

Review Article

New Cholesterol Management Guideline 2013: A Review

SA Fattah¹, AK Saha², MT Alam³, MY Ali⁴

Abstract :

Management of high blood cholesterol is the key point for the treatment and prevention of Atherosclerotic Cardiovascular Disease (ASCVD). Till 2013, Adult Treatment Panel III (ATP III) report was the guideline for the physician for blood cholesterol management. The main feature of this guideline was to achieve a particular target cholesterol level by lifestyle modification, dietary changes and lipid-lowering drugs. But the recently released American College of Cardiology (ACC) and American Heart Association (AHA) guidelines shifted attention to Statin use at high-, moderate- or low-intensity instead of chasing a cholesterol goal. This article reviews the main features of this new guideline comparing to the previous one, where appropriate.

Key words : ASCVD, ACC/AHA, Cholesterol, Statin.

Introduction :

ASCVD that includes coronary heart disease, stroke and peripheral vascular disease is the most important cause of premature death and disability in developed world¹. It is estimated that by 2020 it will be the major cause of death in all the regions of the world². Diseases of the coronary and cerebral arteries are almost always due to atheroma and its complications, particularly thrombosis. High blood cholesterol is one of the major risk factors for ASCVD. So, not surprisingly, management of high blood cholesterol constitutes the centerpiece of prevention and treatment of ASCVD. Till November 2013, ATP III report of the National Cholesterol Education Program (NCEP) released in 2002 was the main guideline for management of high blood cholesterol³. In November, 2013 the ACC and the AHA jointly released a new guideline for managing high blood cholesterol which departed markedly from the prior ATP III report¹. In this article these new developments will be highlighted.

1. Dr. Sk. Abdul Fattah, MBBS, DTCD, FCPS (Medicine), FACP, Professor, Department of Medicine, Faridpur Medical College, Faridpur.
2. Dr. Aloke Kumar Saha, MBBS, FCPS (Paediatrics), Associate Professor, Department of Paediatrics, Faridpur Medical College, Faridpur.
3. Dr. Md. Towhid Alam, MBBS, FCPS (Medicine), Associate Professor, Department of Medicine, Faridpur Medical College, Faridpur.
4. Dr. Md. Yusuf Ali, MBBS, FCPS (Medicine), Professor and Head, Department of Medicine, Faridpur Medical College, Faridpur.

Address of correspondence :

Dr. Sk. Abdul Fattah MBBS, DTCD, FCPS (Medicine), FACP, Professor, Department of Medicine, Faridpur Medical College, Faridpur. Mobile: +88-01720093545, E-mail: skfattah@gmail.com

Methodology :

Since the release of the new guidelines, a lot of articles are published criticizing different aspects of this report. PubMed was searched in July 2014 for all English language publications including the search term "New Statin Guideline", "Cholesterol management guideline" and "ATP IV panel". From the list relevant selected articles were collected and for additional information, articles used as references in those articles were also checked.

Basis of New Guidelines :

The Expert Panel tried to answer three critical questions¹:

1. Whom to treat.
2. With what treatment.
3. How intensively the treatment should be used.

To answer these questions the Expert Panel reviewed the relevant Randomized Clinical Trials (RCT) and the evidences derived from these RCTs were used to formulate the new guidelines. The Panel followed the rules for guideline development published by a committee of the Institute of Medicine that emphasized the necessity for "evidence-based medicine" in guideline development⁴. Thus evidences other than RCTs were virtually excluded and that markedly restricted the scope of this new guideline.

In contrast, the ATP III panel was free to use all types of relevant data including RCTs, epidemiological data, genetic and metabolic studies, and various in vivo and in vitro investigations⁵. So they had the scope to

formulate a comprehensive management guideline. But as all those data were not based on sound evidence-based medicine, question of new evidence-based guideline came forward.

What's new in the Guideline ?

There are many new aspects in the new guidelines, some of which are relevant for advanced studies and researchers. Only some of the more practical points are highlighted here.

1. Focus on ASCVD risk reduction: 4 statin benefit groups¹:

- * Based on a comprehensive set of data from RCTs that identified 4 statin benefit groups which focus efforts to reduce ASCVD events in secondary and primary prevention.
- * Identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention.

2. A New Perspective on LDL-C and/or Non-HDL-C Treatment Goals ⁶⁻⁹:

- *The Expert Panel was unable to find RCT evidence to support continued use of specific LDL-C and/or non-HDL-c treatment targets.
- * The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.
- * Non statin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.

LDL-C Goal vs Statin :

Low-Density Lipoprotein (LDL) elevation was the major focus in ATP-III as a cause of Atherosclerotic Cardiovascular Disease (ASCVD). Epidemiological data from familial or other forms of hypercholesterolemia and from animal studies revealed this relationship between elevated LDL-C and ASCVD. Furthermore Randomized Clinical Trials (RCT) demonstrated that any modalities of intervention including lifestyle changes, diet or drugs that lower LDL-C also lowered the risk for ASCVD. That's why ATP-III fixed LDL-C targets of therapy as the main objective of management. For example, LDL-C goal less than 100mg/dl for high-risk patients with established ASCVD or DM and 10 year risk >20%, LDL-C <70mg/dl for very high risk patients of ASCVD with multiple risk factors⁶.

In formulating new guidelines, the ACC/AHA largely moved away from the connection between LDL-C and ASCVD risk. Instead, statins occupied the center point

of these recommendations. Whether statin imparts its beneficial effect through lowering LDL-C is of no consideration in the new guideline.

This new guideline used the intensity of statin therapy as the goal of treatment rather than LDL-C or non-LDL-C targets. 4 groups of individuals were identified through RCT evidence for whom a reduction of ASCVD were demonstrated with a good margin of safety from moderate- or high- intensity statin-therapy:

4 Statin Benefit Groups¹:

1. Individuals with clinical ASCVD.
2. Individuals with primary elevations of LDL-C equal to or more than 190mg/dl.
3. Individuals 40 to 75 years of age with diabetes and LDL-C 70-189 mg/dl without clinical ASCVD.
4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70 to 189 mg/dl and have an estimated 10-year ASCVD risk of 7.5% or higher.

Lifestyle counseling should be offered at the initial and follow up visits as the foundation for statin therapy and may improve the overall risk factor profile.

High-, Moderate- and Low-intensity Statin Therapy¹⁰⁻¹⁵:

The intensity of statin therapy is defined on the basis of the average expected LDL-C response to a specific statin and

High-Intensity Statin Therapy ¹⁶⁻¹⁹	Moderate-Intensity Statin Therapy ²⁰	Low-Intensity Statin Therapy
Daily dose lowers LDL-C on average, by approximately =/> 50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%	Daily dose lowers LDL-C on average, by approximately < 30%
Atorvastatin -80mg Rosuvastatin - 20mg	Atorvastatin -10mg Rosuvastatin -10mg Simvastatin 20-40mg Pravastatin 40mg Lovastatin 40mg Fluvastatin 40mg bid Pitavastatin 2-4mg	Simvastatin 10mg Pravastatin 10-20mg Lovastatin 20mg Fluvastatin 20- 40mg Pitavastatin 1mg

Major Recommendation for Statin Therapy for ASCVD Prevention¹:

1. For secondary prevention or LDL>190 mg/dl, give 'high-intensity statin' unless age>75 years or intolerant; then use 'moderate-intensity statin'.
2. For diabetes (type-1 or 2, age 40-75 years), use 'moderate-intensity statin' unless 10-year risk >7.5%; then use 'high-intensity statin'.
3. For primary prevention in age group 40-75 years, use 'moderate- to high-intensity statin' if 10-year risk is >7.5%.

If anticipated therapeutic response is achieved, continued adherence to drug therapy should be reinforced and followed up for 3-12 months¹.

If less-than-anticipated response, adherence to medication and intensive lifestyle changes should be reinforced and followed up for 4-12 weeks. If still anticipated response is not achieved, the options are - reinforcement of improved adherence, increasing statin intensity or addition of non-statin drug therapy¹.

Discussion :

ACC/AHA guidelines and ATP III reports, although have many similarities, the two are fundamentally different. ATP III was based on the concept that lowering LDL-C will prevent ASCVD while ACC/AHA guidelines under the influence of IOM paradigm are transformed into statin treatment instructions.

In patient with established ASCVD high-intensity statin is recommended in new guideline. This will definitely reduce the risk but those with high base-line LDL-C may not receive full benefit of LDL-C lowering as non-statin drugs are not recommended¹⁹.

For primary prevention new guideline sets 10-year risk threshold for statin drugs at 7.5%, even $\geq 5\%$ in some cases¹. In ATP III it was $\geq 10\%$. ACC/AHA advocates starting statin therapy at LDL-C >70mg/dl for higher risk patients in contrast to LDL-C ≥ 100 mg/dl in prior guideline. ACC/AHA recommendation is justified by the more recent results of the JUPITER trial²¹. Reduction of both 10-year risk threshold and the level of LDL-C for initiation of statin therapy will expand the use of statin over that of ATP III. However ACC/AHA Panel did not address the cost-effectiveness of this expanded drug use.

ACC/AHA developed a new algorithm for 10-year risk assessment by adding stroke to coronary heart disease^{10,11}, while ATP-III used Framingham risk scoring to estimate 10-year risk for CHD²². It is claimed that the new algorithm overestimates the risk by about

two-folds²³. As a result number of low risk people eligible for statin therapy will be increased further.

Age is an important determinant in the new algorithm, so there will be a progressive increase in number of people of advancing age eligible for statin²². But not all older men and women will benefit from statin, especially those who have very little coronary or carotid atherosclerosis risking them on unnecessary treatment^{24,25}. So this new risk assessment tool may need further review.

Regarding genetic dyslipidaemias and metabolic syndrome ACC/AHA had no comment. So physicians have to rely heavily on other sources of information for their management.

Lifestyle modification was emphasized in ACC/AHA guideline on the basis of a limited number of expert opinion recommendations although no RCT evidence was found²⁶.

The use of non-statin lipid lowering drugs e.g, bile acid sequestrants, ezetimibe, fibrate and nicotinic acids were largely discounted because of lack of supporting RCT studies. Even then use of these drugs are loosely recommended if deemed appropriate by clinical judgment^{27,28}.

Monitoring of patients for anticipated therapeutic response to statin is another field where physicians may feel confused due to lack of any specific target recommendation⁵.

Conclusion :

2013 ACC/AHA Cholesterol management guideline is a long awaited report for this purpose. But as the Expert Panel acknowledged, it did not provide for a comprehensive approach to the detection, evaluation and treatment of lipid disorders as was done in prior ATP III report. Rather it can be viewed as a guide to use statin and the intensity of statin use for reduction of ASCVD risk. It is anticipated that clinicians have to rely markedly on their own expertise and clinical judgment for holistic management of their patients where ATP III guideline may still be relevant.

References :

1. Stone NJ, Robinson J, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH 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 Guideline. *Circulation*. November 12, 2013;1-84.
2. Newby DE, Grubb NR, Bradbury A. *Coronary Heart Disease*. In: Colledge NR, Walker BR, Ralston SH editors. *Davidson's Principles and Practice of Medicine*. 21st ed. Edinburgh: Churchill Livingstone Elsevier; 2010.p.579-80.

3. National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. NIH Publication No. 02-5215. Bethesda, MD: National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health, 2002.
4. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine. Clinical Practice Guidelines We Can Trust: The National Academic Press, 2011.
5. Scott M, Grundy SM. Then and Now: ATP III vs IV. Dyslipidaemia: July 23, 2014. Cardiosource.org.
6. Grundy SM, Cleeman JJ, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
7. National Cholesterol Education Panel. 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; 106:3143-3421.
8. Taylor F, Huffman MD, Macedo AF et al. Statins for the primary prevention of cardiovascular disease. *The Cochrane database of systematic reviews* 2013;1: CD004816.
9. Cholesterol Treatment Trialists Collaboration, Mihaylova B, Emberson 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 randomized trials. *Lancet* 2012;380:581-90.
10. Downs J, Clarfield M, Weis al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/Tex CAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-1622.
11. Nakumary H, Arakawa K, Itakura H et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study) a prospective randomized controlled trial. *Lancet* 2006; 368:1155-1163.
12. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention 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.
13. Shepherd J, Blauw GJ, Murphy MB et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomized controlled trial. *Lancet* 2002;360:1623-30.
14. Forman DE, Rich MW, Alexander KP et al. Cardiac care for older adults: Time for a new paradigm. *J Am Coll Cardiol* 2011;57:1801-10.
15. Miller M, Stone NJ, Ballantyne C et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2011;123:2292-333.
16. 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 randomized trial *Lancet* 2010; 376:1670-1681.
17. La Rosa JC, Grundy SM, Waters DD et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
18. Pedersen TR, Faergeman O, Kast5elein JJP et al. High-dose atorvastatin Vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;2437-45.
19. Baigent C, Blackwell L, Emberson J et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomized trial. *Lancet* 2010;376:1670-81.
20. Canon CP, Brunwal E, Mc Cabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes *N Eng J Med* 2004;350:1495-504.
21. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of stain therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012;380:565-71.
22. Goff DC Jr, Lloyd-Jones DM Benneft G, et al. 2013 ACC/AHA Guideline on the amount of cardiovascular risk: A report of the American college of Cardiology/ American Heart Association Task force on Practice Guideline. *Circulation*. November 12, 2013;1-84.
23. Ridker PM, Cook NR, Statins: New American guidelines for prevention of cardiovascular disease. *Lancet* 2013;382: 1762-65.
24. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomized controlled trials. *Br Med J* 2009;338:b2376.
25. Bukkapatnam RN, Gabler NB, Lewis WR. Statins for primary prevention of cardiovascular mortality in women: a systematic review and meta-analysis. *Prev Cardiology* 2010;13:84-90.
26. Eckel RH, Jakicic J, Ard J, Hubbard VS, Janet M, Jesus de et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk. *J Am Coll Cardiol* 2013; 1-32.
27. Brown BG, Zhao XQ, Chait A et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583-92.
28. AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255-67.