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New Cholesterol Guidelines: A Significant Shift in Cholesterol Management

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The recently published cholesterol treatment guidelines developed by the American College of Cardiology (ACC) and the American Heart Association (AHA) in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) have recommend substantial changes from the 2004 Third Adult Treatment Panel (ATP III) guidelines.[1] The new guidelines abandon specific cholesterol treatment goals and instead focus on four high-risk groups that are most likely to benefit from statin therapy. The new guidelines also emphasize that overall risk of heart disease and stroke should be evaluated on an individual basis and recommend only using medications that have been proven to reduce atherosclerotic cardiovascular disease (ASCVD) risk.

To write the new guidelines, the expert panel focused heavily on high quality evidence from randomized controlled trials (RCTs) and systematic reviews of RCTs to create evidence-based recommendations, while the previous guidelines also included observational studies.[2] This approach led to more uncertainties in areas where high quality evidence is not available.

Should We Continue to Treat-to-Target?

The guidelines argue that multiple RCTs have shown that ASCVD events are reduced by optimizing fixed doses of statin therapy rather than obtaining pre-specified LDL-C goals.[3–5] However, a meta-analysis that evaluated the effects of statin therapy in lowering LDL-C in individuals with low risk for vascular disease conducted by the Cholesterol Treatment Trialists (CTT) Collaborators, supports LDL-C lowering goals.[6] Results showed that incremental reductions in LDL-C produced reductions in major vascular events, such as non-fatal myocardial infarction (MI) or coronary deaths (RR 0.79; 95% CI 0.77-0.81; p<0.0001, per 1.0 mmol/L reduction).[6] Nonetheless, the guideline panel concluded that there is insufficient evidence from RCTs that titration of LDL-C to specific targets further reduces coronary heart disease (CHD) or ASCVD beyond that achieved by simply giving a high-intensity statin. The guidelines also acknowledge that treating to cholesterol targets could potentially result in overtreatment with non-statin therapies which have failed to show a reduction in secondary ASCVD and could result in adverse effects from the use of multiple medications.[6,7]

Furthermore, when evaluating these trials further, the Treating to New Target (TNT) study and Pravastatin or Atorvastatin Evaluation of Infection Therapy (PROVE-IT) trial do indeed seem to support use of further lowering of target LDL-C levels for the reduction in risk of CV outcomes. The TNT study compared the CV benefits of atorvastatin 80 mg verses the lower dose of 10 mg in patients with stable CHD.[3] Results from TNT study demonstrated that treating to a mean target LDL-C of 75 mg/dL reduced the risk of nonfatal MI (HR=0.78; 95% CI 0.66-0.93; p=0.004) and fatal or nonfatal stroke (HR=0.75; 95% CI 0.59-0.96; p=0.02) compared to a target LDL-C of 100 mg/dl with fixed dose statins. [3] The PROVE-IT trial compared the risk reduction in death and CV events in individuals with an acute coronary syndrome taking pravastatin 40 mg with an LDL-C goal of 100 mg/dL compared to atorvastatin 80 mg with an LDL-C goal of 70 mg/dL.[4] Similarly to the TNT study, the results of the PROVE-IT trial suggests that a median LDL-C of 62 mg/dl significantly reduced the risk for requiring revascularizations (RR 0.87; 95% CI 0.76-0.99; p=0.04) and recurrent unstable angina (RR 0.74; 95% CI 0.55-0.99; p=0.02) when compared to a mean LDL-C of 95 mg/dL [4]

Focusing on Risk

The guidelines identified four high-risk populations that benefit from statin therapy: 1) individuals with known ASCVD, 2) adults with LDL-C ≥ 190 mg/dL, 3) individuals with diabetes who are 40 to 75 years old with LDL-C between 70 to189 mg/dL, 4) individuals who are 40 to 75 years old with a 10-year ASCVD risk greater than 7.5% and LDL-C between 70 to 198 mg/dL.[1] These risk categories make it easier to identify individuals who are most likely benefit from treatment with a statin. Rather than focusing on LDL-C targets, the new guidelines take into consideration a patient's overall CV risk.

Based on a review of RCTs included in the CTT meta-analysis, high-, moderate-, and low-intensity statin therapy were defined as a goal percent reduction in LDL-C by approximately ≥50%, 30-50%, and <30%, respectively (Table 1).[1] The meta-analysis provided high quality evidence that atorvastatin 40 mg to 80 mg reduced ASCVD risk significantly more than atorvastatin 10mg, pravastatin 40mg, or simvastatin 20 to 40 mg twice daily (moderate-intensity).

Table 1: Recommended Statins and Doses[8]

High-Intensity Therapy	Moderate-Intensity Therapy	Low-Intensity Therapy
Atorvastatin 40-80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20-40 mg** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* **Pravastatin 10-20mg** **Lovastatin 20 mg** *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

*Statins and doses that are **Bold** were evaluated in RCTs.
**Statins and doses that are *Italics* are approved by the U.S. FDA, but not tested in RCTs reviewed by the guideline panel

It is recommended that patients with established ASCVD and those with LDL-C ≥ 190 mg/dL (groups 1 and 2) should be initiated on high intensity statin therapy. They also recommend considering moderate intensity statin therapy in older patients (>75 years old) with ASCVD and in individuals with diabetes with LDL-C between 70 to 189 mg/dl. In those >75 years old, it is reasonable to continue statin therapy in those who are tolerating it, as the recommendation for starting a lower dose is based on expert opinion and the potential for an increased risk of adverse effects and drug-drug interactions. In those who are intolerant to a high-intensity statin and/or who are receiving concomitant medications that can potentially increase risk of statin related adverse events, moderate intensity therapy is also recommended. There is good evidence to support a benefit from moderate intensity statins if a patient cannot tolerate the higher dose. The guidelines also acknowledge that non-statin drug therapy has not shown a reduction in ASCVD events in RCTs. The lack of evidence for other medications as well as the minimal safety concerns associated with statins is cited as reason for the major emphasis on statin therapy in the guidelines.

For primary prevention in those without clinical ASCVD and LDL-C 70-189 mg/dl (group 4), the expert panel provides a new risk calculator to assess the estimated 10-year risk for an ASCVD event and to identify candidates for statin therapy.[1] Patients calculated as having >7.5% 10-year ASCVD risk are included as a major statin benefit group. [1] This recommendation that people at lower risk for CV should receive a statin comes from the CTT meta-analysis.[6,9] The authors concluded that the significant benefit of statins in low risk patients (five year risk <10%) outweighed any known risks of therapy, based on a reduction in major coronary events (RR 0.61; 99% CI 0.50-074; p<0.0001). However, the data did not demonstrate a significant effect on overall mortality (RR 0.95; 95% CI 0.86-1.04) in low risk patients. A recent article argued that the data supporting this conclusion was based on soft

outcomes such as coronary revascularization procedures, with an increased risk of bias from RCTs predominantly funded by the manufacturer of the statin being studied.[9] In addition, although the meta-analysis resulted in similar adverse effects between placebo and statin groups, generalizing this data to the real world population may be difficult. Study patient selection often results in exclusion of elderly patients, those with medical comorbidities or potential drug-drug interactions, and women.[10]

The peer-reviewed calculator uses the Pooled Cohort Equations which were developed by the Risk Assessment Workgroup of the guidelines. Controversy over the calculator's validity has been raised as it has only been peer-reviewed. There is no high quality evidence supporting its use, but rather the recommendation is based on expert opinion and outdated studies.[9,11] In addition, there has never been a RCT that uses a risk prediction score as inclusion criteria However, this calculator has both strengths and weaknesses. The guidelines state that use of the Pooled Cohort Equations more adequately represents women and African Americans when compared to Framingham calculations.[1] Furthermore, the new risk calculator may also overestimate risk and significantly broaden the patient pool that will qualify for statin treatment; a result that may lead to various unknown implications.

Implications to Practice

The new ACC/AHA recommendations are essentially based on the same body of evidence used by previous ATPIII guidelines, just excluding certain data based on study design. They have taken many steps in the right direction, including focusing on the prevention of stroke as well as heart disease, emphasizing statin therapy rather than agents with no proven benefit on clinical outcomes, and stating the importance of intensive treatment with statins.[12] Conversely, the recommendations for primary prevention and the concern for overestimation of risk remain contentious.

A recent study published by Pencina et al. used data from the National Health and Nutrition Examination Survey to estimate the number of individuals who would be candidates for statin therapy according to the new guidelines, as compared with the previous ATP III guidelines.[13] Of the study sample, 42% of subjects would be eligible for a statin on the basis of the ATP III guidelines, as compared to 56.5% based on the new ACC/AHA guidelines. When extrapolated to U.S. adults, an estimated 56 million adults (48.6% of U.S. population; 95% CI 46.3-51) adults would be eligible for statin therapy based on the ACC/AHA recommendations compared to 43 million (37.5%; 95% CI 35.3-39.7) per the ATP III guidelines [13] This indicates that almost 13 million additional individuals are now eligible for statin therapy; the majority of which now qualify as a result of the new risk calculator. In patients without CV disease, the biggest difference in eligibility was found in older adults between 60 and 75 years of age.

The National Committee for Quality Assurance is proposing retirement of LDL-C monitoring from HEDIS 2015 Criteria in patients 18 to 75 years old with overt ASCVD based upon the recommendation to move away from the treat-to-target method.[14] If approved, this proposal would result in vast changes in the monitoring and quality improvement initiatives involving these patients.

The current pipeline of new lipid lowering drugs is extremely immense, with over 50 new drugs currently in development.[15] Many of these drugs, such as the PCSK9 inhibitors and the cholesterol ester transfer protein (CETP) inhibitors, have novel mechanisms of action. Some of these agents are demonstrating drastic reductions in LDL-C levels (up to 70%).[16] Nevertheless, with the guidelines' shift in focus to ASCVD outcomes rather than reductions in LDL, they may not fit into future guidelines and recommendations unless they can demonstrate ASCVD risk reduction.

In conclusion, the recent ACC/AHA cholesterol guidelines have the potential to greatly simplify and improve care for those patients at a higher risk. The new risk assessment tool significantly expands the number of low risk patients on statin therapy for primary prevention. With the conflicting evidence and uncertainties in the guidelines, it remains essential that health care providers consider the risk benefit ratio for each individual patient until further data is available.

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