

Dyslipidemia management in primary prevention of cardiovascular disease: Current guidelines and strategies

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Author contributions: Hendrani AD and Martin SS drafted this paper and all authors made critical revisions to develop the final manuscript.

Conflict-of-interest statement: No potential conflicts of interest, no financial support.

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Received: June 28, 2015
Peer-review started: July 11, 2015
First decision: September 17, 2015
Revised: November 22, 2015
Accepted: December 4, 2015
Article in press: December 8, 2015

Published online: February 26, 2016

Abstract

Cardiovascular disease is the leading cause of death in the United States. In 2010, the Centers for Disease Control and Prevention estimated that \$444 billion was spent on cardiovascular diseases alone, about \$1 of every \$6 spent on health care. As life expectancy continues to increase, this annual cost will also increase, making cost-effective primary prevention of cardiovascular disease highly desirable. Because of its role in development of atherosclerosis and clinical events, dyslipidemia management is a high priority in cardiovascular prevention. Multiple major dyslipidemia guidelines have been published around the world recently, four of them by independent organizations in the United States alone. They share the goal of providing clinical guidance on optimal dyslipidemia management, but guidelines differ in their emphasis on pharmacotherapy, stratification of groups, emphasis on lifestyle modification, and use of a fixed target or percentage reduction in low density lipoprotein cholesterol. This review summarizes eight major guidelines for dyslipidemia management and considers the basis for their recommendations. Our primary aim is to enhance understanding of dyslipidemia management guidelines in patient care for primary prevention of future cardiovascular risk.

Key words: Dyslipidemia; Guidelines; Cardiovascular diseases

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Core tip: Guidelines for dyslipidemia management have been developed by independent organizations internationally for the purpose of improving patient care and reducing costs related to cardiovascular disease. In

this review article, we briefly summarize the key strategies suggested by each of eight major dyslipidemia guidelines, and the evidence that forms the foundation of the recommendations. We attempt to present a balanced view, commenting on potential strengths and weaknesses of each approach. Overall, we aim to enhance understanding of dyslipidemia management guidelines for primary prevention of future cardiovascular events.

Hendrani AD, Adesiyun T, Quispe R, Jones SR, Stone NJ, Blumenthal RS, Martin SS. Dyslipidemia management in primary prevention of cardiovascular disease: Current guidelines and strategies. *World J Cardiol* 2016; 8(2): 201-210 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v8/i2/201.htm> DOI: <http://dx.doi.org/10.4330/wjc.v8.i2.201>

CLINICAL CASE

A 59-year-old African American man with a history of chronic kidney disease, type 2 diabetes mellitus, and long-standing hypertension presents for a follow-up visit. His blood pressure is 135/80 mmHg, and hemoglobin A1c (HbA1c) is 7.2%. He denies any chest pain or shortness of breath and has no exercise intolerance. His recent fasting lipid panel shows: Total cholesterol 159 mg/dL, triglycerides 190 mg/dL, high density lipoprotein cholesterol (HDL-C) 45 mg/dL, and low density lipoprotein cholesterol (LDL-C) 76 mg/dL. He is currently on atorvastatin 10 mg daily, carvedilol 25 mg twice a day, lisinopril 40 mg daily, and aspirin 81 mg daily. Should he receive a higher dose of atorvastatin?

INTRODUCTION

Cardiovascular disease (CVD) has been recognized as the number one killer in the United States and in the world for decades. Even though there was a 31% decline in CVD deaths from 2001 to 2011 in the United States, CVD still accounted for 1 of every 3 deaths in 2011^[1]. With the decline of cigarette smoking, dyslipidemia has become the number one modifiable risk factor for vascular disease. In the INTERHEART case-control study with 27098 participants in 52 countries, dyslipidemia [elevated apolipoprotein (Apo) ApoB/ApoA1) had the highest mortality odds ratio (3.25), followed by smoking (2.87), psychosocial factors (2.67), and history of diabetes (2.37), and hypertension (1.91)^[2]. In a prospective study of 27673 women, in addition to Apos, CVD risk was also strongly related to nuclear magnetic resonance measures of dyslipidemia and standard lipids (TC/HDL-C)^[3].

Multiple lines of evidence have shown the central role of dyslipidemia in development of atherosclerosis and major CVD events. Traditional management of dyslipidemia includes lifestyle modification and pharmacotherapy based on identification of groups considered at high, medium, or low risk of major cardiovascular events. Guidelines for dyslipidemia management have been developed by

independent organizations internationally for the purpose of improving patient care and reducing costs related to cardiovascular disease. However, many busy clinicians may have difficulty finding the time to read them. Moreover, the existence of multiple different guideline recommendations from different societies can present an added challenge.

In this review article, we briefly summarize the key strategies suggested by each of eight major dyslipidemia guidelines, and the evidence that forms the foundation of the recommendations. We attempt to present a balanced view, commenting on potential strengths and weaknesses of each approach. Overall, we aim to enhance understanding of dyslipidemia management guidelines for primary prevention of future cardiovascular events.

GUIDELINES

American College of Cardiology/American Heart Association 2013

The American College of Cardiology/American Heart Association (ACC/AHA) 2013 guideline recognizes four "statin benefit groups" in whom the risk reduction benefits clearly outweigh the risk of adverse events^[4] (Table 1). Follow-up monitoring includes assessment for the anticipated LDL-C reduction (30%-49% and $\geq 50%$ with moderate- and high-intensity statin therapy, respectively) from baseline after starting the maximal tolerable dose of statin therapy. When such a percentage reduction is not seen, adherence to lifestyle modification and medication should be reinforced, along with evaluation for a secondary cause of dyslipidemia. Non-statin therapy can be considered in high-risk groups if the response to statin therapy is not acceptable. The ACC/AHA guidelines removed fixed target LDL-C levels, although when the baseline LDL-C is not known, the guideline notes that "an LDL-C < 100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs".

The new Pooled Cohort Equations (PCE) are used to calculate 10-year risk of atherosclerotic cardiovascular disease (ASCVD) in this guideline. In contrast to the Framingham Risk Score (FRS) used in adult treatment panel III (ATP III), the PCE use separate equations based on sex and race. Stroke is now included with coronary events in an ASCVD endpoint, whereas the ATP III FRS only predicted coronary events. Along with the ASCVD endpoint, a new cut-point of 7.5% is featured to guide statin decision making. The use of this cut-point is not intended to lead to automatic prescription of a statin, but instead, to serve as the starting point for a clinician-patient risk/benefit discussion and consideration of statin therapy as one management option^[5].

The 7.5% cut-point is derived from three exclusively primary prevention clinical trials: Air Force Coronary Atherosclerosis Prevention Study, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese, and Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trials. It is felt that this new cut-point

Table 1 Fixed-dose strategies

Strategy	ACC/AHA 2013	NICE 2014	VA/DoD 2014
Risk score	PCE to determine 10-yr risk of non-fatal and fatal hard ASCVD events (CHD and CVA)	QRISK2 to determine 10-yr risk of non-fatal and fatal CVD events (CHD, CVA, PAD)	FRS or PCE to determine 10-yr risk of non-fatal and fatal CVD events
Step 1: Identify statin-benefit group	Statin benefit groups: (moderate to high-intensity statin) History of ASCVD; LDL-C \geq 190, age \geq 21; DM at age 40-75 with LDL-C \geq 70; \geq 7.5% of ASCVD risk at age 40-75 with LDL-C; \geq 70 (in some individuals, not all; discussion required) Consider moderate intensity statin as initial dose for: DM with \leq 7.5% ASCVD risk; \geq 7.5% of ASCVD risk without DM Inadequate data to make recommendation (weigh risk, benefit and patient preference) DM at age $<$ 40 or $>$ 75 with LDL-C $>$ 70; Age $<$ 40 or $>$ 75 with LDL-C $>$ 70; 5%-7.4% of ASCVD risk at age 40-75 with LDL-C $>$ 70; $<$ 5% of ASCVD risk at age 40-75 with LDL-C $>$ 70; Age $<$ 40 with low 10 yr ASCVD risk but high lifetime risk based on 1 strong or multiple risk factors; Those with serious co-morbidities and increased ASCVD risk (e.g., HIV, rheumatologic or inflammatory diseases, or solid organ transplantation) Other factors for consideration: family history of premature CVD, hsCRP \geq 2, elevated CAC, ABI $<$ 0.9, LDL-C \geq 160	Statin benefit groups: (initial dose: Atorvastatin 20 mg/d) Type 1 DM; CKD st. III; Risk score $>$ 10%; Age $>$ 85; Familial hypercholesterolemia Elevated risk groups that are underestimated by or not included in QRISK2: Possible benefit with statin HIV; Serious mental problem; On medication that cause dyslipidemia (antipsychotic, corticosteroid, immunosuppressant); Autoimmune disorder and systemic inflammatory disorder; TG $>$ 175; On anti-hypertension or lipid modification therapy; Recently stopped smoking	Statin benefit group: (initial dose: Atorvastatin 10-20 mg/d) Risk score $>$ 12% Moderate dose statin initiation can be considered in patient with 6%-12% risk score after discussion of benefit, risk, and patients' preference
Step 2: Determine adequacy of treatment effect	For group treated with high intensity statin: $>$ 50% \downarrow of LDL-C For group treated with moderate intensity statin: 30%-50% \downarrow of LDL-C If patients are already on statin and baseline LDL-C is unknown, an LDL-C $<$ 100 was observed in most individuals receiving high-intensity statin therapy in RCTs	$>$ 40% \downarrow of non-HDL-C	No objective parameters recommended
Step 3: Follow-up lipids	1-3 mo after initiation therapy Every 3-12 mo as clinically indicated thereafter	3 mo after initiation of therapy Annually when target achieved	Not recommended Lipid measurement can be utilized for compliance monitoring
Step 4: Options if treatment effect judged not adequate	Reinforce lifestyle change and adherence to medication Exclude secondary cause of dyslipidemia Add non-statin agent in those with LDL-C \geq 190 or DM at age 40-75 with LDL-C \geq 70	Discuss adherence to lifestyle and medication Up-titrate statin dose; may go up to a atorvastatin 80 mg/d	No recommendation

ACC/AHA: American College of Cardiology/American Heart Association; NICE: National Institute for Health and Care Excellence; PCE: Pooled Cohort Equations; ASCVD: Atherosclerotic cardiovascular disease; CHD: Coronary heart disease; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; PAD: Peripheral artery disease; FRS: Framingham Risk Score; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; DM: Diabetes mellitus; CKD: Chronic kidney disease; HIV: Human immunodeficiency virus; TG: Triglyceride; hsCRP: High sensitivity C-reactive protein; ABI: Ankle-brachial index; RCT: Randomized controlled trials.

builds in some room for potential overestimation of risk^[6]. A recent study showed that these new guidelines significantly increase the number of potentially eligible adults for statin therapy (12.8 million people), especially in older age groups^[7].

A 2013 Cochrane review on use of statins in primary prevention of ASCVD reported that, for patients with estimated 5% to 10% 5-year ASCVD risk, 15 major vascular events would be avoided per 1000 people treated for five years, which correlates with a number needed to treat (NNT) of 67^[8]. In comparison, a study based on 5 trials with a total of 18564 participants (mean age 46 years)^[9] showed an estimated 5-year NNT of 120 for CVD events when treating patients with mild hypertension (BP 140-160/90-100 mmHg) with anti-

hypertensive medications for primary prevention.

The ACC/AHA guidelines rely on the highest quality randomized control trials (RCTs) and meta-analyses to date to form the foundation of evidence-based guidelines. The fixed-dose strategy promotes the appropriate use of high-intensity statin therapy and avoids overutilization of non-statin drugs, for which evidence is weaker and net benefit is less clear than evidence for statins. Under the "traditional" fixed target level strategy of combining statin and non-statin medications, a patient might receive a lower statin dose because of potential drug interaction with a second agent^[10]. However, on-treatment lipid levels can still be used to motivate additional lifestyle change when statin therapy has been appropriately maximized, and can guide the selective addition of non-

statin therapy. Observational studies have consistently shown a log-linear association of LDL-C level and CVD morbidity^[11].

European Society of Cardiology/European Atherosclerosis Society 2011

The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) 2011 guideline uses a target level strategy^[12] combined with risk stratification based on estimated 10-year risk of a fatal CVD event by the Systemic Coronary Risk Evaluation (SCORE)^[13]. After stratification, ESC/EAS advises group-specific intervention. The initial statin dose is determined by calculating the percentage reduction needed to achieve the target level, and then choosing the intensity of statin accordingly. ApoB and non-high-density lipoprotein cholesterol (non-HDL-C) are alternatives to LDL-C as targets. Up-titration of the statin dose or addition of a non-statin agent may be considered if the target is not attained with the initial statin regimen.

SCORE is based on large European cohorts and can be calibrated to each European country. The rationale for focusing on fatal CVD events is that variation in the definition of non-fatal events makes that parameter less reliable. A 5% risk of fatal CVD events is approximately equal to 15% risk of total (fatal and non-fatal) CVD events^[13]. Recognizing that risk must be interpreted in light of clinical judgment and the pretest probability of CVD, the guideline lists some conditions that are often associated with risk score underestimation, such as elevated high sensitivity C-reactive protein (hsCRP), elevated homocysteine, low HDL-C, family history of premature coronary artery disease, and asymptomatic atherosclerotic disease. High HDL-C and family history of longevity are associated with overestimation of risk.

Overall, the guideline uses an individualized strategy for management, accounting for specific conditions, such as heart failure, diabetes, autoimmune diseases, metabolic syndrome, and HIV. An extensive section of the guideline focuses on management of hypertriglyceridemia and low HDL-C, although the panelists acknowledge that the evidence for these variables impacting future CVD incidence is still weak.

Canadian Cardiovascular Society 2009 Guideline and 2012 Updates

The Canadian Cardiovascular Society (CCS) guideline adopts the traditional approach of risk stratification and group-specific target treatment using LDL-C^[14] (Table 2). Patients are stratified into low, intermediate, or high risk categories using comorbidities in addition to a modified FRS, which includes an additional rule of multiplying the calculated risk by 2 if there is a family history of premature coronary heart disease (CHD)^[15]. The LDL-C level and percentage reduction in LDL-C are the recommended primary targets.

The high-risk and low-risk groups receive interventions according to their respective risk. The intermediate risk group is further refined using LDL-C and, if indicated,

ApoB and/or non-HDL-C to identify candidates for more aggressive intervention. Secondary tests, such as a coronary calcium scan and high-sensitivity C-reactive protein (hsCRP), are optional secondary tests to refine risk assessment in the low- and intermediate-risk groups.

When communicating risk to a patient, a unique aspect of this guideline is the suggestion to use "cardiovascular age" as an easier-to-understand explanation of a patient's ASCVD risk, with the potential to improve awareness and adherence. Cardiovascular age is calculated by age minus the difference between estimated life expectancy and average life expectancy, based on age and sex.

International Atherosclerosis Society 2013

International Atherosclerosis Society (IAS) 2013 makes evidence-based recommendations based on numerous studies from the 1970s to 2013^[16] (Table 2). The risk estimator used is the Lifetime Framingham risk score^[17], which may help call attention to risk in young people and motivate them to improve their lifestyle habits. This score can be recalibrated by nationality.

For those in high and moderately-high risk groups, it is suggested to aim for "optimal" lipid levels (LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL). "Near optimal" levels (LDL-C < 130 mg/dL or non-HDL-C < 160 mg/dL) are considered acceptable for the lower risk group. Statins are the first-line drug when pharmacotherapy is indicated. The initial dose is tailored according to the group-specific lipid target.

National Lipid Association 2014

The National Lipid Association (NLA) guideline uses a multilevel stratification approach to identify patients with a higher CVD risk factor who require more intensive management^[18] (Table 2). First, "very-high" and "high risk" groups are identified based on specified parameters. The remaining patients are then further risk-stratified based on the number of major ASCVD risk factors. People with two major risk factors are deemed to be intermediate risk, but the presence of any secondary risk indicator or a high-risk score places them in the higher risk group. Similar to other guidelines, the goal of treatment in this guideline is group-specific. Non-HDL-C is favored over LDL-C as the therapeutic target, but both are viewed as reasonable.

The NLA guideline is thorough in categorizing groups for whom aggressive intervention is either necessary or optional. The guideline emphasizes the potential for risk score estimation to overestimate or underestimate the risk in certain settings. A general LDL-C goal of < 100 mg/dL or non-HDL-C goal of < 130 mg/dL is recommended for low to high risk groups. LDL-C targets are used to motivate lifestyle change in addition to drug therapy.

National Institute for Health and Care Excellence 2014

The National Institute for Health and Care Excellence (NICE) guideline uses a fixed dose approach similar to ACC/AHA. All people aged \geq 40 years are screened formally with the QRISK2 score^[19] (Table 1). This

Table 2 Target-level strategies

Strategy	EAS/ESC 2011	CCS 2012	IAS 2013	NLA 2014	AACE 2012
Risk score	SCORE chart to estimate 10-yr risk of fatal CVD	Modified FRS to estimate 10-yr risk of non-fatal and fatal CVD	Lifetime FRS to estimate lifetime risk of non-fatal and fatal CVD	PCE or FRS or lifetime FRS	FRS to determine 10-yr risk of non-fatal and fatal CVD
Step 1: Stratify CVD risk	Very-high: $\geq 10\%$ of fatal CVD risk; CHD equivalent risk; DM with microalbuminuria; CKD st. III High: 5%-9% of fatal CVD risk; DM; 1 markedly abnormal risk factor Moderate: 1%-4% of fatal CVD risk Low: $< 1\%$ of fatal CVD risk	High: $\geq 20\%$ risk of CVD; CHD risk equivalent; DM, age > 40 or > 30 with 15 yr DM history; CKD st. III b or III a with microalbuminuria; HTN with ≥ 3 CVD risk factors Intermediate: 10%-19% risk of CVD Low: $< 10\%$ risk of CVD (CVD risk factor: age > 55 , smoker, TC/HDL-C > 6 , LVH, abnormal ECG, microalbuminuria)	High: $\geq 45\%$ lifetime risk of CVD; DM with major risk factor; Familial hyperlipidemia; CKD Moderately-high: 30%-44% lifetime risk of CVD; DM alone; Metabolic syndrome; CKD Moderate: 15%-29% lifetime risk of CVD Low: $< 15\%$ lifetime risk of CVD [Major risk factor: high LDL-C, HDL-C < 40 , HTN, smoker, family history of premature CAD, age (men > 55 , women > 65)]	Very-high: CHD risk equivalent; DM with ≥ 2 major risk factors or evidence of end organ damage High: DM with 0-1 major risk factor; CKD st. III b; LDL-C ≥ 190 ; ≥ 3 major risk factors; ≥ 1 secondary risk (marked major CVD risk, LDL-C > 160 or non-HDL-C > 190 , CAC > 300 , hsCRP > 2 , Lp(a) > 50 , microalbuminuria); High risk score (PCE $> 15\%$, FRS $> 10\%$, lifetime FRS $> 45\%$) Intermediate: 2 major risk factors Low: 0-1 risk factor	Very-high: CHD risk equivalent + ≥ 1 major risk factor High: CAD risk equivalent; ≥ 2 major risk factor + $\geq 20\%$ risk of CVD Moderately-high: ≥ 2 major risk factor + 10%-19% risk of CVD Moderate: ≥ 2 major risk factor + $< 10\%$ risk of CVD Low: ≥ 1 major risk factor
Step 2: Determine target	Very-high: LDL-C < 70 ; Alt: ApoB < 80 , non-HDL-C < 100 ; High: LDL-C < 100 ; Alt: ApoB < 80 , non-HDL-C < 130 Moderate-Low: LDL-C $< 100-115$	High: LDL-C < 77 or $\geq 50\%$ \downarrow ; Alt: ApoB < 80 , Non-HDL-C < 100 Intermediate: LDL-C < 77 or $\geq 50\%$ \downarrow Alt: ApoB < 80 , Non-HDL-C < 100 Low: $\geq 50\%$ \downarrow of LDL-C	High to moderately-high: LDL-C < 100 or non-HDL-C < 130 (goal may be lower for very-high risk) Moderate to low: LDL-C < 130 or non-HDL-C < 160	Very-high: LDL-C < 70 , non-HDL-C < 100 Alt: ApoB < 80 High-Moderate-Low: LDL-C < 100 , non-HDL-C < 130	Very-high: LDL-C < 70 , ApoB < 80 High: LDL-C < 100 , ApoB < 90 Moderately-high: LDL-C < 130 Moderate: LDL-C < 130 ; Low: LDL-C < 160 ; All category: HDL-C > 40 , TG < 150
Step 3: Treat according to risk	Very-high or High: Lifestyle intervention + drug intervention Moderate: Lifestyle intervention; consider drug if uncontrolled with lifestyle Low: Life style intervention only	High: Statin and lifestyle change Intermediate: LDL-C > 135 : Statin if lifestyle change insufficient; LDL-C < 135 : Get ApoB or non-HDL-C: # Apo B > 120 or Non-HDL-C > 165 : Start statin if lifestyle change insufficient # Apo B < 120 or Non-HDL-C < 165 : Lifestyle change Optional use of secondary test for further stratification Low: LDL-C > 190 : Lifestyle change and statin; 5%-9% risk of CVD: Lifestyle change only optional use of secondary test for further stratification; $< 5\%$ risk of CVD: Lifestyle change only	High: Statin and lifestyle change Moderately-high: Lifestyle change; Initiation of statin may be considered Moderate: Lifestyle change; initiation of statin may be considered if LDL-C > 160 Low: Lifestyle change only	Very-high: Statin and lifestyle change; statin optional if baseline LDL-C, non-HDL-C and ApoB below target High: Concurrent statin and lifestyle change or statin after insufficient lifestyle change Moderate: Lifestyle change only; statin may be considered after 3 mo of optimal lifestyle change and LDL-C > 130 Low: Lifestyle change only; statin may be considered after 3 mo of optimal lifestyle change and LDL-C > 160	Exclude secondary cause of hyperlipidemia; Lifestyle change; Lipid lowering agent; Combination lipid lowering agent
Step 4: Follow-up lipids	1-12 wk after initiation; 1-3 mo after every change of dose or change of medication; Annually when target is achieved			Every 3 mo until target is achieved; Every 4-12 mo when target is achieved	6 wk after initiation; Every 6-12 mo when target is achieved
Step 5: Options if target not reached	Up-titration of statin dose; Add non-statin agent			Add non-statin agent; Referral to lipid specialist	

ESC: European Society of Cardiology; EAS: European Atherosclerosis Society; CCS: Canadian Cardiovascular Society; IAS: International Atherosclerosis Society; NLA: National Lipid Association; AACE: American Association of Clinical Endocrinologists; FRS: Framingham risk score; PCE: Pooled Cohort Equations; CVD: Cardiovascular disease; CHD: Coronary heart disease; CKD: Chronic kidney disease; DM: Diabetes mellitus; CAD: Coronary artery disease; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; hsCRP: High sensitivity C-reactive protein; TG: Triglyceride; ApoB: Apolipoprotein B.

estimates 10-year risk of CVD using validated population data in England, taking into account ethnicity and geographical location^[20]. QRISK2 used the same main outcomes as PCE with addition of transient ischemic attack and angina; hence, a 10% risk estimation by the QRISK2 score is approximately equivalent to a 7.5% ASCVD risk estimation by PCE. Both scores are best used in the populations for which they were intended to be implemented. People with a QRISK2 score of $\geq 10\%$ along with those who have other selected risk factors are categorized into a "statin-benefit group" wherein atorvastatin 20 mg is recommended.

The guideline lists conditions that are known to increase risk of cardiovascular disease which are not included in QRISK2, suggesting that risk may be underestimated in people with these conditions. Reducing non-HDL-C $> 40\%$ is used as the target for people who initiate statin therapy. For people who do not attain the target with atorvastatin 20 mg/d, up-titration of atorvastatin to 80 mg/d and/or reinforcement of lifestyle and medication adherence are recommended.

NICE is the first guideline to endorse non-HDL-C as the sole target. The justification is based on epidemiologic evidence supporting non-HDL-C as a cardiovascular risk predictor and the greater practicality for testing because both fasting and non-fasting results are considered reasonable. In targeting non-HDL-C initially, the NICE guideline recommends 20 mg/d of atorvastatin rather than a higher dose for several reasons, including considerations of cost and net clinical benefits^[21].

American Association of Clinical Endocrinologists 2012

The American Association of Clinical Endocrinologists (AACE) guideline uses conventional risk stratification and a group-specific target level strategy^[22] (Table 2). Using a combination of the FRS and presence of major ASCVD risk, the guideline stratifies patients into 5 groups. The entire standard lipid panel is used as the target and for the highest risk population, ApoB can be used as an alternative. AACE 2012 endorses a comprehensive approach to managing dyslipidemia without giving specific criteria for when to initiate pharmacotherapy.

The guideline also does not specify an initial dose for statin therapy. For patients who fail to meet their target after initial management, a non-statin lipid lowering agent can be added. Ezetimibe is recommended as the non-statin agent of choice based on the SHARP (*Study of Heart and Renal Protection*) trial^[23]. The guideline also endorses possible combination therapy with a fibrate, specifically when triglyceride levels are >200 mg/dL and the HDL-C is < 40 mg/dL, due to evidence of non-fatal CVD event reduction in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) trials^[24].

United States Department of Veteran Affairs and United States Department of Defense 2014

Using similar rationale to 2013 ACC/AHA guideline, the

recent United States Department of Veteran Affairs and United States Department of Defense (VA/DoD) guideline advocates the use of a fixed-dose strategy^[25] (Table 1). Men older than 35 years, and women older than 45 years are screened using a 10-year CVD risk calculator (either Framingham or PCE). Patients who have $> 12\%$ estimated 10-year CVD risk are recommended to be started on a moderate dose of statin therapy based on evidence supporting that benefit clearly outweighs risk in this group. For people with intermediate risk (6%-12%), the recommendation for statin initiation is less clear. The guideline's distinct feature is its recommendation against the routine measurement of lipid panel after statin initiation. Thus, neither a target level nor a percentage change from baseline is utilized as a parameter of treatment adequacy. Combination with a non-statin agent is avoided, but a non-statin agent (gemfibrozil or bile acid sequestrant) may be used in patients who cannot tolerate statin.

DISCUSSION

These guidelines approach primary prevention with similar overarching aims. Several adopt traditional risk stratification with group-specific management. ACC/AHA, NICE, and NLA (partially) recommend identifying groups in which benefits of statin therapy clearly outweigh adverse effects. Risk estimation using traditional risk factors to estimate an absolute risk score, secondary testing (including hsCRP, CAC, and ApoB), and secondary risk factors (such as HIV, autoimmune diseases, and medications) are tools that are commonly used to further stratify those in the intermediate risk group to guide management.

Critical role of risk scores

In primary prevention, risk estimators/calculators may have a major impact in determining how many people will be treated with pharmacotherapy. The decision to use one over another could affect treatment of millions of people, and it is worth noting that when a calculator is applied to a given individual, the population from which the calculator was derived may not be representative of that specific individual. For example, a calculator developed from and valid for Asian Americans might not be as well suited to Asian people in general. When using PCE, it is specifically noted that underestimation of ASCVD risk is expected in American Indians, some Asian Americans (*e.g.*, of South Asian ancestry), and some Hispanics (*e.g.*, Puerto Ricans). On the other hand, the overestimation tends to occur in Asian Americans (*e.g.*, of East Asian ancestry) and some Hispanics (*e.g.*, Mexican Americans)^[25].

Ideally, every distinct population would have its own risk calculator; however, this is not practical at this time because of the lack of national representative cohorts in most countries. It is important to realize that the accuracy of a risk calculator in estimating "true" future risk is difficult to ascertain. A risk score is an estimate based

on a population average and the information needs to be contextualized through discussion with a patient and consideration of unique aspects of their case. Concerns with the potential inaccuracies of risk calculators support, in our view, a less calculator-reliant approach^[5].

Pharmacotherapy threshold

Choosing a cut-point of ASCVD risk for stratification can be challenging, and while it can be data driven, it also requires panelist consensus to some extent. In the ACC/AHA guidelines, the cut-point of 7.5% was selected based on a balancing of the estimated NNT and number needed to harm (NNH). By extrapolation from trial data showing the NNT to avoid an ASCVD event with statin therapy vs the NNH for diabetes^[4], comparisons were made for moderate- and high-intensity statin therapy. Again, the cut-point is not intended to automatically trigger a statin prescription, but rather to start a clinician-patient risk discussion.

RCTs are attractive because they allow an unbiased comparison of the NNT and NNH in defined populations. Since there have been over 25 statin trials embracing various populations, guidelines based on high-quality RCTs have merit. But the NNT and NNH have potential shortcomings as the NNT is dependent on the time frame of the trials. In WOSCOPS, there was a significant difference in the NNT at 5 years vs 20 years of follow-up^[26]. The NNH obtained from RCTs may also not reflect the true incidence of adverse effects in a particular case of interest. For example, statin-related diabetes appears to occur in persons with risk factors for diabetes (components of the metabolic syndrome) and, therefore, the NNT vs NNH assessment may not be as relevant to someone without these diabetes risk factors.

Moreover, many patients seen in routine clinical practice may differ from the patients who participated in RCTs. In a recent retrospective cohort study of 107835 statin-treated participants^[27], 17% of patients (18778) reported having a statin-related adverse effect, 40% of which were musculoskeletal. Of these individuals, 6579 subjects were re-challenged with statin. Eventually, over 90% of those previously intolerant patients continued on statin therapy suggesting that many adverse effects were incorrectly attributed to statins. In contrast, in RCTs, people with a history of statin intolerance and those who develop muscle symptoms or elevated CK during run-in phases may be excluded from trials. This selection process limits the ability to generalize such studies to the general population^[28].

Target treatment

Arguments can be made to support a focus on the percentage LDL-C reduction (as in ACC/AHA, NICE) or target LDL-C level (as in EAS/ESC, CCS, IAS, NLA, and AACE). Both approaches inherently acknowledge that the benefit is through LDL-C lowering. Focus on the anticipated response to statin therapy, as reflected by the percentage LDL-C reduction, is felt to be more aligned with evidence from RCTs and high quality meta-

analyses. On the other hand, lack of RCT evidence for efficacy is not the same as RCT evidence for lack of efficacy^[29].

The fixed target LDL-C level could be easier for patients to understand, which theoretically could help maximize adherence to treatment and motivate lifestyle change. Having a target LDL-C level could also be helpful in assessing the success of treatment, particularly when baseline LDL-C is unknown, such as in patients already on a statin. Moreover, some high risk patients with high baseline LDL-C levels may not achieve what would be considered an optimal LDL-C level even with a large percentage change, and without a fixed target LDL-C, the role or timing of the addition of non-statin medications such as ezetimibe becomes less clear. Importantly, patient counseling about the primary goal of LDL-C reduction, which is prevention of future heart attacks and strokes, is critical.

As noted in three guidelines, on-treatment non-HDL-C levels can be a stronger predictor of future cardiovascular events than LDL-C^[30,31]. One contributing factor is that non-HDL-C captures information on triglyceride-rich remnant lipoprotein cholesterol that LDL-C does not. In addition, calculated LDL-C can be inaccurate in the setting of elevated triglyceride levels or low LDL-C levels (particularly levels < 70 mg/dL) as it is derived from Friedewald estimation^[32,33]. Avoiding the issues with such estimation, non-HDL-C is simply a subtraction of total and HDL cholesterol.

Follow-up

Most guidelines advise follow-up at 6 to 12 wk after initiation of treatment and/or dose change and thereafter every 6 to 12 mo when the target is achieved. Reinforcement of lifestyle modification and medical adherence can be done at each follow-up visit. If inadequate time is given to observe the effect of lifestyle changes, this may lead to premature conclusions about the ineffectiveness of lifestyle modification and unnecessary medication changes.

Options for management after maximum statin therapy

In addition to reinforcing intensive lifestyle modification, drug adherence and the possible role of adding a non-statin agent are relevant considerations. Effort to determine a possible secondary cause of dyslipidemia is reasonable when the expected response or target is not achieved (as in ACC/AHA and AACE). This management step may often be overlooked but can be important for treatment. Secondary causes of dyslipidemia include drugs, such as diuretics, steroid, amiodarone, cyclosporine, and protease inhibitors; and diseases, such as nephrotic syndrome, hypothyroidism, biliary obstruction, and anorexia.

Regarding combination therapy, recent evidence showing no overall benefit from the addition of niacin in AIM-HIGH and HPS2-THRIVE to patients with well-controlled LDL-C and fenofibrate in ACCORD^[34-36] has led to less emphasis on routine non-statin therapy. This approach is articulated clearly by ACC/AHA and

NICE. The other guidelines also note the shortage of evidence for the additional use of non-statin agents to background statin therapy, although use of these agents appears to be more of a routine option in their recommendations.

However, the above trials did not test use of a second agent in people who were not at target despite statin therapy. The participants had generally well-controlled LDL-C levels on background therapy. Moreover, pre-specified subgroups with high triglycerides and low HDL-C showed benefit of added therapy. Thus, it may be an overgeneralized conclusion to say that combination therapy has no role in management of adults with mixed hyperlipidemia. Rather, it may be that selective use is reasonable, and indeed the guidelines would generally tend to support such a strategy.

For additional LDL-C lowering, the preferred agent at this time is likely ezetimibe, which showed additional benefit in combination with statin therapy in preliminary reporting of the secondary prevention IMPROVE-IT trial^[37]. Of note, the relative risk reduction was fairly modest, consistent with the fairly modest 20% LDL-C lowering from ezetimibe. Therefore, the additional benefit is most justified in those with high enough absolute risk where such a reduction would be clinically significant.

CASE DISCUSSION

Going back to our case, the patient has three important cardiovascular risk factors: Type 2 diabetes mellitus, chronic kidney disease, and hypertension. By all guidelines, he will be categorized as either high risk or in a statin-benefit group. He has been on chronic statin therapy, and determining a percentage reduction is not possible because baseline LDL-C and non-HDL-C are not known. Per the five guidelines that use a fixed target LDL-C goal (EAS/ESC, CCS, IAS, NLA, and AACE), the most aggressive LDL-C goal is < 70 mg/dL and non-HDL-C goal is < 100 mg/dL. With an LDL-C of 76 mg/dL and non-HDL of 119 mg/dL, the patient's on-treatment lipids are probably not optimal and this should be discussed with the patient. In addition, the on-treatment triglycerides level is elevated and LDL-C may be underestimated by the Friedewald equation. Options include improving medication adherence if there is a need, consideration of up-titrating drug therapy, further addressing lifestyle modification, and addressing a possible secondary cause of dyslipidemia. In this case, after clinician-patient discussion, the patient elected to work even harder on lifestyle modification and increase atorvastatin to 40 mg/d.

CONCLUSION

There is no perfect guideline. Each guideline has advantages and limitations. We hope that, by gathering and elaborating upon current guidelines, important concepts were highlighted about dyslipidemia management to prevent ASCVD. We anticipate that, in the future, having

more congruent guidelines will help avoid confusion among clinicians throughout the world.

ACKNOWLEDGMENTS

We thank Lyn Camire, MA, ELS, of our department for editorial assistance.

REFERENCES

- 1 **Mozaffarian D**, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation* 2015; **131**: e29-322 [PMID: 25520374 DOI: 10.1161/CIR.0000000000000152]
- 2 **Yusuf S**, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364**: 937-952 [PMID: 15364185]
- 3 **Mora S**, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation* 2009; **119**: 931-939 [PMID: 19204302 DOI: 10.1161/CIRCULATIONAHA.108.816181]
- 4 **Stone NJ**, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Tomaselli GF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **129**: S1-45 [PMID: 24222016 DOI: 10.1161/01.cir.0000437738.63853.7a]
- 5 **Martin SS**, Sperling LS, Blaha MJ, Wilson PW, Gluckman TJ, Blumenthal RS, Stone NJ. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. *J Am Coll Cardiol* 2015; **65**: 1361-1368 [PMID: 25835448 DOI: 10.1016/j.jacc.2015.01.043]
- 6 **DeFilippis AP**, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, Kronmal RA, McClelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015; **162**: 266-275 [PMID: 25686167 DOI: 10.7326/M14-1281]
- 7 **Pencina MJ**, Navar-Boggan AM, D'Agostino RB, Williams K, Neely B, Sniderman AD, Peterson ED. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 2014; **370**: 1422-1431 [PMID: 24645848 DOI: 10.1056/NEJMoa1315665]
- 8 **Taylor F**, Huffman MD, Macedo AF, Moore THM, Burke M, Smith GD, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. USA: John Wiley & Sons, Ltd, 2014 [DOI: 10.1002/14651858.CD004816.pub5]
- 9 **Wright JM**, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev* 2009; **8**: CD001841 [PMID: 19588327 DOI: 10.1002/14651858.CD001841.pub2]
- 10 **Martin SS**, Abd TT, Jones SR, Michos ED, Blumenthal RS, Blaha

- MJ. 2013 ACC/AHA cholesterol treatment guideline: what was done well and what could be done better. *J Am Coll Cardiol* 2014; **63**: 2674-2678 [PMID: 24681146 DOI: 10.1016/j.jacc.2014.02.578]
- 11 **Raymond C**, Cho L, Rocco M, Hazen SL. New cholesterol guidelines: worth the wait? *Cleve Clin J Med* 2014; **81**: 11-19 [PMID: 24391101 DOI: 10.3949/ccjm.81a.13161]
 - 12 **Reiner Z**, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011; **32**: 1769-1818 [PMID: 21712404 DOI: 10.1093/eurheartj/ehr158]
 - 13 **Conroy RM**, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003; **24**: 987-1003 [PMID: 12788299]
 - 14 **Anderson TJ**, Grégoire J, Hegele RA, Couture P, Mancini GB, McPherson R, Francis GA, Poirier P, Lau DC, Grover S, Genest J, Carpentier AC, Dufour R, Gupta M, Ward R, Leiter LA, Lonn E, Ng DS, Pearson GJ, Yates GM, Stone JA, Ur E. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2013; **29**: 151-167 [PMID: 23351925 DOI: 10.1016/j.cjca.2012.11.032]
 - 15 **D'Agostino RB**, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; **117**: 743-753 [PMID: 18212285 DOI: 10.1161/CIRCULATIONAHA.107.699579]
 - 16 **Grundy SM**. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia. *J Clin Lipidol* 2013; **7**: 561-565 [PMID: 24314355 DOI: 10.1016/j.jacl.2013.10.001]
 - 17 **Lloyd-Jones DM**, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006; **113**: 791-798 [PMID: 16461820 DOI: 10.1161/CIRCULATIONAHA.105.548206]
 - 18 **Jacobson TA**, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA, Wild RA, Wilson DP, Brown WV. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J Clin Lipidol* 2014; **8**: 473-488 [PMID: 25234560 DOI: 10.1016/j.jacl.2014.07.007]
 - 19 **National Clinical Guideline Centre (UK)**. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London: National Institute for Health and Care Excellence (UK), 2014 [PMID: 25340243]
 - 20 **Hippisley-Cox J**, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007; **335**: 136 [PMID: 17615182 DOI: 10.1136/bmj.39261.471806.55]
 - 21 **Law MR**, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003; **326**: 1423 [PMID: 12829554 DOI: 10.1136/bmj.326.7404.1423]
 - 22 **Jellinger PS**, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW, Shepherd MD, Seibel JA. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. *Endocr Pract* 2012; **18** Suppl 1: 1-78 [PMID: 22522068]
 - 23 **Baigent C**, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Kairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; **377**: 2181-2192 [PMID: 21663949 DOI: 10.1016/S0140-6736(11)60739-3]
 - 24 **Scott R**, O'Brien R, Fulcher G, Pardy C, D'Emden M, Tse D, Taskinen MR, Ehnholm C, Keech A. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care* 2009; **32**: 493-498 [PMID: 18984774 DOI: 10.2337/dc08-1543]
 - 25 **Goff DC**, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Selke FW, Shen WK, Smith SC, Tomaselli GF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **129**: S49-S73 [PMID: 24222018 DOI: 10.1161/01.cir.0000437741.48606.98]
 - 26 **WOSCOPS**: Lifetime clinical and economic benefits of statin-based LDL lowering in 20-year follow-up. Available from: URL: <http://www.acc.org/latest-in-cardiology/articles/2014/11/18/16/45/west-of-scotland-coronary-prevention-study-benefits-of-statin-based-ldl-lowering>
 - 27 **Zhang H**, Plutzky J, Skentzos S, Morrison F, Mar P, Shubina M, Turchin A. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med* 2013; **158**: 526-534 [PMID: 23546564 DOI: 10.7326/0003-4819-158-7-201304020-00004]
 - 28 **Bitzur R**, Cohen H, Kamari Y, Harats D. Intolerance to statins: mechanisms and management. *Diabetes Care* 2013; **36** Suppl 2: S325-S330 [PMID: 23882066 DOI: 10.2337/dcS13-2038]
 - 29 **Ray KR**, Kastelein JJP, Boekholdt SM, Nicholls SJ, Khaw K-T, Ballantyne CM, Catapano AL, Reiner Z, Luscher TF. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. Available from: URL: <http://eurheartj.oxfordjournals.org/content/early/2014/03/16/eurheartj.ehu107>
 - 30 **Ridker PM**, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet* 2013; **382**: 1762-1765 [PMID: 24268611 DOI: 10.1016/S0140-6736(13)62388-0]
 - 31 **Boekholdt SM**, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, Simes RJ, Durrington P, Hitman GA, Welch KM, DeMicco DA, Zwiderman AH, Clearfield MB, Downs JR, Tonkin AM, Colhoun HM, Gotto AM, Ridker PM, Kastelein JJ. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012; **307**: 1302-1309 [PMID: 22453571 DOI: 10.1001/jama.2012.366]
 - 32 **Martin SS**, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, Jones SR. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA* 2013; **310**: 2061-2068 [PMID: 24240933 DOI: 10.1001/jama.2013.280532]
 - 33 **Martin SS**, Blaha MJ, Elshazly MB, Brinton EA, Toth PP, McEvoy JW, Joshi PH, Kulkarni KR, Mize PD, Kwiterovich PO, Defilippis AP, Blumenthal RS, Jones SR. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. *J Am Coll Cardiol* 2013; **62**: 732-739 [PMID: 23524048 DOI: 10.1016/j.jacc.2013.01.079]
 - 34 **Boden WE**, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin

in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; **365**: 2255-2267 [PMID: 22085343 DOI: 10.1056/NEJMoa1107579]

35 **Landray MJ**, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014; **371**: 203-212 [PMID: 25014686 DOI: 10.1056/NEJMoa1300955]

36 **Ginsberg HN**, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz

P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1563-1574 [PMID: 20228404 DOI: 10.1056/NEJMoa1001282]

37 **Cannon DP**, IMPROVE IT Investigators. IMPROVE-IT trial: a comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes after acute coronary syndromes. Available from: URL: <http://circ.ahajournals.org/content/130/23/2105.full>

P- Reviewer: Amiya E, Lin GM, Teragawa H **S- Editor:** Kong JX
L- Editor: A **E- Editor:** Lu YJ





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