Review Article

Atherosclerotic Cardiovascular Disease Risk and Evidence-based Management of Cholesterol

Satyajeet Roy

Department of Medicine, Cooper University Hospital, Cooper Medical School of Rowan University, 1 Cooper Plaza Camden, New Jersey 08103, USA

Abstract

An elevated level of low-density lipoprotein cholesterol is directly associated with development of atherosclerotic cardiovascular disease, which may present as coronary heart disease, stroke, and peripheral arterial disease. The new cholesterol management guidelines from the American College of Cardiology and the American Heart Association aim to address a comprehensive approach to prevent and reduce the risk of atherosclerotic cardiovascular disease. The new guidelines recommend initiation of heart healthy lifestyle modifications and 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitor ("statin") therapy in individuals who are at a high risk for atherosclerotic cardiovascular disease. It is estimated that these guidelines could result in "statin" therapy for one in every three adults in the United States. This article presents a review of the current cholesterol management guidelines, recommendations from relevant randomized controlled trials and meta-analyses obtained from the searches in Medline/PubMed and Cochrane Database of Systematic Reviews, and publications from the Centers for Disease Control and Prevention, the Centers for Medicare and Medicaid Service, and the United States Preventive Services Task Force.

Keywords: Atherosclerotic cardiovascular disease, cholesterol management, statin

Address for correspondence: Dr. Satyajeet Roy, MD, FACP Department of Medicine, Cooper University Hospital, 1103 North Kings Highway, Suite 203 Cherry Hill, NJ 08034, USA. E-mail: roy-satyajeet@cooperhealth.edu

Introduction

Heart disease is the leading cause of death in the United States. High cholesterol increases the risk of developing cardiovascular (CV) disease.[1] About 45% of Medicare beneficiaries have high cholesterol, making it the second most common condition among all of the out-patient medical office encounters.[2] An elevated level of low-density lipoprotein cholesterol (LDL-C) is directly associated with development of atherosclerotic cardiovascular disease (ASCVD), which includes coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD).[3] Although approximately 71 million adults in the United States have elevated LDL-C, less than half receive treatment, and only a third have LDL-C in the desired target level.[4]

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.132916

Old concept

In the United States, cholesterol screening has been recommended for men of ages 35 and older, for women of ages 45 and older, and for men and women of ages 20 and older if they are at increased risk for CHD.[5] The practice of cholesterol management is based on the recommendations to treat elevated LDL-C beyond a specific goal in individuals who fall into a specific cardiovascular disease (CVD) risk category as per the guidelines of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, also known as Adult Treatment Panel-III (ATP-III).[6]

New concept

The goals of the new cholesterol management guidelines include the prevention of ASCVD, improving the management of individuals who have ASCVD, and promoting optimal ASCVD care.[3] An expert panel

was appointed for detection, evaluation, and treatment of cholesterol in adults (Adult Treatment Panel-IV)[7] in order to develop evidence-based guidelines, which follow the practice guidelines and the evidence-based standards set by the Institute of Medicine report.[8] The recommendations made by the expert panel aim to assess CV risk, reduce CV risk by modification of lifestyle factors, guide maintenance of an ideal body mass index, and manage blood cholesterol. After an extensive review of the data from randomized controlled trials (RCTs), systematic reviews and meta-analyses of RCTs, the panel developed these cholesterol management guidelines in order to reduce risk of ASCVD, not just the prevention of CVD alone as proposed by the ATP-III.[9] The RCTs have shown that the increased ASCVD risk is not only associated with elevated LDL-C levels, but also factors such as gender, race, tobacco smoking, hypertension, and diabetes mellitus should be included in the comprehensive management of cholesterol.[10] The guidelines recommend beginning cholesterol screening in all adults who are 21 years or older.[3] The panel did not find evidence to support the titration of cholesterol lowering drug therapy to achieve target LDL-C or nonhigh-density lipoprotein cholesterol (non-HDL-C) levels.[3,6] Lifestyle modifications are the critical components of ASCVD risk reduction.[3] These include adherence to a heart healthy diet, regular exercise, maintenance of a healthy weight, and avoidance of tobacco products.[11] The panel also found that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") are the only cholesterol lowering drugs that have shown ASCVD risk reduction,[12] and each 39 mg/dL reduction in LDL-C by a statin reduces the risk of ASCVD by 20%.[3] In order to reduce the risk of ASCVD an appropriate intensity of statin therapy should be used [Table 1]. As far as the nonstatin cholesterol-lowering drugs are concerned, the panel found no evidence to support the use of this category of drugs either as monotherapy or in combination with a statin.[13,14] The panel also identified the high-risk groups that do not benefit from statin therapy.[3]

New Management Guidelines

The benefits of lipid lowering drug "statin" therapy outweigh the risks in the four groups of patients who are at increased risk of ASCVD [Table 2, Figure 1].[15-38] In patients with LDL-C greater than 190 mg/dL and/or triglyceride greater than 500 mg/dL it is necessary to investigate and correct the common causes of secondary hyperlipidemia [Table 3] before initiation of statin therapy.[48] The panel does not support "statin" therapy in patients who are older than 75 years without clinical ASCVD,[49,50] who are on hemodialysis,[19] and who suffer from New York Heart Association class II, III, or IV heart failure.[51] The role of additional factors, such as biomarkers and noninvasive tests, [Table 4] is limited to patients who either do not qualify in the four statin benefit groups, or in whom it is unclear to make a decision of initiating statin therapy.[3]

Table 1: Intensity of statin therapy

1. High-intensity	Average LDL-C level reduction by > 50% on daily statin therapy
2. Moderate-intensity	Average LDL-C level reduction by 30% to < 50% on daily statin therapy
3. Low-intensity	Average LDL-C level reduction by < 30% on daily statin therapy

LDL-C = Low-Density Lipoprotein Cholesterol
Information from reference 3

ASCVD Risk Assessment

A comprehensive tool, known as Pooled Cohort Risk Assessment Equation (PCRAE),[10] for the prediction and assessment of 10-year risk of an ASCVD event has been developed, which contrasts with the conventional risk

Table 2: Key recommendations: Four statin benefit groups

NHLBI Grading the Strength of Recommendations

Clinical recommendation	Evidence rating	References
1. Individuals with clinical ASCVD HIST is indicated	A	[3,6,8,11,12,14-27]
2. Individuals with primary elevations of LDL-C ≥190 mg/dL HIST is indicated	B	[3,6,21,27-32]
3. Individuals aged between 40 and 75 years with diabetes and LDL-C between 70 and 189 mg/dL MIST is indicated	A	[3,21,28,29,33-37]
4. Individuals without clinical ASCVD or diabetes who are aged between 40 and 75 years with LDL-C between 70 and 189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher M-HIST is indicated	A	[3,27,29,30,32,38-47]

NHLBI = National Heart Lung and Blood Institute; ASCVD = Atherosclerotic Cardiovascular Disease; LDL-C = Low-Density Lipoprotein Cholesterol; HIST = High-intensity statin therapy; MIST = Moderate-intensity statin therapy; M-HIST = Moderate to high-intensity statin therapy.

A = There is high certainty based on evidence that the net benefit is substantial; B = There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate; C = There is at least moderate certainty based on evidence that there is a small net benefit; D = There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits. For information about the NHLBI Grading the Strength of Recommendations, go to http://www.nhlbi.nih.gov. Information from reference 3

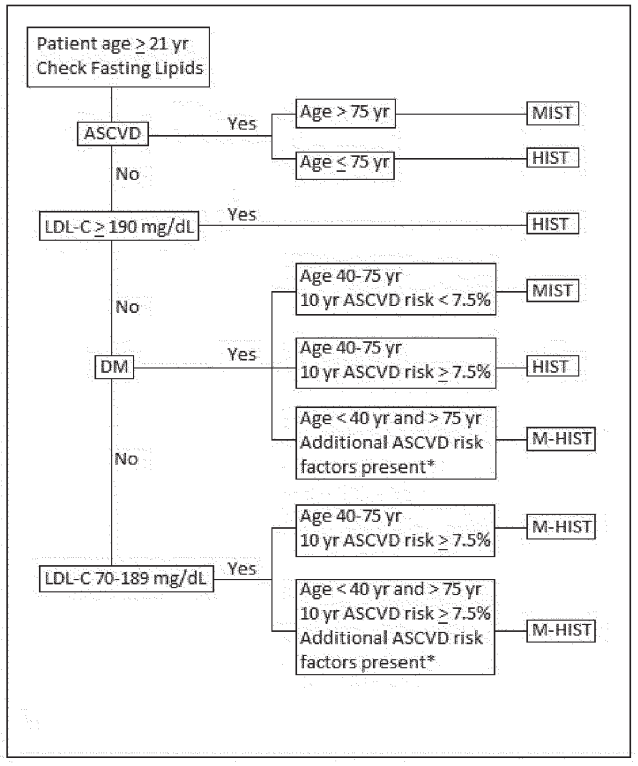

Figure 1: Flow Diagram of Cholesterol Management. (ASCVD = Atherosclerotic Cardiovascular Disease; LDL-C = Low-density Lipoprotein Cholesterol; DM = Diabetes Mellitus; MIST = Moderate-intensity statin therapy; HIST = High-intensity statin therapy; M-HIST = Moderate to high-intensity statin therapy.)

* See Table 4.

Table 3: Common causes of secondary hyperlipidemia

Elevated LDL-C	
Consumption if saturated or *trans* fats	Weight gain
Anorexia	Cholestasis
Nephrotic syndrome	Hypothyroidism
Cyclosporine	Amiodarone
Glucocorticoids	Diurestics
Obesity	Pregnancy
Elevated triglycerides	
Consumption of very low-fat food	Weight gain
Consumption of high amount of refined carbohydrates	Obesity
Consumption of excessive amount of alcohol	Pregnancy
Glucocorticoids	Oral estrogen
Protease inhibitors	Retinoic acid
Bile acid sequestrants	Raloxifene
Thiazide diuretics	Tamoxifen
Beta blockers (except carvedilol)	Nephrotic syndrome
Lipodystrophy	Chronic kidney disease
Poorly controlled diabetes mellitus	Hypothyroidism

Information from reference 3

assessment of CHD alone.[9] This equation was developed after an extensive review of diverse participants from several large studies. This equation should be used in women and men aged 40–79 who have LDL-C levels of 70–189 mg/dL. The equation includes risk factors such as: gender, age, race (African-American or non-Hispanic Caucasian), total cholesterol, HDL-C, systolic blood pressure, receiving treatment for hypertension, diabetes mellitus, and smoking. The risk of ASCVD is generally lower in Hispanic and Asian populations, and higher in American-Indian populations compared with non-Hispanic Caucasians. For the purpose of risk assessment, patients of all other races should be entered as non-Hispanic Caucasian. The PCRAE calculator is easy to download as a Microsoft Excel auto-calculator.[3]

It is evident that gender, age, and race play major role in the risk assessment; changes in lifestyle can modify factors like blood pressure, diabetes mellitus, and smoking, which can alter the calculated 10-year risk of ASCVD in the same patient [Table 5]. The new guidelines are designed to address the context of a patient to be the prime basis of decision-making by the clinicians. Several concerns have been raised regarding potential recruitment of a larger number of the United States' population for statin therapy following the current cholesterol guidelines,[52] but the recommendations are based on the current evidence-based data that supports global CV risk reduction.[3,53]

Most Effective Therapeutic Agent – Statin

The data from RCTs and meta-analysis of RCTs[3] has shown that use of a "statin" provides substantial benefits in primary prevention of ASCVD and risk reduction in patients with LDL-C levels of 70 mg/dL and above.[16,54] Statins have also shown similar benefits in patients with hypertension,[55] diabetes,[39] low HDL-C,[15] elevated C-reactive protein,[38] etc. Additionally, it has been confirmed by the Cochrane meta-analysis[17] and the meta-analysis by the Cholesterol Treatment Trialists[12,18] that statin therapy for primary prevention reduces fatal and nonfatal ASCVD.

Table 4: Additional ASCVD risk factors

1. LDL-C > 160 mg/dL
2. Genetic hyperlipidemia
3. Family history of premature ASCVD in a first degree male member before age 55 years or first degree female member before age 65 years
4. Highly sensitive C-reactive protein (HS-CRP) > 2 mg/L
5. Coronary artery calcium (CAC) score of > 300 Agaston Units or > 75 percentile of age, sex, and ethnicity
6. Ankle-Brachial Index (ABI) < 0.9
7. Elevated lifetime risk of ASCVD

ASCVD = Atherosclerotic Cardiovascular Disease; LDL-C = Low-Density Lipoprotein Cholesterol

Information from reference 3

Table 5: 10-year risk of ASCVD by pooled cohort risk assessment equation

Age (Year)	Race	Gender	TC (mg/dL)	HDL-C (mg/dL)	SBP (mmHg)	Treatment	DM smoking for HTN	Risk (%)	Statin	Therapy recommended
50	AA	M	200	50	130	N	N	Y	9.2	Y
50	AA	M	200	50	130	N	N	N	5.4	N
50	AA	F	200	50	130	N	N	Y	4.6	N
50	AA	F	200	50	130	N	N	N	2.3	N
50	C	M	200	50	130	N	N	Y	7.8	Y
50	C	M	200	50	130	N	N	N	3.6	N
50	C	F	200	50	130	N	N	Y	4.1	N
50	C	F	200	50	130	N	N	N	1.4	N

TC = Total Cholesterol, HDL-C = High-density Lipoprotein Cholesterol, SBP = Systolic Blood Pressure, HTN = Hypertension, DM = Diabetes Mellitus, AA = African-American, C = Non-Hispanic Caucasian, M = Male, F = Female, N = No, Y = Yes. Information from reference 10

An effective dose statin therapy has been defined as high-intensity or moderate-intensity [Tables 1 and 6]. The panel found that both high-intensity and moderate-to-high-intensity statin therapy are effective and safe in ASCVD risk reduction. On the contrary low-intensity statin therapy (e.g., Simvastatin 10 mg, Pravastatin 10–20 mg, Lovastatin 20 mg, Fluvastatin 20–40 mg, Pitavastatin 1 mg) may achieve a target LDL-C goal (as per ATP-III guidelines) without effective ASCVD risk reduction.[3] Similarly, patients may receive an ineffective low-intensity statin therapy with a nonstatin drug combination for presumed safety concerns of statin in order to achieve a specific target LDL-C goal, which does not offer ASCVD risk reduction either.[3] Patients on statin should be monitored for muscle injury, hepatic injury, new-onset diabetes, and other safety concerns [Table 7]. The risk of statin associated myopathy and hemorrhagic stroke is minimal compared with the excess risk of ASCVD due to lack of statin therapy.[12] Additional factors that influence ASCVD risk [Table 4] should be considered in the group of patients in whom the benefit of statin therapy for ASCVD prevention is less clear, such as in the case of patients without clinical ASCVD and without diabetes mellitus who are aged between 21 and 39 years and have LDL-C in the range of 71–189 mg/dL.[3]

Clinical Impact

It is estimated that the new cholesterol management guidelines could result in statin therapy for one in every three adults in the United States.[52] The new cholesterol management approach is primarily geared toward a comprehensive risk reduction of ASCVD, not just to attain a specific LDL-C goal level [Figure 2]. There are some

Table 6: Evidence based recommended statins

High-intensity	Atorvastatin 40–80 mg daily Rosuvastatin 20–40 mg daily
Moderate-intensity	Atorvastatin 10–20 mg daily Rosuvastatin 10 mg daily Simvastatin 20–40 mg daily Pravastatin 40–80 mg daily Lovastatin 40 mg daily Fluvastatin XL 80 mg daily Fluvastatin 40 mg twice daily Pitavastatin 2–4 mg daily

Information from reference 3

Table 7: Statin safety: NHLBI grading the strength of recommendations

Recommendation	Evidence rating	Reference
MIST should be used in patients who are in HIST group if they have severe renal or liver function impairment, stain intolerance or muscle disorder, unexplained elevated ALT >3 times ULN, >75 years of age, history of hemorrhagic stroke, Asian ancestry	A	[17,40,56-60]
CK should not be measured routinely	A	[38,42,43,58,60,61]
Baseline ALT should be checked before initiation of statin therapy	B	[56,59]
Evaluate for new-onset diabetes while on statin therapy	B	[41,62]
Statins should not be used in women of childbearing potential (pregnancy category X) unless effective contraception is used and they are not nursing	A	3

NHLBI = National Heart Lung and Blood Institute; MIST = Moderate-intensity statin therapy, HIST = High-intensity statin therapy, ALT = alanine transaminase, ULN = upper limit of normal, CK = creatinine kinase.

A = There is high certainty based on evidence that the net benefit is substantial; B = There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate; C = There is at least moderate certainty based on evidence that there is a small net benefit; D = There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits. For information about the NHLBI Grading the Strength of Recommendations, go to http://www.nhlbi.nih.gov. Information from reference 3

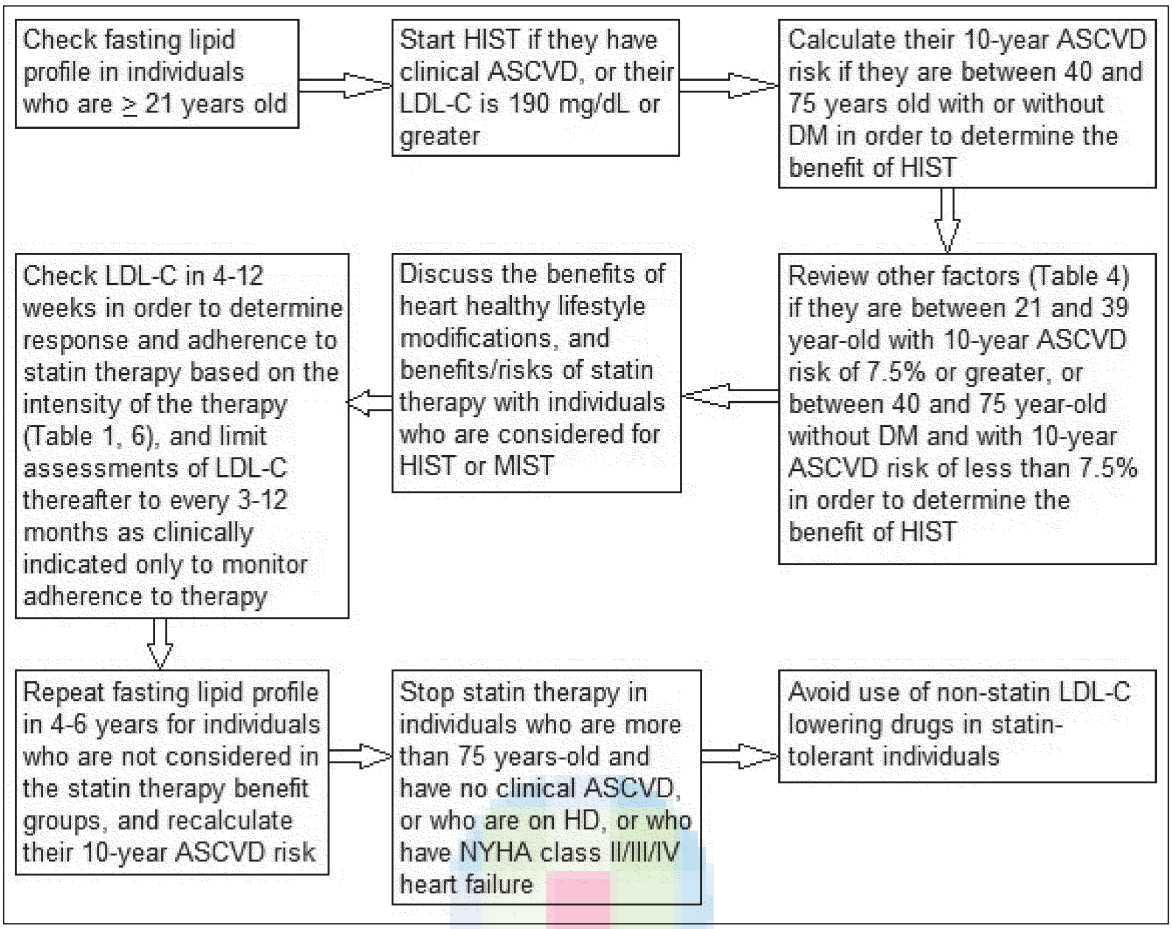

Figure 2: Suggested Steps to Manage Cholesterol. (ASCVD = Atherosclerotic cardiovascular disease, LDL-C = Low-density lipoprotein cholesterol, DM = Diabetes mellitus, HIST = High-intensity statin therapy, MIST = Moderate-intensity statin therapy, HD = Hemodialysis, NYHA = New York Heart Association.) Information from reference 3.

limitations of the new guidelines in specific groups, such as younger adults (aged 21–39 years), individuals with low 10-year ASCVD risk but high lifetime risk based on additional factors, individuals with serious comorbidities, such as HIV infection, rheumatologic disorders, solid organ transplant recipients. Future guidelines may provide management of hypertriglyceridemia, use of non-HDL-C in decision making, or use of therapeutic markers, such as Apo B, Lp(a), LDL particle size. More recent studies suggest a proper method of estimation of LDL-C level based on a calculation that uses a variable ratio of triglyceride (TG) and very low-density lipoprotein cholesterol (VLDL-C), and not just the standard 5:1 ratio of TG:VLDL-C as proposed by the Friedewald equation.[63,64] This may change the estimation of LDL-C level and allow clinicians to assign their patients appropriately into more accurate ASCVD risk category.

Conclusion

The current cholesterol management guidelines provide a comprehensive approach toward ASCVD risk reduction. It is a major shift from the old approach in which a target LDL-C was aimed in order to reduce cardiovascular risk only for the specific cardiovascular risk stratified patient categories. Moderate-intensity and high-intensity statin therapies are safe and effective interventions that have shown major ASCVD risk reduction in statin benefit groups. Clinicians are encouraged to use clinical judgment based on risks, benefits, drug interactions, and patient preference to statin therapy.

References

1. Prevalence of cholesterol screening and high blood cholesterol among adults - United States, 2005, 2007, and 2009. Centers for Disease Control and Prevention. Atlanta, GA.: Morbidity and Mortality Weekly Report, 2012. (Accessed March 20, 2014, at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6135a2.htm).
2. Chronic Conditions among Medicare Beneficiaries. Centers for Medicare and Medicaid Services. Baltimore, MD.: Chartbook, 2012. (Accessed March 20, 2014, at http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-

Reports/Chronic- Conditions/Downloads/2012Chartbook.pdf).
3. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, *et al*. 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 2013 [In Press].
4. Vital signs: Prevalence, treatment, and control of high levels of low-density lipoprotein Cholesterol, United States, 1999 - 2002 and 2005 - 2008. Centers for Disease Control and Prevention. Atlanta, GA.: Morbidity and Mortality Weekly Report, 2011. (Accessed March 20, 2014, at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6004a5.htm).
5. Screening for Lipid Disorders in Adults. United States Preventive Services Task Force. Rockville, MD.: U.S. Preventive Services Task Force Recommendation Statement; 2008. (Accessed March 20, 2014, at http://www.uspreventiveservicestaskforce.org/uspstf08/lipid/lipidrs.htm).
6. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
7. Gibbons GH, Shurin SB, Mensah GA, Lauer MS. Refocusing the agenda on cardiovascular guidelines: An announcement from the national heart, lung, and blood institute. Circulation 2013;128:1713-5.
8. Clinical Practice Guidelines We Can Trust - Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, editors. Institute of Medicine of the National Academics. Washington, DC: The National Academies Press; 2011. p. 1-254.
9. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
10. CV risk calculator. American Heart Association. Dallas, TX.: Prevention Guidelines Tools, 2013. (Accessed March 20, 2014, at http://my.americanheart.org/cvriskcalculator).
11. Eckel RH, Jakicic JM, Ard JD, Miller NH, Hubbard VS, Nonas CA, et al. 2013 AHA-ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology-American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; pii:S0735-1097.
12. Cholesterol Treatment Trialists Collaboration, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.
13. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255-67.
14. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563-74.
15. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615-22.
16. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): A prospective randomised controlled trial. Lancet 2006;368:1155-63.
17. Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. The Cochrane Collaboration. Oxford, UK: Cochrane database of systematic reviews; 2011. (Accessed March 20, 2014, at http://www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD004816.pub4/abstract).
18. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
19. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davy Smith G, et al. Statins for the primary prevention of cardiovascular disease. The Cochrane Collaboration. Oxford, UK.: Cochrane database of systematic reviews, 2011. (Accessed March 20, 2014, at http://www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD004816.pub5/abstract).
20. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet 2002;360:7-22.
21. Lu Z1, Kou W, Du B, Wu Y, Zhao S, Brusco OA, et al. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. Am J Cardiol 2008;101:1689-93.
22. Tikkanen MJ, Holme I, Cater NB, Szarek M, Faergeman O, Kastelein JJ, et al. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged <65 versus >or=65 years with coronary heart disease (from the Incremental DEcrease through Aggressive Lipid Lowering [IDEAL] study). Am J Cardiol 2009;103:577-82.
23. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Arch Intern Med 2006;166:605-9.
24. Akushevich I, Kravchenko J, Ukraintseva S, Arbeev K, Yashin AI. Age patterns of incidence of geriatric disease in the U.S. elderly population: Medicare-based analysis. J Am Geriatr Soc 2012;60:323-7.
25. Robinson JG, Bakris G, Torner J, Stone NJ, Wallace R. Is it time for a cardiovascular primary prevention trial in the elderly? Stroke 2007;38:441-50.
26. Porock D, Oliver DP, Zweig S, Rantz M, Mehr D, Madsen R, et al. Predicting death in the nursing home: Development and validation of the 6-month Minimum Data Set mortality risk index. J Gerontol A Biol Sci Med Sci 2005;60:491-8.
27. Stineman MG, Xie D, Pan Q, Kurichi JE, Zhang Z, Saliba D, et al. All-cause 1-, 5-, and 10-year mortality in elderly people according to activities of daily living stage. J Am Geriatr Soc 2012;60:485-92.
28. Fried T, Bradley E, Towle V, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med 2002;346:1061-6.

29. Ditto PH, Druley JA, Moore KA, Danks JH, Smucker WD. Fates worse than death: The role of valued life activities in health-state evaluations. Health Psychol 1996;15:332-43.
30. Rosenfeld K, Wenger N, Kagawa-Singer M. End-of-life decision making: A qualitative study of elderly individuals. J Gen Intern Med 2000;15:620-5.
31. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: Exploratory analysis of a randomized trial. Ann Intern Med 2010;152:488-96.
32. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. Lancet 2002;360:1623-30.
33. Schonberg MA, Davis RB, McCarthy EP, Marcantonio ER. External validation of an index to predict up to 9-year mortality of community-dwelling adults aged 65 and older. J Am Geriatr Soc 2011;59:1444-51.
34. Fried TR, Tinetti ME, Iannone L, O'Leary JR, Towle V, Van Ness PH. Health outcome prioritization as a tool for decision making among older persons with multiple chronic conditions. Arch Intern Med 2011;171:1854-6.
35. Barry MJ, Edgman-Levitan S. Shared decision making-The pinnacle of patient-centered care. N Engl J Med 2012;366:780-1.
36. Man-Son-Hing M, Gage BF, Montgomery AA, Howitt A, Thomson R, Devereaux PJ, et al. Preference-based antithrombotic therapy in atrial fibrillation: Implications for clinical decision making. Med Decis Making 2005;25:548-59.
37. Gray SL, Boudreau RM, Newman AB, Studenski SA, Shorr RI, Bauer DC, et al. Angiotensin-converting enzyme inhibitor and statin use and incident mobility limitation in community-dwelling older adults: The Health, Aging and Body Composition Study. J Am Geriatr Soc 2011;59:2226-32.
38. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-207.
39. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 2004;364:685-96.
40. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: The IDEAL study: A randomized controlled trial. JAMA 2005;294:2437-45.
41. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and treatment of hypertriglyceridemia: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2969-89.
42. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
43. Rhodes ET, Prosser LA, Hoerger TJ, Lieu T, Ludwig DS, Laffel LM. Estimated morbidity and mortality in adolescents and young adults diagnosed with type 2 diabetes mellitus. Diabet Med 2012;29:453-63.
44. Nease RF Jr, Kneeland T, O'Connor GT, Sumner W, Lumpkins C, Shaw L, et al. Ischemic Heart Disease Patient Outcomes Research Team. Variation in patient utilities for outcomes of the management of chronic stable angina: Implications for clinical practice guidelines. JAMA 1995;273:1185-90.
45. Hippisley-Cox J, Pringle M, Cater R, Coupland C, Meal A. Coronary heart disease prevention and age inequalities: The first year of the National Service Framework for CHD. Br J Gen Pract 2005;55:369-75.
46. Forman DE, Rich MW, Alexander KP, Zieman S, Maurer MS, Najjar SS, et al. Cardiac care for older adults: Time for a new paradigm. J Am Coll Cardiol 2011;57:1801-10.
47. Paynter NP, Mazer NA, Pradhan AD, Gaziano JM, Ridker PM, Cook NR. Cardiovascular risk prediction in diabetic men and women using hemoglobin A1c vs diabetes as a high-risk equivalent. Arch Intern Med 2011;171:1712-8.
48. Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. Am J Cardiol 2012;110:823-5.
49. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395-407.
50. GISSI-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): A randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-9.
51. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-61.
52. Ridker PM, Cook NR. Statins: New American guidelines for prevention of cardiovascular disease. Lancet 2013;382:1762-5.
53. Keaney JF Jr, Curfman GD, Jarco JA. A Pragmatic View of the New Cholesterol Treatment Guidelines. N Engl J Med 2014;370:275-8.
54. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301-7.
55. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. Lancet 2003;361:1149-58.
56. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425-35.
57. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504.
58. Thompson GR, Packard CJ, Stone NJ. Goals of statin therapy: Three viewpoints. Curr Atheroscler Rep 2002;4:26-33.
59. Roffi M, Angiolillo DJ, Kappetein AP. Current concepts on coronary revascularization in diabetic patients. Eur Heart J 2011;32:2748-57.
60. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643-53.

61. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. Circulation 2011;123:2292-333.
62. American Diabetes Association. Standards of medical care in diabetes-2013. Diabetes Care 2013;36:S11-66.
63. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA 2013;310:2061-8.
64. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.

How to cite this article: Roy S. Atherosclerotic cardiovascular disease risk and evidence-based management of cholesterol. North Am J Med Sci 2014;6:191-8.

Source of Support: Nil. **Conflict of Interest:** None declared.