The New ACC/AHA Cholesterol Guideline: A Significant Change with Significant Implications

Prabhjot Singh Nijjar, MD1; Michael D Miedema, MD, MPH2; Daniel Duprez, MD, PhD1

Abstract
The new ACC/AHA cholesterol guidelines were published recently and have been the subject of intense controversy. Earlier guidelines have also led to a passionate debate, 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, it 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.

Keywords — cholesterol, guideline, risk calculator, LDL, statin, high-intensity


I. INTRODUCTION
The 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 citing that guideline development was outside its purview, and transitioned the task to American College of Cardiology (ACC) / American Heart Association (AHA). Later, National Lipid Association (NLA) also pulled out, due to disagreements about the content.2 The expert group was also much more selective about the quality of evidence it considered, including mainly randomized controlled trials (RCT’s) and meta-analyses. In keeping with the Institute of Medicine’s guideline recommendations, the authors largely refrained from giving “expert recommendations”. Only a few specific questions were addressed, and as a result the document is more concise.3

II. TREAT TO TARGET DOSE
This is perhaps the most far reaching and practice changing recommendation. There has been a long-standing debate between proponents of “Treat to Target Level” vs “Treat to Target Dose”. 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, are 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 RCT’s, the guideline writers did not find any evidence to support titration to specific LDL-C targets. Even though there is compelling observational data from all the statin RCT’s that have shown an almost linear association between lower LDL-C levels and lower mortality, the trial designs tested fixed doses without titration to any specific LDL-C level as is commonly done in clinical practice. There is also lower lifetime risk of atherosclerotic cardiovascular disease (ASCVD) in individuals with mutations causing low LDL-C levels such as familial hypobetalipoproteinemia. This controversy 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, used as an unfair performance metric, sometimes encouraged less evidence based non-statin use, and never tested in trials.
Table 1. Summary of major changes in new ACC/AHA guideline on cholesterol treatment compared to ATP III.

<table>
<thead>
<tr>
<th>IN</th>
<th>OUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD prevention</td>
<td>Cholesterol treatment</td>
</tr>
<tr>
<td>Statins</td>
<td>Non-statin</td>
</tr>
<tr>
<td>Treat to Target Dose</td>
<td>Treat to Target Level</td>
</tr>
<tr>
<td>High-intensity statin</td>
<td>LDL monitoring</td>
</tr>
<tr>
<td>Four specific treatment groups</td>
<td>Risk factor tiered groups</td>
</tr>
<tr>
<td>Primary prevention based on global risk</td>
<td>Primary prevention based on LDL level</td>
</tr>
<tr>
<td>Risk score - Pooled Cohorts</td>
<td>Risk score – Framingham</td>
</tr>
<tr>
<td>ASCVD (stroke) prevention</td>
<td>Only CVD prevention</td>
</tr>
</tbody>
</table>

ATP: adult treatment panel, CVD: cardio-vascular disease, ASCVD: athero-sclerotic cardio-vascular disease, LDL: low-density lipoprotein

III. 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 4 well delineated groups most likely to benefit based on their elevated absolute risk for ASCVD. High-intensity statin therapy is recommended for the following patient groups

- Clinically manifest ASCVD.
- Primary elevation of LDL-C >190 mg/dl.
- Diabetics aged 40 to 75 years with LDL-C 70-189 mg/dl, 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%.

This is a significant improvement over the rather cumbersome process outlined by ATP III. High intensity statin is expected to lower LDL-C by > 50%, and moderate intensity statin lowers LDL-C by 30-50% (Table 2). There is strong trial evidence that high-intensity statin therapy with atorvastatin 40 mg to 80 mg reduces ASCVD risk more than moderate-intensity statin therapy with atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20 mg to 40 mg bid (Table 3). Moderate intensity statin therapy is recommended when there are risk factors for statin intolerance [age > 75 yrs, multiple comorbidities such as impaired renal or hepatic function, history of previous statin intolerance or muscle disorders, unexplained alanine aminotransferase (ALT) elevations >3 times upper limit of normal, concomitant use of drugs affecting statin metabolism, or complex medication regimens such as solid organ transplantation or on anti-retroviral therapy]. Caution is also suggested with asian ancestry and prior hemorrhagic stroke. 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.

2. LDL monitoring

Once a target dose statin is initiated, the authors say there is no need to follow LDL-C levels or to use them as a performance measure, other than to ensure compliance. However, there is inter-individual variation in response to statins, and all those initiated on a high intensity statin will not get a > 50% reduction in LDL-C. In high-risk patients, the guideline allows for addition of non-statin agents for further LDL-C reduction, but unfortunately, the evidence base for add-on therapy is weak (Table 4). The practice of checking LDL-C levels is well entrenched in clinical practice, and serves as motivation for physicians and patients alike. It will still be necessary in certain high-risk individuals, and is not likely to change.

3. Non-statin agents

The guideline cites lack of evidence for using non-statin alternatives for reducing cardiovascular disease (CVD) risk in statin-tolerant patients. Ezetemibe and niacin do not reduce mortality despite favorable changes in lipid profile, leading to the current guidelines recommending avoidance of routine use of these drugs. 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 non-statin 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 (Table 5), albeit old, for CVD reduction in statin-naive patients include niacin, gemfibrozil, and cholestyramine. This also signals a shift in focus from cholesterol treatment to CVD prevention.

Table 2. Statin intensity dosing according to the new ACC/AHA guideline on cholesterol treatment.

<table>
<thead>
<tr>
<th>High-Intensity statin therapy</th>
<th>Moderate-Intensity statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Daily dose lowers LDL-C on average, by approximately &gt; 50%)</td>
<td>(Daily dose lowers LDL-C on average, by approximately 30-50%)</td>
</tr>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10-20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
</tr>
<tr>
<td>Simvastatin 20–40 mg</td>
<td>Simvastatin 20–40 mg</td>
</tr>
<tr>
<td>Pravastatin 40-80 mg</td>
<td>Pravastatin 40-80 mg</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td>Fluvastatin XL 80 mg or Fluvastatin 40 mg bid</td>
<td>Fluvastatin XL 80 mg or Fluvastatin 40 mg bid</td>
</tr>
<tr>
<td>Pitavastatin 2–4 mg</td>
<td>Pitavastatin 2–4 mg</td>
</tr>
</tbody>
</table>

Table 3. Statin Dose Intensity Trials comparing high dose statin vs moderate or low dose statin
4. Monitoring for adverse effects
Routine monitoring of creatine kinase (CK) and liver enzymes in asymptomatic individuals is not recommended. Overall, this simplifies the process of statin initiation and follow up for busy primary care physicians.

5. No benefit
Two groups are mentioned to not get benefit from a statin; New York Heart Association class II-IV ischemic systolic heart failure, or those on hemodialysis.

IV. RISK GROUPS

1. Pre-existing CVD
CVD is defined by the inclusion criteria for the secondary prevention statin RCT’s (acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin). There is strong evidence to support high intensity statin therapy in this group. 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 individuals with diabetes (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. 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.

Table 4. Contemporary Non-Statin RCT’s (with control group receiving a statin)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT</td>
<td>Atorvastatin 80 mg vs 10 mg</td>
</tr>
<tr>
<td>IDEAL</td>
<td>Atorvastatin 80 mg vs Simvastatin 40 mg</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>Atorvastatin 80 mg vs Pravastatin 40 mg</td>
</tr>
<tr>
<td>A to Z</td>
<td>Simvastatin 80 mg vs 40 mg</td>
</tr>
<tr>
<td>SEARCH</td>
<td>Simvastatin 80 mg vs 20 mg</td>
</tr>
</tbody>
</table>

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 of 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 non-statin 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 statin-eligible group has clearly been the most controversial and represents the largest paradigm shift compared to prior guidelines. 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 about statin initiation 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. 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 end-points, 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%. The guidelines are clear 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 over-prescription of statin therapy. Moreover, different patients and practitioners will place different weightage on risks of potential ASCVD events and adverse effects of therapy. Hence in the future, performance metrics should consider not measuring the number of eligible patients taking a statin for primary prevention, but rather the number of eligible patients who participate in shared decision making.

Table 5. Non-Statin RCT’s (with control group receiving placebo)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial (year published)</th>
<th>Main inclusion criteria</th>
<th>CHD reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>Coronary Drug Project7 (1975)</td>
<td>Secondary prevention</td>
<td>At 5 yrs - MI, no mortality effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At 9 yrs - mortality</td>
</tr>
<tr>
<td></td>
<td>Helsinki Heart Study 9 (1987)</td>
<td>Primary prevention, LDL -189</td>
<td>34% RRR in MACE</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Lipid Research Clinics10 (1984)</td>
<td>Primary prevention, TC - 270</td>
<td>19% RRR in MACE</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TC: total cholesterol, RRR: relative risk reduction, MACE: major adverse cardiovascular events, MI: myocardial infarction, CHD: coronary heart disease, VA-HIT: Veterans Affairs High-density lipoprotein Intervention Trial

V. RISK CALCULATOR

The guideline writers created a new risk calculator called the Pooled Cohorts Equations (using Atherosclerosis Risk in Communities (ARIC), Cardiovascular Heath Study (CHS), Coronary Artery Risk Development in Young Adults (CARDIA), Framingham Original and Offspring cohorts).3 The risk variables are similar to Framingham risk score, but this pooled cohort also included black participants and hence adds race as a variable. Certain variables are recommended to be considered in individuals in whom the treatment decision is uncertain (hs-CRP > 2 mg/L, family history of pre-mature CAD, ABI < 0.9, CAC score > 300 or 75th percentile, LDL-C > 160 mg/dL, high lifetime risk), while recommending against carotid intima-media thickness (CIMT).

Using data from 3 exclusively primary prevention community based RCT’s,5,18,19 that included individuals with LDL–C between 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 RCT’s. 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.3 It is well known that adverse effects reported in RCT’s are significantly lower compared to real-life observational studies. This has been attributed to exclusion of patients with comorbidities, run-in periods in which people who do not tolerate statins are excluded, and significant dropout rates. However, even though the estimates of myopathy reported in the observational literature has recently been the subject of controversy,20 it is clearly in excess of the modest incidence considered in the guideline. Statins, compared to placebo, have been associated with a higher risk of developing incident diabetes mellitus in many reports. The reason for this is poorly understood. In an analysis of the TNT trial data, weight gain while on statin therapy was an independent predictor of the risk of developing diabetes.21 A recently published meta-analysis of 17 RCT’s found the risk of developing diabetes to be dose and intensity dependent,22 and this was considered in the guideline risk-benefit analysis above. 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. Given that age is the dominant predictor in the risk calculator, 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! This would include roughly 33 million middle-aged Americans without CVD (another 12 million at >5-0–7-4% 10-year risk), or 1 in 3 American adults.23

Besides age, the major drivers of high global risk are smoking and hypertension, for which the primary target should be to eliminate cigarette use and to lower blood pressure. 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.23 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. Risk prediction models are never perfect, and it maybe unfair to hold the new equation to a higher standard.

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 RCT’s. However, such a process is bound to be cumbersome, and as pointed out in the guideline, would lead to overtreatment in low risk individuals and undertreatment in high risk individuals.

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.

VI. CONCLUSIONS

The new guidelines for the management of cholesterol are a significant step in the right direction by focusing appropriately on statin therapy rather than unproven non-statin agents and using absolute risk as the basis for treatment. Allocating statins based on absolute risk is clearly a more evidence-based approach and they simplify the process of follow up by eliminating LDL-C targets and need to follow CK levels. 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 over-estimation 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 over-prescription. This approach is in direct conflict with personalizing the approach to prevention as age is the dominant risk factor in the current calculator and everyone ages at a similar rate. Whether or not the majority of the elderly population should be on statin is a question that has ethical implications in addition to consideration of efficacy, risks, and costs.

VII. ACKNOWLEDGMENTS

Conflicts of interest: PSN, MDM: None. DD has received grants from NIH, Pfizer, Sanofi–Aventis, Regeneron.

References


[4]. Pedersen TR, Cater NB, Faergeman O, et al. Comparison of atorvastatin 80 mg/day versus simvastatin 20 to 40 mg/day on frequency of cardiovascular events late (five years) after acute myocardial infarction (from the incremental decrease in end points through aggressive lipid lowering [IDEAL] trial). Am J Cardiol. 2010;106(3):354-359.


Abramson, Rosenberg et al. Should people at low risk of cardiovascular disease take a statin? BMJ 2013;347:f6123

Ong, Waters et al. Effect of Change in Body Weight on Incident Diabetes Mellitus in Patients With Stable Coronary Artery Disease Treated With Atorvastatin (from the Treating to New Targets Study). Am J Cardiol 2014;113:1593-1598
