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Differential response of cholesterol and particle measures of atherogenic lipoproteins to LDL-lowering therapy: implications for clinical practice

Allan D. Sniderman, MD

Mike Rosenbloom Laboratory for Cardiovascular Research, Room H7.22, McGill University Health Centre, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec H3A 1A1 Canada

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BACKGROUND: Low-density lipoprotein (LDL)–lowering with pharmacologic therapy has been repeatedly shown to substantially reduce risk of vascular disease. LDL cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C) are the cholesterol indices used to measure the adequacy of LDL-lowering therapy, whereas apolipoprotein B (ApoB) is the most widely used index of atherogenic particle number.

OBJECTIVE: This study examines whether LDL-lowering therapy reduces cholesterol indices and ApoB to the same extent. If they are not equally affected, they may not be equally informative about change in risk.

METHODS: Data from 11 studies, which include 17,035 subjects, were analyzed. All the statins in common use were included, as well as all the doses at which they are commonly used. More limited data are presented on combination therapy with statins and ezetimibe.

RESULTS: Reductions in LDL-C, non–HDL-C, and ApoB differed significantly, averaging 42.1%, 39.6%, and 33.1%, respectively ($P < 0.001$ ApoB versus LDL-C or non–HDL-C). Mean value for the measure in question was expressed as the percentile level from a distribution analysis of two reference populations (Framingham Offspring Study and National Health and Nutrition Examination Survey III). The lower the population percentile, the more effective the apparent response. For LDL-C, non–HDL-C, and ApoB, these were the 21st, the 29th, and the 55th percentile of the population, respectively. This value for ApoB was significantly different from both LDL-C and non–HDL-C ($P < 0.001$). Very similar results were obtained in eight studies of LDL-lowering in 889 subjects in which the responses of LDL-C and LDL particle number (LDL-P) assessed by nuclear magnetic resonance spectroscopy were compared. LDL-C was reduced to the 27th percentile of the population, whereas LDL-P was only reduced to the 51st percentile of the population ($P < 0.001$).

CONCLUSIONS: Many patients who achieve LDL-C and non–HDL-C target levels will not have achieved correspondingly low population-equivalent ApoB or LDL-P targets. Reliance on LDL-C and non–HDL-C can create a treatment gap in which the opportunity to give maximal LDL-lowering therapy is lost.

Low-density lipoprotein (LDL)–lowering therapy reduces cardiovascular events; greater lowering produces greater benefit. LDL cholesterol (LDL-C) is the conventional index to judge the adequacy of LDL-lowering therapy. Unfortunately, the LDL-C value calculated in most clinical laboratories often differs substantially in individual patients from the actual LDL-C measured by ultracentrifugation.[1,2] The recently introduced "direct" or "homogenous" methods to measure LDL-C do not fare much better.[1,2] More importantly, because LDL particles differ

E-mail address: allansniderman@hotmail.com
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markedly in the amount of cholesterol they contain, even the most accurate LDL-C values frequently underestimate LDL particle number (LDL-P) and, therefore, may seriously underestimate clinical cardiovascular risk due to LDL.[3,4]

Two other indices, non–high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (ApoB), have been recognized, both of which overcome the technical limitations of LDL-C. However, they do not measure the same thing. Non–HDL-C is the mass of cholesterol within the atherogenic ApoB-containing particles, whereas ApoB equals the number of these particles. They are highly correlated but only moderately concordant—that is, for any given value of one, there is a substantial range of values for the other.[5,6] Moreover, the discordance is not systematic. Agreement, not surprisingly, is greater in normotriglyceridemic compared to hypertriglyceridemic subjects. However, even within the normotriglyceridemic group, there is only moderate concordance between the two methods. Furthermore, all patients with hypertriglyceridemia are not the same. There is less variance in combined hyperlipidemia than in simple hypertriglyceriemia.[7] The net result is that for individuals, the value of ApoB is not accurately predictable from the value for non–HDL-C.

Statins and ezetimibe, either individually or in combination, lower all three measures of the atherogenic ApoB lipoproteins, but are the changes identical? If they are not, they are not equal markers of the effectiveness of therapy. Surprisingly little attention has been paid to this question. Simply put, the degree to which a parameter is lowered determines the potential for further lowering and, therefore, for additional therapy. Target values have been established by the National Cholesterol Education Program Adult Treatment Panel III for LDL-C and non–HDL-C[8,9] and by the Canadian Consensus Group for ApoB.[10] These are generally listed as absolute values, but they can also be expressed as percentiles of the population. Doing so makes them directly comparable, one to the other. The purpose of this work is to examine whether LDL-lowering therapy reduces LDL-C, non–HDL-C, and ApoB equally. Published data on the effects of statin therapy on LDL-P measured by nuclear magnetic resonance spectroscopy are also included.[11]

Methods

Clinical studies

Clinical studies in which lipoprotein lipids and ApoB were measured before and after LDL-lowering therapy were identified.[12–22] These include all the statins in common use at the relevant dosages. Most studies utilized statin monotherapy, but data on combination therapy of statins with ezetimibe are also included. A separate search was made for similar studies[23–29] in which LDL-P was measured by nuclear magnetic resonance.[11]

On-treatment results for LDL-C, non–HDL-C, and ApoB are expressed in milligrams per deciliter and LDL-P in nanomoles per liter. To make the different parameters comparable, they are also expressed as population percentiles. These were based on data from the Framingham Offspring Study.[30,31] These results do not differ significantly for those reported from National Health and Nutrition Examination Survey III survey data.[32] Measurements of ApoB in the National Health and Nutrition Examination Survey III survey data were calibrated with the World Health Organization International Reference Material for ApoB.[33] Measurements of ApoB in studies[11,12,17–21] were similarly standardized.

Statistical methods

Results are expressed as mean ± standard error of mean. Differences in the treatment responses of the alternative lipoprotein measures were assessed by analysis of variance using Prism Plus (Graph Pad Software, Inc, San Diego, California).

Results

Results from 11 studies of LDL-lowering are presented in Table 1. A total of 17,035 subjects are included. Statins used include lovastatin, simvastatin, atorvastatin, and rosuvastatin. Doses used are indicated in Table 1. Statins most commonly used at the present time, at their usual doses, are represented in these studies. Data on combination therapy with ezetimibe are also included. Average percent decrease in LDL-C was 42.1%, which produced an average on-treatment level of 99.2 mg/dL. Average on-treatment level of non–HDL-C was 127 mg/dL. The percent decrease in non–HDL-C was 39.6%. Therefore, the reduction in non–HDL-C was slightly less (94%) than the decrease in LDL-C ($P < 0.001$) (Fig. 1). Average on-treatment ApoB was 101.6 mg/dL, which represents a 33.1% decrease from the starting value. This decrease is significantly less than the decrease in LDL-C (42.1%, $P < 0.001$) or non–HDL-C (39.6%, $P < 0.001$). Figure 1 demonstrates that the decrease in ApoB was 79% of the decrease in LDL-C and 84% of the decrease in non–HDL-C. Therefore, LDL-lowering therapy reduces LDL-C more than non–HDL-C, but both of these are reduced significantly more than ApoB.

These responses can also be expressed in terms of percentile of the population achieved with therapy. As depicted in Figure 2, LDL-C, on average, was reduced to a level equal to the 22nd percentile of the reference population. The corresponding average concentration achieved for non–HDL-C was the 29th percentile value, which was a significantly lesser change than achieved with LDL-C ($P < 0.001$). Both differ substantially with the findings obtained for ApoB. ApoB was only decreased to the 55th percentile of the population, a drop that is significantly less