight	<18.5	Low*	Average
Normal	18.5-22.9	Average	Increased
Overweight (at risk)	23-24.9	Increased	Moderate
Obese I	25-29.9	Moderate	Severe
Obese II	≥30	Severe	Very severe

*But increased risk of other clinical problems

measured using the ratio of waist to hip circumference (WHR). In Caucasians, a WHR >1.0 for men and >0.85 for women indicates abdominal fat accumulation.[24] However, according to *The Asia-Pacific Perspective: Redefining Obesity and its Treatment*, the waist circumference is the preferred measure of abdominal obesity compared to the WHR, and may be used to qualify a patient's risk of associated comorbidities, such as diabetes, metabolic syndrome, CHD, sleep apnea and osteoarthritis.

Physical activity. Regular physical activity is associated with a lower risk of death from CVD and CHD, but the mechanisms behind this are not fully understood and probably multifactorial.[25-30] Physical activity is associated with lower levels of LDL and triglycerides, higher HDL cholesterol, improved insulin sensitivity and lower blood pressure.[31-34] Moreover, exercise-based cardiac rehabilitation in patients with established CAD has been shown to reduce total CV mortality.[6]

For physical activity to be protective, it must be vigorous, aerobic, habitual and continuing.[27,30] A large-scale study suggests that 3 hours a week of moderately vigorous activity or activity equivalent to 3,500 kilocalories is protective.[30] However, this study was done in Caucasians and there are no current local data on this matter.

Moderately vigorous activity includes swimming, basketball, volleyball, badminton, tennis, jogging and running. The equivalent of 3,500 kilocalories is walking 35 miles (56 km) or climbing 438 flights of stairs (20 steps/flight).

Blood pressure

Hypertension should be a concern in dyslipidemic patients because it commonly occurs concomitantly with hypercholesterolemia.[35,36] Particularly after MI, treatment of hypertension, including regimens with ß-blockers or angiotensin-converting enzyme inhibitors, reduces recurrent MI and all-cause mortality, as well as fatal and nonfatal stroke.[12,37] As effective hypertension therapy is available, regular blood pressure screening may be conducted even in apparently healthy individuals.

The above factors – smoking, weight, physical activity and blood pressure – are modifiable. Specific interventions reduce overall CV risk regardless of the individual's present morbid condition or risk profile.[6] Such interventions should be recommended to the general population. Patient advice to reduce overall CV risk should include smoking cessation, maintenance of target weight and prevention of obesity (Tables 2 and 3),[24] regular physical activity and adequate blood pressure monitoring and control.

III. Guideline recommendations for the dietary management of dyslipidemia

Statement 2

For patients at any level of cardiovascular (CV) risk, especially those with established atherosclerosis, a low-fat, low-cholesterol diet is recommended for life.

Statement 3

In poorly nourished and elderly patients, correction of nutritional deficiencies can be achieved even with a low-fat, low-cholesterol diet.

A recent meta-analysis that included 27 studies, comprising a total of 40 intervention arms and 30,901 person-years of data, was the basis for assessing the benefit of dietary fat restriction/modification – which may reduce serum lipid levels – in reducing clinical outcomes, such as CV events and mortality.[38-40]

Dietary interventions in the studies included in this meta-analysis were generally characterized by a recommended total fat intake ranging from 30% to 40% of total caloric intake or a reduction in fat intake to about 35 g/day to 40 g/day.[38] Dietary cholesterol intake recommendations ranged from >300 mg/day, to approximately 450 mg/day, to 100 mg for every 1,000 kilocalories consumed daily.

Validation and appraisal showed that this meta-analysis had high methodological quality. However, Filipinos and females were not represented in the primary studies, which raised the issue of applicability. Long-term follow-up data was also sparse. These issues decreased overall evidence quality, from high to low (with regard to mortality outcomes) and moderate (CV events).

Nonetheless, the study clearly showed that dietary interventions have a protective effect against CV events, with an NNT of as low as 8 among those who maintain dietary interventions for >2 years. No cost-effectiveness study on low- or modified-fat dietary interventions has been made locally, but dietary interventions in the form of advice is generally very cost-effective and should be recommended. As patients vary with regard to nutritional status and lipid levels, there remains the need for clinicians to provide patient-specific and -appropriate dietary advice.

IV. Guideline recommendations for primary prevention

Statement 4

For low-risk* patients without evidence of atherosclerosis, drug therapy is not recommended, regardless of lipid levels.

RISK FACTORS

*** Risk factors: Hypertension, familial hypercholesterolemia,† left ventricular hypertrophy, smoking, family history of premature CAD, male sex, age >55 years, proteinuria, albuminuria, BMI ≥25.**

Low-risk – have <3 of any of the risk factors

† The presence of familial hypercholesterolemia warrants treatment even without other risk factors.

The use of statins in patients with no established atherosclerosis was evaluated using the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) and the West of Scotland Coronary Prevention Study (WOSCOPS).[42,43] The AFCAPS/TexCAPS involved patients with average total cholesterol levels (defined using lipid percentiles of an age- and sex-matched cohort, and conventionally classified as "borderline high").[5,42] On the other hand, the WOSCOPS included men with moderate hypercholesterolemia.[43]

The use of fibrates for primary prevention in patients with dyslipidemia was evaluated via the Helsinki Heart Study (HHS): Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia.[44] The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was used to evaluate the benefit of cholestyramine as a primary prevention intervention in patients with dyslipidemia.[45]

The statin trials showed that statins reduced CV events (by 24%-30%), MI (by 30%-40%) and need for revascularization (by 33%-36%) in patients without established atherosclerosis and risk factors.[42,43] Fibrates reduced the risk of non-fatal MI by 37% while no reductions in total mortality, stroke, CV events and revascularization were demonstrated.[44] Cholestyramine reduced

†Diagnosis based on history of premature CVD, family history, tendon xanthoma, arcus cornealis and LDL >190 mg/dL.[70]

CHD mortality by 25% and nonfatal MI by 19% when evaluated using a 90% confidence interval (CI).[45] However, after standardization to a 95% CI, no significant risk reductions in clinically important outcomes were observed.

Using predicted local rates in computing for NNTs, crude cost-benefit analysis showed that treating 286 patients with the lowest-priced, locally available statin required PHP 12.3 million to prevent around one CV death, one to three MIs, two to three CV events and one revascularization. Treating the same number of patients using the lowest-priced, locally available fibrate required PHP 12.7 million to prevent two MIs.

Appraisal of these four studies revealed problems regarding applicability to Filipinos, which lowered the quality of evidence. Because of this, the net benefit of statins inferred from the AFCAPS/TexCAPS was valued as "uncertain". On the other hand, "trade-offs" were noted using WOSCOPS.

With regard to fibrates, several issues hindered a positive recommendation. The quality of evidence from the HHS was low. This eventually led to treatment being evaluated as having "no benefit". Lastly, fenofibrate and bezafibrate have not been evaluated in randomized controlled trials for primary prevention. Because of the poor benefit compounded by high costs of therapy, the panel's consensus was against drug therapy for primary prevention.

Statement 5

For patients without established atherosclerosis[‡] but with ≥3 risk factors* and total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL, statins may be recommended. (*Please see RISK FACTORS, page 19.)

Evidence on the use of statins on patients with multiple risk factors were derived from the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) and the Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients randomized to Pravastatin versus Usual Care: The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT-LLT).[46,47] ALLHAT-LLT did not demonstrate any significant reduction in important clinical outcomes.[47] However, ASCOT-LLA found that in hypertensive patients with more than 3 additional risk factors and no established CHD, statin therapy significantly reduced MI by 37%, stroke by 27% and CV events by 28%.[46]

Despite the benefits indicated by ASCOT-LLA, there were some difficulties in using this study to formulate primary prevention guidelines for high-risk Filipinos. Although ASCOT-LLA did not have any validity problems, evidence quality was low (very low for the disadvantaged population) because of directness problems. Filipinos have different epidemiological and socioeconomic issues compared with the study population of ASCOT-LLA (which was conducted in Anglo-Scandinavian countries, where CHD risk is twice that of the Philippines). This was further complicated by the inclusion of certain patients, such as those with peripheral artery disease and a history of stroke, which may suggest that ASCOT-LLA is not a purely primary prevention trial. Hence, the benefit indicated by ASCOT-LLA was judged as "uncertain".

On the other hand, ALLHAT-LLT had validity problems, including those concerning study design (open-label), dissimilarity in treatment groups and differences in epidemiological and socioeconomic factors affecting the study population and Filipinos. In addition, there was a 32% crossover from the control group to the statin group. These factors severely impaired the usefulness of ALLHAT-LLT as basis for recommendations.

With little sound evidence on which to base recommendations, expert opinion was given considerable value. According to expert opinion, despite cost-analysis showing that statin treatment for 300 people in order to prevent one stroke, two MIs and two CV events requires PHP 20 million, statins remain as an option and warrants the recommendation "probably do it". Primary physicians are given the option to give a statin. The treatment thresholds of total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL were primarily derived from the Heart Protection Study (HPS).[48] These values approximate one SD from baseline levels of subjects of the trial treatment arm, sufficiently representing those that benefit most from statin therapy.

[‡]Refers to patients with acute coronary syndrome, previous MI or unstable angina, peripheral arterial disease, stroke or transient ischemic attack and evidence of coronary artery disease or revascularization.

Statement 6

For diabetic patients without evidence of atherosclerosis and with total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL, statins are recommended.

Statement 7

Fibrates may be recommended as an alternative to statins in diabetic patients with HDL ≤35 mg/dL AND LDL ≤90 mg/dL.

Statins

Evidence on the benefit of statins for primary prevention in dyslipidemic diabetic patients included AFCAPS/TexCAPS, ASCOT-LLA, the HPS and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), which are studies with large diabetic cohorts.[42,46,48,49] The Collaborative Atorvastatin Diabetes Study (CARDS) was designed primarily for dyslipidemic diabetic patients, and was also included.[50] These studies evaluated statins on a wide range of lipid levels. Patients included in these studies had total cholesterol ranging from 135.1 to 347.5 mg/dL.[42,46,48-50] The quality of evidence from these studies was appraised as moderate.

Although these trials did not show significant reductions in total mortality in patients with diabetes, pooled results showed a 34% reduction in fatal and nonfatal MI, 15% reduction in revascularization, and 28% reduction in CV events.[41,45,47-49] Cost analysis revealed that the use of statins on 90 diabetic patients for the primary prevention of one MI, one revascularization and one CV event may cost PHP 3.9 to 5.3 million. Hence, the consensus recommendation for statins was "do it." Treatment thresholds are primarily based on baseline levels in the HPS, which had the largest diabetic cohort among the above studies.

Fibrates

Sound evidence for the use of fibrates in the primary prevention of CV events among diabetic patients was mostly provided by the Diabetes Atherosclerosis Intervention Study (DAIS) and the St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) study.[51,52] Although primarily intended for patients with diabetes, these trials were not powered for hard clinical outcomes but only for mechanistic or surrogate outcomes.

The pooled estimate for the composite endpoint of CV events indicated a significant 33% risk reduction.[51,52] Data for other outcomes are not available, and adverse events from treatment are minimal and similar to placebo. Hence, fibrate use has a net benefit in the primary prevention of diabetic dyslipidemia. Cost analysis of three-year therapy using bezafibrate 400 mg OD or fenofibrate 200 mg OD on 32 patients to prevent one adverse CV event showed respective costs of PHP 0.88 and 1.0 million.

The recommendation for fibrates was "probably do it", as fibrates are probably more beneficial for patients with low HDL, considering its mechanism. The preference for statins over fibrates is indicated by inherent limitations of evidence for fibrates. As mentioned, DAIS and SENDCAP primarily evaluated mechanistic or surrogate outcomes rather than clinical ones, and were not powerful enough to evaluate clinical outcomes.[51,52] Treatment thresholds were primarily based on DAIS, although cut-offs from the two studies approximate each other.

V. Guideline recommendations for secondary prevention

Statement 8

For patients with established atherosclerosis and total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL, statins are recommended.

Statement 9

Fibrates may be recommended as an alternative to statins if HDL ≤35 mg/dL AND LDL ≤90 mg/dL.

Statins

Evidence on the use of statins for secondary prevention were derived from the HPS, the Scandinavian Simvastatin Survival Study (4S), the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial, the Cholesterol and Recurrent Events (CARE) trial, the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) Study and PROSPER.[49,53-57] Appraised as having moderate evidence quality, these studies indicated a significant overall risk reduction in total mortality, CV death, MI, stroke and

revascularization from statin therapy. Among elderly patients, only CV events were significantly reduced.

Trials for secondary prevention are more cost-effective than those for primary prevention. Considering the HPS, currently the largest, randomized controlled trial on statin use among individuals with established atherosclerosis, crude cost analysis showed that five-year therapy with statins will amount to PHP 2.9 million to prevent 1 death, 4 CV events, 1 MI, 1 stroke and 1 revascularization.

The consensus recommendation for patients with established atherosclerosis is to initiate statin treatment for the following lipid levels: total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL. These levels are based on the baseline characteristics of patients included in HPS,[53] which is relevant for setting cut-offs because of its large size and ability to evaluate the effect of therapy over a wide range of baseline lipid levels. Hence, the patients in this study best represent those that may benefit from statin therapy.

Fibrates

The evidence on fibrates were from the Veteran's Affairs High-density lipoprotein Intervention Trial (VA-HIT) and the Bezafibrate Infarction Prevention (BIP) trial.[58,59] Pooled estimates demonstrated that fibrates reduced the incidence of MI and stroke in patients with established atherosclerosis by 16% and 22%, respectively. No significant effect was seen on the outcomes of total mortality, cardiovascular death, revascularization and serious adverse events.

Crude cost analysis indicated that fibrates taken for 5 to 6 years would cost approximately PHP 2.1 to 2.7 million to prevent one MI and one stroke.

The benefit of fibrate therapy is limited to MI. Furthermore, the magnitude of benefit is small. Hence, after considering costs and marginal benefit, the consensus recommendation was to limit fibrates as an alternative to statins. Baseline HDL levels (-SD) from the two studies approximated each other and those of DAIS and SENDCAP, while HDL and LDL treatment thresholds were harmonized with that of the primary prevention fibrate recommendations. These approximated the baseline values (-SD) from VA-HIT, which was designed for patients with low HDL (the target subgroup for this recommendation).

Nicotinic acid*

The Coronary Drug Project, a study appraised as having moderate-quality evidence, showed that nicotinic acid reduced the risk of MI by 26%, stroke by 24% and revascularization by 60%.[60] The overall estimate cannot be computed from the data provided. Numerous side effects were noted during the study, the most common being flushing, pruritus, gastric irritation, rashes and decreased libido.

A 15-year follow-up study (nine years after the termination of the study) showed that mortality in the nicotinic acid group was lower by 11% (52.0% vs 58.2%, p=0.0004).[61] This late benefit, occurring after discontinuation of the drug, may be a result of a translation of the early favorable effect of nicotinic acid (in decreasing nonfatal reinfarction or lowering cholesterol) into a mortality benefit over subsequent years.

The NNT for MI is 27, 37 for stroke and 73 for revascularization.

Intensive therapy for short-term benefits in acute coronary syndrome (ACS)

The highest rates of death and recurrent ischemic events occur during the period immediately after an ACS.[62,63] To evaluate the benefit of statin therapy in reducing morbidity and mortality after an ACS, two trials were appraised: the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial.[64,65]

Whereas MIRACL was designed to determine the benefit of intensive statin therapy in ACS, PROVE-IT was designed to compare the benefit of standard statin therapy with intensive statin treatment. Hence, results of MIRACL seemed to be a more appropriate basis for indicating the benefit from intensive therapy, whereas PROVE-IT may be less relevant, and was eventually not used.

* At the time of development of these CPGs, nicotinic acid was not available in the Philippine market.

Appraisal indicated that evidence from the MIRACL trial has low quality because of a serious flaw in the study design (censorship of patients who did not experience an endpoint prior to study completion or early withdrawal from study) and identified socioeconomic directness issues regarding the study population.[64]

No significant reductions were observed across all clinically important CV outcomes, but recurrent ischemic angina, an important outcome for ACS patients, was significantly reduced, suggesting some value in intensive therapy.

Cost analysis showed that the cost of preventing recurrent ischemic angina in one patient through 16 weeks of intensive statin therapy is PHP 432,000.00. Because of the low quality of the evidence in the MIRACL study, poorly defined significance of the benefit of treatment, and the results of the cost analysis, the panel gave "no recommendation" with regard to intensive statin therapy for hypercholesterolemic ACS patients.

VI. Guideline recommendations for screening

Statement 10

In patients without risk factors*, history or symptoms of established atherosclerosis, the screening of lipid levels is not recommended.[§] (*Please see RISK FACTORS, page 19.)

Screening is performed to detect unrecognized health risks or asymptomatic disease for prevention and timely intervention.[66] However, because of uncertain benefits and high costs, the panel does not recommend drug therapy for patients with no risk factors, history, or symptoms of established atherosclerosis or previous CVD.[42,43] The only recommended interventions for such patients are nonpharmacological, which should be instituted regardless of lipid levels. Hence, determining lipid levels for screening does not assist decision-making regarding patient management and is therefore not recommended.

[§] Except when familial hypercholesterolemia is suspected.

Statement 11

In patients without established atherosclerosis but with ≥3 risk factors*, lipid profile may be recommended. (*Please see RISK FACTORS, page 19.)

For patients with multiple risk factors but no established atherosclerosis, clinical evidence indicates benefit – although this benefit is uncertain in Filipinos – from the use of statins.[46,47] These guidelines recommend statins as a preventive pharmacological intervention. In this subgroup, statin treatment may be initiated when total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL. Therefore, determining lipid levels may be helpful whenever statin therapy is being considered in this patient subgroup.

Statement 12

In patients with established atherosclerosis or diabetes, the use of lipid profile for screening is recommended.

These guidelines recommend statins for patients with atherosclerosis or diabetes, wherein therapy is initiated in patients with total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL. In addition, fibrates are recommended as an alternative to statins if HDL ≤35 mg/dL and LDL ≤90 mg/dL. Therefore, lipid profiling is helpful in identifying patients where pharmacotherapy is appropriate.

VII. Recommendations for drug therapy

Initiation of therapy

Based on the consensus guidelines on primary and secondary prevention, the initiation of statins is an option in patients with no established atherosclerosis but with multiple risk factors and total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL. It is recommended for diabetic patients and those with established atherosclerosis, when total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL.

However, costs should be considered for the underprivileged. **For patients who opt to defer screening, the initiation of statin therapy may still be given as an option after proper patient education (informed patient choice).**

The following statin doses have been used in outcome trials and have demonstrated an approximate LDL reduction of 30% to 40% from baseline: lovastatin 20 to 40 mg/day; atorvastatin 10 to 80 mg/day; pravastatin 10 to 40 mg/day; fluvastatin 80 mg/day; or simvastatin 20 to 80 mg/day.[42,46,50,53-56,67]

Fibrates may be initiated as an alternative to statins in diabetic patients with no established atherosclerosis and with HDL ≤35 mg/dL and LDL ≤90 mg/dL. The following fibrate regimens were used in clinical studies: gemfibrozil 1,200 mg/day; fenofibrate 200 mg/day; and bezafibrate 400 mg/day. [51,52,58,59]

Target for treatment

The role of LDL in atherogenesis and elevated LDL in CVD is well established.[5] Prestatin and statin trials in which LDL reduction was the major lipid response, resulting in improvements in coronary lesions and clinical outcomes, further validate the role of LDL as a target of therapy. In near-optimal treatment, significant risk reductions are observed with approximately 30% to 40% LDL reduction from baseline.[42,46,50,53-56,67] This may be translated to an approximate LDL reduction of 38 mg/dL (1 mmol/L).

Furthermore, studies that evaluated intensive statin therapy, such as the PROVE-IT and the Treating to New Targets (TNT) trials, showed additional CV benefits, together with slight increases in the frequency of serious adverse events when LDL is decreased to <77 mg/dL through intensive statin therapy (e.g., atorvastatin 80 mg/day instead of 10 mg/day).[63,68] Therefore, a 30% to 40% LDL reduction from baseline or LDL <77 mg/dL are suitable treatment goals.

Patient monitoring

The earliest time to repeat measurements of lipid profile should be within 6 weeks after initiation of therapy.[69] This is a reasonable interval, especially in patients whose therapeutic goal is a 30% to 40% LDL reduction. Less ideal monitoring options (e.g., total cholesterol only) may be used, provided that proper and adequate information and education is provided to help patients make an informed choice. Patients who choose total cholesterol for screening to initiate statin therapy may be given a fixed dose.[46,53] Monitoring may be foregone for such patients. Total cholesterol may also be used for monitoring (to be conducted at the soonest after 6 weeks). Dose titration should aim for at least a 20% reduction of total cholesterol from baseline.[55,56]

VIII. Considerations for the disadvantaged population

The Philippine CPGs on Dyslipidemia consider disadvantaged patients as those with the following characteristics:

- Living below the annual poverty threshold of PHP 12,267.00 (as of 2003);
- Cannot afford laboratory examinations and drug therapy;
- Have limited or no access to health care; or
- Are undernourished (e.g., people with BMI <18.5).

The following are general recommendations for disadvantaged patients:

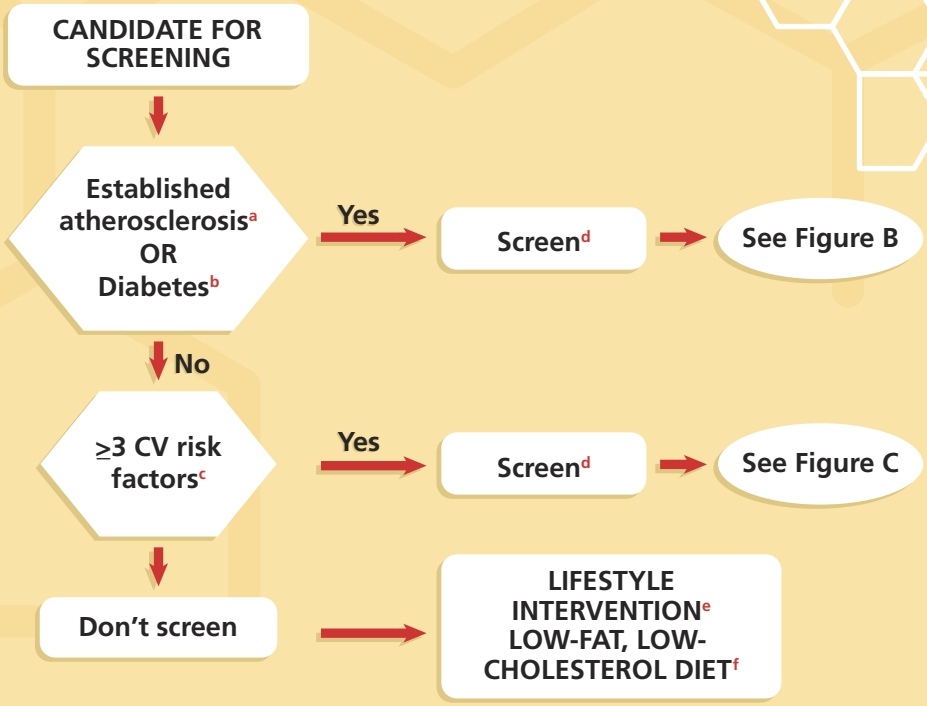
1. Regardless of risk and lipid levels, patients should be advised on smoking cessation, weight management, a low-fat, low-cholesterol diet, correction of nutritional deficiencies, regular physical activity and adequate blood pressure control to reduce overall CV risk.
2. No drug therapy is recommended for patients with <3 risk factors* and without established atherosclerosis.
3. Costs should be considered for patients with ≥3 risk factors* but without established atherosclerosis, as statins may be recommended for primary prevention. Screening with a lipid profile to identify the presence of total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL may also be recommended after careful consideration of costs.

***Please see RISK FACTORS, page 19.**

4. Statins are recommended for patients with diabetes but no established atherosclerosis (if total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL). Fibrates may be recommended as an alternative to statins (if HDL ≤35 mg/dL and LDL ≤90 mg/dL).
5. Statins are recommended for patients with established atherosclerosis and total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL, while fibrates may be recommended as an alternative to statins in patients with HDL ≤35 mg/dL and LDL ≤90 mg/dL.
6. Candidates for drug therapy who are chosen on the basis of the above recommendations may be screened using a lipid profile to identify the presence of specific lipid derangements (e.g., total cholesterol ≥190 mg/dL, LDL ≥100 mg/dL or HDL ≤40 mg/dL). However, the decision to screen and the method of screening should be made after careful patient education and cost consideration. Patients who choose not to be screened may still be given the option to make an informed choice to initiate statin therapy.
7. Monitoring of lipid levels may be recommended. Patients should be provided with proper and adequate information and education regarding monitoring options to be able to make an informed choice. If patients choose total cholesterol for screening, statin therapy may be initiated at fixed dose. Monitoring may be foregone OR it may also be done using total cholesterol, to be conducted at the soonest after 6 weeks. Dose titration should aim for at least a 20% reduction of total cholesterol from baseline.

Decision-making algorithms

Figure A. Screening



All must be advised regarding lifestyle modification

Legends

a Coronary heart disease, thrombotic cerebral stroke, peripheral arterial disease or prior revascularization.
b There is sparse data on patients over 80 years of age and those with type 1 diabetes. There were no data on patients less than 40 years of age. Dyslipidemia management in diabetic patients is considered primary prevention.
c Hypertension, LVH, smoking, family history of premature CAD, male sex, age >55 years, proteinuria/micro-albuminuria, obesity.
d The decision to screen and the method of screening should be made after careful patient education and cost consideration. Patients who choose not to be screened may still be given the option to initiate statin therapy. Total cholesterol can be the relevant screening parameter for patients who only have multiple risk factors. However, total cholesterol, LDL and HDL are recommended for those with established atherosclerosis or diabetes.
e Includes smoking cessation, weight management, regular physical activity and adequate blood pressure monitoring and control.
f See the panel on "Simple Dietary Plan for Fat Modification".

Figure B. Patients with established atherosclerosis or diabetes

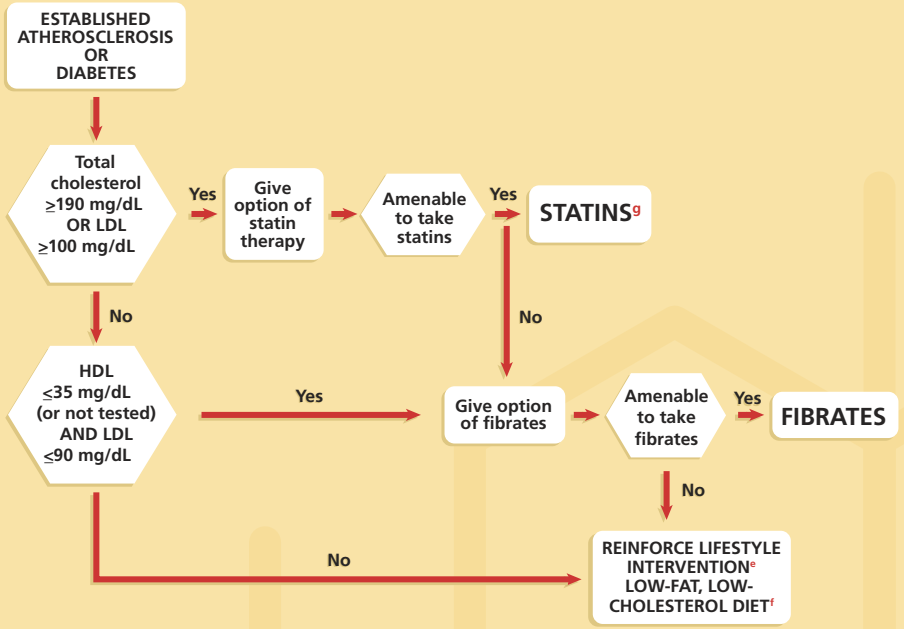


Figure C. Patients with three or more risk factors

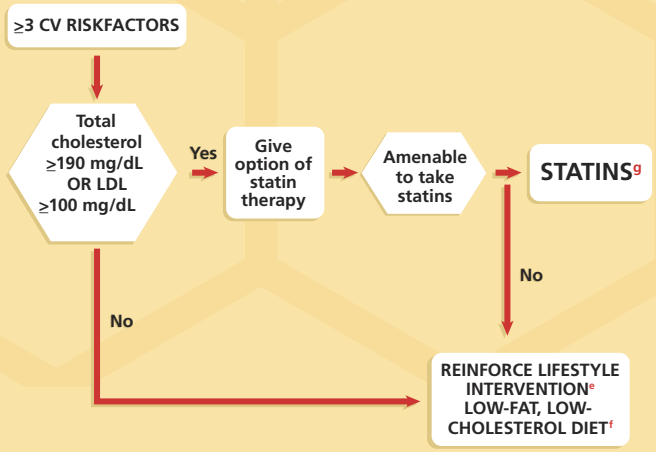


Table A: Screening, lifestyle modification and drug therapy for different risk categories

Category	Screening	Initiate lifestyle modification	Initiate drug therapy when:	Target
Established atherosclerosis or diabetes mellitus	✓	✓	TC† >190 mg/dL OR LDL >100 mg/dL	30%-40% LDL† reduction from baseline (≈77 mg/dL) OR 20% TC† reduction from baseline
>3 risk factors*	✓	✓	TC >190 mg/dL OR LDL >100 mg/dL	30%-40% LDL reduction from baseline (≈77 mg/dL) OR 20% TC reduction from baseline
<3 risk factors*	✗	✓	✗	✗

* Hypertension, LVH, smoking, family history of premature CAD, male sex, age >55 years, proteinuria/microalbuminuria, obesity

† LDL, low density lipoprotein; TC, total cholesterol

✓ YES ✗ NO

Legends for algorithms

a Coronary heart disease, thrombotic cerebral stroke, peripheral arterial disease or prior revascularization.

b There is sparse data on patients over 80 years of age and those with type 1 diabetes. There were no data on patients less than 40 years of age. Dyslipidemia management in diabetic patients is considered primary prevention.

c Hypertension, LVH, smoking, family history of premature CAD, male sex, age >55 years, proteinuria/micro-albuminuria, obesity.

d The decision to screen and the method of screening should be made after careful patient education and cost consideration. Patients who choose not to be screened may still be given the option to initiate statin therapy. Total cholesterol can be the relevant screening parameter for patients who only have multiple risk factors. However, total cholesterol, LDL and HDL are recommended for those with established atherosclerosis or diabetes.

e Includes smoking cessation, weight management, regular physical activity and adequate blood pressure monitoring and control.

f See the panel on "Simple Dietary Plan for Fat Modification".

g Aim for 30% to 40% LDL reduction from baseline (approximately 38 mg/dL or 1 mmol/L). Monitoring may be foregone if total cholesterol was chosen for screening. Total cholesterol may also be used for monitoring. Dose titration should aim for at least a 20% reduction of total cholesterol from baseline. The earliest time to repeat lipid level measurement should be within 6 weeks after treatment initiation.

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Simple Dietary Plan for Fat Modification

The Food and Nutrition Research Institute of the Department of Science and Technology and the Nutritionists-Dietitians Association of the Philippines provide a simple diet guide (Table 4) and meal plan that clinicians can use in advising patients on dietary fat modification.[41] However, patients requiring intensive dietary interventions for whatever reason or condition should be referred to a nutritionist/dietitian for individualized counseling.

Some pointers to observe in planning meals:

1. Choose freely from fruits, vegetables, cereals, breads, dried beans and nuts.
2. Use fish as main dish at least three times a week.
3. May eat chicken meat as a substitute to fish at least three to four times a week.
4. For other kinds of meat, use lean parts and prepare as broiled, boiled or roasted. Trim off any visible fat.
5. Use evaporated filled milk or skimmed milk instead of whole milk and avoid whole milk products such as cheese, butter, cream, etc. Use margarine made with allowed vegetable oil.
6. Use polyunsaturated fats and oils such as corn oil, soybean oil, peanut butter, etc.
7. Limit eggs to only three per week.
8. Avoid rich desserts such as cakes, pastries, cookies, pies, ice cream and chocolate.
9. Always read the nutrition labels of packaged/processed foods.

Table 4. Food selection guide

Food group	Allowed	Restricted/avoided
Fats and oils	• In prescribed amounts: olive, canola, corn, soybean, palm, sunflower and peanut • Coconut oil	• Fats and oils from animal foods; butter; hydrogenated vegetable oils (e.g., margarine, lard, shortening, spread) • Meat and chicken fat drippings used for sauces; bacon fat; "chicharon"
Meat, fish, poultry, eggs, milk, dry beans	• Eat frequently*: Fish (fresh, frozen or canned in water, tomato or vinegar); chicken breast without skin or fat. Dried beans, lentils, fresh or frozen sweetpeas; "vege-meat", tokwa, taho, tofu & other bean products • Eat occasionally**: Very lean, well-trimmed cuts of beef, pork, lamb; crabmeat, shrimp without head; whole eggs up to 3 pieces per week, eggwhite as desired, may be cooked in allowed fat; skimmed milk or low fat milk or cheese	• Fish roe ; crabfat "aligui"; • Fatty meats: cold cuts, canned or frozen meats, sausages; fatty poultry with skin; internal organs (liver, kidney, heart, tripe, sweetbreads) • Whole milk/cow's milk and cheese made from whole milk
Vegetable	• All vegetables prepared without fat or with allowed fats only • Eat frequently*: Green leafy and yellow vegetables (they are good sources of beta-carotene, vitamin C, calcium, iron and dietary fiber among others)	• Buttered, creamed, fried vegetables in restricted fats or cooked with fatty meat and sauces
Fruit	• All fruits; adjust fat allowance when using avocado • Eat frequently*: Vitamin C-rich fruits and deep colored fruits	• Avocado in moderation (due to its high fat content)
Rice, corn, rootcrops, noodles, bread and cereals	• All cereals, roots/tubers, certain noodles/pasta, wheat bread, "pan de sal" except those restricted	• Croissants, muffins, crackers, biscuits, waffles, pancakes, doughnut, rolls made with whole egg, butter, margarine or fat of unknown composition
	• Eat frequently*: Oatmeal, cold cereals, corn and sweet potato	• Fresh mami or miki noodles • Potato chips, french fries, popcorn
Desserts	• Fat-free/low-fat/light dessert; fresh or canned fruits in light syrup only; plain cakes with no icing (angel or sponge cakes), meringue; yogurt; sherbet	• Rich dessert especially those made with cream, butter, solid shortening, lard, whole egg, chocolate cookies and pies made from cream fudge, ice cream; pastillas from whole milk, yema
Soups	• Fat-free broths made from meat or chicken stock, soups prepared with skimmed/ low-fat milk	• Cream soups, fatty broth or stock
Beverage	• Coffee (not more than 3 cups black), decaffeinated coffee, tea, carbonated beverages in moderation • Alcoholic drinks: not more than 1 jigger for women and not more than 2 jiggers for men	• Soda fountain beverages such as milk shake, malted milk and chocolate drinks • Alcoholic drinks in moderation
Miscellaneous	• Nuts (peanuts, cashew, pili, etc.) preferably boiled, roasted/ baked, in moderation • Nondairy cream in moderation • Spices and seasonings in moderation; sauce made with allowed fats and skimmed milk, vinegar, pickles, mustard, catsup, banana sauce	• Sauces and gravies with restricted fats or milk; regular mayonnaise • Butter-dipped foods • Packed dinners or "instant foods" of unknown fat content

*Eat frequently – at least 4 to 5 times a week.
**Eat occasionally – at most, once a month.

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