Journal of Clinical Lipidology (2016) ■, ■–■

Journal of Clinical Lipidology

Original Contribution

An evidence-based analysis of the National Lipid Association recommendations concerning non-HDL-C and apoB

Allan D. Sniderman, MD*, Peter P. Toth, MD, PhD, George Thanassoulis, MD, Curt D. Furberg, MD, PhD

McGill University Health Centre—Royal Victoria Hospital, Montreal, Quebec, Canada (Drs Sniderman, and Thanassoulis); The Department of Preventive Cardiology, CH Medical Center, Sterling, Illinois and Ciccarone Center for Cardiovascular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA (Dr Toth); and Division of Public Health Sciences, Wake Forest School of Medicine, Winston–Salem, NC, USA (Dr Furberg)

KEYWORDS:
ApoB;
Cardiovascular prevention;
Guidelines;
National Lipid Association;
Non-HDL-C

BACKGROUND: The National Lipid Association (NLA) selected non-HDL-C as its prime index of the cardiovascular risk associated with the apoB lipoproteins. ApoB was recommended only as an optional secondary target after low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C) targets were achieved.

OBJECTIVE: The aims of this analysis were to determine whether (1) all relevant uses of apoB were considered by the NLA; (2) all the relevant evidence was considered by the NLA panel; and (3) all the evidence that was considered was interpreted correctly.

RESULTS: (1) The utility of apoB in the diagnosis of the atherogenic dyslipoproteinemias was not considered. (2) All the relevant observational studies were not identified, and some that were cited were incorrectly interpreted. In particular, an equal hazard ratio for two markers in a group does not mean they will predict risk equally in individuals within the group in whom they are discordant. This matters because discordance analysis consistently demonstrates apoB and LDL particle number are more accurate measures of cardiovascular risk than LDL-C/non-HDL-C. (3) The target levels of apoB selected by the NLA are too high relative to the levels selected for LDL-C and non-HDL-C.

CONCLUSIONS: The review of the evidence by the NLA was incomplete. More complete examination of the evidence indicates that apoB is a more accurate marker of cardiovascular risk than non-HDL-C and that the practice of lipidology would be improved by inclusion of apoB along with lipoprotein lipids in routine clinical care.

Introduction

All treatment guideline groups state their recommendations are evidence based. That is the source of their authority. However, correctly identifying and appropriately evaluating all the relevant evidence is challenging. Thus, multiple cholesterol treatment guideline groups have produced recommendations that differ substantially, although

* Corresponding author. McGill University Health Centre - Royal Victoria Hospital, 1001 Decarie Blvd, Montreal, Quebec H4A 3J1, Canada.
E-mail address: allansniderman@hotmail.com

Submitted March 29, 2016. Accepted for publication July 19, 2016.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2016.07.008

they were based on the same evidence.[1] The evidence does not speak for itself.

Nevertheless, given the rate at which information accumulates and the complex forms in which it appears, the guideline process has become essential to medical care. Therefore, we need to understand how it can be improved. That is the purpose of this review, which will examine the evidence on which the recent recommendations of the National Lipid Association (NLA) regarding non–high-density lipoprotein cholesterol (HDL-C) and apoB were based.[2]

The NLA recommended that non-HDL-C be the primary index of the risk attributable to the apoB lipoproteins and the primary index of the adequacy of lipid-lowering therapy. They concluded that non-HDL-C and apoB were both more accurate markers of risk than LDL-C, and that non-HDL-C and apoB were equivalent measures of cardiovascular risk. Given its greater availability and that no extra expense is required for its determination, non-HDL-C was judged superior to apoB.[2] The NLA further determined that the superiority of non-HDL-C over LDL-C was due to VLDL-C. ApoB was recommended as an optional secondary target to assess the adequacy of LDL lowering therapy after non-HDL-C and LDL-C targets were achieved. No other role for apoB was suggested.[2]

Given that the selection of non-HDL-C as the primary index of the atherogenic lipoproteins was one of the principal changes in care advocated by the NLA, examining the quality of their review of the evidence is a fair test of the validity of the process. The only assumption this analysis makes is that the report represents an accurate and complete record of their deliberations.

Role of apoB in diagnosis of the atherogenic dyslipoproteinemias

Diagnosis of the atherogenic dyslipoproteinemias is not considered in the NLA report. For the present exercise, only one clinical consequence of this omission will be noted: remnant lipoprotein disorder (RLD or type III hyperlipoproteinemia or familial dysbetalipoproteinemia).[3,4] RLD becomes manifest typically after early midlife. However, once it appears, the anatomic progression of atherosclerotic disease can be explosive, so explosive that the clinical consequences, both in the coronary and peripheral arterial trees, become evident often within only a few years after the onset of the dyslipoproteinemia. The natural history of RLD is remarkably condensed. However, RLD is treatable. Accordingly, the clinical consequences should be preventable. Presently, RLD cannot be diagnosed in routine clinical care, including care in almost all specialized lipid clinics. The tools that were used previously, ultracentrifugation and/or electrophoresis, are not available. Yet, the diagnosis could be made, simply and inexpensively, by any clinical chemistry laboratory based on measurement of triglyceride, cholesterol, and apoB.[5–7] Indeed, except for Lp(a), diagnosis of all the apoB atherogenic dyslipoproteinemias is possible based on the plasma levels of triglyceride, cholesterol, and apoB.[5]

Clinical significance

Accurate diagnosis is one of the cornerstones of clinical care but the NLA panel did not demonstrate they were aware of and valued this aspect of care.

Comparison of non-HDL-C and LDL-C as markers of cardiovascular risk by the NLA

> "However, a substantial body of evidence has since accumulated to support the view that non-HDL-C is more strongly related to risk for ASCVD than LDL-C and that this relationship is evident in those with and without hypertriglyceridemia"[2]

There is substantial evidence that non-HDL-C is a better marker of cardiovascular risk than LDL-C. However, at multiple points, the NLA report states that VLDL-C accounts for the superiority of non-HDL-C over LDL-C as a marker of cardiovascular risk and that, this constitutes evidence in favor of therapies to reduce VLDL-C. Indeed, the panel identifies four mechanisms that might account for the atherogenic properties of VLDL particles. Nevertheless, although VLDL-C may be the most obvious explanation for the superiority of non-HDL-C over LDL-C, it is not the only one. An alternative hypothesis is that the superiority of non-HDL-C over LDL-C is due, at least in part, to non-HDL-C being a more accurate index of LDL particle number than LDL-C. This hypothesis and the evidence supporting it[8] are not cited in the NLA report.

Indeed, the results of the discordance analysis by Mora et al,[9] which was cited in the NLA report, provide direct evidence against the assumption by the NLA that VLDL-C must entirely account for the superiority of non-HDL-C over LDL-C. In the Mora study, cardiovascular risk was greater in the low LDL-C/high non-HDL-C subgroup than in the low non-HDL-C/low LDL-C subgroup (Table 1). VLDL-C was, in fact, substantially greater in the former than the latter: 51 mg/dL vs 28 mg/dL, $P < .001$, a difference that could contribute to the difference in cardiovascular risk between the two groups as claimed by NLA. However, it is not the only difference between the groups. LDL particle number is also much greater in the high-risk low LDL-C/high non-HDL-C compared to the latter (1356 vs 977 nmol/L $P < .001$; Table 1).

Even when VLDL levels produce substantial hypertriglyceridemia, LDL particles make up the great majority of apoB particles—more than 85%.[11–13] Moreover, hypertriglyceridemia with an elevated apoB is associated with greater atherogenic risk than hypertriglyceridemia