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Editorials

Consensus between the American College of Cardiology and the National Lipid Association on the use of non-statin therapy for atherosclerotic cardiovascular disease prevention

The 2013 ACC/AHA Guideline for the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults[1] and the National Lipid Association recommendations for the patient centered management of dyslipidemia: part I[2] share many similarities. Both the documents emphasize the importance of identifying high-risk patients, including those with atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes, and familial hypercholesterolemia (FH) and recommended that such patients engage in a provider–patient discussion focused on the value of ASCVD preventive treatment with lifestyle therapy and moderate- or high-intensity statins. However, there are differences between the approaches advocated by the 2 organizations, including: the breadth of the evidence base used; the value of using lipoprotein goals; an ASCVD risk assessment and treatment algorithm that focuses on the identification of statin benefit groups vs one that uses risk factor counting for clinical decision-making; the value of dependence on the new risk using American College of Cardiology (ACC)/American Heart Association (AHA) risk calculator to guide treatment decisions; and the indications for use of combination lipid-lowering therapy.

The ACC/AHA Guideline recommends that consideration of non-statin atherogenic cholesterol-lowering therapy for ASCVD prevention be reserved for consideration in: high-risk patients, including those with ASCVD, low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL, or diabetes aged 40 to 75 years who exhibit, after intensified lifestyle therapy, a less-than-anticipated response to maximal tolerated statin therapy (defined as <50% reduction in LDL-C in response to high-intensity statin therapy, or <30% reduction in LDL-C in response to moderate-intensity statin therapy) or unacceptably high on-treatment levels of LDL-C (not defined); or patients who are completely statin-intolerant. The NLA Recommendations—Part I recommend consideration of non-statins for patients on maximum tolerated statin therapy who have not reached their treatment goals for atherogenic cholesterol levels, particularly for those with very high or high ASCVD risk and those who are statin-intolerant. Part I also implies that non-statin therapy might be used in those with progressive atherosclerosis, or recurrent ASCVD events, in whom "very aggressive therapy to lower atherogenic cholesterol well below goal thresholds may be considered".

The NLA Recommendations—Part II[3] advises consideration of non-statin therapy for at-risk patients not at non–high-density lipoprotein cholesterol (non-HDL-C) or LDL-C goals while receiving maximal tolerated statin therapy. In such patients, the recommended order of addition of such therapies is: (1) ezetimibe 10 mg daily; (2) colesevelam 625 mg 3 tablets twice daily or 3.75-g powder form every day or in divided doses; and (3) extended-release niacin titrated to a maximum dose of 2000 mg daily. Niacin add-on therapy is not advised for those taking statin therapy with LDL-C < 70 mg/dL, based on randomized controlled trial (RCT) evidence of lack of benefit and possible harm in such patients. The use of PCSK9 inhibitor therapy is to be considered as a "conservative approach" in selected patients with: (1) ASCVD on maximal tolerated statin therapy with LDL-C ≥ 100 mg/dL or non–HDL-C ≥ 130 mg/dL and (2) heterozygous familial hypercholesterolemia (HeFH) with LDL-C ≥ 130 mg/dL and non–HDL-C ≥ 160 mg/dL. However, the authors suggest that in high-risk patients with recurrent or progressive ASCVD while on evidence-based therapy, clinicians may choose to prescribe PCSK9 inhibitors for those with LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL; or for those with statin intolerance who require substantial additional atherogenic cholesterol lowering.

In 2014, the ACC revised its approach to consensus statements to focus on the creation of concise expert consensus decision pathways (ECDPs) that would provide practical clinical guidance based on "expert opinion in areas in which important clinical decisions are not adequately addressed by the available existing trials". These ECDPs were developed to complement existing

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guidelines and provide clinical guidance during the period between new versions of the guidelines.

On September 16, 2015, the ACC held the second "LDL: Address the Risk Think Tank". This meeting included expert clinicians and stakeholders from key patient advocacy groups, health plans, pharmacy benefit managers, drug manufacturers, electronic health record vendors, and health systems to discuss the impact that newer data might have on the care of high-risk patients with dyslipidemia. The National Lipid Association (NLA) was an invited stakeholder organization at this meeting. During this think tank, the role of non-statin therapies in the management of LDL-C–related ASCVD risk was identified as a critical gap in care. The ACC Task Force on Clinical Expert Consensus Documents, therefore, recommended preparation of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies in the Management of Atherosclerotic Cardiovascular Disease.[4] NLA representation was invited on the Writing Group for preparation of the decision pathway document.

The process used in the creation of this document was supported by the ACC without external funding. All members of the Writing Group volunteered their time to create the document. The document was formulated based on multiple conference calls among committee members and ACC staff. A formal review was completed based on ACC policy, including expert reviewers nominated by the ACC. Two NLA reviewers were sought to provide input on behalf of the NLA. A public comment period was also held to provide additional feedback. All comments were adjudicated by the ECDP Writing Committee, and then, the final document was evaluated and approved for publication by the ACC governing bodies and endorsed by the NLA Board of Directors.

The following key questions were addressed: (1) In what patient populations should non-statin therapies be considered?; (2) In what situations should non-statin therapies be considered, that is, when is the amount of LDL-C lowering (percent LDL-C reduction or LDL-C range achieved on therapy) less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin-intolerant?; and (3) If non-statin therapies are to be added, which agents or therapies should be added and in what order?

Shared ACC and NLA perspectives that are advocated in the ACC Expert Panel Consensus document include: (1) an emphasis on lifestyle intervention as the first step in preventive cardiovascular care for ASCVD prevention; (2) a systematic approach to statin intolerance using the guidance of both the ACC/AHA Guideline and the NLA's 2014 Statin Intolerance Panel[4] and the ACC Statin Intolerance App (http://www.acc.org/StatinIntoleranceApp); (3) consideration of the use of phytosterols and viscous dietary fibers for those who may benefit from modest additional LDL-C lowering and are unable to achieve sufficient LDL-C lowering after using evidence-based statin therapy; (4) the value of patient–provider interaction in clinical decision-making when non-statin therapies are considered, examining the extent of available scientific evidence for net clinical benefit, safety and tolerability, potential for drug–drug interactions, efficacy of additional LDL-C lowering, cost, convenience and medication storage, pill burden, route of administration, and patient preferences; (5) the importance of ongoing LDL-C monitoring to assess adherence and response to therapy; and (6) consideration of referral to lipid specialists of those at very high risk of ASCVD, complex lipid disorders, statin intolerance, multiple lipid medication intolerance, or FH.

An additional important feature of the ACC document is the employment, in selected high-risk patients, of LDL-C and non–HDL-C treatment thresholds for consideration of net clinical benefit. Although the ACC Writing Group endorses the evidence-based findings of statin efficacy from the 2013 ACC/AHA Blood Cholesterol Guideline as a ≥50% reduction in LDL-C for high-intensity statin therapy and 30% to 49% reduction for moderate-intensity therapy, it also recognizes that patients in the RCTs demonstrating safety and efficacy of LDL-C–lowering therapy tended to achieve absolute LDL-C levels within a given range. Those individuals with LDL-C levels above that range might not experience the same risk-reduction benefit and may be candidates for additive non-statin therapy. Thus, the document provides levels of LDL-C, or thresholds, in terms of both percentage of LDL-C reduction and absolute on-treatment LDL-C levels as factors that may affect the decision to consider the use of non-statin therapies. Because of the high prevalence of hypertriglyceridemia in diabetic patients, non–HDL-C treatment thresholds are offered for consideration in higher risk subgroups of diabetic patients, including those with predicted 10-year ASCVD ≥ 7.5% using the Pooled Cohort Equations; strongly positive family history of premature ASCVD; tobacco use; hypertension; chronic kidney disease (CKD); albuminuria; retinopathy; evidence of subclinical atherosclerosis; elevated lipoprotein (a), or elevated C-reactive protein. These lipoprotein treatment thresholds are not to be construed as firm triggers for adding medication but should be interpreted as factors that may be considered within the broader context of the patient's clinical situation.

The ACC Expert Consensus document makes recommendations for consideration of non-statin therapy as an adjunct to evidence-based statins in the 4 statin benefit groups, with a clear emphasis on using such therapy in high-risk populations. Among ASCVD patients on high-intensity or maximal-tolerated statin therapy, the addressed groups include those with: uncomplicated ASCVD; New York Heart Association Class II-III heart failure due to ischemic heart disease; ASCVD and diabetes mellitus; recent (<3 months) acute coronary syndromes or atherothrombotic stroke; ASCVD events while already taking a statin; and ASCVD and concomitant FH. Among patients with LDL-C ≥ 190 mg/dL on high-intensity or maximally