Editorial

The 2013 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines for cholesterol management and for cardiovascular risk stratification: A reappraisal

Manish Bansal [a], K. Sarat Chandra [b,c,*]

[a] Consultant Cardiologist, Medanta – The Medicity, Gurgaon, India
[b] Chief Cardiologist, Indo US Superspeciality Hospital, Hyderabad, India
[c] Editor, Indian Heart Journal

The American College of Cardiology (ACC) and American Heart Association (AHA), in collaboration with the National Heart, Lung and Blood Institute (NHLBI), have recently released a set of four important guideline documents that provide recommendations for blood cholesterol management in adults, management of overweight and obesity, life-style modifications to reduce cardiovascular (CV) risk and the approach to CV risk stratification.[1–4] Of these, the cholesterol guidelines were perhaps the most awaited, given the significant improvements that have taken place in our understanding of lipid management over the past decade, since the previous NHLBI guidelines (adult treatment panel III) were last updated.[5] However, the new recommendations depart heavily from the prevailing concepts in lipid management and in this process have sparked off an intense debate about their rationale and practicality. Therefore, a critical review of these guidelines, along with the related document on CV risk stratification, is warranted before we embark on the task to incorporate them in to our clinical practice.

1. What is new in the new cholesterol guidelines?

In 2008, the NHLBI expert panel set out to review the existing literature on relationship between blood cholesterol levels and CV disease (CVD) and impact of various lipid lowering therapies on CV risk. In order to be the most evidence-based, the NHLBI advisory council required the expert committee to strictly adhere to the highest quality data derived predominantly from randomized controlled trials (RCTs), systematic reviews and meta-analyses of RCTs. Thus, most of the recommendations provided in the current guideline document are based on such data only and, except in few circumstances, no recommendation has been made if a relevant RCT or meta-analysis was not available to answer a particular critical question.[1]

In the pursuit to adhere to data derived mainly from RCTs, the current guidelines have provided recommendations that significantly depart from the existing practice. Unlike the previous ATP III guidelines[5] and all the current guidelines from competent authorities (such as European Society of Cardiology,[6] American Diabetes Association[7]), the present guidelines have completely set aside the need to define any LDL-C thresholds or goals. Instead, four risk groups have been identified that need to be prescribed either moderate or high-intensity statin therapy, regardless of their baseline LDL-C levels and without aiming for a particular pre-defined LDL-C target. These risk groups include – 1) patients with clinically evident atherosclerotic cardiovascular disease (ASCVD), 2) those with primary elevations of LDL-C > 190 mg/dl, 3) diabetics aged 40–75 years and having LDL-C between 70 and 189 mg/dl, and 4) for everyone who is 40–79 years old, has LDL-C above 70 mg/dl and in whom estimated 10-year risk of hard CV disease is >7.5% (and even those with 5.0–7.5% risk) according to the new risk algorithm. At the same time, the guidelines have also identified patients for whom available data do not support statin therapy and for whom no

recommendation is made. These include chronic kidney disease patients requiring maintenance hemodialysis and those with symptomatic heart failure. Finally, the panel also cited the lack of RCT evidence to support the use of non-statin cholesterol lowering drugs, either in combination with statins or as mono-therapy in statin-intolerant patients.[1]

2. What are the practical issues with these recommendations?

The major strength of these guidelines is that they are based on RCT data and also promise to simplify lipid management by eliminating any need to focus on LDL-C targets and by simplifying available therapeutic options for lipid lowering. However, there are several practical challenges with this approach as outlined below.

The elimination of LDL-C goals aims to prevent under-treatment of individuals with LDL-C levels close to the 'goals' and unwarranted over-treatment of those with very high baseline LDL-C levels who have achieved a significant fall in LDL-C but LDL-C still remains above the 'target' level. However, the reverse is also true. According to the new guidelines, a patient with significantly elevated LDL-C (e.g. 180 mg/dl) but without other CV risk factors will not be a candidate for lipid lowering therapy whereas another patient with marginally elevated LDL-C (80 mg/dl) but without overt ASCVD will qualify for high-dose statin therapy, if overall 10-year risk of hard CV events is >7.5%. These observations are clearly contradictory to available trial data that show benefit with statin therapy in patients with high baseline LDL-C irrespective of other CV risk factors.

Further, these recommendations are based on the premise that in appropriately selected patients, high-intensity (defined as the one resulting in ≥50% reduction in LDL-C from baseline) or moderate-intensity (one that is expected to reduce LDL-C by 30—50%) statin therapy provides the most favorable risk-benefit ratio. However, it is well known that individual responses and tolerability to statin therapy vary considerably, translating into variable magnitude of LDL-C reduction with variable degree of CV risk reduction. In the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis of 26 statin trials, it was found that each 1 mmol/l (~39 mg/dl) reduction in LDL-C was associated with a 22% proportional reduction in major vascular events.[8] Thus, the net benefit achieved correlated directly with the magnitude of LDL-C reduction. Hence, a patient having sub-optimal response to a particular statin dose is likely to benefit from further intensification of life-style measures, an increment in the statin dose and/or change of statin preparation to achieve adequate LDL-C reduction. However, in absence of a pre-defined LDL-C goal, it will be difficult to determine whether a particular patient has achieved a desired fall in LDL-C or not. In addition, successful achievement of LDL-C goal provides the patient with a sense of accomplishment, boosts his/her morale and motivates him/her further to continue with the treatment regimen. At the same time, persistently elevated LDL-C above the goal can help improve patient compliance to the treatment, esp by the adoption of a healthy life-style.

The notion that the current guidelines do not recommend any LDL-C goal is actually not entirely correct. As mentioned above, the present guidelines define high-intensity statin therapy as the one that is expected to reduce LDL-C levels by ≥50% and moderate-intensity statin therapy as the one likely to reduce LDL-C by 30 to <50%. Therefore, if moderate-intensity statin therapy is initiated in two patients with baseline LDL-C of 150 mg/dl and 100 mg/dl respectively, their LDL-C levels are expected to fall to approximately 80 mg/dl and 50 mg/dl, respectively. Thus, the current guidelines do also implicitly suggest what LDL-C level to expect in a patient initiated on statin therapy but unlike the previous guidelines, do not recommended any fixed LDL-C goals and do not emphasize on rigidly following LDL-C levels. Nevertheless, for the reasons mentioned above, it will be desirable to measure LDL-C in patients on statin therapy but their interpretation will now be problematic in many ways:

- The treating physician is now required to keep track of the patient's baseline LDL-C level during each follow-up visit to be able to take decisions about the further course of lipid lowering treatment.
- If a patient who is already on a statin visits a physician's clinic, the treating physician has to first find out his baseline LDL-C level to determine whether his current LDL-C level is acceptable or not. For example, if a patient on moderate dose statin therapy has LDL-C 90 mg/dl, it does not tell us whether the statin dose needs to be increased or continued as such.
- It is not uncommon to find statin therapy being initiated without obtaining baseline LDL-C levels. In such cases, it will be difficult to make subsequent therapeutic decisions.

These issues are particularly relevant for Asian populations in whom lower statin doses are very frequently used, both because of poorer tolerability as well as more marked LDL-C reduction as compared to western populations.[9—11] In such patients, adequacy of statin therapy cannot be determined without measuring on-treatment LDL-C.

Another controversial aspect of the new guidelines is the complete denouncement of the role of non-statin drugs in the management of dyslipidemia. Although it is true that there is only limited RCT data to support use of non-statin drugs for lipid lowering, some of these agents have shown promise. For example, in the ACCORD Lipid study, when fenofibrate was added to background statin therapy, it significantly reduced the incidence of CV events in patients who had atherogenic dyslipidemia.[12] This is consistent with the data from older studies comparing gemfibrozil and bezafibrate with placebo, which showed significant CV risk reduction with these agents, with more marked effects seen in those with elevated triglyceride levels.[13—15] Furthermore, fibrates have been shown to have additional non-cardiac benefits also, such as reduced progression of diabetic retinopathy. These findings suggest that fenofibrate may be a reasonable alternative in statin-tolerant patients, particularly in diabetic subjects with atherogenic dyslipidemia. Similarly, ezetimibe can be very helpful in lowering LDL-C in patients who are not able to achieve desired LDL-C reduction with maximally tolerated statin dose. However, it is important to remember that no lipid lowering drug can match statins in their efficacy to prevent CVD and hence, use of non-statin drugs at the expense of statins is not desirable and must be avoided.

Finally, the new guidelines propose statin use (at least moderate intensity) for everyone who is 40–79 years old, has LDL-C above 70 mg/dl and in whom estimated 10-year risk of hard CV disease is >7.5% (and even those with 5.0–7.5% risk) according to the new risk algorithm. This is a major deviation from the existing recommendations that had proposed much higher thresholds for initiation of statin therapy in primary prevention setting in absence of diabetes.[6,16] Data presented in the accompanying CV risk assessment document shows that >45% of the non-pregnant US population in the age group 40–79 years had an estimated 10-year risk of hard CV event ≥5.0%, translating into nearly 45 million middle-aged Americans potentially being prescribed a statin.[4,17] This is a huge number, appears rather irrational and has already invited sharp criticism from several quarters.

3. Guidelines on approach to CV risk assessment

The current guidelines for CV risk assessment have proposed a new risk calculator which is based on data collected from several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies, including the ARIC (Atherosclerosis Risk in Communities) study, Cardiovascular Health Study and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts.[4] The risk score is based on same risk factors as in previous scorings systems and includes smoking status, diabetes, systolic blood pressure (along with treatment status) with total and high-density lipoprotein cholesterol level, apart from age, gender and race. The purpose of the new risk score is to provide risk estimates which are more contemporary and therefore more representative of the true CV risk status of the present population. However, similar to the cholesterol guidelines, these too have several contentious issues that need to be addressed:

1. An intense debate has already ensued about the accuracy of the new risk calculator. Several leading researchers, including Dr Paul Ridker from Brigham and Women's Hospital, USA, have suggested that the new risk calculator overestimates CV risk.[17] They applied the new risk algorithm to patients included in three large-scale primary prevention studies, namely Women's Health Study,[18] the Physicians' Health Study,[19] and the Women's Health Initiative Observational Study[20] and found that the new scoring system overestimated risk by 75–150%. While this may relate to the fact that the patients included in these three studies were healthier than the general US population, more data and more analyses are required to provide the final answers.

2. The new risk algorithm cannot be applied to Asians as the Asian populations were not adequately represented in the studies used for developing this algorithm. It is already known that because South-Asians tend to develop CV disease at an earlier age than their western counterparts, most of the commonly available risk assessment tools such as Framingham risk score underestimate CV risk in South-Asians.[21,22] Strategies such as using a correction factor to recalibrate CV risk in South-Asians have been proposed in the past.[23] In this context, the accuracy of new risk score in Asians needs to be documented separately.

3. One of the major limitations of strategies aimed at primary prevention of CVD has been the general indifference and poor compliance of the common public towards preventive measures. The problem is greatest in persons at intermediate risk, who, because of the absence of overt CV disease, tend to under-recognize the risk of developing the disease in future. A potential way to overcome this challenge is to identify additional risk markers that can help further refine CV risk so that those at 'higher risk' of developing CVD could be specifically targeted. While numerous such risk markers are being evaluated currently, the new guidelines have suggested that only family history of premature CV disease, coronary artery calcium (CAC) score, high-sensitive c-reactive protein (hs-CRP) level and ankle-brachial index (ABI) have sufficient discriminatory value to be included in routine clinical practice.[4] Of these, family history of premature CVD is a known major CV risk factor and is easy to obtain, the other three tools have some or other practical limitation to their wide-spread use. CAC score, though sufficiently robust, is expensive, not easily available and requires radiation exposure which seriously limits its repeatability and therefore applicability for monitoring patients requiring primary prevention of CVD. Similarly, hs-CRP has also been shown to have a strong relationship with the risk of adverse CV events and is a target for statin therapy also but is readily influenced by any inflammatory condition compromising its specificity. The ABI, which measures the fall in systolic blood pressure in lower limbs, indirectly detects hemodynamically significant occlusive disease of lower limb arteries. Thus, it is really not a tool for early detection of atherosclerosis and has limited sensitivity in apparently asymptomatic patients undergoing CV risk stratification. This is highlighted in the ABI collaboration meta-analyses cited by the guideline document. In spite of the significantly high mortality risk (20% over 10 years) in the studied population, only 7.7% had ABI <0.9.[24]

In contrast, carotid intima-media thickness is a simpler tool, easily available, inexpensive and free from any side-effects. Numerous large-scale studies have demonstrated its utility for prediction of CV risk and most of the current guidelines, including the previous AHA guideline on CV risk stratification, endorse utility of CIMT in risk stratification of the patients otherwise considered to be at 'intermediate risk'.[25,26] Moreover, by providing visual, structural evidence of atherosclerosis, CIMT has also been shown to be useful in improving patient compliance to treatment.[27,28] Unfortunately, the current guidelines have not recommended CIMT as a routine test citing lack of outcome data and also because of apprehensions related to standardization of measurement technique. Possibly, a more rational approach would have been to emphasize upon its standardization rather than to exclude it.

4. Conclusions

"The absence of evidence to show benefit does not mean evidence of absence of benefit"

The recently published ACC/AHA guidelines for cholesterol management and CV risk stratification have taken a bold step by departing from the current clinical practice, in order to adhere strictly to data derived from large-scale RCTs. At the same time, these guidelines have also simplified lipid management approach by eliminating any need to define fixed LDL-C goals and by simplifying therapeutic options. However, in this process, these guidelines have raised several questions that need to be answered before they could receive widespread adoption in to regular clinical practice.

REFERENCES

1. Stone NJ, Robinson J, Lichtenstein AH, 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.

2. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/ American heart Association Task Force on practice guidelines and the Obesity Society. *Circulation.* 2013.

3. Eckel RH, Jakicic JM, Ard JD, 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. *Circulation.* 2013.

4. Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. 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.* 2013.

5. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program adult treatment panel III guidelines. *Circulation.* 2004;110:227—239.

6. Reiner Z, Catapano AL, De Backer G, et al. 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.

7. Standards of medical care in diabetes—2013. *Diabetes Care.* 2013;36:S11—S66.

8. Baigent C, Blackwell L, Emberson J, et al. 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—1681.

9. Matsuzawa Y, Kita T, Mabuchi H, et al. Sustained reduction of serum cholesterol in low-dose 6-year simvastatin treatment with minimum side effects in 51,321 Japanese hypercholesterolemic patients. *Circ J.* 2003;67:287—294.

10. Wu CC, Sy R, Tanphaichitr V, Hin AT, Suyono S, Lee YT. Comparing the efficacy and safety of atorvastatin and simvastatin in Asians with elevated low-density lipoprotein-cholesterol—a multinational, multicenter, double-blind study. *J Formos Med Assoc.* 2002;101:478—487.

11. Deedwania PC, Gupta M, Stein M, Ycas J, Gold A. Comparison of rosuvastatin versus atorvastatin in South-Asian patients at risk of coronary heart disease (from the IRIS Trial). *Am J Cardiol.* 2007;99:1538—1543.

12. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1563—1574.

13. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med.* 1987;317:1237—1245.

14. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med.* 1999;341:410—418.

15. Tenenbaum A, Motro M, Fisman EZ, Tanne D, Boyko V, Behar S. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med.* 2005;165:1154—1160.

16. 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.

17. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet.* 2013;382:1762—1765.

18. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;352:1293—1304.

19. Final report on the aspirin component of the ongoing physicians' health study. Steering committee of the physicians' health study Research group. *N Engl J Med.* 1989;321:129—135.

20. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol.* 2003;13:S107—121.

21. Kanjilal S, Rao VS, Mukherjee M, et al. Application of cardiovascular disease risk prediction models and the relevance of novel biomarkers to risk stratification in Asian Indians. *Vasc Health Risk Manag.* 2008;4:199—211.

22. Bansal M, Shrivastava S, Mehrotra R, Agarwal V, Kasliwal RR. Low Framingham risk score despite high prevalence of metabolic syndrome in asymptomatic North-Indian population. *J Assoc Physicians India.* 2009;57:17—22.

23. Enas EA, Singh V, Munjal YP, et al. Recommendations of the second Indo-U.S. health summit on prevention and control of cardiovascular disease among Asian Indians. *Indian Heart J.* 2009;61:265—274.

24. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA.* 2008;300:197—208.

25. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography carotid Intima-Media thickness Task Force Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr.* 2008;21:93—111.

26. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol.* 2010;56:e50—103.

27. Bovet P, Perret F, Cornuz J, Quilindo J, Paccaud F. Improved smoking cessation in smokers given ultrasound photographs of their own atherosclerotic plaques. *Prev Med.* 2002;34:215—220.

28. Wyman RA, Gimelli G, McBride PE, Korcarz CE, Stein JH. Does detection of carotid plaque affect physician behavior or motivate patients? *Am Heart J.* 2007;154:1072—1077.