The editors of the Revista del Hospital Italiano de Buenos Aires invite readers to reflect on issues currently under debate within the scientific community. To this end, we invited two distinguished experts with differing perspectives on cholesterol-lowering pharmacotherapy to present their arguments based on a hypothetical clinical scenario. Below, we share the perspectives of Drs. Karin Kopitowski* and Walter Masson on the following case:

> *A healthy, asymptomatic 24-year-old man presents for a routine health checkup. He does not smoke, exercises regularly, and has no history of hypertension, diabetes, or obesity. His LDL cholesterol levels are 175 and 180 mg/dL on two separate occasions. He has no family history of premature cardiovascular disease. His short-term cardiovascular risk is very low. However, persistently elevated LDL cholesterol may lead to greater cumulative exposure over his lifetime. In this situation, should a statin be prescribed to a young adult with elevated LDL cholesterol, or is it preferable to continue lifestyle interventions and periodic monitoring?*

LDL-C: The Level Matters, but So Does the Duration of Exposure

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The decision to initiate lipid-lowering therapy in a young adult with an LDL-C level of 180 mg/dL, without a diagnosis of familial hypercholesterolemia—which substantially simplifies the decision—raises a question that goes beyond simply applying a guideline-defined cutoff: Should we wait until LDL-C reaches 190 mg/dL before intervening, or should we consider the magnitude and, more importantly, the duration of exposure to atherogenic lipoproteins? This distinction is particularly relevant in a 24-year-old individual, whose 10-year cardiovascular risk will inevitably be low—in fact, most risk scores cannot even be calculated at this age—but whose cumulative exposure over the coming decades may be considerable.

Of course, the first step is to rule out secondary causes. When an identifiable cause is present, it makes sense to address it and subsequently reassess the lipid profile. Similarly, lifestyle and dietary interventions are an essential part of management regardless of whether pharmacological treatment is prescribed, although, in this particular case, there may be limited scope for substantially reducing LDL-C through lifestyle changes alone. The central question, then, is whether pharmacological treatment should be initiated. In my opinion, it should.

The LDL-C threshold of ≥190 mg/dL, traditionally used in guidelines to define severe hypercholesterolemia, is not a biological threshold below which LDL-C ceases to be atherogenic. In other words, although 190 mg/dL represents a clinical cutoff for identifying a population at particularly high risk, lower concentrations can also contribute to the development of atherosclerosis when exposure persists over prolonged periods.

Each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol (LDL-C) reduces major cardiovascular events by approximately 22%, regardless of baseline LDL-C levels. Even among individuals at lower risk, the proportional reduction in events was similar. These findings demonstrate that the magnitude of LDL-C reduction matters, but they do not, in themselves,

*Comments by Dr. Karin Kopitowski, "The Patient Is More Than His LDL: The Case for Active Monitoring" [link]

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answer a fundamental question when considering young individuals: How much does the duration of exposure to elevated LDL-C levels matter?

In this context, data from the CARDIA study provide relevant evidence. Cumulative exposure to LDL cholesterol (LDL-C × duration of exposure) is a well-established cardiovascular risk factor. The timing of exposure also appears to influence risk: for the same cumulative exposure, exposure at younger ages was associated with a greater increase in risk than exposure later in life. Another analysis of the CARDIA study, which included 4,366 young adults aged 18 to 40 years, showed that greater cumulative exposure to atherogenic particles, such as apolipoprotein B and LDL, during the first 22 years of adulthood was associated with a significant increase in the risk of cardiovascular disease after age 40. Each one-standard-deviation increase in cumulative exposure was associated with an approximately 30% higher risk of cardiovascular events.

This perspective substantially changes how we interpret an LDL-C level of 180 mg/dL at age 24. The difference between 180 and 190 mg/dL is small from a biological standpoint, but it may take on disproportionate importance if 190 mg/dL is used as an absolute threshold separating "treat" from "do not treat." Moreover, contemporary guidelines have begun to explicitly incorporate an earlier prevention strategy, emphasizing the importance of reducing cumulative exposure to atherogenic lipoproteins and considering pharmacotherapy in young adults with persistently elevated LDL-C levels (>160 mg/dL).

Therefore, in a 24-year-old man with an LDL-C level of 180 mg/dL, the discussion should not be limited to determining whether his LDL-C exceeds the 190 mg/dL threshold or to estimating his 10-year cardiovascular risk. Rather, it should focus primarily on the concept of lifetime exposure (Fig. 1). At the same time, clinicians should engage patients in shared decision-making, explaining the potential benefits of reducing lipid exposure early in life, as well as the possible adverse effects, the need for long-term treatment, and the importance of individual preferences. In this context, initiating statin therapy can be viewed not as a means of addressing immediate cardiovascular risk, but as a strategy to reduce cumulative LDL-C exposure and potentially alter the trajectory of cardiovascular risk over the course of a lifetime. Ultimately, the question is not simply how much LDL-C this patient has today, but how many years of atherogenic exposure we are willing to allow before intervening.

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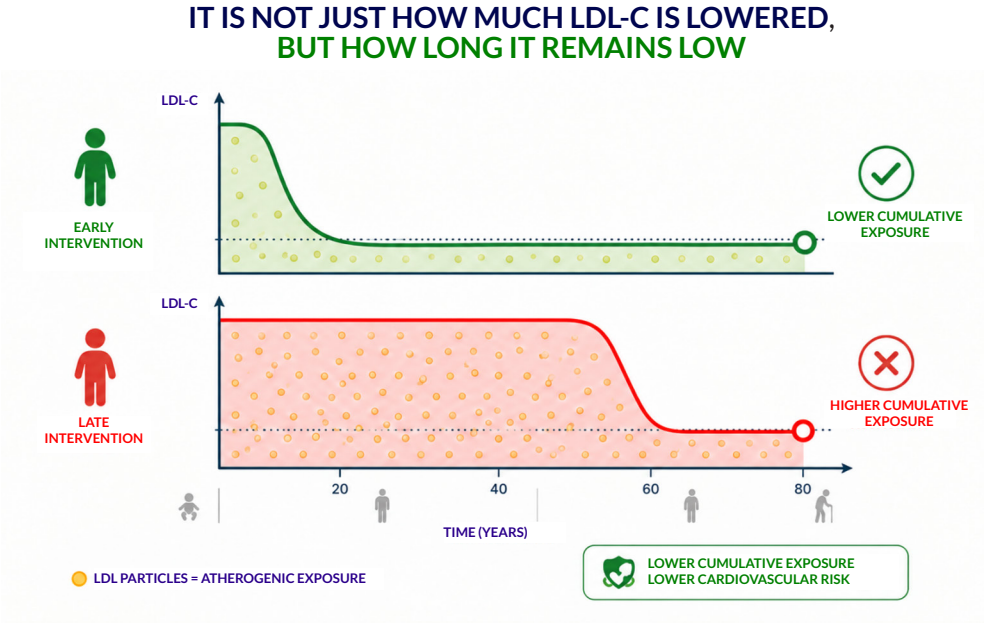


Figura 1. Conceptual framework illustrating the principle "the earlier we lower LDL-C, the better." Source: Created by the author with assistance from ChatGPT; freely adapted version.

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