A Review of the 2005 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines

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Abstract

Cardiovascular disease is a leading cause of mortality in the Philippines with an upward trend in the prevalence of atherosclerosis-related risk factors. In the national survey done in 2008, the prevalence of dyslipidemia is also increasing. As such, there is a need to increase awareness of the risk factors for cardiovascular disease among health care professionals. The development of Philippine guidelines were part of the strategy to improve overall cardiovascular risk and dyslipidemia management that is relevant to the Philippine setting. This article summarizes the 2005 Dyslipidemia guidelines, discusses some updates since its release and emphasizes equity issues when considering management of dyslipidemia in a Filipino patient.

Keywords: Dyslipidemia, clinical practice guidelines, Philippines, cardiovascular disease, Asia

INTRODUCTION

The Philippine Clinical Practice Guidelines (CPG) for the management of dyslipidemia was published in July 2005. The guidelines, based on the best available evidence at that time, was part of the strategy to improve cardiovascular disease (CVD) risk and dyslipidemia management that is more appropriate and relevant for Filipinos. It took into consideration the Philippines' demographic, socioeconomic and health situation. The CPG also dealt with equity issues and considered the disadvantaged groups who live below the annual poverty threshold, those who cannot afford laboratory examinations and drug therapy and have limited or no access to health care or are undernourished. The guidelines were not meant to be viewed as absolute rules and the recommendations should supplement, but not replace, sound clinical judgment.

Summary of Methodology of CPG Development

The Philippine CPGs' stated objectives were to develop valid and applicable dyslipidemia CPGs for Filipinos with special consideration for existing health inequities. The CPG considered lifestyle and diet modification as the cornerstone for total CVD risk management as well as primary and secondary prevention of dyslipidemia. The guidelines also outlined screening and drug therapy recommendations, as well as considerations for the disadvantaged population.

The guidelines were spearheaded by the Philippine Heart Association (PHA) Council on Preventive Cardiology in cooperation with partner organizations. Technical and financial support was provided by the International Clinical Epidemiology Network (INCLEN). A technical research committee comprising cardiologists, endocrinologists, social scientists and epidemiologists was formed. Panelists were composed of appointed representatives of partner organizations and government stakeholders.

The Philippine CPG on Dyslipidemia were developed using the INCLEN Guideline Development Cycle, referred to as the Knowledge Management Plus (KM+).[1] In this development cycle, clinical trial evidence available at that time were appraised for validity as well as applicability to the Philippine setting. The quality of evidence was graded as high, moderate, low or very low. Evaluation of treatment benefit and harm were prepared from data in literature following the KM+ process and were determined as net benefits (the intervention clearly does more good than harm), trade-offs (trade-offs exist between benefit and harm), uncertain net benefits (uncertainties whether the intervention does more good than harm) or no net benefits (the intervention clearly does not do more good than harm). After the evaluation of intervention was described, crude cost benefit was analyzed and a balance of net benefits and costs were made to determine if incremental health benefits were worth the costs. Recommendations formulated following the KM+ process

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included: Do it, Probably do it, No recommendation, Probably don't do it or Don't do it.

INCLEN Guideline Development Cycle Knowledge Management Plus (KM+)
1.a. Identification of the Topic
1.b. Organization of the panel members
1.c. Appraisal of previous guidelines
1.d. Identification of research questions
2. Literature search and retrieval of studies
3. Validity appraisal of literature
4. Appraisal of literature in terms of validity
5. Preparation of evidence-based summaries
6. Preparation of balance sheets for intervention
7. Developing judgment by consensus
8. Presentation of guidelines in a public forum
9. Plan for guideline implementation, disseminate guidelines
10. Monitor guideline implementation and impact

This paper summarizes the guidelines of 2005 and the basis and quality of evidence for each recommendation.

Summary of the 2005 Clinical Practice Guidelines

Current Epidemiology of Cardiovascular Disease (CVD) and Dyslipidemia

Cardiovascular disease is the leading cause of mortality in the Philippines.[2] In 2009, the cause-specific mortality rate for diseases of the heart was 109.4 deaths/100,000 population and 71.0 deaths/100,000 population for diseases of the vascular system.[1] This was much higher compared to the report in the CPG of 78.4 and 58.4 deaths/100,000 population in 1999.

The reported prevalence for atherosclerosis-related risk factors is also increasing. In the NNHES survey in 2008, the prevalence of dyslipidemia was 72% which was higher than the survey done in 2003 (62%).[3,4] In both surveys, the prevalence of dyslipidemia was caused by a high prevalence of low HDL-C levels.

Total CVD Risk Management for the General Population

The CPG in 2005 recommended that all patients regardless of their risk profile should be advised on lifestyle modification including smoking cessation, maintenance of target weight and prevention of obesity, regular physical activity and adequate blood pressure monitoring and control to reduce their overall risk.

Lifestyle Management Recommendations

1. Smoking
   There is an increased cardiovascular risk associated with smoking in a dose dependent manner.[5] To be able to reduce this risk, the CPG recommended complete smoking cessation and passive smoking avoidance.

2. Weight Management
   Abdominal Obesity is more strongly correlated with CV risk than BMI.[6-8] The CPG recommended the use of waist circumference as the measure of abdominal obesity rather than waist-hip circumference ratio (WHR). This is to be used as a tool to assess a patient's risk associated with co-morbidities such as diabetes, metabolic syndrome, CHD, sleep apnea and osteoarthritis.[8]

3. Physical Activity
   Regular physical activity is associated with lower levels of LDL and triglycerides, higher HDL cholesterol, improved insulin sensitivity and lower blood pressure.[9-12] It is also associated with lower risk of CVD and CHD.[13-18] The CPG therefore recommended that for physical activity to be protective, it should be moderately vigorous, done 3x a week or an activity equivalent to 3,500 kilocalories.[18] Examples of these types of activities included swimming, basketball, volleyball, badminton, tennis, jogging and running. Walking for 56 km (35 miles) or climbing 438 flights of stairs with 20 steps per flight is equivalent to 3,500 kilocalories.

Blood Pressure Recommendations

Hypertension is an associated condition in patients with hypercholesterolemia.[19-20] The CPG recommended that regular blood pressure screening should be done in apparently healthy individuals.

Dietary Management of Dyslipidemia

At the time of publication, evidence for dietary interventions showed cardioprotection.[21-23] Advice on dietary interventions was considered cost effective and highly recommended. The CPG enumerated that:

1. Low fat, low cholesterol diet is recommended for life for patients at any level of cardiovascular risk especially in patients with established atherosclerosis.

2. Low fat, low cholesterol diet can still achieve correction of nutritional deficiencies among poorly nourished and elderly patients.

Use of the Food and Nutrition Research Institute of the Department of Science and Technology (FNRI-DOST) Simple Dietary Plan for Fat Modification (2000)[24] pointers in planning meals:

1. Choose freely from fruits, vegetables, cereals, root crops, bread, dried beans and nuts.

2. Use fish as main dish at least 3 times a week.

3. May eat chicken meat as a substitute to fish at least three to four times a week. Eat chicken preferably without skin.

4. For other kinds of meat, use lean parts and prepare as boiled, baked, broiled 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. Use margarine in moderation instead of butter.
6. Use polyunsaturated fats and oils such as olive oil, corn oil, canola oil and peanut oil.
7. Limit egg yolk consumption to only three pieces per week.
8. Avoid rich desserts such as cakes, pastries, cookies, pies, ice cream and chocolates.
9. Always read the nutrition labels of packaged/processed foods.

Primary Prevention

1. The CPG stated that for low risk patients without evidence of atherosclerosis, drug therapy is not recommended regardless of lipid levels.

   The 2 statin trials (AFCAPS/TexCAPS, WOSCOPS), 1 fibrate trial (HHS) and 1 cholestyramine trial (LRC-CPPT) that were included in the appraisal showed problems of applicability to Filipinos which lowered the quality of evidence.[25-28] Crude Cost benefit analysis showed that to prevent 1 CV death, 1-3 MIs, 2-3 CV events and one revascularization, it would cost PhP 12.3 M to treat 286 Filipinos with a statin. Moreover, treating the same number of patients with a fibrate would cost PhP 12.7 M to prevent 2 MIs.

   On this basis, the CPG recommended against drug therapy for primary prevention because of the poor benefit and high cost of treatment. However, for patients with familial hypercholesterolemia, treatment is recommended even without risk factors.

2. The CPG stated that statins MAY BE recommended among patients without established atherosclerosis but with more than 3 risk factors and total cholesterol ≥190 mg/dl or LDL ≥100 mg/dl.

   Established atherosclerosis referred 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.

   The evidence for this recommendation was based on 2 statin trials (ASCOT-LLA and ALLHAT-LLT).[29-30] ASCOT-LLA showed that statin therapy significantly reduced MI (37%), stroke (27%) and CV events (28%) among hypertensive patients with more than 3 additional risk factors and no established CVD. ALL-HAT LLT on the other hand

did not demonstrate important clinical outcomes. Even if the ASCOT-LLA demonstrated benefits, the CPG rated the evidence quality as low because of epidemiological and socioeconomic issues that are not applicable to the Filipinos thus benefit was judged as "uncertain."

With little evidence to work with, the basis for this recommendation was expert opinion, statins remain an option and was given the recommendation "probably do it."

3. Diabetic Patients
   a. The CPG recommended statins for diabetic patients without evidence of atherosclerosis and with total cholesterol ≥190 mg/dl or LDL ≤100 mg/dl .

      The basis for the above recommendation came from 4 statin trials (AFCAPS/TexCAPS, ASCOT-LLA, HPS, PROSPER) with large diabetic cohorts and 1 trial (CARDS) designed for diabetic patients with dyslipidemia.[25,29,31-33] The pooled results of these trials showed reduction in fatal and nonfatal MI (34%), revascularization (15%) and CV events (28) though no significant reductions in mortality. The CPG rated the quality of evidence as moderate and treatment thresholds were based on baseline levels in HPS.

      Cost analysis showed that to prevent 1 MI, revascularization and CV event, it would cost PhP 3.9-5.3 M to treat 90 diabetic patients, thus the CPG recommendation for statins was "do it."

   b. The CPG stated that for diabetic patients fibrates MAY BE recommended as an alternative to statins in those with HDL ≤35 mg/dl AND LDL ≤ 90mg/dl.

      The CPG's recommendation for fibrates as "Probably do it" was considered beneficial to patients with low HDL given its mechanism of action. Clinical trials appraised and evaluated for this recommendation included the Diabetes Atherosclerosis Intervention Study (DAIS) and the St. Mary's, Ealing, Northwick, Park Diabetes Cardiovascular Disease Prevention (SEND CAP) Study.[34-35]

Secondary Prevention

1. The CPG recommended that for patients with established atherosclerosis and total cholesterol ≥ 190 mg/dL or LDL ≥100 mg/dL, statins are indicated.

Evidence included in the appraisal for the use of statin in secondary prevention was the Heart Protection Study (HPS)[36] where crude cost analysis showed that the five year therapy with statins will amount to PhP 2.9 million to prevent one death, four CV events, one MI, one stroke and one revascularization.

After appraisal, the quality of evidence was downgraded based on the issues of directness with a significant difference between the study population and Filipinos socioeconomic characteristics. The quality of evidence in the disadvantaged population was regarded to be low. Despite this, on the basis of established "net benefit" of statin therapy, the panel decided to recommend statins in patients with established atherosclerosis.

2.   The CPG stated that fibrates may be recommended as an alternative to statins if HDL levels are ≤35 mg/dL AND LDL ≤90 mg/dL.

The evidence for fibrates were from the Veteran's Affairs High-Density Lipoprotein Intervention Trial (VA-HIT)[37] and the Bezafibrate Infarction Prevention (BIP)[38] Trial where crude cost-analysis indicated that fibrates taken five to six years would cost approximately PhP 2.1 to 2.7 million to prevent one MI and one stroke.

Similar to the statin group, the quality of evidence was downgraded due to the difference in socioeconomic characteristics between populations. After considering costs and the marginal benefit of fibrate therapy, the consensus recommendation was to limit fibrates as an alternative to statins.

Screening

1.   The CPG elucidated that in patients without risk factors (Table 2), history or symptoms of established atherosclerosis, screening of lipid levels was not recommended.

The only recommended intervention for such patients were non-pharmacological which should be instituted regardless of lipid levels.

2.   The CPG affirmed that in patients without established atherosclerosis but with ≥3 risk factors (table 2), lipid profile may be recommended.

Clinical evidence indicated benefit of statin therapy in patients with multiple risk factors, specifically in patients with total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL. Therefore, the panel recommended determining lipid levels for screening purposes in patients with multiple risk factors but no

established atherosclerosis. Total cholesterol was also considered a relevant screening parameter based on the Anglo-Scandinavian Cardiac Outcome Trial – Lipid Lowering Arm (ASCOT-LLA)[39] trial.

3.   The CPG advocated that in patients with established atherosclerosis or diabetes, screening with lipid profile is recommended.

The panel recommended statin therapy for patients with atherosclerosis or diabetes if total cholesterol > 190 mg/dL or LDL > 100 mg/dL and fibrate therapy if HDL <35 mg/dL and LDL < 90 mg/dL. Lipid profiling was deemed appropriate in identifying patients where pharmacotherapy was indicated.

Table 2. 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

Drug Therapy

Initiation of Therapy

The CPG gave the following recommendations in the initiation of pharmacotherapy:

1.   Statin therapy may be initiated in patients with no established atherosclerosis but have ≥ 3 risk factors and total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL.
2.   Statin therapy initiation is recommended for diabetics with no established atherosclerosis but with total cholesterol ≥190 mg/dL or LDL ≥100 mg/dL.
3.   Statin therapy initiation is recommended for patients with established atherosclerosis and with 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).**
4.   Fibrates may be initiated as an alternative to statins in diabetics patients with no established atherosclerosis if HDL ≤35 mg/dL and LDL ≤90 mg/dL.

Targets for Treatment

The CPG gave the following targets for LDL-C:
1.   A 30 to 40% LDL reduction from baseline **OR**

2. < 77 mg/dL

The CPG endorsed a 30% to 40% LDL reduction from baseline as a suitable treatment goal based on significant risk reductions in randomized clinical trials[25,33,39-44] with approximately 30 to 40% LDL reduction from baseline.

The CPG recommended <77 mg/dL as a target for treatment on the basis of the Treating to New Targets (TNT)[45] trial where additional CV benefits were achieved when LDL was decreased to <77 mg/dL. Although TNT and PROVE-IT[46] were appraised as having low evidence quality due to poor applicability to Filipinos, a significant benefit was observed making <77 mg/dL a suitable treatment goal in pharmacotherapy. Crude cost analysis showed that shifting patients from usual statin therapy to intensive therapy using atorvastatin 80 mg/day on 167 individuals for 3.45 years to reduce one stroke, two MIs and seven CV events require PhP 16.8 million.

Patient Monitoring

The CPG recommended the earliest time to repeat measurements of lipid profile is within six weeks after initiation of therapy. In patients where total cholesterol was used as a basis for initiating statin therapy, fixed dose was recommended and dose titration aim of at least a 20% reduction of total cholesterol from baseline.

Considerations for Disadvantaged Populations

The CPG considered disadvantaged patients as 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 healthcare
- Are undernourished (i.e., People with BMI <18.5)

Recommendations for the disadvantaged population are similar to the general population with greater cost consideration for screening, medical therapy and lipid monitoring. Patients should be provided with proper and adequate information and education regarding options to be able to make an informed choice.

CONCLUSION

The strength of the Clinical Practice Guidelines for the management of dyslipidemia in the Philippines (2005) lies in the process by which recommendations were made, taking into full consideration the applicability of international clinical trials in the local setting and the cost-analysis of implementing these practices among Filipinos.

The recommendations of the 2005 Guidelines are currently being updated based on new clinical trial evidence using the same process of critical appraisal as the 2005 CPG. These updates will take into consideration existing international guidelines prioritizing its applicability in the Philippine setting. The updated version of the guidelines is expected to be available by 2015.

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