Lipids in Health and Disease

EDITORIAL

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Methodological challenges in studies of the role of blood lipids variability in the incidence of cardiovascular disease

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It has long been known that high levels of total and LDL-cholesterol, and low levels of HDL increase the risk of developing atherosclerotic cardiovascular diseases [1]. Recent studies suggest that high intra-individual variability in blood lipids may increase the risk of major cardiovascular events (MACE: non-fatal myocardial infarction, stroke, or cardiovascular death), independently of individual average levels [2]. Here we discuss some methodological challenges in studies of the causal effect of blood lipids variability (BLV) on the risk of MACE, and suggest possible solutions.

Studies of the BLV-MACE association have shown that high intra-individual blood lipids variability (BLV) is independently associated with MACE in different types of patients [3–7], as well as in the general population [8, 9].Visit to visit BLV has been measured by conducting serial measurements of blood lipids and calculating their measure-to-measure variability as the standard deviation (SD), the coefficient of variation (CV), the average successive variability (ASV = $\sum(X_i - X_{i+1})/n$) or the variance Independent of the mean (VIM = (k SD/ $\bar{x}^p$), where $k = M^p$, and p is the regression coefficient of log (SD) over the log($\overline{X}$) [9, 10]. These estimates of individual BLV are then included in regression models to estimate the between-subject effect of BLV. Measures such as SD and CV are strongly related to the mean of visit values, while VIM is independent of the mean [2].

An accurate assessment of individual BLV requires multiple measurements at given intervals of time. Unfortunately, there is considerable uncertainty about how many measurements are needed and how long the intervals should be in order to get an assessment of BLV that is accurate and also etiologically relevant. Researchers should not assume that because data are available, BLV based on that data is accurate or biologically and clinically relevant. Average lipid levels, at a given point in time, reflects accumulated exposure up to that time, and is unequivocally related to the risk of MACE [1]. In contrast, it is uncertain whether BLV measured over a period of weeks or months accurately reflects a cumulative exposure, particularly in patients receiving cholesterol-lowering drugs. This uncertainty is due in part to our limited knowledge on BLV over time. In a meta-analysis conducted by Smith et al. [11] the coefficient of variation (CV = standard deviation/mean) for HDL were 5.5, 5.8, and 7.8% when measurements were conducted daily, weekly, and monthly, respectively. Corresponding values for LDL were 6.1, 6.2, and 10.8%. Similar findings have been reported in more recent studies [12, 13]. These studies seem to indicate BLV is low, at least when measured in a relative scale. On the other hand, studies on age-related BLV indicate that LDL cholesterol levels increase with age and reach a plateau in men between the age of 50 and 60 years, and in women between the age of 60 and 70 years [14], while HDL cholesterol levels diminish or have minimal changes with age [15, 16]. Taken together, these studies suggest BLV measured in intervals of even years may be small and of little clinical significance, after accounting for age-related changes. Therefore, well-designed studies describing the accuracy of BLV patterns are highly desirable. Knowledge generated in those studies would inform the design and interpretation of future studies, identify high-risk individuals, and determine what measurement intervals and indicators of BLV are clinically relevant.

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Evidence of mechanisms explaining a BLV-MACE association is limited. One proposed hypothesis is that high BLV promotes the development and progression of atherosclerotic plaques. Clark et al. showed that BLV was associated with progression of coronary atherosclerotic plaques, measured as the proportion of the arterial wall occupied by the plaque, in patients included in trials assessing the effect of intensive lipid lowering with statins [17]. However, the BLV effects on plaque development were weak, were not present in individuals who achieved treatment target, and were not independent of average levels of blood lipids. On the other hand, in patients receiving cholesterol-lowering drugs, the BLV-MACE association may also be just a consequence of poor treatment adherence [18].

The BLV-MACE association observed in several studies, though statistically significant, has been consistently weak. The average increases in risks of MACE associated with LDL-variability ranged between 10 and 34% in studies in cardiovascular patients [3–6], and between 6 and 11% in the general population [8, 9]. Associations from studies in treated patients should be cautiously interpreted. Interventions to reduce the risk of MACE in these patients are guided by their levels of cardiovascular risk factors. If those interventions are more frequent or intense in patients with high levels of blood lipids, the risk of MACE in patients with high BLV may be underestimated, since BLV increases with average blood lipid levels. This implies that data on co-interventions must be collected at the times blood lipids are measured, to control for their confounding effect. On the other hand, the effect of BLV from studies in the general population are too weak (maximum hazard ratio of 1.11) and could be explained by a confounding factor that increases the proportion of individuals with high BLV and the risk of MACE by just 46% [19].

It is also uncertain whether BLV is a modifiable therapeutic target, beyond the modification of average levels, and how this may be achieved. Moreover, before implementation of BLV measurement in the clinical context it is necessary to ascertain whether different measures of BLV improve predictability of MACE to the same degree, and which may be easier to use in patient care. Implementation is also hampered by the fact that BLV measures, such as SD, CV, and VIM are study-population specific and, therefore, their values cannot be applied to other populations. Moreover, the BLV-MACE association observed in several studies, though statistically significant, may not improve the performance of models excluding BLV or predictions from a cardiovascular risk score [20].

On the other hand, in most studies, BLV has been evaluated through short-time intervals and taken as the baseline exposure. This implies, without due justification, that BLV is a time-fixed variable that does not change or changes little over the follow-up period. Longitudinal follow-up studies, with repeated evaluations of BLV, time-dependent risk factors, and MACE or surrogates of MACE, such as carotid artery intima-media thickness and plaque stability, could be used to test this assumption and elucidate both the stability of BLV and its within-individual effects. In addition, Cox proportional hazard model has been used to assess the BLV-MACE association in most studies [3, 5–9, 21]. Although appropriate for the analysis of survival data, Cox regression does not take advantage of the correlation across the repeated measurements of blood lipids or the observed trajectory in average lipid levels. Moreover, Cox regression only considers between group variability, leaving out the estimation of within-individual and total effects of BLV. Other analytical approaches, such as multilevel/mixed linear regression models [22], joint modelling [23, 24], and g methods [25, 26], could be helpful to address the limitations of Cox regression. In particular, these methods could be useful to estimate the potential impact of pharmacological interventions to reduce BLV using data from observational studies.

Authors' contributions

The author(s) read and approved the final manuscript.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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