2020 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines

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CLINICAL RECOMMENDATIONS

The 2020 Clinical Practice Guidelines for the management of dyslipidemia in the Philippines is created for primary care physicians and specialists managing and treating dyslipidemia. It is the goal of this CPG to holistically manage dyslipidemia, both for primary and secondary intervention.

Topics	Recommendations
Lifestyle Modification	• For individuals at any level of cardiovascular risk, a low-fat, low cholesterol diet, rich in fruits and vegetables, is RECOMMENDED. o Intermittent fasting may be used as a weight loss strategy for obese individuals without established atherosclerotic cardiovascular disease (ASCVD). We do not recommend the use of ketogenic diets as a weight loss strategy • For individuals at any level of cardiovascular risk, cigarette smoking cessation is STRONGLY RECOMMENDED. o For individuals at any level of cardiovascular risk, e-cigarette

	smoking/vaping CESSATION IS RECOMMENDED • For individuals at any level of cardiovascular risk, adequate exercise is RECOMMENDED.
Primary Prevention	• For individuals without diabetes aged ≥ 45 years with LDL-C ≥ 130 mg/dL AND ≥ 2 risk factors*, without atherosclerotic cardiovascular disease, statins are RECOMMENDED for the prevention of cardiovascular events. • For individuals with diabetes without evidence of ASCVD, statins are RECOMMENDED for primary prevention of cardiovascular events. • For individuals identified to have familial hypercholesterolemia, statin therapy is STRONGLY RECOMMENDED for the prevention of cardiovascular events. • Among pediatric population (≤ 17 years old) at risk for development of atherosclerosis and premature cardiovascular disease, screening with a fasting lipid profile is RECOMMENDED. • Among chronic kidney disease individuals not on dialysis (CKD-ND), statins are RECOMMENDED for the prevention of cardiovascular events.

Secondary Prevention	• For individuals with acute coronary syndrome, early high intensity statin that is maximally-tolerated is RECOMMENDED and should not be discontinued. • Statins should be given to ACS patients immediately • For individuals with documented ACS, and target LDL-C has not been reached despite maximally-tolerated high-intensity statin therapy, ezetimibe may be added on top of statin therapy to get to goal LDL-C.
Use of Non-statin Therapies	• Among individuals without diabetes not at goal LDL-C, routinely adding fibrates on top of statin therapy is not recommended for primary or secondary prevention of cardiovascular disease • Among individuals with diabetes, routinely adding fibrates on top of statin therapy is not recommended for primary or secondary prevention of cardiovascular disease However, adding fibrates to statins may be considered among men with controlled diabetes, low HDL-C (<35 mg/dl) and persistently high triglycerides (>200 mg/dl) for prevention of CV disease

	• Among individuals with ASCVD, omega fatty acids (EPA+DHA) given on top of statin therapy is not recommended Among individuals with ASCVD on statin therapy at goal LDL-C, but with persistently high triglyceride levels of 135-499 mg/dl, omega fatty acids (pure EPA) MAY be given. • Among individuals with ASCVD not at goal LDL-C, adding ezetimibe on top of statin therapy is RECOMMENDED for secondary prevention of cardiovascular disease
Adverse Events on Statins	• Treatment with statins is associated with a low risk of developing statin-associated muscle symptoms (SAMS), but the benefits of cardiovascular risk reduction outweigh the risk. • Treatment with statins is associated with an increased risk of new onset diabetes mellitus, but the benefits of statin treatment for cardiovascular risk reduction outweigh the risk. • Treatment with statins is not associated with the development of dementia and cognitive dysfunction

	• Treatment with statins is not associated with an increased risk of intracerebral hemorrhage
Use of Other Lipid Parameters	• Among individuals on statin therapy who have achieved their LDL-C goal, an elevated computed non-HDL-C may be used as an additional therapeutic target to further reduce CV events • Among individuals on statin therapy who have achieved their LDL-C goal, an elevated apolipoprotein B-100 may be used as an additional therapeutic target to further reduce CV events.

Keywords: dyslipidemia, high cholesterol, cardiovascular disease, LDL, HDL, triglycerides, statins

BACKGROUND

The 2020 Clinical Practice Guidelines (CPG) for dyslipidemia is a collaboration of different stakeholders in the field of dyslipidemia, particularly the Philippine Heart Association (PHA), the Philippine Lipid and Atherosclerosis Society (PLAS), and the Philippine Society of Endocrinology, Diabetes, and Metabolism (PSEDM). Because of the different issues regarding special populations, the Philippine Society of Nephrology (PSN), Philippine Neurological Association (PNA), and the Philippine Pediatric Society (PPS) became part in this guideline formation.

These guidelines are meant to provide physicians with a review of the latest available research in the field of dyslipidemia to produce recommendations adaptable locally in the Philippines. In keeping with the 2015 Clinical Practice Guidelines on the Management of Dyslipidemia in the Philippines (2015 CPG)[1], experts in the fields of dyslipidemia, cardiology, endocrinology, pediatrics, neurology, nephrology and clinical epidemiology assembled to comprise the technical research committee (TRC). These experts were tasked to review the most updated, available clinical evidence on cholesterol

management. Together with a steering committee, the TRC developed specific statements answering key clinical questions regarding the treatment of dyslipidemia among various risk groups. The main objective for this document is to enhance earlier local clinical guidelines in the management of Filipino patients who are diagnosed with dyslipidemia which may influence standards and national policies for optimal patient care and cardiovascular health.

It is the hope of this 2020 CPG that the Filipino physician may use the recommendations confidently in caring for most patients and is meant to guide practices that meet the needs of patients in most but not all circumstances. The ultimate decision must be made by the physician and patient together and should not be a replacement for clinical judgment.

OBJECTIVES OF THE GUIDELINES

The objective of the 2020 CPG on Dyslipidemia is to provide evidence-based recommendations to effectively manage individuals with dyslipidemia. These recommendations aim to identify effective and feasible treatment regimens, both non-pharmacologic and pharmacologic, in dyslipidemia treatment. The recommendations developed in this CPG are applicable to all patient groups with a focus in the Philippine setting.

SCOPE OF THE GUIDELINES

The scope of this CPG includes statements on screening and monitoring using lipid profile determination, identification of high-risk groups for cardiovascular (CV) events which will be targeted for prevention and treatment and recommendations for locally available therapies for the treatment of dyslipidemia and their adverse effects. The guidelines will also include novel therapies and cholesterol targets which were not included in the previous guidelines.

Primary prevention refers to interventions in patients without prior coronary heart disease (CHD) or other clinical atherosclerotic cardiovascular disease (ASCVD). Primary prevention of CV events targets individuals who are considered to be part of at-risk populations including those with diabetes mellitus (DM) or those with multiple risk factors (i.e., advanced age, male gender, smoking, hypertension, body mass index [BMI] $\geq$ 25 kg/m^2, family history of premature CHD [first-degree relatives with fatal or non-fatal myocardial infarction, coronary angioplasty, coronary artery bypass surgery or stroke

before the age of 55 years in male relatives or before 65 years of age in female relatives][2], those identified to have familial hypercholesterolemia [an elevated cholesterol level ≥ 190 mg/dL, the presence of xanthomas and a family history of premature cardiovascular disease][3], those with laboratory findings of proteinuria, menopausal women and those with left ventricular hypertrophy.

Secondary prevention refers to interventions in patients with known ASCVD in order to prevent another CV event, those with prior CHD, history of transient ischemic attack, stroke, acute coronary syndrome (ACS), and documented carotid artery disease and clinical peripheral arterial disease (PAD)[4].

This new set of guidelines also looked at the most common adverse events caused by the medications, particularly on the musculoskeletal, endocrine, renal and neurologic systems.

As seen in the previous guidelines, only major classes of locally available medications are mentioned, focusing on those that are widely used in practice, and those that would provide the most benefit in terms of CV risk reduction. Furthermore, clinical questions that were most relevant to clinical practice were identified, as well as the applicability of recommendations to local clinical scenarios. Novel therapies and new biomarker targets were included if available in our local setting.

METHODS

Organization of the Process

The creation of this guidelines is based on the Department of Health's outline for guideline development, which is divided into four (4) phases; 1. Preparation and prioritization, 2. CPG generation, 3. CPG appraisal and 4. Implementation in the manual for CPG development. For the first phase, the steering committee together with the officers of PLAS set the CPG objectives, scope, target audience and clinical questions. The working groups were identified and finalized the recommendations for each clinical question.

The technical working group were tasked to reviews randomized clinical trials and systematic reviews, appraise, and summarize the evidence, and draft the initial recommendations. These summaries were presented to the consensus panel to finalize the recommendations. The consensus panel were comprised of multisectoral representatives tasked to review the evidence summaries and develop recommendations

during the meeting. They discussed necessary considerations and voted on each recommendation, and strengths.

Composition of Technical Review Committee

The technical review committee (TRC) was composed of different experts in the field of cardiology, nephrology, endocrinology, neurology, pediatrics, and clinical epidemiology selected as representatives by the different specialties to create the latest guidelines.

The TRC reviewed the recommendations in the 2015 CPG[1], gathered questions frequently asked in lipid fora conducted in the past five years and discussed challenges in cholesterol management in the Philippines before proposing critical clinical questions to be answered by the 2020 CPG. These questions were presented to the steering committee for comments. Clinical questions were formulated by identifying the specific population, intervention and outcomes for each question. Systematic searches for relevant studies were carried out. All relevant clinical trials and meta-analysis were included and were evaluated using the GRADE-PRO[5].

Standardized tables were used to present the quality of the evidence and key results in a transparent and reproducible fashion. The statements were presented to a panel of experts who voted as to the level of recommendation using the Modified Delphi technique[6]. This technique utilizes consensus strategy that systematically uses literature review, opinion of stakeholders and judgment of experts within a field to reach an agreement. It relies on the collective intelligence of group of members resulting in increased content validity.

Stakeholder Involvement

Several stakeholders were consulted prior to the creation and even after the voting panel of the guidelines. Physicians who are actively managing dyslipidemia, particularly general practitioners, internists, cardiologists, endocrinologists, and nephrologists were engaged. We actively sought their advice particularly on non-pharmacologic and pharmacologic interventions in dyslipidemia and these were done during continuous medical education (CME) activities of the different medical societies. We also involved patients during lay fora activities and inquired their concerns in cholesterol management, thus, the statements on adverse event management of statin treatment. The pharmaceutical industry was also engaged by

the guidelines on the local availability of the medications and the prices of each medication.

Creation of Evidence Summaries

The clinical questions were developed using the PICO (population, intervention, comparator, and outcome) format. The TRC searched and appraised available best evidence of randomized controlled trials and systematic reviews. If the clinical trials were of good quality done within the last ten years, they were included in the search.

One of the gaps identified in the creation of this guidelines is to identify patient related outcomes through surveys or Patient-related outcome researches.

LITERATURE SEARCH

The TRC searched for all published studies, both local and international, pertaining to the clinical questions, with the use of electronic search engines and manual search. The literature search was conducted using the search engines Pubmed, Scopus, Medline, Google Scholar, Cochrane reviews and other medical engines using search words relevant to each clinical question, such as dyslipidemia, LDL-c, adverse reactions. The cut-off date of the search was February 1, 2020. Unpublished data were also retrieved, whenever possible. To formulate the recommendations, the Work Group used randomized controlled trials (RCTs), meta-analyses, and systematic reviews of studies carried out in individuals with or without established coronary heart disease/CVD and with or without risk factors for coronary heart disease/CVD, and diagnosed with elevated blood cholesterol.

Excluded from the search are clinical trials more than ten years old, non-English journals, case reports and series.

Prospective cohorts relevant to the clinical questions are discussed but were not included in the GRADE-PRO analysis.

At least two reviewers worked on each clinical question. The TRC appraised the directness, methodological validity, results and applicability of the article. GRADE Pro were used for quantitative synthesis of clinical outcomes. The quality of evidence was assessed using the GRADE approach.

CLINICAL QUESTIONS

The following questions were deemed critical to be addressed. Some questions were retained to be answered with the latest clinical data, others are new questions, particularly on adverse events of statins, novel treatment options and available new

biomarkers. Questions that had been answered previously will be referenced back to the earlier released guidelines.

Table 1. Clinical Questions

Clinical Questions	
CQ1	Among individuals with dyslipidemia, regardless of their present condition or risk profile, should lifestyle modification (ie, reduced fat diet, smoking cessation, regular physical activity) be advised to reduce overall cardiovascular risk?
CQ2	Among individuals without diabetes without ASCVD but with multiple risk factors, should statin therapy be given? Among individuals with diabetes without ASCVD, should statins be recommended?
CQ3	Among high risk individuals identified to have familial hypercholesterolemia, should statin therapy be initiated?
CQ4	Among pediatric population at risk for premature cardiovascular disease, should screening with fasting lipid profile be recommended?
CQ5	Among non-dialytic CKD individuals, should statins be given to reduce CV risk?
CQ6	Among individuals with acute coronary syndrome (ACS), should statin therapy be given?
CQ7	Among individuals with ASCVD, should ezetimibe be given on top of statin therapy? Among individuals with ASCVD, should fibrates be given on top of statin therapy once LDL-C goal is achieved? Among individuals with ASCVD, should omega fatty acids be given on top of statin therapy once LDL-C goal is achieved?
CQ8	Among individuals taking statin therapy, what is the risk of developing adverse effects? a. Statin associated Muscle Symptoms

	b. New onset Diabetes c. Dementia/cognitive dysfunction/intracerebral hemorrhage
CQ9	Among individuals on statin therapy with LDL-C goal achieved, should non-HDL-C be used as additional target to reduce CV events? Among individuals on statin therapy with LDL-C goal achieved, should apolipoprotein B-100 be used as additional target to reduce CV events?

Several of these CQs were retained from the 2015 CPG[1], such as Clinical questions (CQ) 1, 2, and 6 to review the latest data involving these issues. Management of special groups of patients such as Familial Hypercholesterolemia (FH), pediatric population, and chronic kidney disease (CQ 4-6) are highlighted in this guideline. We created several questions on adverse events in statin use since this is a recurrent question among local physicians and looked at the latest clinical trials pertaining these concerns. We also created questions on new treatment options for dyslipidemia management (CQ 8) and the importance of novel biomarkers as targets of treatment (CQ9).

CLINICAL OUTCOMES

Various clinical outcomes were rated and ranked using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE)[5] categories of importance. The clinical outcomes were rated numerically on a 1-to-9 scale following the GRADE categories, where a score of 7-9 is critical; 4 -6 important; and 1- 3, of limited importance. According to GRADE, ranking outcomes by their relative importance can help to focus attention on those outcomes that are considered most important and help to resolve or clarify disagreements.

Table 2. Clinical Outcomes Included in the 2020 Clinical Guidelines

Clinical Outcomes	GRADE Category	Score
Total Mortality	Critical	9
Cardiovascular Death	Critical	9
Fatal and no-fatal Myocardial Infarction	Critical	9
Stroke or Cerebrovascular	Critical	9

disease		
Major Adverse CV events	Critical	7
Coronary Revascularization	Important	6

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

Data on these six outcomes were extracted from the retrieved studies.

The TRC members also looked at the most common adverse events affecting individuals on statin treatment. The following outcomes were analyzed using the GRADE-PRO software and were given the following scores:

Table 3. Adverse Events Outcomes Included in the 2020 Clinical Guidelines

Adverse Event Outcomes	GRADE Category	Score
Hepatotoxicity	Critical	8
Rhabdomyolysis	Critical	8
Hemorrhagic Conversion	Important	6
New Onset Diabetes	Important	6
Myopathy	Important	6
Intracranial hemorrhage	Important	6
Elevated liver transaminases	Important	6
Risk of Dementia	Low	3

DATA ANALYSIS

The extracted data from retrieved studies were pooled and analyzed using the GRADE-PRO software[5]. The quality of evidence and risks of biases were also evaluated using GRADE-PRO. Evidence quality and risk of bias were based on:

- Study design;
- Study limitations – These could include lack of allocation concealment; lack of blinding particularly for subjective outcomes; losses to follow-up; failure to adhere to an intention to treat analysis; stopping early for benefit; failure to report outcomes;
- Study inconsistencies – Widely varying effects or study heterogeneity;

- Indirectness of evidence – Applicability of the study to the specific clinical question based on various study characteristics (e.g., ethnicity, choice of comparators, etc.);
- Study imprecision – Few included patients or reported events; and,
- Other identified limiting characteristics.

Standardized summary of evidence tables was used to present the quality of the evidence and key results in a transparent and reproducible fashion. These are presented in the subsequent sections.

To aid in quantifying treatment effect, numbers-needed-to-treat (NNTs) were reported in interventions with significant benefit to specific outcomes. By convention, NNTs are adjusted to the local prevalence of disease and outcomes. According to the 2008 National Nutrition and Health Survey, the prevalence of CHD in the Philippines was 1.1%.[2] This is around a third of the reported prevalence in the United States. However, the TRC believes that the local prevalence could be underestimated, since the NNHES definition of CHD was a diagnosis by a physician or nurse (e.g., from a previous heart attack). Furthermore, should a Filipino patient experience acute coronary syndrome (ACS) and was admitted to a tertiary hospital, the mortality rate as reported by the ACS registry is 7.8%, which is only slightly higher than the mortality reported in the United States (6.3%).[4] Hence, the NNTs from Western studies were not adjusted, under the assumption that local prevalence rates and mortality rates were not significantly different from Western countries.

FORMULATION OF RECOMMENDATIONS

Recommendations based on the 9 clinical questions were formulated, taking into account the following results in each summary of evidence table:

- Quality of evidence for each outcome;
- Treatment effect for each outcome; and,
- Relative importance of outcomes.

Table 4. Criteria for recommendation

Quality of Evidence	Outcome	NNT	Recommendation
High	Critical	Low	Strongly Recommend

Moderate	Critical	Low	Recommend
Moderate	Important	Low	May Recommend
Low	Critical or important	High or not significant	Do not recommend

CONSENSUS BUILDING/COMPOSITION OF THE CPG PANEL

Draft recommendations were written and presented to the members of the TRC and were subsequently modified. These guideline recommendations were then subjected to external review by a panel of experts representing local stakeholders in the care of dyslipidemia. During the panel meetings, the process of guideline development and the method for consensus building was first presented. The members of the TRC presented the questions, the answers to the question (recommendations) based on the summary of the evidence and the GRADE table of appraisal. Comparison of the recommendations with other guidelines was provided if applicable. The expert panel then voted on the recommendations. Any proposed changes to the recommendation were also voted on after thorough discussion. The results of the panel meetings are presented here as the final recommendations. **The panel meetings included representatives from the different specialty divisions of the Philippine College of Physicians (PCP), PPS, PNA, Food Nutrition and Research Institute of the Department of Health, Philippine Health Insurance Corporation, and some head of hospitals in Manila**.

A modified Delphi approach was used throughout consensus building. Whenever a consensus was not reached after discussion and 2 rounds of voting, then recommendation and the summary of the evidence is then sent to the panelists to study, and then afterwards, the guideline developer will either modify the recommendation based on feedback from the panelists, or more typically, revise the strength of the recommendation based on any additional evidence which was provided. During the discussions, majority of the draft recommendations and the strength of recommendations were modified during the panel meetings, and there were very few recommendations which were tabled for further discussion in subsequent meetings

External Review

Three reviewers, independent from the technical working group, comprised the external review committee. One epidemiologist, one cardiologist, and one endocrinologist were nominated by the steering committee and by their medical societies to review and critique the full Dyslipidemia guidelines. They utilized the ADAPTE method to guide them in reviewing the guidelines. Their recommendations were included in the final revision of the guidelines

The draft guidelines were also presented in different CME/fora conducted by the technical review committee. The comments from these activities were collected and taken into consideration during the final creation of the guidelines.

DISSEMINATION AND IMPLEMENTATION OF GUIDELINES

Guideline Utilization

The Executive Summary of the Dyslipidemia guidelines has already been published in the Journal of ASEAN Federation of Endocrine Society (Volume 36, Issue 1, May 2021). The PLAS and other societies plan to discuss with relevant stakeholders such as the Department of Health and Philhealth to prepare a dissemination plan that will actively promote the adoption of this guidelines. This will include copyright strategies. The guidelines once published will be available on websites, social media sites, professional society conventions, and press conferences. The 2020 CPG guidelines will be disseminated in the different meetings of the main stakeholders of the guidelines. The final paper will also be available for download in the websites of the PCP, PLAS, PHA, PSEDM and other relevant medical societies in the Philippines.

Additional Materials

The Executive Summary and the full paper will be available for free in the medical society websites. A quick reference guide for the updated algorithm will also be made available in the websites.

Guidelines applicability

It is the hope that these guidelines be used in the clinical practice of both the general practitioner, internist, family doctor, and specialist who handle cholesterol problems of individuals. Recommendations for follow up and monitoring of lipid panel were initially discussed in the 2015 guidelines and will not be tackled in this update. It is recommended that difficult to treat cholesterol issues be handled by an expert in dyslipidemia and follow up in their clinics.

Economic Assessment

As there were no local data on health economy assessment in the management of dyslipidemia, this was not included in the latest guidelines. This is one of the research gaps identified in this guidelines, and will be included in the next update.

Intended audience

The 2020 CPG is designed to be a guide for clinicians; general practitioners, family practitioners, internists, cardiologists, endocrinologists, neurologists, nephrologists, pediatricians and other medical healthcare workers in managing dyslipidemia for the Filipino patient.

Guideline monitoring

In clinical practice, the parameters presented in Table 18 will serve as the targets in dyslipidemia management. These targets will guide the clinician in lowering the cardiovascular morbidity and mortality.

In monitoring the guidelines, PLAS and the other medical societies plan to conduct small group discussions, mini lectures, and convention lectures. The questions and feedback gathered from these fora will be analyzed by the TRC to come up with updates. The updating of the dyslipidemia guidelines is recommended after three (3) years.

MANAGING CONFLICTS OF INTEREST

The steering committee facilitated the whole formulation process, but their members had no direct participation in assessing and analyzing the evidence, generating the summaries and evidence-based recommendations of the TRC. The voting panel were nominated from the relevant medical societies to become part of the consensus panel.

Each TRC and consensus panelist were required to fill out and sign a declaration of interest form and submit their curriculum vitae. The PLAS officers screened the nominees for any possible conflict of interest. Those with significant potential COI were not allowed to join the consensus panel members.

The funding bodies (PLAS, PHA, PSEDM, PSN, PPS, and PNA) did not have an influence in the analysis and generation of evidence created by the TRC.

Any conflicts of interests were addressed by the steering committee and the officers of the PLAS.

DYSLIPIDEMIA IN THE PHILIPPINES

Cardiovascular disease is considered the number one cause of death globally, with an estimated 17.5 million people dying of heart disease in 2016 alone[4]. Unfortunately, over three quarters of CVD deaths take place in low- and middle-income countries, like the

Philippines. According to the World Health Organization Non-Communicable Diseases (WHO-NCD) Country Profiles of 2014, cardiovascular disease make up about 33% of all mortality in the Philippines[8]. In 2017, the Philippine Statistics Authority reported ischemic heart disease as the top leading cause of mortality in the Philippines[9].

Controlling modifiable risk factors for the development of CVD, such as dyslipidemia, is of prime importance in-keeping with the United Nations Sustainable Development Goal to reduce premature mortality due to CVD by at least a third before 2030[10]. Several correlation studies have been conducted in Filipino households over the years. A cross-sectional study in the Philippine General Hospital screened over 130 Filipino patients with hypertension and metabolic syndrome. They showed that clustering of hypertension, obesity, dyslipidemia and sedentary lifestyle is frequent, with 66% of subjects have this clustering of risk factors. Half of the patients were at high risk of coronary artery disease, and those with metabolic syndrome had a coronary heart disease of 18.2%[12].

The prevalence of dyslipidemia was described in the 2015 CPG[1] showing an increasing trend of lipid levels.

Table 5. Trends of Lipid Profiles of Filipinos Based on NNHeS Data[12]

Lipid parameter	Prevalence, %		
	2003	2008	2013
Borderline (200-239 mg/dL) to High (≥ 240 mg/dL) Total Chol	33.5	41.6	46.9%
Bordeline (130-159) to high (≥ 160 mg/dL) LDL-Cholesterol	43.2	43.2	47.2%
HDL-C < 40 mg/dL	54.2	64.1	71.3
Elevated Triglyceride ≥ 150mg/dL	30	46.5	38.6

Reconstructed from the 2003, 2008 and 2013 FNRI NNHES data

* Based on ATP-III cut –off values

The prevalence of other risk factors were as follows[12-13]:

- 6.8% for obesity (defined as a BMI of 30 or higher) and peaking at age 40-45 years;
- 22.3% for hypertension (defined as a systolic BP of at least 140 or a diastolic BP of at least 90) accelerating at age 40-49 years;

- 5.4% for diabetes (defined as a fasting blood sugar of at least 126 mg/dL) accelerating at age 40-49 years and peaking at age 60-69 years;
- 25.4% for smoking, with a relatively even age distribution; and,
- 45.2% for insufficient physical activity, with an inverted distribution peaking at ages 20-29 years, and 70 years and above.

As a general trend, risk factors tend to surpass the national averages at the age group of 40-49 years, making individuals in this age group an important lower threshold for preventive care[11].

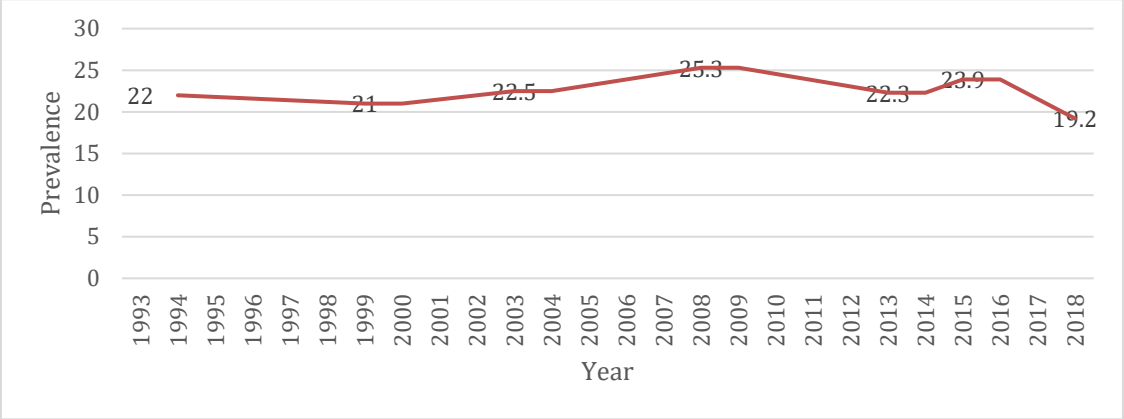


Figure 1. Trend in the Prevalence of Elevated Blood Pressure among Adults, 20 Years Old and Above: 1993-2018[12]

*Based on a single-visit blood pressure measurement of 140/90mmHg or higher (JNC VII. 2004)

Clinical Question 1

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

The importance of lifestyle modifications, such as proper diet and exercise, has been repeatedly emphasized and been given increasing attention because of their relation to cardiovascular disease. The TRC recommends that patients with dyslipidemia should undertake lifestyle modification regardless of their risk profile**.** Specific recommendations for this clinical question are on diet, exercise and smoking. For this 2020 guidelines, we will also summarize the recommendations on fad diets, particularly on the popular

ketogenic diet and intermittent fasting. The Philippine Heart Association released a consensus statement on these specific diets to address questions surrounding its role in cardiovascular disease prevention[14].

Statement 1.1 Diet

For individuals at any level of cardiovascular risk a low-fat, low cholesterol diet, rich in fruits and vegetables, is RECOMMENDED.

Summary of Evidence

The importance of lifestyle change has been advocated by several guidelines, including the previous Philippine guidelines, which counseled that patients diagnosed with dyslipidemia should undertake lifestyle modification regardless of their risk profile. A low fat, low cholesterol diet rich in fruits and vegetables is recommended by the TRC. A meta-analysis of 48 studies with 71,770 patients was used in the previous recommendation[15]. However, there is paucity of new randomized clinical trials focusing on hard end points since the 2015 CPG, but there are new observational studies focusing on the impact of dietary patterns on cardiovascular mortality. These studies will be discussed but will not be included in the GRADE table of appraisal.

<u>Clinical trial updates for Nutrition</u>

Plant-based and Mediterranean diets have been associated with the lower risk of all-cause mortality than control or standard diet. The diets included an increase in the serving of fruits, nuts, vegetables, legumes and lean vegetable or animal protein (preferably fish) consumption. The Prevencion con Dieta Mediterranea (PREDIMED) trial[16], which was included in the previous meta-analysis in the 2015 guidelines, randomized patients to a Mediterranean diet (MD) with either extra virgin olive oil (EVOO) or nuts. The results showed reduction of 30% (MD + EVOO) and 28% (MD + nuts) in the combined endpoint of myocardial infarct, stroke or cardiovascular mortality. The improved outcomes were largely driven by a reduction in stroke, with no significant results in MI or cardiovascular mortality.

A re-analysis of the PREDIMED study[16] was conducted due to protocol deviations and the latest report revised effect estimates based on analyses that not all patients included in the study were randomized. The primary endpoint was major adverse cardiovascular events (MACE) myocardial infarct, stroke or cardiovascular mortality and

occurred in 288 participants, with 96 events occurring in the MD+EVOO arm, 83 events in the MD + nuts arm, and 109 events in the control arm. There was benefit of 31% in the MD+EVOO arm (hazard ratio 0.69, 95% CI 053-0.91) and a 28% benefit in the MD+nuts (hazard ratio 0.72, 95% CI 0.54-0.95) as compared to the control diet. Secondary endpoints were comparable for all groups. The PREDIMED study showed that in patients with high cardiovascular risk, the incidence of major cardiovascular event was lower in patients receiving a Mediterranean diet supplemented with extra virgin olive oil or nuts than those assigned reduced fat[16].

Dietary intake of fat has been correlated with higher mortality based on previous studies. The Prospective Urban Rural Epidemiology (PURE) study was a large, epidemiological cohort of 135,335 individuals in eighteen countries and was followed up with a median of 7.4 years[17]. They looked at the relationship of macronutrients, particularly fat and carbohydrates, and cardiovascular morbidity and mortality. They used a validated food frequency questionnaire to assess the primary outcomes of total mortality and major cardiovascular events. Results showed a higher risk of mortality in individuals eating a high carbohydrate diet (Hazard Ratio 1.28, 95% CI 1.12-1.46), but this was not driven by cardiovascular mortality or cardiovascular disease mortality. The fat intake was divided into total fat and its component of saturated, monounsaturated and polyunsaturated fat. Intake of diets rich in fat were associated with lower risk of mortality; total fat (HR 0.77, 95% CI 0.67-0.87), saturated fat (HR 0.86, 95% CI 0.76-0.99), monounsaturated fat (HR 0.81, 95% CI 0.71-0.92), and polyunsaturated fat (HR 0.80, 95% CI 0.71-0.89). A diet rich in saturated fat also lowers the risk of stroke (HR 0.79, 95% CI 0.64-0.98). Intake of fat did not significantly lower the risk of cardiovascular mortality and myocardial infarction. There are several limitations in this cohort study worth pointing out. The use of a questionnaire is not a measure of absolute intake and may lead to random errors that could dilute associations in real outcomes. Dietary patterns were only measured during baseline and changes in their diet may have occurred during the follow up period. The issue of confounding factors in particular income, education, culture and conscientiousness, despite the extensive adjustments may have significantly impacted the results[17].

Table 6. Summary of Evidence for Diet

Outcome	Evidence Quality	Relative Importance	Relative Risk	NNT
Total Mortality	High	9	0.98 (0.93,1.04)	NS
Cardiovascular Deaths	High	9	0.94 (0.85,1.04)	NS
Fatal and non-fatal MI	High	9	0.9 (0.72,1.11)	NS
Strokes (Fatal and nonfatal)	High	9	0.99 (0.89, 1.11)	NS
Cardiovascular events (MACE)	Moderate	7	0.86 (0.77, 0.96)	209
Coronary intervention	Moderate	6	NS	NS

CPG Recommendation

This CPG stands by our previous recommendation of a low-fat, low cholesterol diet, rich in fruits and vegetables. The Food and Nutritional Research released a simpler version of the food pyramid with is called the Pinggang Pinoy[18] described in the 2015 CPG[1]. A nine-inch plate is advised, and distributing foods proportionally among the food groups provides approximately 1,200 to 1,500 calories per day. It is advised that half of the plate is composed of green leafy vegetables and one serving of fruit per meal. For fruits, 4 to 6 servings are encouraged per day.

Figure 2. Pinggang Pinoy

For a detailed guide to serving portions, please see Appendix 1.

Recommendations from other Guidelines

The latest guidelines from the American College of Cardiology/American Heart Association Task Force on Practice Guidelines[19] emphasized that lifestyle modifications, particularly heart healthy diets, remain a critical component of health promotion atherosclerotic cardiovascular disease, both prior to and in concert with the use of cholesterol-lowering therapy. The International Atherosclerotic Society[20] released a position paper recommending a reduction of saturated fat in the diet to <7%, decreasing trans fat by 1%, and dietary cholesterol to < 200 mg/day of the daily total calorie intake. This is similar to the recommendations of the National Institute for Health and Care Excellence of the United Kingdom 2014[21]. In line with the World Health Organization advocacy to eliminate artificial trans fats from the global food supply by 2023 for worldwide eradication, the Philippines has required labeling of trans fat on packaged food[8].

Statement on FAD Diets

A Philippine consensus on the use of ketogenic diets and intermittent fasting was created last 2019, and this guideline adheres to their recommendations[14]. This is available in the Philippine Lipid and Atherosclerosis Society website for access.

Intermittent fasting (IF) is defined as an interventional strategy in which individuals are subjected to varying periods of fasting[22]. This approach to weight loss involves short periods of substantial energy restriction, defined as >70% of the total energy, interspersed with normal eating[23]. It is successful in reducing weight for obese adult individuals and based on a recent meta-analysis, it can achieve an average weight loss of 4.1 kg. In observational studies, the use of intermittent fasting may increase HDL-C between 1 to 14 mg/dl, LDL-C may decrease between 1 to 47 mg/dl, total cholesterol may decrease between 5-88 mg/dl and triglyceride levels may decrease between 3 to 64 mg/dl[24]. However, two published small non-randomized controlled trials showed contradicting results in cholesterol reductions. One study showed an elevation of HDL-C levels, but no effect on the LDL-C and triglyceride levels, while the other one showed no effect on the lipid levels. There are ongoing clinical trials on the impact of intermittent fasting to cardiovascular disease. Thus, we are waiting for the results of the large clinical trial on intermittent fasting[25-26].

In this light, similar to the consensus statement, **IF (i.e. alternate day fasting or modified fasting regimens) may be used as a weight loss strategy in obese adult individuals without established ASCVD for a period of 6 to 12 months.** However,

because of lack of evidence, **the guidelines do not recommend IF for diabetic individuals and in individuals with clinical ASCVD for ASCVD protection.**

Ketogenic diet (KD) is defined by a low carbohydrate and high fat content diet and was first used by Dr. Russel Wilder in the treatment of epilepsy. Classical KD is defined as < 130 gm carbohydrate per day or less than 26% of caloric intake, while a very low-carbohydrate ketogenic diet (VLCKD) is composed of 20-50 g/day of carbohydrate[27]. Several mechanisms are involved in the weight loss effect of KD including reduction in lipogenesis and increased lipolysis, appetite suppression effects of a higher protein intake, increased metabolic costs of gluconeogenesis and the thermic effect of proteins[27]. A meta analysis of 13 randomized controlled trials involving adult obese individuals showed a significant weight loss using Ketogenic diet by an average of 1 kg up to 12 kg in morbidly obese adults. There were significant decreases in the triglycerides, LDL-C and an increase in HDL-C. However, in ketogenic diets using saturated fats as source of fat, they showed an either a neutral effect or an increase of LDL-C[28].

In light of these conflicting evidence, similar to the consensus statement, **we do not recommend KD as a weight loss strategy in adult individuals for ASCVD protection.**

Statement 1.2 Smoking Cessation

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

Summary of Evidence

Traditional cigarette smoking continues to be a major public issue with its documented pathogenic and negative effects on cardiovascular health. Cigarette smoking is one of the most preventable risk factors for heart disease. The previous CPG[1] strongly recommended cessation from cigarette smoking, and we continue to support this stand. Randomized controlled trials on smoking cessation and their effect on cardiovascular morbidity and mortality were included in the review for this recommendation. As with the previous CPG, there remains 1,355 clinical trials on smoking cessation but, only three (3) trials had relevant outcomes and were thus included. All three trials looked at primary prevention outcomes. Two of the studies looked at multiple risk factors, such as diet and smoking cessation, while the last one also included respiratory and cancer outcomes.

The clinical trials included in the CPG are seen in the appendix. Two clinical trials, Multiple Risk Factor Intervention Trial (MRFIT) and Oslo study[29-30] included men with multiple risk factors, while the Lung Health Research Study Group[31] had both men and women in the study. The interventional group had an intensive treatment program for smoking cessation, which include behavior modification and may use devices such as nicotine gum or patches.

The table below summarizes the review and relevant outcomes. Statistically significant results are seen in the total mortality (N=18,023; RR 0.90 [95% CI 0.82, 0.99)], and acute major CV events (N=18,023; RR 0.85 [95% CI 0.76, 0.95). There was a trend towards benefit of cigarette cessation in CV mortality. Only one trial looked at secondary outcomes such as MI and stroke, and the former outcome showed a trend in favor of cigarette cessation.

Table 7. Summary of evidence on the effects of smoking cessation

Outcome	Evidence Quality	Relative Importance	Relative Risk	NNT
Total Mortality	Moderate	9	0.90 [0.82, 0.99]	9
Cardiovascular deaths	Moderate	9	0.92 [0.76, 1.12]	500
Fatal and nonfatal myocardial infarction	Moderate	9	0.92 [0.80, 1.07]	NS
Cardiovascular events	Moderate	7	0.85 [0.76, 0.95]	100
Stroke	Moderate	9	1.20 [0.79, 1.81]	NS

Total cigarette smoking cessation is still recommended to patients with all levels of CV risk factors.

Statement 1.2.1

For individuals at any level of cardiovascular risk, e-cigarette smoking/vaping CESSATION IS RECOMMENDED

Alternatives to tobacco smoking has skyrocketed in the recent years, and electronic cigarettes (e-cigarettes) have become more popular due to their perceived safety compared with traditional cigarette smoking. As of 2018, the National Youth

Tobacco Survey reported that 20.8% of the same population reported current use of e-cigarettes[32]. Although advertised to contain less toxic compounds, a variety of potentially toxic compounds have yet to be thoroughly studied in research.

There is a paucity of long-term clinical trials on the impact of e-cigarettes to cardiovascular morbidity and mortality. The Cardiac and LUng E-cig Smoking **CLUES Trial[33]** is an ongoing prospective case-control study on the impact of e-cigarettes on cardiovascular diseases. In small cohorts of e-cigarette smokers, there is an observed significant increase in blood pressure, pulse wave velocity, increased cardiac sympathetic nerve activity and oxidative stress compared to non-users[33]. In the National Health Interview Surveys conducted in the years 2014 and 2016[34], daily e-cigarette users were 1.79 times more likely to experience a myocardial infarction compared to individuals who had never used e-cigarettes. Despite the lack of hard data, the CPG does not recommend e-cigarette use as well as tobacco products.

The Philippine College of Chest Physicians issued a position statement that they do not support making e-cigarettes widely available and these products be regulated as a "drug", which means that they pass the same approval process if they are to be marketed as a form of tobacco alternative[35].

Statement 1.3. Exercise

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

Summary of Evidence

Literature review revealed 48 articles that evaluated the benefit of exercise on the risk of cardiovascular outcomes. Mostly were observational and cohort studies. The lack of randomized controlled trials was mostly attributed to poor long-term adherence to exercise programs. Furthermore, only a few studies evaluated hard cardiovascular outcomes. Thus, only four studies were included in the analysis: the Action for Health in Diabetes (LookAhead) trial, the Instensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria (STENO2) trial, the Chengdu trial, and the study by Fowler and colleagues (2002)[36-40].

In general, these studies recommended approximately 150 minutes of moderate- to high-intensity exercise per week. Pooled analysis revealed that such an exercise regimen reduced major acute coronary events by 25%, and non-fatal myocardial infarction by 71% (Table 8).

Table 8. Summary of evidence on the effects of exercise

Outcome	Evidence Quality	Relative Importance	Effect Estimate (RR, 95% CI)	NNT
All cause mortality	Moderate	9	0.95 [0.86, 1.05]	NS
Cardiovascular mortality	Moderate	9	0.97 [0.85, 1.09]	NS
Cardiovascular events	Moderate	7	0.75 [0.62, 0.91]	48
Non-fatal myocardial infarction	Moderate	9	0.29 [0.11, 0.76]	7
Stroke	Moderate	9	0.88 [0.67, 1.17]	NS
Coronary intervention	Moderate	6	0.99 [0.84, 1.15]	NS

Quality of evidence for the important outcome of major adverse cardiovascular events was moderate, with an NNT of 48. Additionally, exercise was found to marginally reduce LDL-C by 17.4 mg/dL (0.45 mmol/L), triglycerides by 20.37 mg/dL (0.23 mmol/L) and increase HDL-C by 0.7 mg/dL (0.02 mmol/L).

Thus, exercise of approximately **150 minutes** of moderate- to high-intensity exercise per week is recommended in individuals to improve patients' outcomes.

Exercise prescription

Compliance is one of the major difficulties when prescribing exercise to patients. It is important to highlight that consistency and regularity are important so that exercise becomes an integral part of a patient's lifestyle. One way to achieve this is to explain that the time allotted per week should be split into several exercise sessions. In this case, 150 minutes per week should be cumulated from around five sessions per week with a duration of 30 minutes. This will also ensure that the exercise sessions do not interfere with a person's daily routines. Furthermore, physical activity may be integrated into their daily routine, such as climbing of stairs or brisk walking.

It is important to specify that the patient should exert moderate to intense activity during exercise. A general rule is that they should have difficulty speaking during the exercise. However, at the same time, they should not be experiencing symptoms such as chest pain, difficulty of breathing, or dizziness/syncope. Examples of exercises may include swimming, jogging, brisk walking, stair-climbing, cycling, dancing, sports activities, and supervised aerobic exercise programs. Slow exercises such as yoga or tai chi may

improve strength and flexibility, but may be inadequate in intensity as the patient becomes physically stronger.

The physician should assess the functional capacity and overall risk of patients before prescribing exercise. If assessment reveals that a patient is physically incapable of safely performing moderate to intense exercise, refer the patient for physical rehabilitation and strengthening to a qualified physiatrist.

Clinical Question 2

CQ 2.1. Among individuals without diabetes without ASCVD but with multiple risk factors, should statin therapy be given?

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

Statement 2.1

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

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

**Patients who fulfil the criteria for the diagnosis of familial hypercholesterolemia (see statement 6 on screening and lipid monitoring for familial hypercholesterolemia) should be initiated therapy for aggressive LDL-C lowering.*

Summary of evidence

In the previous guidelines, randomized controlled trials evaluating statins in individuals without ASCVD with at least a minimum duration of 1-year follow-up were used in the analysis and a total of 8 RCTs were included[41-48]. All of these trials either used total cholesterol (TC) and/ or LDL-C as part of their inclusion criteria with the lowest levels seen in the Justification for the use of Statin in Prevention: An interventional trial evaluating Rosuvastatin (JUPITER) trial[47] which were 168 mg/dl for TC and 94 mg/dL for LDL-C. This 2020 guideline included the Heart Outcomes Prevention Evaluation (HOPE)-3 study[48], which is a randomized trial using a statin in intermediate risk individuals without cardiovascular disease. The study used rosuvastatin 10 mg versus placebo, were followed

up for a median of five (5) years and all cardiovascular events were adjudicated. Based on the HOPE-3 trial[48], the mean cholesterol level was 201.4 mg/dl, baseline LDL-C levels for both arms were 127.8 mg/dl and apolipoprotein B level was 102 g/L. The use of low to medium-dose of the rosuvastatin resulted in a significant reduction of the lipid levels, with end of trial results showing reduction of LDL-C by 26.5% (mean difference 34.6mg/dl), triglyceride reduction was 21.2 mg/dl, and apolipoprotein B was 0.23 g/L.

The quality of evidence was mostly moderate owing to indirectness in the enrolled population which mostly included Caucasians with the exception of the MEGA study which enrolled Japanese. Cardiovascular events as an outcome was graded to be low due to its issue of inconsistency having a large I^2 of 59% since CV events was a secondary outcome in all of these trial with the exception of Air Force/ Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS)[43]. All of the outcomes were deemed critically important except for coronary revascularization which was important since it is an outcome least likely to happen if these individuals were treated optimally.

As for the desired outcomes, statins in individuals without ASCVD showed a siginificant reduction in all cause mortality by 8%, cardiovascular death by 14%, myocardial infarction by 24%, stroke by 15%, cardiovascular (CV) events by 15% and coronary revascularization by 17%. The numbers needed to treat (NNT) is highly significant. Prevention of stroke has an NNT of 14. You need to treat 62 individuals with statins to prevent any cardiovascular event.

Thus, this guideline continues to recommend the use of low to medium dose of statin to individuals who have risk factors for cardiovascular disease.

Table 9. Summary of Evidence on Treatment Effects of Statins in Primary Prevention.

Outcome	Evidence Quality	Relative Importance	Effect Estimate (RR, 95% CI)	NNT
Total Mortality	Moderate	9	0.92 (0.87, 0.97)	37
CV death	Moderate	9	0.86 (0.79, 0.92)	17
MI	Moderate	9	0.76 (0.71,0.83)	21
Stroke	Moderate	9	0.85 (0.78,0.92)	14
Cardiovascular events	Moderate	7	0.85 (0.81,0.88)	62
Coronary intervention	Moderate	6	0.83 (0.79, 0.88	32

The TRC and Voting Panel decided to implement LDL-C and age cut-offs to better target patients who have no evidence of atherosclerotic disease but would benefit from statin therapy for primary prevention.

The LDL-C level chosen was from the Anglo-Scandanavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOTT-LLA) trial[44], where patients had a mean LDL-C of 131.3 mg/dL to represent patients at higher risk of development of cardiovascular outcomes in light of additional risk factors.

The recommended cut-off age of 45 years old was on the basis of the epidemiology of dyslipidemia among Filipinos and the age consideration of patients in the different primary prevention trials appraised. Forty-five years was decided to be the representative age at which patients with multiple risk factors for development of atherosclerotic cardiovascular disease would benefit from statin therapy.

Lastly, the primary prevention trials on statins only included patients with at least 2 risk factors. The TRC was not able to find data on patients with one or no risk factors. Hence, the TRC recommendations only encompass patients with 2 or more risk factors. It should be emphasized that although the TRC has no recommendations for patients <45 years with less than 2 risk factors, individuals in this group are still eligible for lifestyle interventions, as discussed in the previous section. To date, there are no international risk calculators validated in Filipinos. The TRC do not recommend the use of any calculators in computing CV risk as there are no calculators that have been validated for Filipino cohorts.

Thus, the use of statins for individuals with no clinical ASCVD (primary prevention) is recommended for patients aged 45 years and above with 2 or more risk factors with an LDL-C $\geq$ 130 mg/dL.

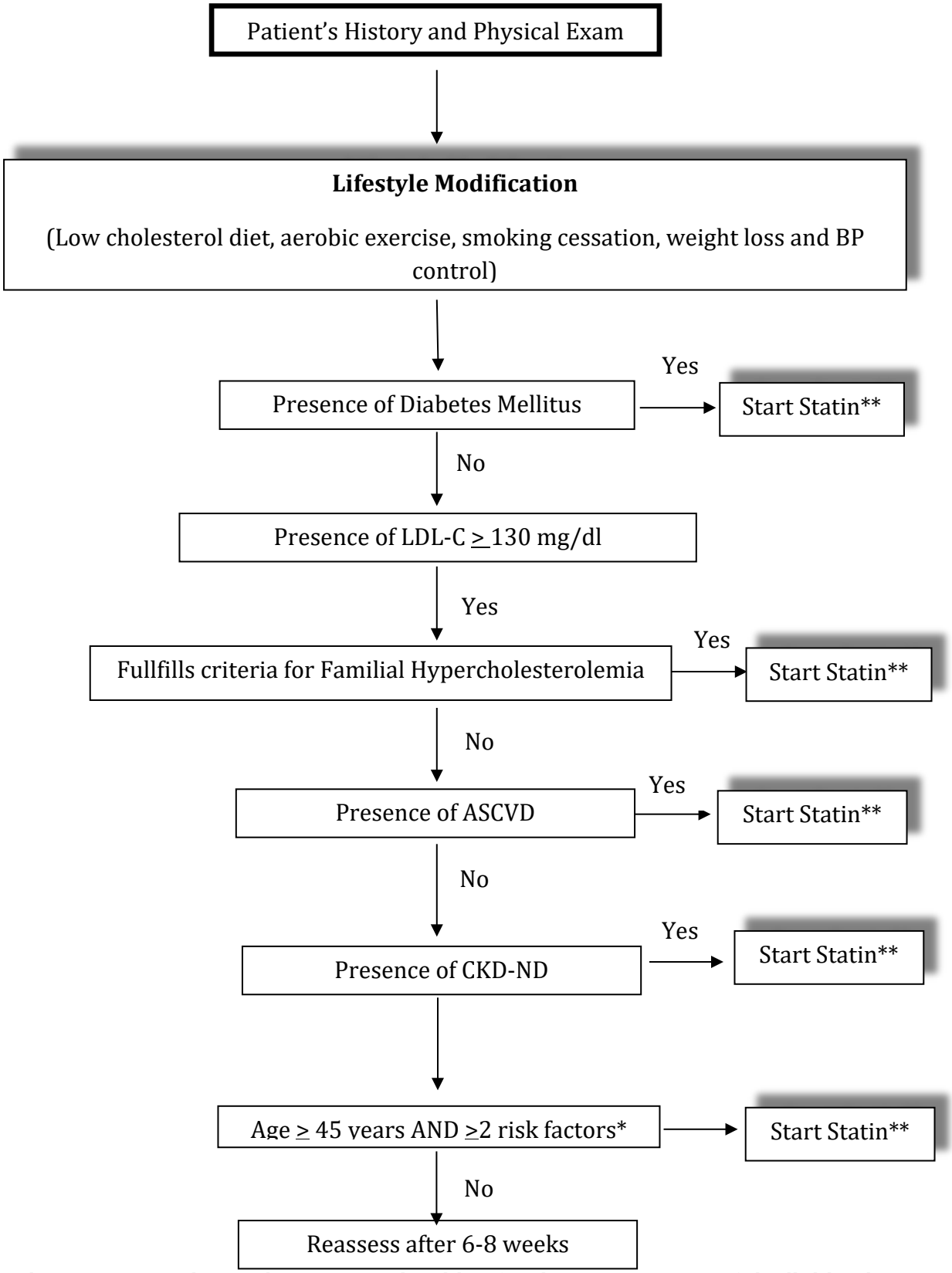


Figure 3. Screening and treatment algorithm for the management of dyslipidemia

Legend:

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

** The guideline recommends maximally-tolerated statin therapy to reach recommended target LDL-C levels

Clinical Question 2.2

CQ 2.2 Among individuals with diabetes without ASCVD, should statins be recommended?

Statement 2.2

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

Summary of the evidence

Evidence on the use of statins for primary prevention of cardiovascular outcomes were derived from 8 different clinical trials. In the original guideline published in 2015, only 5 studies were included; this has been updated in the current recommendation.

Of the eight studies that were included, five were sub-studies from a larger group of individuals who had no previous cardiovascular events (AFCAPS/TEXCAPS[43], ALLHAT-LLA[49] ASCOT-LLA[44], PROSPER, MEGA[46]) while the other three were primarily studies done on individuals with diabetes (ASPEN[50], CARDS[51], HPS[52]). Whenever a study involved a combination of patients for primary and secondary prevention, then only the data for primary prevention was obtained and analyzed (e.g., ASPEN).

Appendix Table 1.5 summarizes the characteristics of the studies that were included in this review. Different statins of various daily doses were used including lovastatin 20-40 mg, pravastatin 10-20 and 40 mg, atorvastatin 10 mg, and simvastatin 40 mg. The baseline lipid values also varied across the studies with the mean baseline total cholesterol ranging from 195 ±31 to 227 ±33.8 mg/dL; and the baseline mean LDL-C ranging from around 115 ±26.6 mg/dL to a high of 150 ±31 mg/dL. The studies included both genders, and the age range for most of the studies is from 45 to late 70's, with the PROSPER study being specific for elderly 70-82 years.

Table 10 summarizes the results of the review and the relevant outcomes. Statistically significant results are seen from the outcomes of fatal and nonfatal MI (N=27,810, RR 0.73 [0.64, 0.83]), stroke (N=27,810, RR 0.75 [0.63, 0.89]), acute major CV events (MACE) (N= 16,095, RR=0.78 [0.70, 0.86]) and coronary revascularization

(N=25,783, RR= 0.84 [0.73, 0.97]). A trend to benefit is seen for the outcomes of total mortality, and CV death. Significant impact on clinical outcomes was achieved using even low to moderate intensity statins.

Table 10. Summary of Evidence on Treatment Effects of STATINS in Individuals with Diabetes without ASCVD

Outcome	Evidence Quality	Relative Importance	Effect Estimate (RR, 95% CI)	NNT
Total Mortality	Moderate	9	0.73 (0.53-1.010)	NS
Fatal CHD/CV death	Moderate	9	0.98 (0.68, 1.41)	NS
Fatal & Nonfatal MI	Moderate	9	0.73 (0.64, 0.83)	100
Stroke	Moderate	9	0.75 (0.63, 0.89)	200
Cardiovascular events	Moderate	7	0.78 (0.70, 0.86)	45
Coronary intervention	Moderate	6	0.84 (0.73, 0.97)	200

The GRADE balance sheet combines the appraisal of the studies included in the guideline recommendation with the outcomes. Generally, the quality of the evidence is **moderate** with the downgrade due to the question of directness. The studies were all done in Caucasian populations and Asians, and in particular Filipinos were not included in the samples that were included in these trials. Likewise, 5 out of the 8 studies were subgroup analysis of diabetic individuals from a larger group of individuals with no previous cardiovascular events.

Thus, the recommendation is only moderate for the use of statins for primary prevention. **For persons with diabetes but without evidence of atherosclerosis (ASCVD), statins are RECOMMENDED for primary prevention of cardiovascular events.**

The statin dose should be optimized to reach the LDL goal of less than 100 mg/dL for most persons with diabetes for primary prevention. For individuals with diabetes with > 1 risk factor or target organ damage, LDL-C goal of less than 70 mg/dL is recommended. LDL-C of < 55 mg/dL should be attained for those who have diabetes and are at extremely high risk of having recurrent CV events due the previous occurrence of major cardiovascular events such as myocardial infarction, unstable angina or CVD (stroke).

Recommendation from other guidelines

Other guidelines have similar recommendations but add on a layer of risk on top of diabetes mellitus. For example, the Canadian Diabetes Association guidelines recommend statin therapy for diabetic individuals with an indication for lipid-lowering therapy.[53] The American Diabetes Association on the other hand recommends high-intensity statin for patients of all ages with diabetes and overt CVD, or for those who are at least 40 years old and with additional CV risk factors (total of 3 risk factors: $\geq$ 40 years old, diabetes and another CV risk factor).[54] Those who have diabetes and are aged 40-75 years old should consider using moderate-intensity statins. It is silent though for diabetic individuals who are less than age 40.

The recommendations in this local guideline is to give statin therapy for ALL adult diabetic individuals for primary prevention especially among those with Type 2 diabetes mellitus, without regard for age nor duration of diabetes. The justification for this recommendation is the frequent observation that both macrovascular and microvascular complications, as well as various CV risk factors are prevalent even among newly diagnosed diabetics. For example, the Complications and Cardiovascular Risk Factors among newly diagnosed type 2 diabetics in Manila (CANDI Manila) study among newly diagnosed adults with type 2 diabetes mellitus (mean age of 50 years) demonstrated a high prevalence of diabetic complications and CV risk factors.[55] The electrocardiographic findings showed that 2% had myocardial infarcts, 3% had ischemic changes, and 6% had left ventricular hypertrophy. Hypertension was found in 42% of individuals with a mean BP of 144/88 mm Hg, and 80% of all subjects had LDL-C of at least 100 mg/dL, with another 38% with elevated triglyceride of at least 150 mg/dL.

Clinical Question 3

Among high risk individuals identified to have familial hypercholesterolemia, should statin therapy be initiated?

Statement 3

For individuals identified to have familial hypercholesterolemia, statin therapy is STRONGLY RECOMMENDED.

Summary of the evidence

Familial hypercholesterolemia (FH) is a dominantly inherited gene disorder resulting from gene mutations in the LDL-receptor pathway that cause markedly elevated LDL-C from birth. Untreated FH leads to premature death from coronary artery disease due to accelerated atherosclerosis. Early diagnosis and treatment is vital in prevention of CV events in this high-risk population (Dutch Lipid Network Criteria)[56].

Evidence on the use of statins for primary prevention of cardiovascular outcomes in patients with identified FH was derived from the retrospective cohort study of 2146 adults with FH followed for 8.5 years[57]. This long-term cohort studied patients with FH without prevalent coronary heart disease (CHD) measuring risk for development of CHD in statin-treated and "untreated" (delay in starting statin treatment) FH patients. During 7473 person years of statin-treated patients and 9319 person years of untreated patients, 408 patients had an incident coronary event, 161 of these patients had been using statins for an average 3.4 years (median 2.7 years, range 1 month to 11.6 years). The absolute risk of first onset of coronary heart disease was 11/1000 person years in statin-treated patients compared with 119/1000 person years in untreated patients. Incident coronary heart disease occurred at younger age in untreated patients (48.6 *v* 50.9 years, P=0.05). The statin-treated group had a significantly better event-free survival (P<0.001). After adjustment for year of birth and sex, statin treated patients had a 76% reduction in risk of coronary heart disease compared with untreated patients (hazard ratio 0.24 (95% confidence interval 0.18 to 0.30), P<0.001).

Earlier studies of smaller cohorts reflect reduction in mortality in patients with FH treated with statin therapy[57-58]. Despite lowering LDL-C with statins, mortality was still higher than the general population.

Recommendations from other guidelines

Various organizations recommend treating patients with FH with high doses of high-intensity statins, which are capable of lowering LDL-C by 50% to 60%[59]. Given that many patients with FH will have documented CAD and will continue to be at very high risk for future ASCVD, the guidelines suggest the use of an LDL-C threshold of 70 mg/dL (1.8 mmol/L) and for the addition of non-statins to statin therapy to get to goal levels. Non-

statins include ezetimibe and PCSK9 inhibitors[60-61]. It is estimated that 80% of these patients will not reach LDL-cholesterol targets despite efficacious therapy[62].

The recommendations in this local guideline is to give statin therapy for all identified FH patients for primary prevention. Recognizing the increased risk for this population with additional co-morbidities cumulatively intensifying probability of CV events, the TRC recommends lowering LDL-C targets in those with FH with target organ damage and established ASCVD.

Table 11. Dutch Lipid Network Criteria on the Diagnosis of Heterozygous Familial Hypercholesterolemia

CRITERIA	**POINTS**
Family history	
First-degree relative with known premature* coronary and vascular disease, OR First-degree relative with known LDL-C level above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C level above the 95th percentile	2
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C $\geq$ 330 mg/dL ($\geq$8.5)	8
LDL-C 250 – 329 mg/dL (6.5–8.4)	5
LDL-C 190 – 249 mg/dL (5.0–6.4)	3

LDL-C 155 – 189 mg/dL (4.0–4.9)	1
DNA analysis	
Functional mutation in the LDLR, apo B or PCSK9 gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6-8
Possible Familial Hypercholesterolemia	3-5
Unlikely Familial Hypercholesterolemia	<3

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

Clinical Question 4

Among pediatric population at risk for premature cardiovascular disease, should screening with fasting lipid profile be recommended?

Statement 4

Among pediatric population (< 18 years old) at risk for development of atherosclerosis and premature cardiovascular disease, screening with a fasting lipid profile is RECOMMENDED.

(Risk factors: Obesity, diabetes type 1 and type 2, hypertension, FH, family history of premature CVD, CKD, Kawasaki disease, HIV, adolescent depressive and bipolar disorder)

Summary of the evidence

The screening for dyslipidemia in childhood is made on the basis of early identification and control of pediatric dyslipidemia that will reduce the risk and severity of cardiovascular disease (CVD) in adulthood. There has been no solid evidence so far with regards the screening recommendation for dyslipidemia among the pediatric age group.

In our literature review, the screening guidelines that have been suggested are the following: 1. Selective screening for those at risk (see table 1) and 2. Universal screening to identify those with risk factors for familial hypercholesterolemia at 9-11 years old and 17-21 years old[63].

Selective screening is done the first time the risk factor has been identified beyond two years of age. For children without any risk factors for CVD but with strong family history of premature CVD, the first screening is done between the age of 9 and 11 years and the second between age 17 and 21 years. It is not recommended to perform routine screening for ages 12 to 16 years because changes in lipid levels that normally occur during puberty decrease the sensitivity and specificity for predicting adult low-density lipoprotein cholesterol (LDL-C) levels and increase false-negative results in this age group[64].

Table 12. Risk Factors for Cardiovascular disease in the Pediatric Population

Traditional Risk Factors	**Other conditions**
Dyslipidemia	Familial Hypercholesterolemia
Obesity	Chronic kidney disease
Diabetes Mellitus (Type 1 or 2)	Kawasaki disease
Hypertension	Childhood cancer
Family History of premature CVD	Transplant vasculopathy
Smoke exposure	Certain congenital heart disease defects (eg: coarctation of the aorta, aortic stenosis)
	Cardiomyopathy
	Chronic inflammatory disorders
	HIV infection
	Adolescent depressive and bipolar disorders

Clinical Question 5

Among CKD individuals not on dialysis, should statins be given to reduce CV risk?

Statement 5

Among CKD individuals not on dialysis (CKD-ND), the use of statins to reduce CV risk is RECOMMENDED

Summary of the evidence

Individuals suffering from kidney impairment have a higher risk of cardiovascular disease. In a meta-analysis with 1.4 million people, there was a linear increase in cardiovascular mortality seen with decreasing estimated glomerular filtration rate (eGFR) below 75 ml/min/1.73m^2, with mortality rates twice as high in stage 3 Chronic Kidney Disease (CKD), and three times as high in stage 4 CKD[65]. These individuals have also been shown to have similar rates of myocardial infarction or coronary heart disease compared to diabetic individuals. While CKD is often a result of hypertension or diabetes, both a decline in kidney function and albuminuria are considered independent risk factors for cardiovascular disease. Thus, presence of CKD is considered a CHD equivalent.

Dyslipidemia is common but not universal in CKD. Kidney dysfunction leads to a profound dysregulation of lipoprotein metabolism, resulting to multiple lipoprotein abnormalities. Changes in lipid metabolism occur significantly in early stages of kidney disease, and significant changes in apolipoproteins precede changes in lipid levels. The major abnormalities in CKD is a decrease in HDL-C and elevation of triglyceride-rich lipoproteins. Levels of LDL-C in CKD are not elevated and may be even low in hemodialysis because of poor nutrition and chronic inflammation[66]. However, in patients in peritoneal dialysis, elevations of LDL-C levels result from constant dextrose absorption during peritoneal dialysis.

For this consensus statement, we were able to identify thirteen (13) studies, mostly post-hoc analysis of non-dialytic individuals, and three studies were primary studies. These include 4S[67], AFCAPS/TEXCAPS[68], ALLIANCE[69], CARDS[51], JUPITER[47,70], MEGA[46], LIPS[71], PPP[72], PREVEND IT[45], PANDA[73], TNT[74] and IMPROVE-IT[75], SHARP[76] and Asuca et al, Suzuki et al, and Sawara et al[77-79] Four studies, IMPROVE-IT, PANDA, TNT, and Suzuki et al were studies on moderate dose statins comparing them to high intensity studies in CKD patients.

Table 13. Summary of Evidence for the Use of Statins in Individuals with CKD

Outcome	Evidence Quality	Relative Importance	Relative Risk	NNT
Total Mortality	Moderate	9	0.80 (0.74 to 0.86)	55
Cardiovascular Deaths	Moderate	9	0.78 (0.69 to 0.88)	77
Fatal and non-fatal MI	Moderate	9	0.55 (0.42 to 0.73)	71
Strokes (Fatal and nonfatal)	Moderate	9	0.60 (0.42 to 0.87)	166
Cardiovascular events	Moderate	7	0.76 (0.73 to 0.80)	2
Coronary intervention	Moderate	6	0.56 (0.41 to 0.77)	23

Table 12 summarizes the results of the review and the relevant outcomes. Statistically significant results are seen from reduction all-cause mortality of 20%, reduction of CV death by 22%, myocardial infarction by 54%, stroke by 40%, major cardiovascular events by 24% and coronary revascularization by 44%. The GRADE balance sheet combines the appraisal of the studies included in the guideline recommendation with the outcomes. Generally, the quality of the evidence is **moderate** with the downgrade due to the question of directness. In particular Filipinos were not included in the samples that were included in these trials.

The recommendations in this local guideline is to give statin therapy for individuals with CKD not on dialysis. For individuals who are on renal replacement therapy and post-transplant, this local guideline recommends referring patients to nephrologists for lipid management[80].

Clinical Question 6

Among individuals with Acute Coronary Syndrome, should statin therapy be given?

Statement 6

For individuals with acute coronary syndrome, early high intensity statin that is maximally-tolerated is RECOMMENDED and should not be discontinued.

Statement 6.1

Statins should be given to ACS patients immediately

Summary of the evidence

Timing of therapy is critical among patients with acute coronary syndrome. Early intervention is advocated to optimize recovery and minimize complications. The adage "time is muscle" is based on the principle of the necessity for immediate action during the golden period in which myocardial ischemic damage is still potentially reversible or myocyte necrosis can still be contained and much of the myocardium in the ischemic penumbra can still be salvaged.

Evidence on the use of statins for the secondary prevention of cardiovascular outcomes were derived from 18 clinical trials comparing statins against placebo in secondary prevention populations[81-97]. Five studies assessed the use of statins for secondary prevention in individuals with type 2 diabetes[50,97-100].

Appendix 5 Table 1 summarizes the characteristics of the studies that were included in this current guideline. Statin preparations available locally were the only ones included in the review, which includes the following statins; fluvastatin 80 mg, pravastatin 20 to 40 mg, atorvastatin 10 to 80 mg, and simvastatin 10 to 20 mg. The baseline lipid levels in the included studies varied, with the mean baseline LDL-C ranging from 199.3$\pm$39.0 mg/dL to 387.1$\pm$73.5mg/dL. The studies included both genders.

Statin treatment in those with ASCVD resulted in a statistically significant reduction in the critical outcomes of total mortality (RR 0.87; 95% CI 0.83-0.91), cardiovascular mortality (RR 0.79; 95% CI 0.75-0.84), myocardial infarction (RR 0.70; 95% CI 0.66-0.75) and stroke (RR 0.78; 95% CI 0.72-0.84), with NNTs ranging from 46 for myocardial infarction, to 88 for stroke (Table 11). Hence, in patients with ASCVD, statin therapy is recommended.

For those with DM, statistically significant results are seen for the outcomes of total mortality (RR 0.87; 95% CI 0.79 – 0.91) and stroke (RR 0.67; 95% CI 0.49 – 0.90) (Table 14).

Table 14. Summary of Evidence on treatment effect of statins for secondary prevention

Outcome	Studies	Total Participants	Effect Estimate (RR, 95% CI)	NNT
General population				
All cause Mortality	15	60,166	0.87 (0.83 – 0.91)	67
CV death	14	59,949	0.79 (0.75 – 0.84)	62
Myocardial infarction	13	54,018	0.70 (0.66 – 0.75)	45
Stroke	11	52,426	0.78 (0.72 – 0.84)	83
Patients with diabetes				
Cardiovascular events	5	4,351	0.85 (0.79 – 0.91)	16
Myocardial infarction	5	1,091	0.73 (0.53 – 1.00)	NS
Stroke	5	2,370	0.67 (0.49 – 0.90)	37
All-cause mortality	5	707	0.78 (0.53 – 1.14)	NS

The GRADE balance sheet for the appraisal of evidence on the use of statins in secondary prevention among patients with ASCVD and DM showed that the quality of evidence is moderate for both subgroups, with the quality downgrade resulting from questions of directness. The studies included were all performed on Caucasian populations. Asians, particularly Filipinos, were not well-represented in these trials. Heterogeneity of pooled studies also resulted in serious inconsistencies and a further downgrade of the evidence.

Evidence on the appropriate statin intensity for secondary prevention in individuals with ASCVD were obtained from 4 trials that compared varying statin regimens, as defined in Table 12: Armitage et al [101], Phase Z of the A-Z trial[102], TNT [103] and IDEAL [104] clinical trials. These abovementioned studies compared high intensity (atorvastatin 80 mg or

simvastatin 80 mg) to medium intensity (atorvastatin 10 mg or simvastatin 20 mg) statins. High intensity statins reduce LDL-C by >40%, compared to low intensity statins which reduces LDL-C by 20-30%.

Table 15. Statin treatment intensity

Treatment intensity	% LDL-C reduction	Drug regimen
Low intensity	< 30 %	Fluvastatin 20-40 mg Pravastatin 10-20 mg Simvastatin 10 mg
Moderate intensity	30% - 50%	Atorvastatin 10 -20 mg Fluvastatin 80 mg Rosuvastatin 5 - 10 mg Simvastatin 20 - 40 mg Pravastatin 40 - 80 mg Pitavastatin 2 – 4 mg
High intensity	>50%	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

Analysis of the evidence on high-intensity vs moderate intensity statin therapy using GRADE Pro showed that the quality of evidence is moderate, with quality downgrade due to the question of directness. Filipinos where not well represented in the clinical trials and were mostly done in Caucasians. The evidence was able to show a net benefit **favoring high-intensity statin therapy** in reducing the critical outcome of myocardial infarction (RR 0.85; 95% CI 0.78-0.92).

Despite of the early use of high intensity statins among patients with ACS, there is a low prevalence among patients reaching target LDL-C <70 mg/dl. Data from Thailand (26.7%) and Hongkong (45.1%) showed low rates of patients reaching target.

This guideline recommends that high-intensity statin therapy be used in secondary prevention of patients diagnosed with ASCVD. It should be emphasized that the definition of statin treatment intensity rests on the degree of LDL-C reduction, and less on the drug dose used. Evidence that Asians may require lesser dose to achieve target LDL-C goals has only been shown locally in one trial in Filipinos looking at the efficacy of simvastatin and atorvastatin 20 mg once daily. LDL-C levels were reduced by 34.8% and 42.5% respectively, however, the sample size was small. Until a bigger trial is conducted, statin

intensity remains as percentage LDL-C reduction from baseline as presented in the 2015 CPG (Table 14). It is recommended that physicians use the appropriate statin dose that will achieve the needed treatment reduction goal with minimal risk of adverse events.

Statement 6.1.2

For individuals with documented ACS and target LDL-C has not been reached despite maximally-tolerated high-intensity statin therapy, ezetimibe may be added on top of statin therapy to get to goal LDL-C.

Summary of evidence

Ezetimibe is an important adjunct medication in lowering LDL-C in the body[105]. It blocks a critical mediator of cholesterol absorption, the Niemann-Pick C1 like-1 Protein (NCP1L1) on the gastrointestinal tract epithelial cells, as well as in hepatocytes. It also blocks aminopeptidase N and interrupts a caveolin 1-annexin A2 complex involve in cholesterol synthesis[105]. Presently, the use of this drug is to lower LDL-C in combination with statins in select high risk patients.

For this CPG, three studies satisfied our clinical question: IMPROVE-IT using ezetimibe+simvastatin vs simvastatin monotherapy[106], NSTE-ACS using rosuvastatin 10 or 20 mg alone vs ezetimibe+rosuvastatin combination[107], and HIJ-PROPER using pitavastatin+ezetimibe vs pitavastatin alone[108].

Baseline LDL-c in the three clinical trials differ with high baseline LDL-c of 205-208 mg/dl in the three arms of NSTE-ACS compared to the two other clinical trials where the baseline LDL-c was below 100 mg/dl. Table 13 summarizes the results of the review and the relevant outcomes. Statistically significant results are seen from reduction of total mortality, fatal and non-fatal MI, stroke, MACE, and coronary revascularization. The GRADE balance sheet combines the appraisal of the studies included in the guideline recommendation with the outcomes. Generally, the quality of the evidence is **moderate** with the downgrade due to the question of directness, based on suitability for Filipino patients in particular Only 4.9% of the population in the IMPROVE-IT study belong in the Asia-Pacific region, HIJ Proper trial included Japanese subjects, while NSTE-ACS included Chinese subjects.

Table 16. Summary of Evidence in the Use of Ezetimibe in Individuals with ASCVD

Outcome	Evidence Quality	Relative Importance	Relative Risk	NNT
Total Mortality	High	9	**0.97 (CI 0.91 to 1.05)**	NS
Cardiovascular Deaths	High	9	0.99 (CI 0.89 to 1.12)	NS
Fatal and non-fatal MI	High	9	0.87 (CI 0.81 to 0.95)	66
Strokes (Fatal and nonfatal)	High	9	0.86 (CI 0.74 to 1.00)	NS
Major Adverse CV events	Moderate	7	0.93 (CI 0.89 to 0.97)	48
Coronary intervention	Moderate	6	0.94 (CI 0.90 to 0.99)	83

This guideline recommends that ezetimibe be given to patients with documented ACS on maximally tolerated statin therapy not at goal LDL-C levels.

Non-Statin Therapies

Clinical Question 7.1

Among individuals with ASCVD, should ezetimibe be given on top of statin therapy?

Statement 7.1

For the secondary prevention of CV events, the use of ezetimibe on top of maximally tolerated high intensity statins is RECOMMENDED to achieve target LDL-C goal

Clinical Evidence – please see statement 6.1.2

Clinical Question 7.2

Among individuals, can fibrates be given on top of statin therapy once LDL-C goal is not achieved?

Statement 7.2.1

Among individuals not at goal LDL-C, adding fibrates on top of statin therapy is not recommended for primary or secondary prevention for cardiovascular disease

Summary of Evidence

The evidence on fibrates was taken mainly from the Veteran's Affairs High-density lipoprotein Intervention Trial (VA-HIT)[109] and a subgroup of patients with pre-existing ASCVD in the Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (FIELD) study.[110] The LOCAT[111] study also

contributed a small number of patients. In the 2015 guidelines[1], the study on bezafibrate was included in the analysis. In this guideline, bezafibrate study was excluded (not locally available). In VA-HIT[109], gemfibrozil reduced nonfatal myocardial infarction (OR 0.77 [95% CI 0.61, 0.97]) and cardiovascular events (OR 0.73 [95% CI 0.6, 0.88]) among 2,531 men with coronary heart disease, a HDL-C of 40 mg/dL or less, and an LDL-C level of 140 mg/dL or less. There was no effect on all-cause mortality, stroke, CHD death and revascularization. In the FIELD study[110], 22% of both fenofibrate and placebo arms have prior cardiovascular diseases. Among these patients, the authors reported cardiovascular event rates of 25.5% in the fenofibrate group and 25.1% in the placebo group. This is the only outcome reported under the specific subgroup of patients with ASCVD (Table 17). In the LOCAT[111] study, no mortality was noted during the study for either arm.

Table 17. Summary of study outcomes for the use of fibrates versus placebo among individuals with ASCVD

Outcome	Evidence Quality	Relative Importance	Effect Estimate (RR, 95% CI)	NNT
Total Mortality	Moderate	9	0.90 [0.76, 1.08]	NS
Fatal CHD/CV death	Moderate	9	0.89 [0.69, 1.15]	NS
Nonfatal MI	Moderate	9	0.80 [0.65, 0.97]	34
CHD death	Moderate	9	0.79 [0.61, 1.02]	NS
Stroke	Moderate	9	0.76 [0.55, 1.07]	NS
Coronary revascularization	Moderate	6	0.93 [0.80, 1.08]	NS

The GRADE Pro balance sheet shows the quality assessment of the evidence on the use of fibrates in secondary prevention. Generally, the quality of the evidence is moderate with the downgrade due to the question of directness. The studies were all done in Caucasian populations and Asians, and in particular Filipinos were not included in the samples that were included in these trials.

Thus, given the moderate quality of evidence, fibrates are not recommended as an alternative to statin therapy in patients with established ASCVD.

Clinical Question 7.2

Among individuals with diabetes, can fibrates be given on top of statin therapy once LDL-C goal is not achieved?

Statement 7.2.2

Among individuals with diabetes, routinely adding fibrates to statins is not recommended for primary or secondary prevention of cardiovascular disease

Among individuals with diabetes, routinely adding fibrates on top of statin therapy is NOT RECOMMENDED for primary or secondary prevention of cardiovascular disease.

However, adding fibrates to statins may be considered among men with controlled diabetes and low HDL-C (<35 mg/dl) and persistently high triglycerides (>200 mg/dl) for additional prevention of CV disease

Summary of Evidence

An updated review of literature was done which revealed only 4 studies which address this issue. These studies include the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[112-113], and its follow up study, the Action to Control Cardiovascular Risk in Diabetes Follow-on Study (ACCORDION)[114], the Acute Coronary Syndrome Israel Trial, and a study on bezafibrate and simvastatin combination therapy for diabetic dyslipidemia published in 2000. The latter was excluded because bezafibrate is no longer available in our local market, while the Israeli study was actually derived from a registry of patients who were followed up after acute coronary syndrome.

This question is answered directly by the ACCORD lipid trial, and the post-trial follow-up of this trial, the ACCORDION. This study randomly assigned 5518 patients with type 2 diabetes who were being treated with open-label simvastatin to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. This was a clinical trial on persons with high CV risk enrolling both those with subclinical CV disease or 2 or more risk factors, as well as persons with diabetes and previous cardiovascular events. The latter comprised 36.5% of the included subjects and the mean follow-up was 4.7 years.

Overall, the ACCORD[112] Lipid trial was negative with the conclusion that there is

no evidence to indicate that fenofibrate should be routinely added to a statin for the treatment of dyslipidemia in patients with type 2 diabetes mellitus. For the primary outcome of major fatal or nonfatal cardiovascular event, the hazard ration is 0.92 (95% CI 0.79-1.08), p-value 0.32 (NS). The results for the secondary outcomes which included major coronary disease event, nonfatal myocardial infarction, stroke, total mortality and death CV diseases, or fatal or nonfatal congestive heart failure, were likewise not statistically significant.

The pre-specified subgroup analysis showed heterogeneity in the treatment effect according to sex, with a benefit for men and possible harm for women (men had an ~16% lower primary event rate on fenofibrate, whereas women had an ~38% greater primary event rate on fenofibrate). There is also a possible benefit for persons with both a high baseline triglyceride level and a low baseline level of HDL cholesterol.

The ACCORDION[114] study is a passive follow up of the original ACCORD Lipid Trial participants, enrolling 4644 surviving participants. Similar to the original cohort, 35% had pre-existing cardiovascular events. Total post randomization follow-up duration was a median of 9.7 years. Only 4.3% of study participants continued treatment with fenofibrate following completion of ACCORD, and thus, the results of ACCORDION reflect the long-term effects of the previously randomized treatment. The results of this follow up study confirm the original neutral effect of fenofibrate in the overall study cohort. Similar too, to the original study, there is still an observation of heterogeneity of treatment response in that fenofibrate appeared to reduce CV events among those with baseline hypertriglyceridemia (TG $\geq$ 200 mg/dL) and low HDL cholesterol < 35 mg/dL. The investigators concluded that a definitive trial of fibrate therapy in this patient population is needed to confirm these findings.

Thus, until more data are available, there appears to be no evidence to recommend routinely adding fibrates to statins once LDL-C goals have been reached. However, it may be considered among persons with diabetes (especially men) with high baseline TG and low HDL-C, once LDL-C goals have been reached. This statement is based on the experts' panel consensus during the presentation of the clinical practice guidelines.

Clinical Question 7.3

Among individuals with ASCVD, should omega fatty acids be given on top of statin therapy?

Statement 7.3.1

Among individuals with ASCVD, omega fatty acids (EPA+DHA) given on top of statin therapy is not recommended

Summary of the evidence

Three meta-analyses on omega 3 fatty acids for secondary CVD prevention were reviewed to answer the above clinical question but most come from the latest 2019 meta-analysis[115]. Thirteen randomized controlled trials with 127,777 participants. were analyzed. All except one study (VITAL[116]) can be considered as secondary prevention trials involving participants with previous cardiovascular diseases or those with diabetes mellitus and at high risk of developing CVD. Hu et al showed a dose-response relationship between omega 3 fatty acids and several cardiovascular disease outcomes. This may explain the findings of previous meta-analyses and studies showing no clinical benefit when utilizing lower doses. Thus, the present analysis included secondary prevention studies that utilized at least 1 g EPA/DHA omega 3 fatty acid in the intervention group. The four studies included are DOIT[117], AREDS2[118], JELIS[119] and REDUCE-IT[120].

Table 18. Summary of Evidence in the Use of Omega Fatty Acids in Individuals with ASCVD

Outcome	Evidence Quality	Relative Importance	Relative Risk	NNT
Total Mortality	Moderate	9	0.97 (0.86-1.10)	**NS**
Cardiovascular Deaths	Moderate	9	0.93 (0.56-1.55)	143
Fatal and non-fatal MI	Moderate	9	0.70 (0.61-0.81)	111
Strokes (Fatal and nonfatal)	Moderate	9	0.89 (0.75-1.05)	NS
Cardiovascular events	Moderate	7	0.76 (0.68-0.84)	71

The cardiovascular outcomes are myocardial infarction, stroke, CHD death, CVD death, total CVD and all cause mortality. The summary of findings table showed benefit on myocardial infarction, total CVD and CVD death. However, the number needed to treat

for the three outcomes are high (MI- 111, CVD – 71 and CVD death- 143). The benefit for CV outcomes was largely impacted by the JELIS and REDUCE-IT with a significant number of participants in the trial, both using pure EPA, a formulation currently not available in our local setting.

Thus, until more data are available and if the formulation of pure EPA becomes available in the Philippines, this guideline does not recommend routinely administering omega-fatty acids (EPA + DHA) in patients with ASCVD for secondary prevention. However, it may be recommended to specific populations with clear indications for its use such as those with hypertriglyceridemia (TG > 500 mg/dL). This statement is based on the experts' panel consensus during the presentation of the clinical practice guidelines.

Statement 7.3.2

Among individuals with ASCVD on statin therapy at goal LDL-C but with persistently high triglyceride levels of 150-499 mg/dl, omega fatty acids (pure EPA) MAY be given.

Summary of the evidence

The REDUCE-IT[120] trial addressed individuals with ASCVD at-goal on maximally-tolerated statin therapy with persistently elevated triglycerides. 8179 statin-treated patients with qualifying triglycerides ≥135 and <500 mg/dL and LDL-C >40 and ≤100 mg/dL and a history of atherosclerosis or diabetes mellitus were randomized to icosapent ethyl 4 g/d or placebo. After a median of 4.9 years, a primary end-point event occurred in 17.2% of the patients in the pure icosapent ethyl group (EPA), as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001). Among patients with elevated TG, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 4 gm of icosapent ethyl daily than among those who received placebo on top of statin therapy. Unfortunately, pure EPA used in both this trial and JELIS is currently not available in the Philippines.

In patients with ASCVD at-goal LDL-C on statin therapy but with persistently high triglyceride (TG 135-499 mg/dl), omega fatty acids (pure EPA) MAY be given once this formulation of omega fatty acids becomes locally available.

The use of PCSK-9 inhibitors in individuals with ASCVD

Other lipid lowering agents, the Proprotein Convertase Subtilisin/Kexin Type 9 inhibitors (PCSK9-I), are available worldwide as an adjunct to statins in lowering cholesterol levels. These are monoclonal antibodies which bind to and inactivate an enzyme in the liver called proprotein convertase subtilisin kexin 9 (PCSK-9), which inactivates the need receptors on the liver cell surface that transport LDL-C into the liver for metabolism. Evolucumab is already available in the country, while Alirocumab, the other PCSK-9 inhibitor, is only available in other countries. Bococizumab showed no benefit in cardiovascular morbidity and mortality in phase 3 clinical trials.

The use of PCSK-9 inhibitors can lower LDL-C by < 70mg/dl (59% lower than the baseline) and can go as low as 30 mg/dl. The addition of these monoclonal antibody to statins can reduce the risk of major adverse coronary events by 15%, and a 20% reduction in cardiovascular death, stroke, and myocardial infarction[121-122]. Unfortunately, the cost of these therapies and the availability in the Philippines may limit the use of these drugs. Thus, this guideline recommends maximizing oral therapy (ie. high-intensity statin therapy and Ezetimibe) prior to considering the use of PCSK-9 inhibitors.

Cholesterol Target Levels

Based on the clinical trials discussed above and the expert panel opinions, the following table is the summary of cholesterol level targets for the different patient groups discussed above.

Table 19. Cholesterol Targets for Different Patient Groups

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
DM individuals With ≥1risk factors/target organ damage With ASCVD	< 100 mg/dL < 70 mg/dL < 55 mg/dL		
Individuals with clinical ASCVD	< 55 mg/dL		
FH Individuals without ASCVD or without major risk factor/target organ damage	< 70 mg/dL		

FH With ASCVD or with ≥1risk factors/target organ damage	< 55 mg/dL		

Clinical Question 8

Among individuals taking statin therapy, what is the risk of developing adverse events?

a. **Statin-associated Muscle Symptoms (SAMS)**
b. **New onset Diabetes Mellitus**
c. **Dementia/cognitive dysfunction**
d. **Intracerebral hemorrhage**

Statement 8.1

Treatment with statins is associated with a low risk of developing statin-associated muscle symptoms (SAMS), but the benefits of cardiovascular risk reduction outweigh the risk.

Statin-associated muscle symptoms (SAMS) are classified as myalgias, myopathies, myositis, or rhabdomyolysis. In patients at risk for development of statin myopathies, baseline creatine phosphokinase and subsequent monitoring should only be performed when symptoms are present[123]. The diagnosis of SAMS is subjective for both patient and physician because there are no validated clinical tests or diagnostic criteria. Creatine Kinase (CK) levels are normal in patients with possible SAMS, whereas many asymptomatic patients on statin therapy have elevated CK levels[124].

In RCTs, the risk of developing myalgia ranges from 1-5% while in observational studies and in the clinical setting, myalgia frequency ranges from 10-15%[125] The risk of myopathy compared to placebo is less than 0.1% [47,126-127], while myositis and rhabdomyolysis are rare with the risk of rhabdomyolysis at 0.01%[128] or 1 patient per 100,000 treated with statins. [129]. In a systematic review of 42 clinical trials of statin therapy, the incidence of statin associated muscle symptoms were the same as that of placebo (12.7% in statin treatment group vs. 12.4% in the placebo group). [130]

One note-worthy study to mention is the Prediction of Muscular Risk in Observational Conditions (Predictio du Risque Musculaire en Observationnel PRIMO). This was an observational survey of muscular symptoms in 7924 hyperlipidemic patients receiving high-dosage statin therapy in an outpatient setting in France. They used a validated questionnaire in obtaining patients' demographics, treatment history and muscular symptoms. Multivariate analyses revealed that the strongest predictors for muscular symptoms are history of muscle pain during treatment, unexplained cramps, and elevation of creatine kinase levels. Muscle symptoms were recorded by 832 patients with a median onset of one month after initiation of statin therapy. Muscle pain prevented 38% of the patients from moderate exertion during everyday activities while 4% of the patients were bed-ridden or unable to work. Fluvastatin XL was associated with the lowest rate of muscular symptoms compared to atorvastatin and pravastatin XL. High dose simvastatin was associated with the highest risk of muscular symptoms. The results of the PRIMO study indicate that mild to moderate muscular symptoms may be more common and exert a greater influence in the quality of life of patients on high dose statins[131].

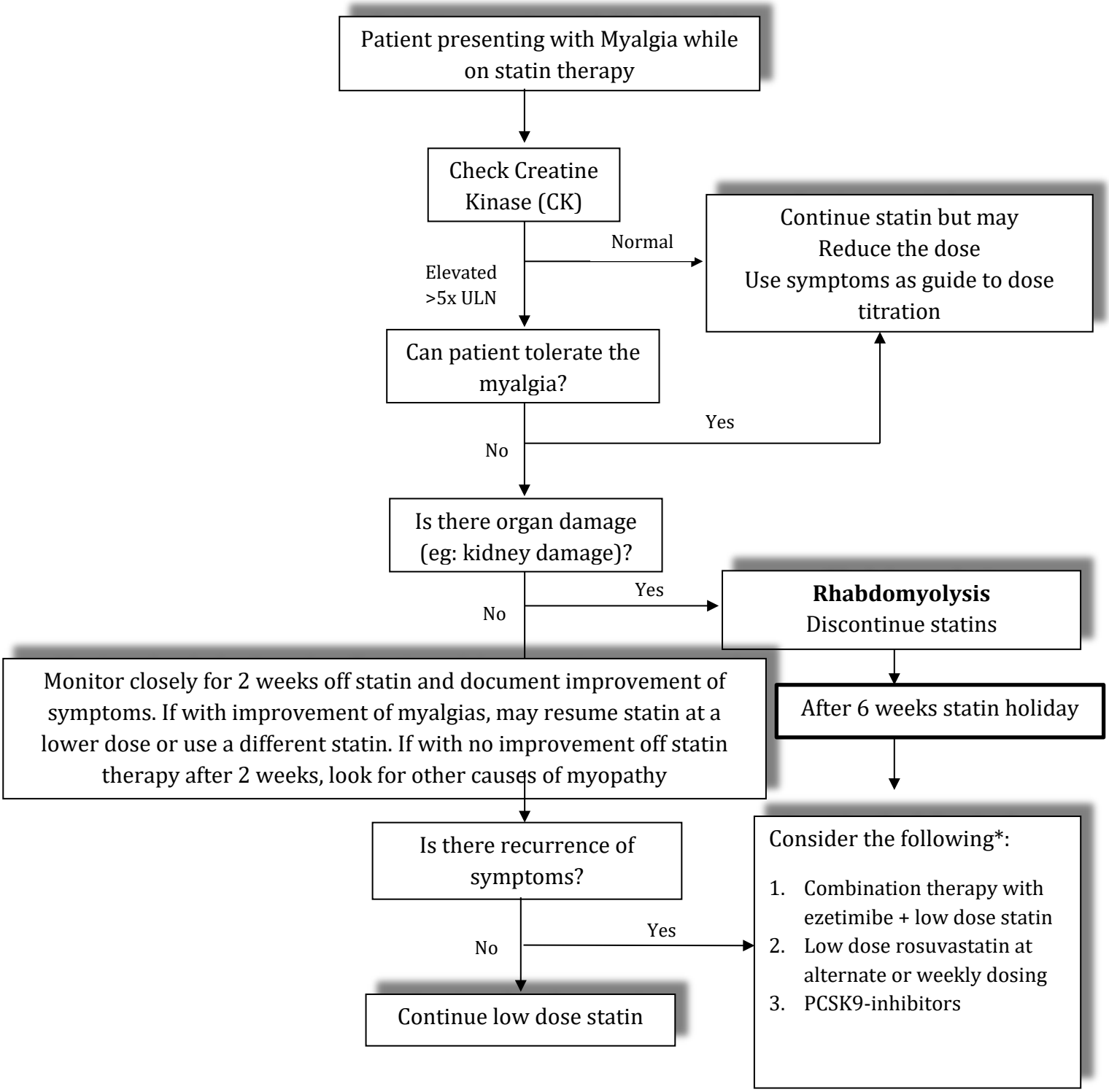
Table 20. Classification of statin myopathies

<table>
<tr><th></th><th>Myalgia</th><th>Myopathy</th><th>Myositis</th><th>Rhabdomyolysis</th></tr>
<tr><td>ACC/AHA NHLBI[132]</td><td>Focal or diffuse muscle aches or weakness with normal CK</td><td>Any disease of muscle</td><td>Muscle pain with CK elevation</td><td rowspan="2">Severe muscle damage with damage to another organ (i.e., kidney) and CK > 10 x ULN</td></tr>
<tr><td>NLA[133]</td><td></td><td rowspan="2">Myalgia with CK > 10x ULN</td><td></td></tr>
<tr><td>US FDA[134]</td><td></td><td></td><td>CK >50x ULN + organ damage</td></tr>
</table>

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

With the low prevalence rate of statin-associated myopathies in clinical trials contrasted to the benefit of statin therapy such as in a meta-analysis comparing patients who were adherent to statin therapy and those with low adherence showing 15% reduction

in CVD risk among patients who were adherent to statin therapy[134], this guideline concludes that the benefit of statins outweigh the risks of developing muscle side effects.



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

Figure 4. Algorithm for Statin-induced Myopathy

The TRC also recommends, as in the previous guideline, a localized management algorithm for statin-treated patients with muscle symptoms. The most common risk factors for SAMS include advanced age, female sex, low BMI, high- risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, pre-existing myopathy), Asian descent, excess alcohol, high levels of physical activity and trauma[129-130]. This algorithm has been updated to include the option of a recently made-available therapy, PCSK9-inhibitors, after 6 weeks statin-holiday.

Statement 8.2

Treatment with statins is associated with an increased risk of new onset diabetes mellitus, but the benefits of statin treatment for cardiovascular risk reduction outweigh the risk.

Summary of Evidence

Statins are beneficial in patients with diabetes mellitus, but also appear to increase risk for new onset diabetes (NOD). It might disrupt insulin signaling pathways and may reduce insulin secretion and/or systemic insulin sensitivity. The risk of NOD may be dose dependent and dependent on the baseline DM risk and statin potency. The first report on association between statin use and incident diabetes was derived from a post hoc analysis of the WOSCOPS in 2001[41]. In the trial, a risk ratio of 0.7 (95% CI 0.5-0.99, p=0.042) was reported on patients taking pravastatin versus placebo. A recent meta-analysis on the use of statins and development of NOD resulted in the analysis of 236,864 patients of which 180,811 were in the control group, while 56,053 were in the statin group. The cumulative fixed effect for use of statin therapy and incident NOD was an OR 0f 1.61 (95% CI 1.55-1.68, p <0.001), suggesting that statin therapy is associated with NOD. However, the patients included in the analysis have other diabetes risk factors, such as obesity and hypertension, contributing the development of NOD. Thus, it is recommended to monitor patients with NOD[135]

Various studies suggest that factors such as hydrophilicity (pravastatin and rosuvastatin) or lipohilicity (atorvastatin, lovastatin, pitavastatin, and simvastatin) may influence the risk of NOD. In a retrospective study examining low doses of atorvastatin 10 mg/day, pravastatin 10 mg/day and pitavastatin 2 mg/day on glucose control over 3 months, random blood sugar and HbA1C levels were elevated in the atorvastatin group while the other two arms were not. Intensive dose statin therapy has also been observed to cause NOD, compared to moderate or low dose of the statin. In the CORALL study, both high dose rosuvastatin and high dose atorvastatin were associated with significant increases in HbA1C, but not in the mean fasting glucose. In the PROVE-IT TIMI 22 study, a post hoc analysis showed that patients on atorvastatin 80 mg/day has an increased risk of developing HbA1C >6% compared with pravastatin[136].

Thus, the use of statins may cause NOD, however, the risk benefit of statin therapy favored its use in high-risk patients and in secondary prevention. It is thus important to monitor patients, especially if they have risk factors for diabetes.

Statement 8.3

Treatment with statins is not associated with the development of dementia and cognitive dysfunction

Dementia is a neurodegenerative condition associated with decline in cognitive function, behavior, personality and sensorimotor functions[137-138]

Post marketing case reports have implicated statin use as a cause of reversible cognitive impairment in some patients. In contrast, several phase III clinical trials with statin did not report any significant increase in the incidence of cognitive impairment among study participants when compared against placebo. Paradoxically, a number of observational studies have cited evidence that statin use may be associated with protective effect against the development of dementia. However, subsequent clinical trials and re-evaluation of previous clinical statin trials failed to show decreased risk of dementia with statin use. In 2013, the American Heart Association / American College of Cardiology released a statement in their guidelines citing they did not find evidence linking statin use with development of cognitive dysfunction or the increased risk of dementia. Moreover, they recommended against the consideration of dementia as a symptom or adverse event to be considered when prescribing statins[132].

We have reviewed four recent meta-analyses[137-140] of various observational studies investigating the association between statin use and risk of dementia. All these four recent and updated metanalyses of observational studies showed no increase in the incidence of dementia or cognitive impairment among statin users. It is also important to note that these meta-analyses were consistent in showing the opposite observation, that there is **reduction in risk of dementia with statin use**.

Poly et al published the largest and most recent meta-analysis of statin use and risk of dementia[138] with 23 cohort and 7 case-control studies, they found out that patients taking statins are 17% less likely to develop dementia [**RR 0.83** (95% CI 0.79-0.87, p<0.0001)]. In terms of type dementia, the meta-analyses found out that statin use is associated with statistically significant lesser risk for Alzheimer disease [**RR 0.69** (95% CI 0.60–0.80, p < 0.0001)] but a non-significant and small decrease risk for vascular dementia [**RR 0.93**, 95% CI 0.74–1.16, p=0.54)]. The association of lesser risk of dementia development among statin users is seen both in the subgroup analysis according to type of studies (cohort vs case-control), gender (male vs female), and ethnicity or region (North America vs Europe vs Asia). In terms of individual statins, subgroup analysis shows that the association of lesser dementia risk is statistically significant only among rosuvastatin and atorvastatin users. No statistically significant reduction in the risk of dementia is associated with statin use duration of less than 1 year [**RR 1.04**, 95% CI 0.95–1.14, p=0.35)] when compared to those who had statins for 2-3 years [**RR 0.66**, 95% CI 0.52–0.83, p<0.0001)]. The largest dementia risk decrement was seen among patients with statin use of more than 3 years [**RR 0.37**, 95% CI 0.19–0.73, p<0.004)][141].

In summary, based on the available evidences from observational studies and subgroup analyses of clinical trials, there is no increased risk of dementia and cognitive dysfunction both with the use of statins and LDL-C lowering as low as 30mg/dL.

Statement 8.4

Treatment with statins is not associated with an increased risk of intracerebral hemorrhage

Statin therapy has been recommended by both American and European guidelines to reduce the risk of stroke and cardiovascular events in patients with cerebrovascular disease. However, 2 large randomized trials, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)[142] and Heart Protection Study (HPS)[52], showed that the

benefit in reducing recurrent stroke was offset in part by an increased risk of intracerebral hemorrhage (ICH). On the other hand, meta-analyses of randomized trials involving patients without prior stroke showed no significant association between statins and intracerebral hemorrhage with significant reductions in all-stroke and all-cause mortality with statin therapy[143-145].

There are several mechanisms that can explain the association between statins and intracerebral hemorrhage. Statins are mildly antithrombotic agents that inhibit platelet aggregation, enhance fibrinolysis, and reduce thrombosis. Moreover, cholesterol may be essential for blood vessel integrity in the brain. Intracerebral hemorrhage occurs from small breaks in the walls of perforator arteries that branch orthogonally from the major cerebral vessels, intraparenchymal bleeding may occur when clotting mechanisms are unable to compensate for this disruption[143]. Epidemiological data also pointed out the association of low LDL-C and the increase risk of ICH. By reducing serum cholesterol, statins may reduce the integrity of the vasculature leading to arterial necrosis and microaneurysm formation.[142]

Therefore, in an attempt to settle the aforementioned uncertainty over the adverse effects of statins, we reviewed various articles on the systemic reviews and meta-analyses of randomized controlled trials and observational studies with regard to statins and the risk of intracerebral hemorrhage with or without history prior stroke.

Table 21. Summary of Evidence of Statins causing ICH

Year	Author	Included Studies	Results
2019	Ziff, OJ, et al[146]	35 Observational Studies, 15 RCTs	Statins had no significant impact on the pooled RR with recurrent ICH (1.04, 95% CI 0.86 to 1.25, p=0.70) Statins were associated with non-significant increase of ICH in patients with previous stroke (RR 1.36 95% CI 0.96 to 1.91 p=0.08)
2012	McKinney, JS, et [143]	31 RCT	No significant difference in incidence of ICH in statin group (OR, 1.08; 95% CI 0.88 to 1.32 p=0.47)
2011	Hackam, DG, et al[145]	23 RCT, 19 Observational Studies (12 cohort, 6 case-control, 1 case crossover study)	Statins were not associated with increased risk of ICH in RCT (RR 1.10 95% CI 0.86 to 1.41 p=0.09), Cohort studies (RR 0.94; 95% CI 0.81 to 1.10 p=0.48), Case-control studies (RR 0.60; 95% CI 0.41 to 0.88 p=0.01)

Based on this wide range of current studies, we found no significant association between statin therapy and intracerebral hemorrhage among individuals with or without prior stroke infarct or ICH. We found no effect of statin therapy on ICH risk related to the degree of decline in LDL or to the achieved level. And finally, statins should be recommended in those with a previous stroke including ICH to reduce the mortality and improve functional outcome. However, caution should be advised in individuals with predisposing factors for intracerebral hemorrhage such as elderly individuals > 80 years age, with concomitant anticoagulants and uncontrolled hypertension or presence of cerebral amyloid angiopathy.

Clinical Question 9.1

Among individuals on statin therapy with LDL-C goal achieved, should non-HDL-c used as additional target to reduce cardiovascular events?

Statement 9.1

Among individuals on statin therapy who have achieved their LDL-C goal, an elevated non-HDL-C may be used as an additional therapeutic target to further reduce CV events

Non- high density lipoprotein cholesterol (Non-HDL-c) is the difference between the total cholesterol levels and HDL-C and quantifies all atherogenic lipoprotein particles. Target non-HDL in various guidelines set it as 30 mg/dL above target LDL-C. Rationale for difference of 30 mg/dL between LDL-C and non-HDL-C goals was based on the assumption that VLDL-C was the principal atherogenic lipoprotein after LDL-C. The average weight ratio of triglyceride to cholesterol in VLDL particle is 5 to 1. Assuming the weight of triglyceride is 150 mg in VLDL, the weight of cholesterol content in VLDL particle should be around 30 mg. However recent findings that optimal fasting TG is less than 150 mg/dL[147].

One of the first studies to show that non-HDL-C can be a predictor for cardiovascular disease mortality was the Lipid Research Clinics program involving a total of 2406 men and 2056 women aged 40 to 59 years with follow-up over 19 years involving 2046 men and 2056 women. It showed that non-HDL-C was a better predictor for all-cause mortality than LDL-C[146]. The Framingham Heart Study which included 2,693 men and 3,101 women aged ≥ 30 years without coronary heart disease at baseline, showed that

non-HDL-c is a better predictor than LDL-C for incident coronary heart disease[148]. In a retrospective study among 868 Thai patients after an MI, showed that non-HDL-C of greater than 130 mg/dL compared to those less than 100 mg/dL had a high incidence of major adverse cardiac event (MACE) HR 3.15 (95% CI 1.46-3.8). There was stronger association of non-HDL-C compared to LDL-C with regards to (MACE) when a direct pairwise comparison was made.[149].

In a meta-analysis of relationship between non-HDL-C and coronary heart disease (CHD) reduction, a subgroup analysis of those taking statins showed that for each 1% decrease in non-HDL-C resulted in a 1% relative decrease in estimated 4.5 year coronary heart disease RR 0.99% (95% CI 0.98-1)[150]. An updated meta-analysis of statin trials with complete lipid profile at baseline and after 1 year was done. Risk of major cardiovascular event was higher among those with non-HDL-C greater than or equal to 130 mg/dL regardless of their LDL-C levels[151].

Formula:
NON-HDL-C = (Total Cholesterol levels) – (HDL-C levels)

Recommendations from other guidelines

Both the 2018 American College of Cardiology/American Heart Association[19] and the 2019 European College of Cardiology[61] lipid guidelines recommends the value of obtaining non-HDL-cholesterol levels. In patients with high triglycerides (greater than177 mg/dl), diabetic individuals, obese individuals and with low LDL-C, particularly less than 70 mg/dl, non-HDL-c determination is recommended as a general risk assessment before initiation of statin therapy in individuals with clinical ASCVD. The non-fasting sample seem to have the same prognostic value as the fasting sample and may have the practical advantage because of patient acceptability. However, the use of non-fasting samples may lead to potential imprecision for some patients and may compromise the determination of some key electrolytes.

Clinical Question 9.2

Among individuals on statin therapy with LDL-c goal achieved, should apolipoprotein B-100 be used as additional target to reduce CV events?

Statement 9.2

Among individuals on statin therapy who have achieved their LDL-C goal, an elevated apolipoprotein B-100 may be used as an additional therapeutic target to further reduce CV events.

Apolipoprotein B-100 (Apo B-100) is an essential component of the atherogenic lipoprotein particles which is synthesized in the liver. Particles of VLDL, VLDL remnants, IDL, LDL-C and lipoprotein (a) each carry one molecule of Apo B that acts to facilitate attachment of these particles to cellular receptors. In different guidelines, Apo B-100 levels are pegged at <65 mg/dl (very high risk), < 80 mg/dl (high risk), and < 100 mg/dl (moderate risk), and a relative indication in measuring Apo B-100 is if the triglyceride level is > 200 mg/dl [152].

In the Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction (INTERHEART) study[152], using discordance analysis, showed the apo B-100 is a more accurate marker of CV risk than non-HDL-C [OR 1.58 (95% CI 1.38 – 1.78)]. Discordance is defined either as the phenotype when percentile Non-HDL-C > percentile apo B (cholesterol-enriched apo B particles) or percentile Non-HDL-C < percentile apoB (cholesterol-depleted apo B particles). Measurement of atherogenic particles are important to certain populations, particularly in diabetes mellitus, metabolic syndrome and dyslipoprotenemia wherein LDL-C and non-HDL-C are low but low density lipoprotein protein (LDL-P) are elevated. In a meta-analysis, of lipid lowering therapies involving 25 trials, a 10 mg/dL decrease in apo B was associated with a 9% decrease risk in coronary heart disease, no decrease in stroke and 6.3% decrease in overall CV risk[153]. However, no study has demonstrated improved outcomes and cost-effectiveness of using atherogenic particles as compared with traditional lipid goals in CHD risk management.

Recommendations from other guidelines

Guidelines have recognized the value of apolipoprotein B determination in risk evaluation of patients with ASCVD. In the 2019 European guidelines[54], apoB analysis is an alternative to LDL-c as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high triglycerides, diabetes, obesity or very low LDL-c levels. Nevertheless, apoB measurement carries extra expense and its measurement in some laboratories may not be reliable. The American guidelines recommends the determination of apoB if triglyceride levels is $\geq$ 200 mg/dl, and apoB levels of >130 mg/dl corresponds to an LDL-C value of > 160 mg/dl and may constitute a risk enhancing factor[17].

Limitations of the Guidelines

Several limitations were encountered during the process of creating the 2020 CPG. The evidence obtained from the trials only involved randomized controlled trials and some meta-analyses. Observational studies were only used as references. This approach, however, resulted in a comprehensive set of evidence based clinical recommendations. The clinical trials analyzed do not involve Filipino patients, thus analysis and grading of evidence were downgraded. Thus, we can only RECOMMEND the statements in this guideline. We hope in the future that more clinical trials be made with Filipino patients as subjects.

CONCLUSIONS

The nine clinical statements were made by the TRC and the recommendations revolve around the holistic management of dyslipidemia. Lifestyle modification should be recommended to all patients regardless of their CVD risk. Dosing of Statin therapies should be based on individual risk factors. We recommend a lower LDL-C target, particularly for secondary prevention, as tabulated in Table 8. The simplified algorithm was provided to serve as a quick reference in the management of clinicians.

The 2020 CPG is designed to be a guide for clinicians in managing dyslipidemia for the Filipino patient. This, however, should not replace sound clinical judgment by doctors and the ultimate decision for treatment should involve both clinician and the patient.

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- Nemencio Nicodemus – speaking engagement from Abbott
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Appendix 1. Dietary Meal Plan

Rice and alternatives 	1 serving of any of the following: • 1 cup cooked rice • 4 pcs of pandesal (17 g each) • 4 slices of loaf bread (17 g each) • 1 cup of cooked macaroni or spaghetti noodles • 1 piece of root crop (e.g., kamote, kamoteng kahoy, gabi, ubi)
Fish and alternatives 	Two servings of any of the following: • 1 pc. of small fish (e.g., galunggong) • 1 pc. Of small chicken leg or 1 matchbox size of chicken breast • 1 matchbox size of meat (e.g., beef or pork) • 1 pc. of small chicken egg
Vegetables 	• ¾ to 1 cup of cooked or raw vegetables
Fruits 	1 serving of any of the following: • 1 medium-sized fruit (e.g., banana, dalanghita, kaymito) OR • 1 slice of big fruit (e.g., watermelon, papaya)
Water and beverages 	8 or more glasses of water daily

Appendix 2. Included Studies for Lifestyle Changes

Table 1.1 Characteristics of included studies/substudies on diet modification

Study/Year	Methods	Participants	Interventions	Outcomes
Anderson 1990	Randomized controlled trial	107 moderately hypercholesterolaemic, non-obese Caucasian men and women aged 30-50	Reduced fat diet vs usual diet	Total mortality, cardiovascular mortality, total and non-fatal MI, stroke, total, LDL and HDL cholesterol
Azadbakht 2007	Randomized controlled trial	100 overweight and obese people	Reduced fat diet vs modified fat diet	Weight, metabolic risk, total mortality, CV mortality. total MI, stroke, cancer diagnoses, cancer deaths
Ball 1965	Randomized controlled trial	252 men who have recently recovered from their first MI	Reduced fat intake vs. dietary advice	Reinfarction, death, MACE, CV deaths, non-fatal MI, total MI
BDIT Pilot Studies 1996	Randomized controlled trial	295 women with mammographic dysplasia	Reduced fat intake vs usual diet	Dietary fat, serum cholesterol, total mortality, weight, BMI, total and HDL cholesterol
beFIT 1997	Randomized controlled trial	409 women and men with mild hypercholesterolemia	Reduced and modified fat vs usual diet	Lipids, total mortalit
Black 1994	Randomized controlled trial	133 people with non-melanoma skin cancer	Reduced fat intake vs usual diet	Incidence of actinic keratosis and non-melanoma skin cancer, total mortality, CV mortality
Boyd 1988	Randomized controlled trial	21 women with severe cyclical mastopathy for at least 5 years	Reduced fat vs usual diet	Mastopathy symptoms, plasma hormone and lipids, total mortality, CV deaths
BRIDGES 2001	Randomized controlled trial	106 women diagnosed with stage I or II breast cancer over the past 2 years	Reduced fat vs usual diet	Diet and BMI , total mortality, CV deaths, total and non-fatal MI, stroke, cancer deaths

CARMEN 2000	Randomized controlled trial	290 healthy overweight people, BMI 26-34	Reduced fat vs usual diet	Weight, body composition, lipids , total mortality, CV mortality, cancer deaths and diagnoses
CARMEN MS sub-study 2002	Randomized controlled trial	23 people with at least 3 risk factors for metabolic syndrome	Reduced fat vs usual diet	Weight, body composition, lipids, total mortality, CV mortality, cancer deaths and diagnoses, non-fatal MI, stroke, heart failure, PVD
Curzio 1989	Randomized controlled trial	135 hypertensives with cholesterol >6.5mmol/L	Unclear	Blood pressure, weight, lipids , total mortality, CV mortality, cancer deaths
DART 1989	Randomized controlled trial	2033 men recovering from an MI	Reduced and modified fat vs usual diet	Mortality, reinfarction, CV mortality, MACE, cancer deaths, total MI, non-fatal MI
DO IT 2006	Randomized controlled trial	249 patients with hyperlipidaemia and high risk of CVD	Reduced fat vs usual diet	CVD, total mortality
Due Low fat 2008	Randomized controlled trial	73 young overweight adults who had lost at least 8% of body weight	Reduced fat vs usual diet	CVD risk, diabetes risk, weight, total mortality, CV mortality, total MI, stroke, cancer deaths and diagnoses, total and non-fatal MI
Due Low vs Mod 2008	Randomized controlled trial	100 young overweight adults who had lost at least 8% of body weight	Reduced fat intake vs modified fat	CVD risk, diabetes risk, weight, total mortality, CV mortality, total MI, stroke, cancer deaths and diagnoses, total and non-fatal MI
Due Mod fat 2008	Randomized controlled trial	77 young overweight adults who had lost at least 8% of body weight	Modified fat vs usual diet	CVD risk, diabetes risk, weight, total mortality, CV mortality, total MI, stroke, cancer deaths and diagnoses, total and non-fatal MI
Dullaart 1992	Randomized controlled trial	38 Type I diabetics with elevated urinary albumin	Modified fat vs usual fat	Albuminuria and serum lipoproteins, total mortality, CV mortality, non-fatal MI,

				stroke, cancer deaths
Frenkiel 1986	Randomized controlled trial	36 people with radiolucent gallstones taking ursodeoxycholic acid	Modified fat vs average diet	Bile acid kinetics, total mortality
Houtsmuller 1979	Randomized controlled trial	102 adults with newly diagnosed diabetes	Modified fat vs usual diet	Progression of diabetic retinopathy, total MI and angina
Lean 1997	Randomized controlled trial	110 healthy women, BMI >25	Reduced fat vs usual diet	Weight loss, CV risk factors, total mortality, CV mortality, total and non-fatal MI, stroke, cancer deaths
Ley 2004	Randomized controlled trial	176 people with impaired glucose intolerance or high normal blood glucose	Reduced fat vs usual diet	Lipids, glucose, blood pressure, total mortality, CV death, total MI, stroke, cancer diagnoses, cancer deaths
McAuley 2005	Randomized controlled trial	62 overweight and insulin-resistant women	Reduced fat vs Modified fat diet	Weight loss, lipids, total mortality, CV mortality, non-fatal and total MI, stroke, cancer deaths and diagnoses
McKeown-Eyssen 1994	Randomized controlled trial	201 people after adenomatous colorectal polypectomy	4-monthly counseling to encourage a nutritionally balanced diet vs monthly counseling on diet to achieve fat goals	Recurrence of neoplastic polyps, total mortality, CV mortality, cancer diagnoses, cancer deaths
MeDiet 2002	Randomized controlled trial	112 healthy postmenopausal women with above median serum testosterone	Reduced and modified fat vs usual diet	Breast cancer, weight, lipids, wellbeing, total mortality, CV mortality, cardiovascular deaths, non fatal MI, stroke, ventricular fibrillation, ventricular overload
Minnesota Coron men 1989	Randomized controlled trial	4,393 institutionalised men living in a mental hospital	Modified fat diet vs. usual diet	MI, total mortality, sudden deaths, CV mortality, stroke, cancer deaths, total MI
Minnesota Coron women 1989	Randomized controlled trial	4,664 institutionalised women living in a mental hospital	Modified fat diet vs. usual diet	MI, total mortality, sudden deaths, CV mortality, stroke, cancer deaths, total MI

Moy 2001	Randomized controlled trial	267 middle-aged siblings of people with early CHD, with at least one CVD risk factor	Reduced fat intake vs. usual diet	Dietary intake, total mortality, CV mortality, cancer diagnoses (no events), cancer deaths, stroke, total and non-fatal MI
MRC 1968	Randomized controlled trial	395 men who have survived a first MI	Modified fat vs usual diet	MI or sudden death, total mortality, CV mortality, total and non-fatal MI
MSFAT 1997	Randomized controlled trial	240 healthy people aged 20-55	Reduced fat vs usual diet	Weight, vitamin and fatty acid intake, anti-oxidative capacity, total mortality, CV mortality, stroke, MI, cancer diagnoses and deaths
NDHS Faribault 1968	Randomized controlled trial	224 men living in a mental health institute	Modified fat vs usual diet	Lipid levels and dietary assessment, total mortality
NDHS Open 1st L&M 1968	Randomized controlled trial	436 men	Reduced and modified fat diet vs. usual diet	Lipid levels and dietary assessment, total mortality, CV mortality, total or non-fatal MI, peripheral vascular events
NDHS Open 1st mod 1968	Randomized controlled trial	782 men	Modified fat diet vs. usual diet	Lipid levels and dietary assessment , CV mortality, cancer diagnoses, total and non-fatal MI
NDHS Open 2nd L&M 1968	Randomized controlled trial	489 men	Reduced and modified fat vs usual diet	Lipid levels and dietary assessment , CV mortality, cancer diagnoses, total and non-fatal MI
NDHS Open 2nd Mod 1968	Randomized controlled trial	431 men	Modified fat vs usual diet	Lipid levels and dietary assessment, total mortality, CV mortality, total or non-fatal MI, peripheral vascular events
Nutrition & Breast Health	Randomized controlled trial	122 pre-menopausal women at increased risk of breast cancer	Reduced fat vs usual diet	Body weight, dietary compliance , total mortality, CV mortality, non-fatal and total MI, stroke, cancer diagnoses and deaths

Ole Study 2002	Randomized controlled trial	30 moderately obese healthy men	Reduced fat vs usual diet	Body weight, body fat, lipids, glucose, insulin , total mortality, CV mortality, non-fatal and total MI, stroke, cancer diagnoses and deaths
Oslo Diet-Heart 1966	Randomized controlled trial	412 men with previous MI	Modified fat diet vs control	Coronary heart disease morbidity and mortality, total mortality, non-fatal and total MI, stroke
Oxford Retinopathy 1978	Randomized controlled trial	498 newly diagnosed non-insulin dependant diabetics	Reduced and modified dietary fat vs average diet	Retinopathy, total mortality
Polyp Prevention 1996	Randomized controlled trial	2079 people with at least one adenomatous polyp of the large bowel removed	Low fat vs usual diet	Recurrence of polyps, prostate cancer, total mortality, cancer diagnoses
PREMIER 2003	Randomized controlled trial	537 adults with above optimal BP or stage 1 hypertension	Reduced fat vs usual diet	Blood pressure, total mortality, cardiovascular mortality, cancer deaths, cancer diagnoses, diabetes, stroke, total and non-fatal MI
Rivellese 1994	Randomized controlled trial	63 adults with primary hyperlipoproteinaemia	Reduced fat vs Modified fat diet	Metabolic effects, total mortality, CV mortality, stroke, total and non-fatal MI
Rose 1965	Randomized controlled trial	53 men with angina or following MI	Modified fat vs. usual diet	Cardiac events, total mortality, CV mortality, cardiovascular deaths, non-fatal MI, angina, stroke
Sacks high protein 2009	Randomized controlled trial	403 overweight or obese adults	Reduced fat vs Modified fat diet	Weight, total mortality, CV mortality, cancer deaths and cancer diagnoses
Sacks low protein 2009	Randomized controlled trial	408 overweight or obese adults	Reduced fat vs Modified fat diet	Weight, total mortality, CV mortality, cancer deaths and cancer diagnoses
Sarkkinen Fat Mod 1995	Randomized controlled trial	78 people aged 30-60 with serum total cholesterol levels 6.5-8.0 mmol/L	Modified fat vs usual diet	Lipids and blood pressure , total mortality

Sarkkinen Red & Mod 1995	Randomized controlled trial	78 people aged 30-60 with serum total cholesterol levels 6.5-8.0mmol/L	Reduced and modified fat vs usual diet	Lipids and blood pressure , total mortality
Sarkkinen Red Fat 1995	Randomized controlled trial	78 people aged 30-60 with serum total cholesterol levels 6.5-8.0mmol/L	Reduced fat vs usual diet	Lipids and blood pressure , total mortality
Sarkkinen Red vs Mod 1995	Randomized controlled trial	81 people aged 30-60 with serum total cholesterol levels 6.5-8.0mmol/L	Reduced fat vs modified fat	Lipids and blood pressure , total mortality
Seppelt 1996	Randomized controlled trial	70 women with BMI 24-29	Reduced fat vs usual diet	Weight, total mortality, CV mortality, total and non-fatal MI, stroke, cancer deaths
Simon 1997	Randomized controlled trial	194 women with a high risk of breast cancer	Reduced fat vs usual diet	Total mortality, cancer diagnosis
Sondergaard 2003	Randomized controlled trial	131 people with IHD plus total cholesterol at least 5mmol/L	Reduced and modified fat intake vs. usual diet	Endothelial function , total mortality, CV mortality, cancer diagnoses and deaths, stroke, total MI
STARS 1992	Randomized controlled trial	60 men with angina referred for angiography	Reduced and modified fat diet vs usual diet	Angiography , total mortality, CV mortality, cancer deaths, stroke, total MI
Strychar 2009	Randomized controlled trial	32 people with well controlled type I diabetes mellitus	Reduced fat vs Modified fat diet	Triglycerides and other CVD risk factors, total mortality, CV mortality, cancer deaths and diagnoses
Sydney Diet-Heart 1978	Randomized controlled trial	458 men with previous MI	Modified fat diet vs usual diet	Cardiovascular mortality and morbidity, total mortality
THIS DIET 2008	Randomized controlled trial	101 people following a first MI	Low fat vs modified fat	Mortality and morbidity , CV mortality, cancer deaths, stroke, total and non-fatal MI
Veterans	Randomized	844 men living at the Veterans Administration	Modified fat vs. usual diet	Total mortality, heart disease, CV mortality, cancer deaths, cancer

Admin 1969	controlled trial	Centre (USA)		diagnoses, stroke, non-fatal MI, total MI
WHEL 2007	Randomized controlled trial	3,112 women with previously treated early breast cancer	Reduced fat intake vs usual diet	Total mortality, invasive breast cancer, CV mortality
WHI with CVD 2006	Randomized controlled trial	2,277 post-menopausal women aged 50-79 with CVD at baseline	Reduced fat vs. usual diet	Breast cancer, total mortality, other cancers, cardiovascular events, diabetes, CV mortality, cancer deaths, cancer diagnoses, stroke, non-fatal MI
WHI without CVD 2006	Randomized controlled trial	58,835 post-menopausal women aged 50-79 with CVD at baseline	Reduced fat vs. usual diet	Breast cancer, total mortality, other cancers, cardiovascular events, diabetes, CV mortality, cancer deaths, cancer diagnoses, stroke, non-fatal MI
WINS 2006	Randomized controlled trial	2,437 women with localised re-sected breast cancer	Reduced fat intake vs. usual diet	Dietary fat intake, total cholesterol, weight and waist, total mortality, cancer diagnoses

Table 1.2. Summary of Clinical Trials for Smoking Cessation

Clinical Trials	Methods	Participants	Intervention	Outcomes
Lung Health Study Program	Randomized controlled trial	5,887 patients	Intensive smoking cessation program versus usual care	Total mortality, COPD, lung cancer, CV Death
MRFIT	Randomized controlled trial	12,866 men	In-depth multifactor intervention program aimed at lowering serum cholesterol, BP and smoking cessation	CV mortality, Fatal and nonfatal MI, stroke, revascularization and total mortality
OSLO Study	Randomized controlled trial	1232 high risk middle-aged Oslo men	diet and smoking cessation	Total mortality, CV Events, CV deaths

Table 1.3. Summary of Clinical Trials on Exercise

Clinical Trials	Methods	Participants	Intervention	Outcomes
LOOK Ahead	Randomized controlled trial	5,145 overweight or obese patients with type 2 diabetes to participate	Intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity	Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina (composite)
STENO2	Randomized controlled trial	160 diabetic patients with microalbuminuria	Stepwise implementation of exercise program	Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization, and amputation.
Chengdu trial	Randomized controlled trial	1232 high risk middle-aged Oslo men	diet and smoking cessation	Total mortality, CV Events, CV deaths
Fowler et al/2002	Randomized controlled trial	882 men with early peripheral arterial disease	A "stop smoking and keep walking" regime - a combined community-based intervention of cessation of smoking and increased physical activity.	Maximum walking distance, myocardial infarction, stroke

Table 2.1 Grade Pro Summary of Evidence on Reduction of Trans/Modified Fat

Bibliography: Cochrane Database Syst Rev. 2012 May 16;5:CD002137

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects** *(6 months duration)*	
							With Control	**With Reduced dietary fat**		**Risk with Control**	**Risk difference** (95% CI)
Major Acute Coronary Event(MACE) (CRITICAL OUTCOME; assessed with: reduction of fat vs control diet)											
65508 (31 studies) 8 years	no serious risk of bias	no serious inconsistency	Serious	no serious imprecision	Undetected	⨁⨁⨁⊖ **MODERATE** due to indirectness	2867/37402 (7.7%)	2020/28106 (7.2%)	**RR 0.86** (0.79 to 0.96)	**Study population**	
										77 per 1000	**11 fewer per 1000** (3 fewer to 16 fewer)
										Moderate	
Total mortality (CRITICAL OUTCOME; assessed with: reduction of dietary fat vs control diet)											
71790 (21 studies) 11 years	no serious risk of bias	no serious inconsistency	Serious[1]	no serious imprecision	Undetected	⨁⨁⨁⊖ **MODERATE**[1] due to indirectness	2404/40957 (5.9%)	1888/30833 (6.1%)	**RR 0.98** (0.93 to 1.04)	**Study population**	
										59 per 1000	**1 fewer per 1000** (4 fewer to 2 more)
										Moderate	

Cardiovascular mortality (CRITICAL OUTCOME; assessed with: reduced/modified fat vs usual diet)										
65978 (16 studies) 11 years	no serious risk of bias	no serious inconsistency	Serious[1]	no serious imprecision	Undetected	⨁⨁⨁⊖ **MODERATE**[1] due to indirectness	774/37840 (2%)	633/28138 (2.2%)	**RR 0.94** (0.84 to 1.04)	**Study population** **20 per 1000** / **1 fewer per 1000** (3 fewer to 1 more) **Moderate**
Fatal and Nonfatal MI (CRITICAL OUTCOME; assessed with: reduction of fat in diet)										
64891 (19 studies) 8 years	no serious risk of bias	no serious inconsistency	Serious[1]	no serious imprecision	Undetected	⨁⨁⨁⊖ **MODERATE**[1] due to indirectness	894/27611 (3.2%)	1174/37280 (3.1%)	**RR 0.90** (0.72 to 1.11)	**Study population** **32 per 1000** / **3 fewer per 1000** (from 9 fewer to 4 more) **Moderate** **-**
Stroke (CRITICAL OUTCOME; assessed with: reduction of dietary fat vs control)										
59853 (11 studies) 8 years	no serious risk of bias	no serious inconsistency	Serious[1]	no serious imprecision	Undetected	⨁⨁⨁⊖ **MODERATE**[1] due to indirectness	457/25063 (1.8%)	683/34790 (2%)	**RR 0.99** (0.89 to 1.11)	**Study population** **18 per 1000** / **0 fewer per 1000** (from 2 fewer to 2 more) **Moderate**

										-

[1] No Filipinos included in the study population

Table 2.2 GRADE PRO summary of evidence on the benefit of smoking cessation

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publica-tion bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticip effects**
							With Control	**With Smoking cessation**		Risk with Control
Total mortality (CRITICAL OUTCOME)										
18023 (3 studies) 7 years	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	Unde-tected	⨁⨁⨁⊖ **MODERATE**[1] due to indirectness	918/9030 (10.2%)	826/8993 (9.2%)	**RR 0.90** (0.82 to 0.99)	**Study p** **102 per 1000**
Cardiovascular deaths (CRITICAL OUTCOME)										
18023 (2 studies) 7 years	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	Unde tected	⨁⨁⨁⊖ **MODERATE**[1] due to indirectness	219/9030 (2.4%)	200/8993 (2.2%)	**RR 0.92** (0.76 to 1.11)	**Study p** **24 per 1000**
CV Events (CRITICAL OUTCOME										

18023 (3 studies) 7 years	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[1] due to indirectness	599/9030 (6.6%)	506/8993 (5.6%)	**RR 0.85** (0.76 to 0.95)	**Study p** **66 per 1000**

[1] No Filipinos included in the study.

Table 2.3. Grade PRO Summary of Evidence on the Benefit of Exercise

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated abso**
							With Control	**With Exercise**		**Risk with Control** / **Ris Ex** (95
All cause mortality (CRITICAL OUTCOME; assessed with: Moderate exercise vs usual care)										
	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected		624/3016 (20.7%)	594/3011 (19.7%)	**RR 0.95** (0.86 to 1.05)	**Study population** **207 per 1000** / **10 100**

6027 (2 studies) 9 years						⨁⨁⨁⨀ **MODERATE**[1,2] due to indirectness				(fro 10
CV Mortality (CRITICAL OUTCOME; assessed with: Moderate exercise versus usual care)										
5305 (2 studies) 9 years	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, indirectness	425/2655 (16%)	410/2650 (15.5%)	**RR 0.97** (0.85 to 1.09)	**Study population** **160 per 1000** **5 fe** (fro 14
Major Acute Coronary Event (CRITICAL OUTCOME; assessed with: Moderate exercise versus usual care)										
5305 (2 studies) 9 years	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1,2] due to indirectness	226/2655 (8.5%)	170/2650 (6.4%)	**RR 0.75** (0.62 to 0.91)	**Study population** **85 per 1000** **21** **100** (fro 32 **Moderate** -
Non-fatal MI (CRITICAL OUTCOME; assessed with: Moderate exercise versus usual advice)										
160 (1 study)	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, indirectness	17/80 (21.3%)	5/80 (6.3%)	**RR 0.29** (0.11 to 0.76)	**Study population** **212 per 1000** **151** **100** (fro 189

Stroke (CRITICAL OUTCOME; assessed with: Moderate exercise versus advice)										
5305 (2 studies) 9 years	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁⊖⊖ **LOW**[1,2] due to risk of bias, indirectness	100/2655 (3.8%)	88/2650 (3.3%)	**RR 0.88** (0.67 to 1.17)	**Study population** **38 per 1000** **5 fe** (fro 6 m
Revascularization (CRITICAL OUTCOME; assessed with: Exercise versus usual care)										
5312 (2 studies) 9 months	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[1] due to risk of bias	289/2659 (10.9%)	284/2653 (10.7%)	**RR 0.99** (0.84 to 1.15)	**Study population** **109 per 1000** **1 fe** (fro 16

Appendix 3. Clinical Studies and GRADE Pro Table for Primary Prevention

Table 1. Clinical Studies for Primary Prevention

Study/Year	Inclusion Criteria	Intervention	Age (mean)	Baseline Lipids (mean)	After treatment Lipids (mean)	Outcomes	Remarks
WOSCOPS 1995	6595 men, aged 45-64 years old, fasting LDL cholesterol level of at least 4 mmol/L during the second and third visits, with at least one value of ≥4.5 mmol/L and one value of ≤6.0 mmol/L; no serious ECG abnormalities according to Minnesota code 1 (pathologic Q waves), arrhythmia such as atrial fibrillation; and no history of myocardial infarction or other serious illness, although men with stable angina who had not been hospitalized within the previous 12 months	Intervention: 40 mg of pravastatin Control: placebo Follow-up: 5 years	55 y/o ± 5.5 All men	TC- 272 ± 22 LDL-C 192 ± 17 HDL-C 44 ± 10 TG – 162 ± 70	TC - □ 20% LDL-C □ 26% HDL-C □ 5% TG - □ 12%	non-fatal MI CHD death coronary revascularization any death	1% DM 78% smoker 15% HPN Mean BMI 26 kg/m^2
KAPS 1995	447 men, LDL-C > 4.25 mmol/L, total cholesterol < 8.0 mmol/L, body mass index < 32 kg/m2, and liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) not exceeding 1.5-fold the laboratory upper normal limit	Intervention: 40 mg of pravastatin Control: placebo Follow-up: 3 years	57 y/o (44-65) All men	TC – 258.7 (5.2-8.5) LDL-C 189.2 (2.3-6.7) HDL-C 46.3 (0.4-2.2) TG- 150.4 (0.5 – 5.9)	TC – 200.8 (22%) LDL-C 131.3 (31%) HDL-C 42.5 TG – 132.7	IMT of carotid and femoral arteries myocardial infarction cardiac death stroke coronary revascularization	3% DM 79% smoker 35% HPN 9% prior MI

AFCAPS/TexCAPS 1998	6605 participants, men aged 45-73 years old, postmenopausal women aged 55-73 years old, total cholesterol 4-65-6.82 mmol/L, LDL-C 3.36-4.91 mmol/L, HDL-C ≤ 1.16 mmol/L for men, HDL-C ≤ 1.22 mmol/L for women, triglyceride ≤ 4.52 mmol/L, TC/ HDL ratio >6 Intervention: 20-40 mg of lovastatin Control: placebo	Intervention: 20-40 mg of lovastatin Control: placebo Follow – up: 5 years	58 y/o Men 58 ± 7 Women 63 ± 5	TC – 220.5 LDL-C 150.2 HDL-C Male – 36.3 Female – 39.8 TG – 157.5	After 1 year TC – 184 (17%) LDL-C 115 (24%) TG – 143 HDL-C 39	fatal and non-fatal MI unstable angina sudden cardiac death cardiovascular mortality coronary heart disease mortality coronary revascularization cardiovascular events coronary events	85% male 2-3% DM 15% family history of premature CHD 22% HPN 12% smoker
ASCOT-LLT 2003	10, 305 participants, aged 40-79 years old, with either untreated HPN (SBP ≥160 mmHg or DBP ≥100 mmHg or both), or treated HPN (SBP ≥140 mmHg or DBP ≥90mmHg or both), total cholesterol of 6.5 mmol/L or lower, not currently taking statin or fibrate, at least 3 CV risk factors (LVH, other specified abnormalities on ECG, type 2 DM, PAD, previous stroke or TIA, male sex, 55 years or older, microalbuminuria or proteinuria, smoking, ratio	Intervention: 10 mg of atorvastatin Control: placebo Follow-up: 3.5 years	63 y/o > 60 (64%) ≤ 60 (36%)	TC – 212.3 LDL-C 131.3 HDL-C 50.2 TG- 150.4	After 3 years TC – 161.4 (24%) LDL-C 88 (34%) HDL-C 50.2 TG – 116.8	Primary: Non-fatal MI and fatal CHD	81% men 24% DM 33% smoker All HPN 14% LVH on ECG 5% PAD 10% previous CVA

	of TC/ HDL ≥6, premature family history of CHD						
PREVEND IT 2004	864 participants, aged 28-75 years old, persistent microalbuminuria (a urinary albumin concentration 10 mg/L in 1 early morning spot urine sample and a concentration of 15 to 300 mg/24 hours in 2 24-hour urine samples at least once), blood pressure 160/100 mm Hg and no use of antihypertensive medication, and a total cholesterol level 8.0 mmol/L, or 5.0 mmol/L in case of previous myocardial infarction, and no use of lipid-lowering medication.	Intervention: 40 mg of pravastatin Control: placebo Follow-up: 4 years	52.1 ± 11.9	TC – 223.9 (5.8 ± 1) LDL-C 158.3 (4 ± 1) HDL-C 38.6 (1 ± 0.4) TG- 123.9 (0.9-2)	After 4 years TC – 185.3 (17%) LDL-C 119.7 (24%)	cardiovascular mortality myocardial infarction and/ or myocardial ischemia heart failure peripheral vascular disease stroke	65% male 2-3% DM 2-4% prior CVD
MEGA 2006	7832 Japanese men and post-menopausal women (3966 control, 3866 intervention), aged 40-70 years old, total cholesterol concentration 5.69-6.98 mmol/L	Intervention: NCEP step I diet plus 20 mg of pravastatin Control: NCEP step I diet Follow-up: 5 years	58 y/o	TC – 242 LDL-C 156.4 HDL-C 57.5 TG – 127.4	After 9 years TC – 208.9 (14%) LDL-C 122.4 (23%) HDL-C 62.2 TG – 107	coronary heart disease fatal and non-fatal myocardial infarction angina stroke sudden cardiac death coronary revascularization	69% women 21% DM 42% HPN 20% smoker

JUPITER 2008	17,802 participants, LDL-C <3.4 mmol/L, hsCRP ≥ 2 mg/L, triglyceride <5.6 mmol/L	Intervention: 20 mg of rosuvastatin Control: placebo Follow-up: 1.9 years	66 y/o (60-71)	TC- 186 (168-200) LDL- C 108 (94-119) HDL-C 49 (40-60) TG- 118 (85-169)	After 4 years LDL-C 55 (49%) HDL-C 50 TG- 99	non-fatal MI non-fatal stroke hospitalization for unstable angina coronary revascularization cardiovascular mortality	38% female 16% smoker 12% family history of premature CHD Mean BMI 28 kg/m^2 41% MetS

Table 2. Grade PRO Summary of Evidence on Primary Prevention

Quality assessment							№ of patients		Effect		Quality	Impor
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total mortality												
4	randomised trials	not serious	not serious	serious [1]	not serious	none	544/21237 (2.6%)	673/21297 (3.2%)	**RR 0.81** (0.72 to 0.90)	6 fewer per 1000 (from 3 fewer to 9 fewer)	⊕⊕⊕◯ MODERATE	CRITIC
								3.4%		7 fewer per 1000 (from 3 fewer to 10 fewer)		
Cardiovascular death												

7	randomised trials	not serious	not serious	serious [1]	not serious	none	240/25198 (1.0%)	357/25252 (1.4%)	**OR 0.67** (0.57 to 0.79)	5 fewer per 1000 (from 3 fewer to 6 fewer)	⊕⊕⊕◯ MODERATE	CRITICA
								0.9%		3 fewer per 1000 (from 2 fewer to 4 fewer)		
Myocardial infarction												
7	randomised trials	not serious	not serious	serious [1]	not serious	none	367/25198 (1.5%)	598/25252 (2.4%)	**RR 0.61** (0.54 to 0.70)	9 fewer per 1000 (from 7 fewer to 11 fewer)	⊕⊕⊕◯ MODERATE	CRITICA
								2.9%		11 fewer per 1000 (from 9 fewer to 13 fewer)		
Stroke												
6	randomised trials	not serious	not serious	serious [1]	not serious	none	227/21894 (1.0%)	306/21951 (1.4%)	**RR 0.74** (0.63 to 0.88)	4 fewer per 1000 (from 2 fewer to 5 fewer)	⊕⊕⊕◯ MODERATE	CRITICA
								1.6%		4 fewer per 1000 (from 2 fewer to 6 fewer)		
Cardiovascular events												
4	randomised trials	not serious	serious [2]	serious [1]	not serious	none	1028/21239 (4.8%)	1411/21305 (6.6%)	**RR 0.73** (0.67 to 0.79)	18 fewer per 1000 (from 14 fewer to 22 fewer)	⊕⊕◯◯ LOW	CRITICA
								3.6%		10 fewer per 1000 (from 8 fewer to 12 fewer)		

Coronary revascularization													
6	randomised trials	not serious	not serious	serious [1]	not serious	none	660/24765 (2.7%)	925/24821 (3.7%)	**RR 0.71** (0.65 to 0.78)	11 fewer per 1000 (from 8 fewer to 13 fewer)	⊕⊕⊕◯ MODERATE	IMPORT
								2.3%		7 fewer per 1000 (from 5 fewer to 8 fewer)		

Appendix 4. Summary of Evidence in the use of Statins in Diabetes without ASCVD

Table 1.GRADE PRO Summary of Evidence in the use of Statin in Diabetes without ASCVD.

Quality assessment							**№ of patients**		**Effect**		**Quality**	**Im**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total Mortality												
1	randomised trials	not serious	not serious	serious[1]	not serious	none	61/1428 (4.3%)	82/1409 (5.8%)	**RR 0.73** (0.53 to 1.01)	16 fewer per 1000 (from 1 more to 27 fewer)	⊕⊕⊕◯ MODERATE	C
Fatal CHD/Cardiovascular death												
3	randomised trials	not serious	not serious	serious[2]	not serious	none	60/3645 (1.6%)	58/3629 (1.6%)	**RR 0.98** (0.68 to 1.41)	0 fewer per 1000 (from 5 fewer to 7 more)	⊕⊕⊕◯ MODERATE	C

Fatal and Non-fatal MI												
4	randomised trials	not serious	not serious	serious[3]	not serious	none	378/13914 (2.7%)	518/13896 (3.7%)	**RR 0.73** (0.64 to 0.83)	10 fewer per 1000 (from 6 fewer to 13 fewer)	⊕⊕⊕◯ MODERATE	C
CVD/Stroke												
4	randomised trials	not serious	not serious	serious[5]	not serious	none	224/13914 (1.6%)	298/13896 (2.1%)	**RR 0.75** (0.63 to 0.89)	5 fewer per 1000 (from 2 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	C
Acute Major CVD Events (composite)												
8	randomised trials	not serious	not serious	serious[5]	not serious	strong association	597/8083 (7.4%)	766/8012 (9.6%)	**RR 0.78** (0.7 to 0.86)	21 fewer per 1000 (from 13 fewer to 29 fewer)	⊕⊕⊕⊕ HIGH	C
Coronary revascularization (Interventional) Procedures												
3	randomised trials	not serious	not serious	serious[5]	not serious	none	328/12908 (2.5%)	390/12875 (3.0%)	**RR 0.84** (0.73 to 0.97)	5 fewer per 1000 (from 1 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	IM

RR – relative risk

1. No explanation was provided
2. All the studies are on DM but none were done locally or included Filipinos
3. All the studies except for HPS, were done on DM patients. However, NONE of these studies were done locally or included Filipinos
4. All the studies except for ASCOT were done on DM but none were done locally or included Filipinos
5. None of the studies included Filipinos or were done locally

Appendix 5. Summary of Evidence and GRADE Pro Table in the Use of Statins in Secondary Prevention

Table 1 Summary of Clinical Trials in the Use of Statins in Secondary Prevention.

Study Name	Method	Intervention group (N)	Intervention Intervention details	Comparison group (N)		Follow-up
Trials on individuals with ASCVD						
4S, 1994[55]	Randomized Controlled Trial	2,221	Medium-intensity statin	Simvastatin 20 mg	2,223	5.4 years
LIPID, 1998[56]	Randomized Controlled Trial	4,512	Low-intensity statin	Pravastatin 40 mg	4,502	6.1 years
GISSI, 2000[57]	Randomized Controlled Trial	2,138	Low-intensity statin	Pravastatin 20 mg	2,133	Mean 23 months
Amarenco et al, 2006 (SPARCL)[58]	Randomized Controlled Trial	2,365	High-intensity statin	Atorvastatin 80 mg	2,366	Median 4.9 years
Athyros et al, 2002 (GREACE)[59]	Randomized Controlled Trial	800	High-intensity statin	Atorvastatin 20 mg	800	Mean 3 years
Byington et al, 1995 (PLAC II)[60]	Randomized Controlled Trial	75	Low-intensity statin	Pravastatin 40 mg	76	3 years
Koren et al, 2004 (ALLIANCE)[61]	Randomized Controlled Trial	1,217	High-intensity statin	Atorvastatin 80 mg	1,225	Mean 51.5 months
Lemos et al, 2003 (LIPS)[62]	Randomized Controlled Trial	844	Medium-intensity statin	Fluvastatin 80 mg	833	3-4 years
Meade et al, 1999 (HPS)[63]	Randomized Controlled Trial	10,269	Medium-intensity statin	Simvastatin 40 mg	10,267	5 years
Pitt et al, 1995 (PLAC I)[64]	Randomized Controlled Trial	206	Low-intensity statin	Pravastatin 40 mg	202	3 years

Rieggeret al, 1999[65]	Randomized Controlled Trial	187	Low-intensity statin	Fluvastatin 40 mg	178	1 year
Sacks et al, 1996 (CARE)[66]	Randomized Controlled Trial	2,081	Low-intensity statin	Pravastatin 40 mg	2,078	5 years
Shepherd et al, 2002 (PROSPER)[67]	Randomized Controlled Trial	2,891	Low-intensity statin	Pravastatin 40 mg	2,913	Mean 3.2 years
Shukla et al, 2005[68]	Randomized Controlled Trial	75	Medium-intensity statin	Atorvastatin 10 mg	75	1 years
Sola et al, 2006[69]	Randomized Controlled Trial	54	High-intensity statin	Atorvastatin 20 mg	54	1 year
Teo et al, 2000 (SCAT)[70]	Randomized Controlled Trial	230	Low-intensity statin	Simvastatin 10 mg	230	3 - 5 years
Yamada et al, 2007[71]	Randomized Controlled Trial	19	Medium-intensity statin	Atorvastatin 10 mg	19	3 years
Yokoi et al, 2005[72]	Randomized Controlled Trial	186	Low-intensity statin	Pravastatin 20 mg	187	3 years
Trials on patients with diabetes mellitus						
4S, 1997[73] T1/T2, 60 years, MI or AP, Baseline TC 6.7 mmol/L, LDL-C 4.8 mmol/L	Randomized Controlled Trial	105	Medium-intensity statin	Simvastatin 20 mg	97	5.4 years
ASPEN, 2006[74] T2, 63 years, MI or IP, Baseline TC 4.9 mmol/L, LDL-C 2.9 mmol/L	Randomized Controlled Trial	252	Medium-intensity statin	Atorvastatin 10 mg	253	4.0 years
CARE, 1998[75] T1/T2, 61 years, MI, Baseline TC 5.3 mmol/L,	Randomized Controlled Trial	282	Low-intensity statin	Pravastatin 40 mg	304	5.0 years

LDL-C 3.6 mmol/L						
HPS, 2003[76] T1/T2	Randomized Controlled Trial	972	Medium-intensity statin	Simvastatin 40 mg	1009	5.0 years
LIPID, 2003[77] T1/T2, 64 years, MI or UAP, Baseline TC 5.6 mmol/L, LDL-C 3.7 mmol/L	Randomized Controlled Trial	542	Low-intensity statin	Pravastatin 40 mg	535	6.0 years

T1, Type 1 diabetes; T2, Type 2 diabetes; MI, myocardial infarction; AP, angina pectoris; IP, interventional procedure; UAP, unstable angina pectoris.

Table 2. GRADE PRO Summary of evidence on the use of statins for secondary prevention in individuals with ASCVD.

Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importan**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**statins**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total mortality												
15	randomized trials	not serious	not serious	serious [1]	not serious	none	2978/30085 (9.9%)	3436/30081 (11.4%)	**RR 0.87** (0.83 to 0.91)	15 fewer per 1000 (from 10 fewer to 19 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Fatal coronary heart disease or cardiovascular death												
14	randomized trials	not serious	not serious	serious [1]	not serious	none	1812/29980 (6.0%)	2287/29969 (7.6%)	**RR 0.79** (0.75 to 0.84)	16 fewer per 1000 (from 12	⊕⊕⊕◯ MODERATE	CRITICAL

										fewer to 19 fewer) [1]		
myocardial infarction												
13	randomized trials	not serious	serious [2]	serious [1]	not serious	none	1377/27009 (5.1%)	1960/27009 (7.3%)	**RR 0.70** (0.66 to 0.75)	22 fewer per 1000 (from 18 fewer to 25 fewer)	⊕⊕◯◯ LOW	CRITICAL
Stroke												
11	randomized trials	not serious	not serious	serious [1]	not serious	none	1060/26221 (4.0%)	1356/26205 (5.2%)	**RR 0.78** (0.72 to 0.84)	11 fewer per 1000 (from 8 fewer to 14 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

ASCVD, atherosclerotic cardiovascular disease; RR=relative risk.

[1]Caucasian population; Asians were not well-represented; different socio-economic population (first world vs third world)

[2]Heterogeneity I^2=57%

Table 3. GRADE Pro summary of evidence on the use of high-intensity (atorvastatin 80 or simvastatin 80 mg) vs medium-intensity (atorvastatin 10 mg or simvastatin 20 mg) statin therapy for secondary prevention in ASCVD

Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importan**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**high intensity statin**	**medium intensity statin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total mortality												
4	randomized trials	not serious	not serious	serious [1]	not serious	none	1678/17562 (9.6%)	1711/17543 (9.8%)	**RR 0.98** (0.92 to 1.04)	2 fewer per 1000 (from 4 more to 8 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Cardiovascular mortality												
4	randomized trials	not serious	not serious	serious [1]	not serious	none	972/17730 (5.5%)	1026/17720 (5.8%)	**RR 0.95** (0.87 to 1.03)	3 fewer per 1000 (from 2 more to 8 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Myocardial infarction												
4	randomized trials	not serious	not serious	serious [1]	not serious	none	1058/17730 (6.0%)	1247/17720 (7.0%)	**RR 0.85** (0.78 to 0.92)	11 fewer per 1000 (from 6 fewer to 15 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Stroke												
3	randomized trials	not serious	not serious	serious [1]	not serious	none	388/12735 (3.0%)	439/12714 (3.5%)	**RR 0.88** (0.77 to 1.01)	4 fewer per 1000 (from 0 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

ASCVD, atherosclerotic cardiovascular disease; RR=relative risk.

Appendix 6. Clinical Studies and GRADE Pro Table in the Use of Fibrates in Diabetic Individuals

Table 1. Summary Table of Prevention Trials Using Fibrates Among Individuals with Diabetes

Study/year	Population	Baseline lipid values Mean (SD) mg/dL	Intervention	Duration of follow up	Outcome Measures
INCLUDED					

SENDCAP (1998)	164 Type 2 diabetes patients, 35 to 65 years old without history of clinical CV disease Primary prevention study Fatal and Non-fatal MI 0.51 (0.10, 2.72)	TC 223.3 mg/dL LDL 141.3 mg/dL HDL 39.5 mg/dL TG 198.5 mg/dL	Bezafibrate 400 mg OD for 3 years	3 years	Change in the carotid intima-media thickness (IMT) measured by B-mode ultrasound, incidence of CHD
DAIS (2001)	418 diabetic patients, 40 to 65 years old with or without previous coronary intervention 100% DM; 48% with CVD (combined primary & secondary prevention)	TC 3301. mg/dL LDL 130.5 mg/dL HDL 39.0 mg/dL TG 229.5 mg/dL	Micronized fenofibrate 200 mg/day for 3 years	3.3 years	Mean segment diameter, mean lumen diameter, percentage stenosis
FIELD (2005)	9795 Type 2 diabetes patients, mean age of 62 years without history of CV disease 22% with history of CV disease (combined primary & secondary prevention)	TC 194 mg/dL LDL 118 mg/dL HDL 42.5 mg/dL TG 154 mg/dL	Fenofibrate 200 mg per day	5 years	CHD death, non-fatal MI
REVIEWED BUT EXCLUDED					
BIP (2000)	10% with history of diabetes (N=309) (subgroup analysis), mean age of 60 years Secondary Prevention study	TC 213.2 mg/dL LDL 147.5 mg/dL HDL 34.5 mg/dL TG 156.1 mg/dL	Bezafibrate 400 mg/day	6.2 years	MI (fatal and nonfatal), sudden death
VA-HIT (2002)	Men with average age of 64 years, 25% of subjects with DM (N= 769) with CV disease	TC 213.2 mg/dL LDL 147.5 mg/dL	Gemfibrozil 1,200 mg/day	5.1 years	Combined incidence of nonfatal MI &

	Secondary Prevention study	HDL 34.5 mg/dL TG 156.1 mg/dL			death from CAD
HHS (1987)	Men with an average age of 47 years, 3% with a history of DM (N=135), without CV disease Primary Prevention study	TC mg/dL LDL mg/dL HDL mg/dL TG mg/dL	Gemfibrozil 600 mg/day	5 years	MI (fatal and nonfatal), cardiac death

Table 2. GRADE Summary table for the Use of Fibrates for the Primary Prevention of Cardiovascular Events Among Diabetic Individuals.

Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importa**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	Indirectness	**Imprecision**	Other considerations	**Fibrates**	**Placebo**	**Relative (95% CI)**	Absolute **(95% CI)**		
Total mortality												
3	randomised trials	not serious	not serious	serious [1]	serious [2]	strong association	362/5183 (7.0%)	333/5194 (6.4%)	**RR 1.09** (0.94 to 1.26)	6 more per 1000 (from 4 fewer to 17 more)	⊕⊕⊕◯ MODERATE	CRITIC
Cardiac Mortality												
3	randomised trials	not serious	not serious	serious [1]	serious [2]	strong association	143/5183 (2.8%)	132/5194 (2.5%)	**RR 1.09** (0.86 to 1.37)	2 more per 1000 (from 4 fewer to 9 more)	⊕⊕⊕◯ MODERATE	CRITIC
Stroke												
1	randomised trials	not serious	not serious	serious [1]	not serious	none	158/4895 (3.2%)	175/4900 (3.6%)	**RR 1.1** (0.87 to 1.4)	4 more per 1000 (from 5 fewer to 14 more)	⊕⊕⊕◯ MODERATE	CRITIC

Major adverse CV events												
3	randomised trials	not serious	not serious	serious [1]	serious [2]	none	300/5183 (5.8%)	355/5194 (6.8%)	**RR 0.85** (0.73 -0.98)	10 fewer per 1000 (from 1 fewer to 18 fewer)	⊕⊕◯◯ LOW	CRITIC

MD – mean difference, RR – relative risk

1. None of the trials involved Asians specifically Filipinos
2. DAIS & SENDCAP are small studies

Appendix 7. Summary of Evidences and GRADE Pro in the Use of Ezetimibe in Secondary Prevention

Table 1. Summary of Evidence in the Use of Ezetimibe

STUDY	mean Baseline LDL-C between groups	Population	Other remarks
IMPROVE-IT	93.8 mg/dL vs 93.8 mg/dL *Simvastatin monotherapy vs Simvastatin-Ezetimibe	18,144	P: max LDL-C for participants on lipid-lowering tx = 100mg/dL (2.6mmol/L); those not receiving lipid-lowering therapy = 125mg/dL (3.2mmol/L)
NSTE-ACS	205±37 mg/dL vs. 20±46 mg/dL vs. 207±32 mg/dL	1,734	P: excluded those who received lipid-lowering therapies within 6 months

	*Rosuvastatin 10mg vs. Rosuvastatin 20mg vs. Ezetimibe 10mg + Rosuvastatin 10mg		
HIJ - PROPER	135.6±30.0 mg/dL vs. 134.8±29.3mg/dL *Pitavastatin monotherapy vs. Pitavastatin-Ezetimibe	125	P: LDL-C measured within 24H of hospitalization for the ACS event at least 100mg/dL (2.6mmol/L)

Table 2. GRADE PRO Evidence Table for the Use of Ezetimibe in Secondary Prevention

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statin**	**placebo or no statin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Major CV Events												
13	randomised trials	not serious	serious [a]	serious [b]	not serious	none	2526/18071 (14.0%)	3360/18279 (18.4%)	**RR 0.76** (0.73 to 0.80)	**44 fewer per 1,000** (from 50 fewer to 37 fewer)	⊕⊕◯◯ LOW	CRITICAL
All-cause death												

9	randomised trials	not serious	not serious	serious [c]	not serious	none	1005/14142 (7.1%)	1279/14291 (8.9%)	**RR 0.80** (0.74 to 0.86)	**18 fewer per 1,000** (from 23 fewer to 13 fewer)	⊕⊕⊕◯ MODERATE	

Cardiovascular death

6	randomised trials	not serious	not serious	serious [d]	not serious	none	440/9558 (4.6%)	572/9657 (5.9%)	**RR 0.78** (0.69 to 0.88)	**13 fewer per 1,000** (from 18 fewer to 7 fewer)	⊕⊕⊕◯ MODERATE	

CHD death and nonfatal myocardial infarction

7	randomised trials	not serious	not serious	serious [e]	not serious	none	75/4623 (1.6%)	138/4673 (3.0%)	**RR 0.55** (0.42 to 0.73)	**13 fewer per 1,000** (from 17 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	

Fatal and nonfatal stroke

6	randomised trials	not serious	serious [f]	serious [g]	not serious	none	44/4478 (1.0%)	74/4514 (1.6%)	**RR 0.60** (0.42 to 0.87)	**7 fewer per 1,000** (from 10 fewer to 2 fewer)	⊕⊕◯◯ LOW	

Coronary Revascularization

3	randomised trials	not serious	not serious	serious [h]	not serious	none	51/913 (5.6%)	94/940 (10.0%)	**RR 0.56** (0.41 to 0.77)	**44 fewer per 1,000** (from 59	⊕⊕⊕◯ MODERATE	

										fewer to 23 fewer)		

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Test for statistical heterogeneity is significant at P = 0.05

b. Of the 13 studies, 8 are post hoc and 1 subgroup analysis

c. Of the 9 studies, 8 are post hoc

d. 5 of the six studies are post hoc

e. 6 of the 7 studies are post hoc

f. There was significant (P = 0.06) and important (I2 = 76%) statistical heterogeneity.

g. 6 of the 7 studies are post hoc

h. All 3 studies are post hoc

Appendix 8. Summary of Evidence and GRADE PRO Table in the use of Statins in Chronic Kidney disease- not in dialysis

Table 1. Summary of Evidence

Study	Intervention	Control	Inclusion Criteria	Remarks on N	Setting	GFR(ml/min)	Crea	Albu-minuria	Follow-up	Outcomes
4S, 2007 post hoc	Simvastatin 20-40 mg n = 1143	Placebo n = 11	Hx of angina or AMI		Scandinavia	<60	----	---	65.5 mos	1. Major CV events 2. All-cause death
AFCAPS/TEXCAPS, 2009 post hoc	Lovastatin 20-40 mg	Placebo N=159	Dyslipidemic	eGFR <60 (1 excluded due to	US	15 - 60	----	---	64 mos	1. Major CV events

	n=145			eGFR <15)						2. CV death 3. CHD death & nonfatal MI 4. Coronary Revascularization
ALLIANCE, 2009 POST HOC	Atorvastatin 10-80 mg N=286	Usual Care N=293	With known CHD pts		UK	<60	----	-----	54.3 mos	1. Major CV events 2. All-cause death 3. CV death 4. CHD death & nonfatal MI 5. Fatal & nonfatal stroke 6. Coronary revascularization
ASUCA, 2017 (PRIMARY STUDY)	Atorvastatin + diet N=168	Nonstatin therapy N=166	No statin + proteinuria with eGFR ≥ 60 ml/min OR GFR < 60 ml min + DL C >150 w/o statins / LDL C ≥ 100 on nonstatin regimen	Excluded: egfr < 30	Japan	≥ 30	---	some	2 yrs	1. Major CV events 2. All-cause death 3. CV death 4. CHD death & nonfatal MI 5. . Fatal & nonfatal stroke
CARDS, 2009 post-hoc	Atorvastatin 10 mg N=482	Placebo N=488	DM + hpn/ smokers/microalb	eGFR ,60 (n=1 for eGFR <30)	UK	<60	-----	Some	48 mos	1. Major CV events 2. All-cause death

										3. CHD death & nonfatal MI 4. . Fatal & nonfatal stroke 5. Coronary revascularization
HPS , 2003 subgroup	Simvastatin 40 mg N=646	Placebo N=683	DM nephro-pathy with sCrea < 200	sCrea >200 umol/L were excluded	UK	----	F: >110 umol/L M: > 130 umol/L	-----	60 mos	1. Major CV events
JUPITER, 2010 post hoc	Rosuvastatin 20 mg N=1638	Placebo N=1629	No CVD hx, LDL <130, hsCRP > 2	eGFR ,60 (n=14 for eGFR < 30)	26 countries	<60	---	---	1.9 yrs median ff up	1. Major CV events 2. All-cause death 3. CHD death & nonfatal MI 4. . Fatal & nonfatal stroke
MEGA, 2009 post hoc	Pravastatin 10-20 ng N=1471	Diet N=1507	TC 5.69 to 6.98 mg/dL	SCr > 1.5 mg/dl excluded from original study, 16 excluded from sub-analysis due to eGFR <30)	Japan	<60	-----	----	5.3 yrs	1. Major CV events 2. All-cause death 3. CHD death & nonfatal MI 4. . Fatal & nonfatal stroke
LIPS, 2005 post hoc	Fluvastatin 20 mg N=150	Placebo N=160	CHD Post 1st successful PCI px with CKD		International	<55.9	---	---	4-5 yrs	1. Major CV events 2. All-cause death 3. CV death

PPP, 2004 post hoc pooled data	Pravastatin 40 mg N=8376	Placebo N=8448	CARE and LIPID: with ACS WOSCOPS: non CHD		International	30 – 89.9 ml/min	-----	---	5 yrs	1. Major CV events 2. All-cause death 3. CV death
PREVEND IT, 2000 post hoc	Pravastatin 40 mg N=433	Placebo N=431	Microalb pxs with or without CVD	- Excluded if creatinine clearance < 60 - CKD defined by proteinuria	Netherlands	>60 ml/min	----	Microalb 15-300 mg in 24 hrs	46 mos	1. Major CV Events 2. All-cause death 3. CV death 4. CHD death & nonfatal MI 5. . Fatal & nonfatal stroke
Sawara, 2008 (Primary study)	Rosuvastatin 2.5 mg N=11	No lipid lowering drug N=16	CKD px		Japan	> 15 to < 90 ml/min	----	---	12 mos	1. Major CV Events
SHARP, 2010 (Primary study)	Simvastatin + Ezetimibe N=1533	Placebo N=1490	CKD px		international	----	Men: ≥ 150 umol/L Females: ≥130 umol/L	--	4.9 yrs	1. Major CV Events
PANDA, 2011 (post hoc)	Atorvastatin 80 mg n-60	Atorvastatin 10 mg N=59	T2dm with albuminuria	Excluded: sCrea > 200 umol/L and urinary protein > 2g/day	UK	I: 54-85 C: 44-76	ACR > 5 mg/mmol	Y	36 mos	1. Major CV events
TNT, 2005 (post-hoc)	Atorvastatin 80 mg N=1602	Atorvastatin 10 mg N=1505	Clinically evident CHD		International	<60	---	---	4.9 yrs	1. Major CV events

IMPROVE-IT (Post-hoc)	Simvastatin 40 mg + Ezetimibe N=6694	Simvastatin 40 mg + Placebo N=6639	CVD px		International	> 30 – 89 ml/min	---	---	7 yrs	1. Major coronary event
Suzuki, 2013 (Primary study)	Statin (any statin) + Ezetimibe N=145	Statin uptitration (any statin) N=141	LDL > 120 + albuminuria/GFR < 60; dialysis px excluded wi		Japan	<60 ml/min, nondialytic	---	some	12 mos	Major coronary event

Table 2. GRADE PRO Table of Evidence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statin	placebo or no statin	Relative (95% CI)	Absolute (95% CI)		
Major CV Events												

13	randomised trials	not serious	serious [a]	serious [b]	not serious	none	2526/18071 (14.0%)	3360/18279 (18.4%)	**RR 0.76** (0.73 to 0.80)	**44 fewer per 1,000** (from 50 fewer to 37 fewer)	⊕⊕◯◯ LOW	CRITICAL

All-cause death

9	randomised trials	not serious	not serious	serious [c]	not serious	none	1005/14142 (7.1%)	1279/14291 (8.9%)	**RR 0.80** (0.74 to 0.86)	**18 fewer per 1,000** (from 23 fewer to 13 fewer)	⊕⊕⊕◯ MODERATE	

Cardiovascular death

6	randomised trials	not serious	not serious	serious [d]	not serious	none	440/9558 (4.6%)	572/9657 (5.9%)	**RR 0.78** (0.69 to 0.88)	**13 fewer per 1,000** (from 18 fewer to 7 fewer)	⊕⊕⊕◯ MODERATE	

CHD death and nonfatal myocardial infarction

7	randomised trials	not serious	not serious	serious [e]	not serious	none	75/4623 (1.6%)	138/4673 (3.0%)	**RR 0.55** (0.42 to 0.73)	**13 fewer per 1,000** (from 17 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	

Fatal and nonfatal stroke

6	randomised trials	not serious	serious [f]	serious [g]	not serious	none	44/4478 (1.0%)	74/4514 (1.6%)	**RR 0.60** (0.42 to 0.87)	**7 fewer per 1,000** (from 10 fewer to 2 fewer)	⊕⊕◯◯ LOW	

Coronary Revascularization

3	randomised trials	not serious	not serious	serious [h]	not serious	none	51/913 (5.6%)	94/940 (10.0%)	**RR 0.56** (0.41 to 0.77)	**44 fewer per 1,000** (from 59 fewer to 23 fewer)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Test for statistical heterogeneity is significant at P = 0.05

b. Of the 13 studies, 8 are post hoc and 1 subgroup analysis

c. Of the 9 studies, 8 are post hoc

d. 5 of the six studies are post hoc

e. 6 of the 7 studies are post hoc

f. There was significant (P = 0.06) and important (I2 = 76%) statistical heterogeneity.

g. 6 of the 7 studies are post hoc

h. All 3 studies are post hoc

Appendix 9. Evidence Table for Omega 3 Fatty Acid

Table 1. Summary of Evidences

Outcome/Number of Participants	Relative Effect (95% CI)	Anticipate absolute Effects (95% CI)	Certainty

MI of at least 1 event 31,590 (4 trials)	OR 0.71 (062 – 0.82)	3.2%	2.3% (2 to 2.6%)	0.9 fewer (1.2 fewer to 0.6 fewer)	HIGH
CHD Death 23411 (4 RCTs)	OR 0.85 (0.56 to 1.28)	0.4%	0.4% (0.2 to 0.5%)	0.1% fewer (0.2 fewer to 0.1 more)	HIGH
CVD Death 12945 (3 RCTs)	OR 0.81 (0.67 to 0.99)	3.7%	3.0% (2.5 to 3.7)	0.7% 91.2 fewer to 0 fewer)	HIGH
Stroke 31590 (4 RCTs)	OR 0.91 (0.78 to 1.07)	2.2%	2.0% (1.7 to 2.3)	0.2% fewer (0.5 fewer to 0.1 fewer)	HIGH
All cause mortality 26824 (3 RCTs)	OR 0.97 (0.86 to 1.10)	4.3%	4.2% (3.7 to 4.7)	0.1% fewer (0.6 fewer to 0.4 more)	MODERATE
Total CVD 31590 (4 RCTs)	OR 0.79 (0.72 to 0.86)	7.3%	5.9% (5.4 to 6.4)	1.4% fewer (1.9 fewer to 1 fewer)	HIGH

Table 2. Grade PRO Evidence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EPA DHA	placebo/control	Relative (95% CI)	Absolute (95% CI)		
MI2												
2	randomised trials	serious [a]	not serious	serious [b]	not serious	none	321/13415 (2.4%)	448/13409 (3.3%)	**OR 0.70** (0.61 to 0.81)	**10 fewer per 1,000** (from 13 fewer to 6 fewer)	⨁⨁◯◯ LOW	CRITICAL
all death												
2	randomised trials	serious [c]	not serious [d]	serious [e]	not serious [b]	none	560/13415 (4.2%)	575/13409 (4.3%)	**OR 0.97** (0.86 to 1.10)	**1 fewer per 1,000** (from 6 fewer to 4 more)	⨁⨁◯◯ LOW	CRITICAL
chd death												

1	randomised trials	not serious	not serious	not serious	not serious	none	29/9326 (0.3%)	31/9319 (0.3%)	**OR 0.93** (0.56 to 1.55)	**0 fewer per 1,000** (from 1 fewer to 2 more)	⨁⨁⨁⨁ HIGH	CRITICAL

chd2

2	randomised trials	serious [c,f]	not serious	serious [b]	not serious	none	480/13415 (3.6%)	620/13409 (4.6%)	**OR 0.75** (0.67 to 0.86)	**11 fewer per 1,000** (from 15 fewer to 6 fewer)	⨁⨁◯◯ LOW	CRITICAL

cvd death2

1	randomised trials	not serious	not serious	not serious	not serious	none	174/4089 (4.3%)	213/4090 (5.2%)	**OR 0.81** (0.66 to 0.99)	**9 fewer per 1,000** (from 17 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

stroke2

2	randomised trials	serious [c]	serious [d]	serious [b]	not serious	none	264/13415 (2.0%)	296/13409 (2.2%)	**OR 0.89** (0.75 to 1.05)	**2 fewer per 1,000** (from 5 fewer to 1 more)	⨁◯◯◯ VERY LOW	CRITICAL

total cvd2

2	randomised trials	serious [c]	not serious	serious [b]	not serious	none	721/13415 (5.4%)	929/13409 (6.9%)	**OR 0.76** (0.68 to 0.84)	**16 fewer per 1,000** (from 21 fewer to 10 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

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