Published in final edited form as:

Coron Artery Dis. 2014 June ; 25(4): 360–363. doi:10.1097/MCA.0000000000000086.

A controversial step forward: a commentary on the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults

Philip A. Ades

Division of Cardiology, University of Vermont College of Medicine, Fletcher Allen Health Care, Burlington, Vermont, USA

Abstract

The 2013 ACC/AHA guidelines on the treatment of blood cholesterol in adults is a major step forward in the field of preventive cardiology but it is not without controversy. It should be well accepted that in individuals with established atherosclerotic vascular disease, individuals with a low-density lipoprotein cholesterol of greater than 190 mg/dl and individuals with diabetes, treatment with an appropriate fixed dose of a statin, without titration to a specific low-density lipoprotein goal, will provide substantial protection against future atherosclerotic vascular disease events. More controversial is the utilization of a risk calculator in primary care to determine which individuals will require a statin. For as long as these risk calculators are in question, primary care practitioners will struggle to make treatment decisions. Factors such as cardiovascular fitness, measures of adiposity, and details of the family history will aid in treatment decisions.

Keywords

atherosclerotic risk; cardiac prevention; cholesterol management; clinical guidelines

Introduction

It has been more than 10 years since the last full version of the NCEP guidelines for cholesterol management was published [1]. Certainly enough, new data have emerged to justify a new version to better target lipid management therapies for the reduction of cardiovascular events in our adult population [2]. The HMG CoA-reductase inhibitor classes of medications (statins) were the mainstay of treatment in 2002 and they are more firmly entrenched as the mainstay of therapy in 2013. While one might have predicted that genotyping or new classes of medications would have led to the targeting of new drugs or multidrug regimens to specific genotypes or phenotypes, the opposite is actually true. A single class of drugs is so powerful and so effective that when they are tolerated and taken in

high doses, the addition of other drug classes to the regimen does not appear to further reduce cardiovascular risk.

The development of these new guidelines was based on an extensive review of randomized controlled trials (RCTs) that assessed their effect on major atherosclerotic events rather than on the effect of drug regimens on optimization of the lipid profile. No longer need we titrate drug doses to their individualized effect on low-density lipoprotein (LDL)-cholesterol or non-high-density lipoprotein (non-HDL)-cholesterol as the RCT studies were simply not designed that way. Rather, research participants took fixed doses of statins and were compared with placebo or other fixed doses of statins without titration to a specific level of LDL-cholesterol. Somewhat similar to antibiotics or antidepressants, one administers a medication (statin) for the treatment and prevention of a condition [atherosclerotic vascular disease (ASCVD)] and one need not titrate to a specific endpoint of LDL-cholesterol any more than we titrate antibiotics dose to a bacteria count in the lungs in the setting of bronchitis or pneumonia.

This commentary addresses in particular the highlights and strengths of the new cholesterol guidelines. It also addresses what is controversial about the new guidelines. Finally, it addresses what is not addressed in the present guidelines and makes suggestions for the next version.

Highlights and strengths of the new cholesterol guidelines

Highlights of the new cholesterol management guidelines include that there are four classes of patients for whom treatment of cholesterol with statins is recommended (Table 1):

1. Individuals with established ASCVD.
2. Individuals aged between 40 and 75 years with an LDL-cholesterol of at least 190.
3. Individuals aged between 40 and 75 years with diabetes mellitus.
4. Individuals with a predicted 10-year ASCVD event rate of 7.5% or above.

The strengths of the guidelines include their simplicity, particularly as they apply to individuals with ASCVD, individuals with very high LDL levels, and individuals with type 1 or type 2 diabetes. In these three settings, the questions of who should be treated and how they should be treated are clearly addressed and the benefits of treatment have been very well documented in RCTs.

What is controversial?

Not treating to goal

Many combined analyses of RCTs show that the lower the LDL, the lower the ASCVD event rate; thus, many physicians have adopted the philosophy that 'lower is better'. Yet, as the writers of the present guideline point out, none of the RCTs that were used to establish the benefits of statins treated and titrated dosing to an LDL goal. Rather, established doses were administered and the long-term event rates were calculated. Although this is a change in how physicians will behave, it is supported by the data and makes sense. It will be

relatively easy to implement, although changes in drug doses in individuals already on a statin for ASCVD will need to be discussed with patients. It is also a change for patients with established coronary artery disease (CAD) who have been taught for many years to strive to reach their LDL goal. In many cases, patients have been advised to adhere strictly to dietary and exercise habits as it may allow them to minimize the dose of medication needed to attain their goal. As an example, a 60-year-old patient with established ASCVD (s/p percutaneous coronary intervention) with excellent lifestyle habits and on atorvastatin 10 mg was found in follow-up to have an LDL-cholesterol of 69 mg/dl. This patient should be advised that his/her efforts are beneficial and should be continued but that his/her coronary risk can be further reduced by increasing the atorvastatin to an intensive level of 40 or 80 mg daily. Alternatively, the patient could remain on his/her present dose but he/she may miss out on supplemental preventive benefits of a higher dose statin such as has been shown in newer RCTs.

The risk calculator

In recommendation #4, individuals 75 years of age or younger and with no established ASCVD but a predicted 10-year ASCVD event rate of at least 7.5% are advised to take a statin. This differs from the last NCEP guideline where patients at a 10-year risk of greater than 10% were considered as candidates for therapy. A criticism is that although, on one hand, we do away with titration of LDL to pre-established goals because none of the studies were so designed, we are deciding upon the use of statins in primary prevention using a risk calculator despite the fact that none of the studies were so designed. That is, risk calculators were not used to determine eligibility for the RCTs upon which these guidelines were based.

What is particularly controversial about recommendation #4 is the accuracy of the risk calculators that are located at the following web addresses: https://www.heart.org/gglRisk/main_en_US.html and <http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx>.

Concern has been expressed that these risk calculators generally overpredict ASCVD risk because of their use of older data to predict risk [3]. Indeed, according to the risk calculator, every 65-year-old man in the USA, no matter how well controlled his risk factors, is in a risk category where a statin is recommended. It matters not how fit or how fat he is (both independent risk predictors of ASCVD risk). It matters not that he never smoked, has a normal blood pressure and blood glucose. It matters not that his parents lived into their 90s. A statin is recommended. Certainly the writers of this guideline acknowledge that there is a bell-shaped curve around this risk prediction number, but it is nonetheless problematic that powerful risk predicting information such as fitness and waist circumference is not taken into account in the risk prediction instrument [4,5]. In contrast to a 65-year-old man, a 60-year-old woman whose parents died in their 50s and has an LDL of 175, an HDL of 40 but no other risk factors has a 5-year risk prediction of 3% and would not be treated with a statin according to the new guidelines. This despite the fact that she would represent the type of individual who would have been randomized in one of the primary prevention trials upon which these guidelines are based. A more updated risk predictor may partially solve these contrasting situations, but the risk calculator controversy is not confidence inducing for

primary care physicians who are told to discuss recommendations with their patients based both on contemporary data and on 'patient preferences'. The primary care physician needs accurate data as the foundation of this discussion. The availability of 'number needed to treat' (NNT) data would help in this discussion, although individual patients may not well understand this concept.

Overall, using data from primary prevention trials, the NNT to prevent a single cardiovascular disease (CVD) event is roughly 50 individuals over 5 years in a setting where the 10-year risk of CVD events was 15% [6]. If the CVD risk is 10%, the NNT would be 75 and if the risk is 7.5% it would be much higher. This is in contrast to the situation in secondary prevention where the NNT is much lower, in the range of 15–25 [7], to prevent an ASCVD event over 5 years. In this latter situation, the absolute risk reduction would be far greater than in primary prevention because of the higher baseline risk of ASCVD events in this higher risk population. Similarly, a cost-effectiveness analysis would vary on the basis of the NNT of the individual patient.

Conflicts of interest

The writing group of the present guidelines includes seven of 15 writers with conflicts of interest (although not the Chair or Co-Chairs), such as relationships with industry, speakers bureaus, and research funding. Although the writers believe that they can write and recommend impartially, it would have been preferable to remove these potential biases by only engaging individuals, who, in their professional lives, have chosen not to be funded by the lipid pharmaceutical industry. A large enough pool of lipid experts would remain to be able to put together an equally expert panel. This concern is partly balanced by the fact that many of the statins in question are generic drugs, but generic drugs are also huge business and in some cases generic companies are owned by well-known large pharmaceutical companies. While conflicts of interest were disclosed by the writing groups, it does not fully eliminate potential bias.

Also relevant to this topic is the extremely high cost of designing and carrying out large RCTs of drug therapies of hyperlipidemia. Only pharmaceutical agents with a large future sales potential will be deemed 'worth the effort' by pharmaceutical companies. Independent funding agencies such as the National Institutes of Health or the American Heart Association will often defer and leave the funding of large pharmaceutical trials to pharmaceutical companies. This results in a bias toward the funding of studies primarily for brand name agents as was the case for all of the statin medications. Other agents such as generic niacin, which is made by many different small vitamin companies and sells for pennies per pill, will have only very few studies available.

What is not addressed in the guidelines?

What is not addressed in the present cholesterol guidelines includes the following:

1. How to treat patients with statin intolerance, and
2. studies before 1995.

Treatment of patients with statin intolerance

Roughly 10% of individuals cannot tolerate statins long term [8]. Although this focuses therapeutic energy in these individuals on optimizing lifestyle treatments such as the quality and quantity of the diet, long-term exercise, smoking prevention, and blood pressure control, it also begs the question of whether other classes of lipid-lowering agents such as niacin, red rice yeast (RRY), bile resin-binding agents, fibrates, and cholesterol absorption inhibitors are effective in preventing ASCVD events.

Statin intolerance and the primary prevention of atherosclerotic vascular disease

Nonstatin treatments that have been assessed in an RCT format for the primary prevention of ASCVD include trials of cholestyramine and gemfibrozil.

The Lipid Research Clinics Coronary Primary Prevention Trial [9] published in 1984 assessed the effect of cholestyramine in 3806 middle-aged men with hypercholesterolemia and found that treatment was associated with a 19% reduction over 7 years of the primary endpoint, which was a combination of coronary heart disease death and nonfatal myocardial infarction (MI). The Helsinki Heart Study, published in 1987 [10], found that gemfibrozil reduced cumulative cardiac endpoints by 34% over 5 years in individuals with a non-HDL-cholesterol of at least 200 mg/dl. It is recommended that individuals who cannot take the recommended dose of statin because of intolerance consider first a lower dose of a less potent statin such as lovastatin or pravachol or alternatively consider agents such as cholestyramine or gemfibrozil, the latter for individuals with a non-HDL-cholesterol of at least 200 mg/dl.

Statin intolerance and the secondary prevention of atherosclerotic vascular disease

Nonstatin treatments that have been assessed in an RCT format for the secondary prevention of ASCVD include trials of niacin, RRY, and colestipol.

Whereas there has been considerable controversy as to whether niacin provides supplemental benefits when added to a high-intensity statin regimen such as in the AIM-HIGH where individuals had a mean statin-induced preniacin LDL level of 74 mg/dl [11,12], there are convincing data that in the absence of statin therapy, niacin reduces coronary events in study individuals with established CAD. Niacin has been assessed in the secondary prevention of ASCVD as a single agent in the Coronary Drug Project [13] and as part of nonstatin combination therapy in the FATS trial [14]. In the Coronary Drug Project study of 8341 men with previous MI, niacin treatment decreased nonfatal recurrent MI at 5 years and reduced the total mortality by 11% at 15 years 9 years after discontinuation of study drug. In the FATS trial of 146 men with documented CAD and hyperlipidemia, two treatment arms were compared with placebo on their effects on angiographic disease and coronary events at 2½ years. The treatment arms consisted of a combination of niacin–colestipol in one arm and lovastatin–colestipol in the other arm. Clinical events were

reduced both in the niacin–colestipol arm and in the lovastatin–colestipol arm compared with placebo. Angiographic progression of disease was also reduced in both treatment arms.

RRY was assessed in a secondary prevention trial in China published in 2008 [15]. In this multicenter study of almost 5000 individuals with a previous MI, an extract of RRY versus placebo was administered. After 4.5 years of follow-up, the RRY group showed a 45% reduction of the primary endpoint, which was a combination of coronary heart disease death or nonfatal MI. At issue with this study is the difficulty of translating the dose of the RRY extract used in China into the available preparations of RRY available in the US vitamin stores, health food coops, and over-the-counter pharmacies.

As described above, colestipol was assessed as a part of nonstatin combination therapy for secondary prevention in the FATS trial and was associated, in both arms, with a decreased rate of coronary events; however, one cannot sort out the independent effect of the colestipol versus effects of niacin and lovastatin [14].

For patients with ASCVD who cannot tolerate the recommended high-intensity statin, it is recommended that they first consider a low dose of a less potent statin such as lovastatin or pravachol. If even a low dose of a nonpotent statin is not tolerated, agents such as RRY, niacin, or a resin binder should be considered alone or in combination.

By not including studies from before 1995 such as the Coronary Drug Project, FATS, and the Lipid Research Clinics, there is an excessive focus on the benefits of statins versus nonstatin agents. If for no reason other than to provide useful information for individuals intolerant of statins, these data are of use in both primary and secondary prevention.

Summary

The new cholesterol treatment guidelines are a step forward in pharmacologic prevention as they focus on the singular primary outcome of preventing ASCVD events. However, by limiting studies to those published after 1995, they forego the lessons learned from earlier studies that are of great value, particularly for patients who cannot tolerate statin medications. The recommendations are least evidence based where they base primary care treatment recommendations on a risk calculator that may be faulty and may overestimate the number of patients who would benefit from statin treatment. It is certainly of concern that this risk calculator would recommend statin treatment for literally every man in the US aged between 65 and 74 years of age. Treatment decisions in primary care should be informed by the provision of NNT and cost-effectiveness data for age-stratified, race-stratified, and sex-stratified categories. The next version of these cholesterol guidelines should take these issues into account (Table 2).

Acknowledgments

This study was supported by the Vermont Center on Behavior and Health (NIH-NIGMS P20GM103644-01).

References

1. 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. [PubMed: 12485966]
2. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *J Am Coll Cardiol*. 2013 2013. [Epub ahead of print].
3. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet*. 2013; 382:1762–1765. [PubMed: 24268611]
4. Blair SN, Kampert JB, Kohl HW III, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*. 1996; 276:205–210. [PubMed: 8667564]
5. Dhaliwal SS, Welborn TA. Central obesity and multivariable cardiovascular risk as assessed by the Framingham prediction scores. *Am J Cardiol*. 2009; 103:1403–1407. [PubMed: 19427436]
6. Taylor FC, Huffman M, Ebrahim S. Statin therapy for primary prevention of cardiovascular disease. *JAMA*. 2013; 310:2451–2452. [PubMed: 24276813]
7. Rembold CM. Number-needed-to-treat analysis of the prevention of myocardial infarction and death by antidiyslipidemic therapy. *J Fam Pract*. 1996; 42:577–586. [PubMed: 8656168]
8. Eckel RH. Approach to the patient who is intolerant of statin therapy. *J Clin Endocrinol Metab*. 2010; 95:2015–2022. [PubMed: 20444930]
9. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984; 251:351–364. [No authors listed]. [PubMed: 6361299]
10. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, 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. [PubMed: 3313041]
11. AIM-HIGH Investigators. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011; 365:2255–2267. [PubMed: 22085343]
12. Genest J. High-density lipoprotein and residual cardiovascular risk: de minimis non curat medicus or the COURAGE to be SMART? *J Am Coll Cardiol*. 2013; 62:1842–1844. [PubMed: 23973697]
13. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986; 8:1245–1255. [PubMed: 3782631]
14. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990; 323:1289–1298. [PubMed: 2215615]
15. Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, et al. Chinese Coronary Secondary Prevention Study Group. 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; 101:1689–1693. [PubMed: 18549841]

Table 1

Recommendations for statin therapy

Patient classification	Intensity of therapy	Agents to consider
Clinical ASCVD	Age 75 years: high intensity ^a	Atorva 40 and 80, Rosuva 10–40
Age > 21 years	Age >75 years: moderate intensity ^b	Atorva 10, Simva 20–40, Rosuva 5
LDL-C 190 mg/dl	High-intensity statin	Atorva 40–80, Rosuva 10–40
Age > 21 years		
Diabetes (type 1 or 2)	If 10-year risk < 7.5%: moderate intensity	Atorva 10, Simva 20–40, Rosuva 5
Age 40–75 years	If 10-year risk >7.5%: high intensity	Atorva 40 and 80, Rosuva 10–40
Estimated 10-year risk > 7.5%	Moderate to high intensity	Atorva 10–80, Simva 20–40, Rosuva 5–40
Age 40–75 years		

ASCVD, atherosclerotic vascular disease; Atorva, Atorvastatin; LDL-C, low-density lipoprotein cholesterol; Rosuva, Rosuvastatin; Simva, Simvastatin.

^a High-intensity statin lowers LDL-C by >50%.

^b Moderate-intensity statin lowers LDL-C by 30–50%.

Table 2

Pertinent quotes for each theme

Distressing Symptoms	1) Patient: "Shortness of breath and chest pain, flown here a few days ago... I just couldn't get any air, so I went to local hospital to try to figure out if I just needed some oxygen or if something else was going on."
Unavoidable Progression of Chronic Disease	2)Patient: "I am at the later stages of it now. They say my heart is getting real stiff." 3)Patient: "Diabetes [has a] deteriorating effect on your life. If you have high blood pressure, that has to be controlled. So they all have an impact on weight. Weight gain puts pressure on your heart It's all integrated and interconnected and one has an effect on another down the stretch."
Influence of Psychological and Social Environment Factors	4)Patient: "I have a problem getting to the pharmacy, and paying... am not working, without money, you can't buy medication." 5)Caregiver; "It's impossible to eat a good, proper, nice balanced diet when you are trying to scrape and save every penny on food stamps. You don't have the luxury to be able to buy fresh vegetables." 6)Patient: "When I think about it, it is when I'm depressed that I eat stuff I shouldn't and drink too much. ... I just want to feel better, I just want to get to some kind of normal life."
Self-Care and Adherence with Medical Recommendations	7)Patient: "Yeah, I was meeting goals for most part, but did go over a few times. I'm not going to lie." 8)Patient: "I eat more salt in the hospital than I do at home! I follow the rules always when doctor tells me what to eat. Salt is not my problem. Diet is not my problem. It is hard to limit my salt intake but not as hard as it was."
Health System Factors	9)Caregiver; "Last time, he had been here 15 days and they just wanted to get us out. But he had already started to gain, 2lbs, before he even left. But it never stopped; it just kept going up and up and up." 10)Patient: "When I left I thought I was ok, but doc said that in retrospect she should have kept me a few more days." 11)Patient: "I wasn't ready, but there wasn't much they could do." 12)Patient: "I had a PCP there and it was really easy to get back and forth from his office. So I went there and they had no idea what to do with me." 13)Patient: "Patients are humans. Doctors forget, ... they are so into their routines and dealing with [sick] people every day, and spitting out orders ..." 14)Patient: "Biggest problem, our doc at home, he is a great communicator and talks to people up here before he does anything, but his lack of knowledge of heart disease, he doesn't do something or doesn't do something enough."