Review Article

Critical Review of the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Lower Atherosclerotic Cardiovascular Risk in Adults

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ABSTRACT

Background: The new lipid guidelines were published late last year, and were immediately the subject of intense controversy. Cardiologists in general tend to be an opinionated lot, but the hue and cry in response to these guidelines was unprecedented. These were updated after a period of 11 years, and were far reaching in their conclusions. As with all such important documents, they will likely have a significant impact on the way we practice medicine. Here, we try to distill the lengthy document to some take-home points for the busy readers of this Journal, touching on the evidence-base for the recommendations and the controversies surrounding them. (J Clin Prev Cardiol. 2014;3(2):43-8)

Introduction

The last Adult Treatment Panel (ATP) III recommendations were published in 2002 (1), and given how much the evidence-base has expanded since then, the new guidelines were eagerly awaited. The framework of the current guidelines differed significantly from prior iterations. National Heart Lung and Blood Institute (NHLBI) was given the task of development and convened the expert group in 2008; however it pulled out in 2013 mainly due to financial constraints, citing that guideline development was outside its purview. Later, National Lipid Association (NLA) also pulled out due to disagreements about the content (2). The American College of Cardiology (ACC)/ American Heart Association (AHA) task force was engaged to finally compile the evidence, formulate the guidelines and to make them available to the widest possible constituency. Apart from this, the expert group was also much more selective about the quality of evidence it considered, including mainly randomized controlled trials (RCTs) and meta-analysis. Only a few specific questions were addressed, and as a result the document is less vast and more accessible (3).

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Treat to Target Dose

This is perhaps the most far-reaching and practice-changing recommendation. The debate between "treat to target level" versus "treat to target dose" is not new in cardiology. The established practice, supported by ATP III, has been to titrate treatment doses to "treat to target low-density lipoprotein cholesterol (LDL-C) levels." A whole generation of practitioners, and patients, has got accustomed to following LDL-C levels and adjusting medications. However, "treat to target dose" has been declared the ultimate victor by the current guideline. After reviewing all the evidence, including 19 RCTs, the guideline writers did not find any evidence to support titration to specific LDL-C targets. Even though all the statin RCTs have shown an association between lower LDL-C levels and mortality, the trial design tested fixed doses without titration to any specific LDL-C level as is commonly done in clinical practice. There is observational data from RCTs and genetic studies showing mutations causing low LDL-C levels decrease lifetime risk of atherosclerotic cardiovascular disease (ASCVD), and this was one of the main reasons listed by NLA for not endorsing the guideline. However, even though the relative risk reduction for ASCVD is proportional to the degree of LDL-C lowering, the currently used targets were arbitrary, and never tested in trials.

Strategy for LDL-C reduction

1. *Who and how to treat*: The guideline simplifies the process of deciding who to initiate on a statin, by outlining four well-delineated groups most likely to benefit. This is a significant improvement over the rather cumbersome process promoted by ATP III. Once that decision is made, the only other decision to be made is of a high-intensity versus moderate-intensity statin.

   High-Intensity statin therapy (daily dose lowers LDL-C on average, by approximately >50%) includes the following:

   - Atorvastatin 40–80 mg
   - Rosuvastatin 20–40 mg

   Moderate-intensity statin therapy (daily dose lowers LDL-C on average, by approximately 30% to <50%) includes the following:

   - Atorvastatin 10–20 mg
   - Rosuvastatin 5–10 mg
   - Simvastatin 20–40 mg
   - Pravastatin 40–80 mg
   - Lovastatin 40 mg
   - Fluvastatin XL 80 mg or fluvastatin 40 mg bid
   - Pitavastatin 2–4 mg

   There is strong trial evidence that high-intensity statin therapy with atorvastatin 40–80 mg reduces ASCVD risk more than moderate-intensity statin therapy with atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg bid (4). High-intensity statin therapy is recommended for the following patient groups:

   - Those with clinically manifest ASCVD,
   - Those with primary elevations of LDL-C >190 mg/dL,
   - Diabetics aged 40–75 years with LDL-C 70–189 mg/dL and without ASCVD, and estimated 10-year ASCVD risk >7.5%, or
   - Those without clinically manifest ASCVD or diabetes with LDL-C 70–189 mg/dL and estimated 10-year ASCVD risk >7.5%.

   Moderate-intensity is recommended in the following scenarios: age >75 years, potential for drug–drug interactions, and risk factors for statin intolerance (multiple comorbidities, including impaired renal or hepatic function, history of previous statin intolerance or muscle disorders, unexplained alanine aminotransferase [ALT] elevations more than three times upper limit of normal, concomitant use of drugs affecting statin metabolism, >75 years of age). Everyone will not tolerate high-intensity statins, and hence the guideline calls for titrating statin dose to maximally titrated dose. For those unable to tolerate high- or medium-intensity statin, low-intensity should still be used as it also decreases ASCVD (5).

2. *LDL monitoring*: Once a target dose statin in initiated, there is no need to follow LDL-C levels or to use them as a performance measure, other than to ensure compliance. Even though this recommendation is evidence-based, the practice of checking LDL-C levels is well-entrenched in clinical practice and is bound to cause confusion among patients. But history has taught us that practice patterns, when evidence-based, can change over time, as they did with infective endocarditis prophylaxis guidelines.

3. *Non-statin agents:* The guideline cites lack of evidence for using nonstatin alternatives for reducing cardiovascular disease (CVD) risk in statin-tolerant patients. Given the failure of ezetemibe and niacin to reduce mortality despite favorable changes in lipid profile, it was just a matter of time before the death knell sounded for these drugs (6). However, in patients unable to tolerate statins, the benefit of these drugs is untested. The guideline gives the option (based on expert opinion only, recognizing the lack of any RCT evidence) to use nonstatin alternatives in statin-intolerant individuals, and in those at high risk and unable to achieve a 50% LDL-C reduction with the maximally tolerated statin dose. Medications that have RCT evidence, albeit old, for CVD reduction in statin-naive patients include niacin (7), gemfibrozil (8,9) and cholestyramine (10). This also signals a shift in focus from cholesterol treatment to CVD prevention.

4. *Monitoring for adverse effects*: Routine monitoring of creatine phosphokinase and liver enzymes in asymptomatic individuals is not recommended. Overall, this simplifies the process of statin initiation and followup for busy primary care physicians.

5. *No benefit:* Two groups are mentioned to not get benefit from a statin: New York Heart Association

class 2–4 systolic heart failure (11) or those on hemodialysis (12).

Specific-risk Groups

1. Pre-existing CVD

CVD is defined by the inclusion criteria for the secondary prevention statin RCTs (acute coronary syndromes, or a history of myocardial infarction [MI], stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack [TIA], or peripheral arterial disease presumed to be of atherosclerotic origin). There is strong evidence to support high-intensity statin therapy in this group (13,14). This is similar to ATP III, and most patients with CVD are already prescribed a statin. The only difference is how to treat, as outlined above.

2. Diabetes

This includes all diabetics (type 1 and 2), aged 40–75 years, with LDL levels >70 mg/dL. There is strong evidence to support moderate-intensity statin therapy for primary prevention in this group (15,16). The only trial of high-intensity statin therapy in primary prevention was performed in a population without diabetes.
There is an option for high intensity if the calculated 10-year ASCVD risk (covered later) is >7.5%, based on the risk–benefit analysis done for the primary prevention group.

3. LDL-C >190 mg/dL

Individuals with severe elevations of LDL-C (>190 mg/dL) arising from genetic causes have a high lifetime risk for ASCVD events. Although no RCTs included only individuals with LDL-C >190 mg/dL, many trials did include individuals with LDL-C >190 mg/dL and all these trials consistently demonstrated a reduction in ASCVD events. A high-intensity statin should be prescribed, with the option of titrating to a 50% reduction in LDL-C and considering nonstatin alternatives to achieve this. This is consistent with clinical practice, and similar to ATP III.

4. Primary Prevention in Patients with High Estimated CV risk

This part of the guideline is probably the most controversial, and was responsible for all the hysteria featured in the media. In individuals 40–75 years of age with LDL-C > 70 mg/dL who are without clinical ASCVD or diabetes, initiation of statin therapy based on estimated 10-year ASCVD risk is recommended, regardless of sex, race or ethnicity. This is a big departure from earlier guidelines and current clinical practice. In essence, this takes LDL-C out of the equation when deciding for primary prevention. In defense, the guideline writers quote the Cholesterol Treatment Trialists (CTT) 2010 meta-analysis that found the relative risk reduction in ASCVD events to be similar across the spectrum of LDL-C levels >70 mg/dL (14).

Secondly, whereas earlier risk tools such as Framingham risk score included only coronary events as an endpoint, the new risk score adds stroke to the traditional endpoints, making it more clinically relevant, but at the same time increasing the at-risk population. ASCVD event is now defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke (17).

Thirdly, in Framingham risk scoring, a 10-year risk of >20% was considered to convey high risk and an indication for therapy, and a 10–20% risk conveyed intermediate risk and generally called for additional testing to decide for therapy. However, the current guideline drops the threshold significantly to a calculated 10-year risk of ASCVD event of >7.5%. In defense of the guideline writers, they do write that this threshold should not be an automatic trigger for therapy and should lead to a discussion with the patient. But given how guideline thresholds impact practice patterns, and with physicians constrained for time, there is a genuine concern about overprescription of statin therapy. Moreover, different patients and practitioners will pay different weightage to risks of potential ASCVD events and adverse effects of therapy. Hence in the future, performance metrics should not measure the number of eligible patients taking a statin for primary prevention, but rather the number of eligible patients who participate in shared decision-making.

The guideline writers came up with a new risk calculator called the Pooled Cohorts Equation. Using data from three exclusively primary prevention community based RCTs (5,18,19) that included individuals with LDL-C of 70–190 mg/dL, an estimate of the expected 10-year ASCVD event rates was derived from the placebo groups. The net benefit of statin therapy is the risk reduction for CVD compared with the excess risks of therapy. The relative risk reduction is in the range of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy. The rates of excess adverse events in the statin treatment groups were obtained

from meta-analyses of statin RCTs. The excess risk of diabetes was considered at ~0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 year. The risk of hemorrhagic stroke (~0.01 excess case per 100) and myopathy (~0.01 excess case per 100) were also considered. However, the estimate of myopathy is extremely conservative, and at odds with reports of upto 15-20% in clinical practice.

The risk–benefit analysis of therapy was found to be favorable at a threshold of >7.5% 10-year risk. For those with a 5–7.5% 10-year risk, moderate-intensity statin therapy (and not high-intensity) was found to have a favorable risk–benefit analysis. However, virtually all men older than 66 years and women older than 70 years have a calculated 10-year risk greater than 7.5%, even with optimal risk factors! Besides age, the major drivers of high global risk are smoking and hypertension, for which the target should be to eliminate cigarette use and to lower blood pressure, rather than statin therapy. The panel cites paucity of evidence to recommend therapy for primary prevention in elderly individuals with age >75 years.

Ridker and Cook calculated predicted 10-year risks of the same ASCVD events using this new ACC/AHA risk prediction algorithm and compared these estimates with observed event rates in three large-scale primary prevention cohorts (Women's Health Study, Physicians' Health Study, Women's Health Initiative Observational Study). In all three of these primary prevention cohorts, the new ACC/AHA risk prediction algorithm systematically overestimated observed risks by 75–150%, roughly doubling the actual observed risk (20). The guideline writers acknowledge this discrepancy, and retort that the external validation cohorts are more contemporary and motivated than the cohorts used in the risk prediction algorithm and thus reflect improved lifestyle and overall health.

Moreover, this strategy of using a global risk prediction score as an enrollment criterion has never been tested in a statin RCT. Instead, Ridker and Cook recommend using enrollment criteria of major primary prevention RCTs. However, such a process is bound to be cumbersome, and difficult to apply as a general guideline.

The risk calculator also gives an estimate of lifetime risk for ASCVD for adults 20–59 years old, as opposed to a 10-year risk. This is shown as the lifetime risk for a 50-year old without ASCVD who has the risk factor values entered into the spreadsheet, and gives 4 potential quartiles of risk. This provides a valuable tool to engage in a preventive therapy discussion with younger adults with risk factors, who will have a low 10-year risk but potentially a high lifetime risk. A downloadable spreadsheet for estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator.

Indian Perspective

1. *High intensity statin therapy.* There is evidence that Asians have an exaggerated response to statins as compared to their western counterparts. Among Asians, atorvastatin 10–20 mg/d and rosuvastatin 5–10 mg/d have been shown to result in as much as 40–50% reduction in the LDL-C. In the Investigation of Rosuvastatin in South Asians study (IRIS study), the largest statin efficacy trial in an exclusively South Asian population, 740 patients in North America received 6 weeks of treatment with rosuvastatin 10 or 20 mg/d and atorvastatin 10 or 20 mg/d (21). Nearly 40%, 47% and 45% reduction in LDL-C was seen with atorvastatin 10 mg, 20 mg and rosuvastatin 10 mg/d dose, respectively. Lower body mass index and slower statin metabolism may be possible reasons for this exaggerated statin response in Asians.

   No large-scale study has compared CVD event reduction with low-dose versus high-dose statin therapy exclusively in Asian populations. However, it is noteworthy that the observed benefit on CVD risk reduction is directly proportional to the reduction in LDL-C, suggesting that it may be possible to achieve a similar degree of CVD risk reduction with lower dosages of statins in Asian populations. Indeed, in the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) trial enrolling 7832 individuals, 10-20 mg pravastatin resulted in 33% reduction in CVD events as compared to diet alone (5).

   Exaggerated statin response in Asians also raises concerns of increased risk of adverse effects. Given these observations, coupled with the increased costs of higher statin doses, the strategy to routinely recommend high dose statin therapy for Indian patients may not be appropriate, as the desired LDL-C reduction can be achieved with much lower dosages. A more prudent approach could be to start

with commonly used dosages and then up-titrate to the desired magnitude of LDL-C reduction.

2. *LDL targets*. In the Indian population, lower statin doses are used frequently and baseline lipid levels are often not available. In the absence of a reference value, it becomes difficult to determine whether a particular patient has achieved a desired reduction in LDL-C. For example, if a patient on moderate-intensity statin therapy has LDL-C of 90 mg/dL, it does not tell us whether therapy needs to be intensified further or not.

3. *Non-statin agents*. Two large trials (Fenofibrate Intervention and Event Lowering in Diabetes [FIELD] and Action to Control Cardiovascular risk in Diabetes [ACCORD]) evaluated fenofibrate in diabetic patients. While most patients in FIELD were not on any statin (22), in ACCORD fenofibrate was added on top of simvastatin (23). In both these trials, fenofibrate did not result in any significant reduction in the primary end-point in the overall study population, but subgroup analysis showed benefit for those with atherogenic dyslipidemia (high triglycerides and low HDL-C). Given the high prevalence of atherogenic dyslipidemia in India, fenofibrate can be a useful adjunct. However, it must be emphasized that treatment with any nonstatin agent should not be at the cost of adequate statin therapy.

Conclusion

The new guidelines for the management of cholesterol are a significant step in the right direction by recommending prevention of stroke in addition to CVD, and focus appropriately on statin therapy rather than unproven nonstatin agents.

They simplify the process of initiating statin therapy by defining groups proven to get benefit, and of followup by eliminating LDL-C targets and need to follow CPK levels, thereby simplifying preventive care. The removal of arbitrary LDL-C treatment targets, though bound to cause confusion, is evidence-based and will get accepted over time. The mandate to titrate to high-intensity statin therapy in many patients will not change the practice of checking LDL-C levels.

The recommendation for statin therapy in individuals with >7.5% calculated 10-year ASCVD risk is controversial. There is concern for risk overestimation that will require continuous validation and recalibration of the risk prediction model. By lowering the risk threshold and placing emphasis on global risk that relies less on LDL-C levels, there is a genuine concern for overprescription. Whether we want to have most of our elderly population on statin therapy for primary prevention is a decision that each one of us has to make.

In addition, there may be practical challenges in application of these recommendations in countries, such as India, that have significant differences in CV epidemiology, prescription patterns, patient beliefs and the socioeconomic milieu.

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