LETTER TO THE EDITOR

Low-density Lipoprotein Cholesterol (LDL-C) and Atherosclerotic Cardiovascular Disease: is More Evidence Necessary to Attribute its Causal Role?

Colesterol asociado a lipoproteína de baja densidad (cLDL) y enfermedad cardiovascular aterosclerótica: ¿es necesaria más evidencia para atribuir su rol causal?

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Atherosclerosis can be defined as a chronic and progressive disease of the elastic arteries, characterized by the accumulation and retention of cholesterol in apolipoprotein B (ApoB) containing lipoproteins, mainly low-density lipoproteins, in the subendothelial space of these arteries. This concept seems so simple that Jan Borén and Kevin Jon Williams chose "a triumph of simplicity" as part of the title of an interesting review that describes the aforementioned. (1) Accordingly, William Clifford Roberts, modifying one of the phrases that brought Bill Clinton to the presidency of the United States at the beginning of the last decade of the 20th century, titled an editorial "*It's Cholesterol, Stupid*" in which he used four arguments to explain the causal role of cholesterol associated with low-density lipoproteins (LDL-C) in atherosclerosis. (2) In his review, Borén claims that it is a fact, not a hypothesis, that elevated cholesterol levels transported by lipoproteins with Apo B have a causal role in the genesis of atherosclerosis, and that lowering LDL-C also reduces the risk of cardiovascular events. Similarly, Clifford Roberts implies something similar when he quotes the word cholesterol "hypothesis" in the development of atherosclerosis.

This view of atherosclerosis is not universally accepted, it has its detractors, and this has motivated the publication of new studies, which seem to contribute to Jan Borén's "triumph of simplicity".

Along these lines, a study published in JAMA, some months ago, adds to the body of evidence that for years has supported the causal role of LDL-C in the development of atherosclerotic cardiovascular disease (ASCVD). This interesting study analyzed the impact on a group of people with variations in two genes (APOB -apolipoprotein B- and PCSK9 –proprotein convertase subtilisin/kexin type 9) related to lipid metabolism, more precisely in reference to LDL-C levels. (3)

For this analysis, two large databases were considered (the National Heart, Lung, and Blood Institute -NHLBI- and the UK Biobank), with a total number of 209 537 analyzed individuals. (3)

The analysis found in 0.4% of participants (n=801) a variant or mutation in the APOB or PCSK9 genes, associated with a decrease in the LDL-C level (47 mg/dL on average) compared with individuals without the genetic variant. Carriers of the genetic variant had an average of 80 mg/dL LDL-C, whereas non-carriers had an average of 128 mg/dL LDL-C. After a mean follow-up of 21.5 years, the incidence of coronary events reported was 8.6% in mutation carriers and 16% in non-carriers, which corresponds to a reduction of 49% in the adjusted risk of developing coronary heart disease. Interestingly, this result was observed despite an 8-fold greater use of statins and other lipid-lowering agents in the group not carrying the variants. (3) (Figure)

This finding is in line with previous studies of similar characteristics and design, which analyzed the impact of having a genetic variant associated with lower levels of LDL-C and the benefit in terms of decreased risk of atherosclerotic cardiovascular events. (4-6)

When we refer to the consistency of studies and scientific evidence, we observe that once again science shows us the preponderant and central role of LDL-C in the genesis and progression of ASCVD, which unfortunately continues to be the first cause of morbidity and mortality in Argentina and across the world. (7)

From the first purely epidemiological studies, through genetic evidence (Mendelian randomization

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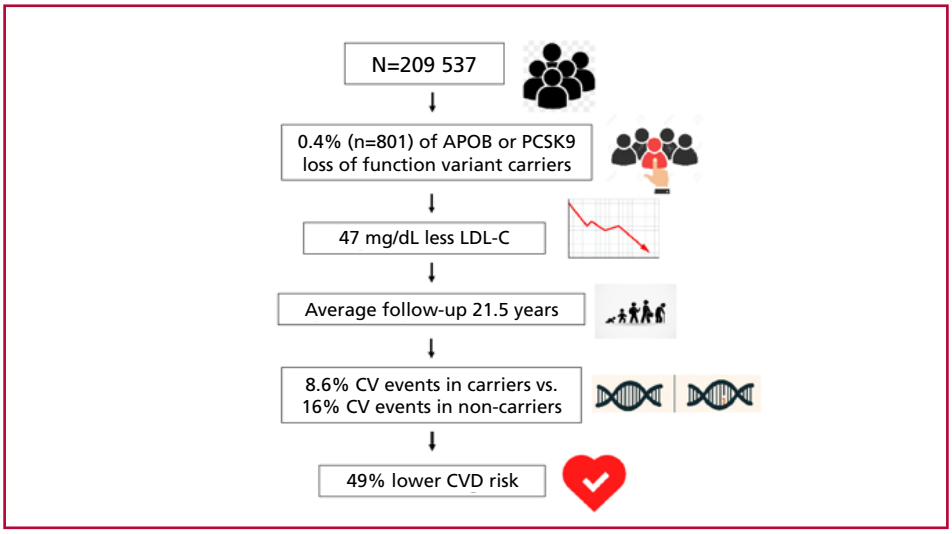

Fig. 1. Prognostic impact of a genetic variant associated with LDL-C decrease.

CVD: cardiovascular disease

studies and genetic disorders of lipid metabolism) and finally the evidence derived from pharmacological intervention, science has shown us concordance, until now irrefutable, of this causal association between LDL-C and CVD of atherosclerotic origin. And it is the accumulated atherogenic load of LDL-C over the years (mg/dL/years) that determines the risk of suffering from atherosclerosis, which is difficult to observe when it is <5000 mg/dL/years. (8) For more than five years now, a reduction in the risk of cardiovascular events in studies with non-statin drugs such as ezetimibe, PCSK9 inhibitors and recently bempedoic acid has been found in pharmacological intervention studies. This last study included a population of patients at high cardiovascular risk but without established cardiovascular disease, with partial or total intolerance to statins. A benefit was observed in a proportion similar to that expected for equivalent reductions in LDL-C levels with statins. (9-12) Once again this reinforces that, regardless of the pleiotropic effect that each pharmacological group may have, the final common pathway responsible for most of the benefit is explained by the reduction of plasma levels of LDL-C and ApoB.

The benefit then of being aggressive in terms of beginning lipid-lowering therapy (*the sooner, the better*) and in terms of intensity (*the lower, the better*) is evidenced again in the observational study that we present, with an unquestionable methodology and design, and with clear implications when assessing the potential beneficial effect of reducing LDL-C levels in our patients. (3)

The above mentioned clearly adds to the basic and elementary recommendation of adopting a healthy lifestyle in which we can include an adequate diet, systematic physical activity, avoiding smoking and maintaining a good rest, among other actions. The synergy of these two strategies clearly has the power to modify the natural course of ASCVD and in this way combat the number one cause of morbidity and mortality in our country and worldwide. (13)

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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