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CURRENT OPINION

Statins, LDL Cholesterol Control, Cardiovascular Disease Prevention, and Atherosclerosis Progression: A Clinical Perspective

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Abstract

Despite the longstanding and widespread use of statins, they are used quite inefficiently in everyday clinical practice. This might be because of a lack of robust evidence or the wide variety of different guidelines that are frequently changed. Using data from clinical trials and some simple mathematical modeling, we sought to expand upon the relation between low-density lipoprotein cholesterol (LDL-C) control and cardiovascular risk to offer a firm basis for independent decision making in everyday clinical practice. Analysis of the dose–response curves of different statins indicated that doubling the dose will provide a < 5% extra LDL-C gradient and that the relationship among different statin dose equipotencies is fourfold in the lower range and threefold in the higher range. Thus, the use of potent statins at very low doses might overcome patient statin reluctance. Moreover, whereas statins lower LDL-C percentwise, the prevention of atherosclerosis-related cardiovascular events (ARCVEs) depends on the absolute LDL-C gradient produced and the level of risk. Consequently, and counterintuitively, the lower the baseline LDL-C and/or ARCVE risk, the higher the statin therapy strength required, and approach that is also cost effective. We discuss the issue of threshold versus gradient in terms of clinical trials on plaque regression and speculate on the relationship between LDL-C and atherosclerosis.

Key Points

Statins are used quite inefficiently in clinical practice; however, with some simple mathematical modeling, their use can be rational and cost effective.

Statins lower low-density lipoprotein cholesterol (LDL-C) percentwise while preventing atherosclerosis-related cardiovascular events in proportion to the absolute LDL-C gradient.

Counterintuitively, the lower the baseline cardiovascular risk, the higher the potency of the statin required. It is possible to overcome patient statin reluctance by using potent statins at very low doses.

Stabilization is more likely to be obtained via LDL-C lowering than by plaque regression.

A working hypothesis of atherosclerotic plaque formation congruent with the clinical data is offered.

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1 Introduction

Statins remain the most prescribed low-density lipoprotein cholesterol (LDL-C)-lowering drugs worldwide, as they are effective in both primary and secondary cardiovascular disease prevention [1, 2]. Large clinical trials have consistently shown that statins can reduce the incidence of atherosclerosis-related cardiovascular events (ARCVE), demonstrating that the benefit is proportional to the achieved (and maintained) plasma LDL-C concentration gradient with respect to baseline LDL-C values [3]. Consequently, guidelines unanimously support the use of statins in subjects with prior cardiovascular events (secondary prevention) or those at high risk for a first ARCVE (primary prevention). However, they do differ in their suggestions as to whether physicians should aim at targets [4] or only select the adequate treatment potency [5, 6], thus possibly generating uncertainty about the best strategy to adopt in routine clinical practice. Through careful review of the literature and data modeling, we aim to offer physicians firm evidence-based information to support autonomous patient-oriented decision making. We first analyze the main characteristics of the dose–response curves of statins with regard to plasma LDL-C control and then discuss the relationship between LDL-C-lowering therapy and

ARCVE prevention as it stems from clinical trials. Finally, we present some thoughts on the threshold-versus-gradient controversy and on atherosclerosis pathophysiology.

2 Effect of Statins on Plasma Low-Density Lipoprotein Cholesterol (LDL-C)

Statins reduce the synthesis of cholesterol in hepatocytes by competitively inhibiting the activity of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase. The subsequent depletion of the intracellular cholesterol pool induces an increased translocation of LDL receptors on hepatocyte membranes, increasing the removal of LDL particles from the serum and reducing circulating LDL-C levels. Although the statins primarily act to reduce serum LDL-C, a number of ancillary and potentially important effects have been suggested, known as "pleiotropic effects" [7]. In particular, anti-inflammatory and antioxidant effects have been observed in vitro and in experimental studies, but their actual clinical relevance remains controversial.

We used data from the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial [8] to investigate the effects of the different statins. This study evaluated the LDL-C-lowering effect of 6 weeks of treatment with either rosuvastatin, atorvastatin, simvastatin, or pravastatin at the most commonly used daily doses in 2268 adult subjects with hypercholesterolemia (LDL-C 160–250 mg/dL [4.13–6.46 mmol/L]; triglycerides < 400 mg/dL [4.52 mmol/L]) divided into 15 treatment groups of approximately 150 subjects each. Figure 1a shows the different dose–response curves for each of the four drugs, gained by plotting all available data. As expected, the four statins differ widely in potency. Remarkably, after log transformation, the dose–response curves are very well-represented—and fitted—by straight and almost parallel lines (Fig. 1b), which has interesting implications. First, the doubling of the dose of any statin produces an effect that is extremely similar and easily predictable. Provided that $\ln(x \times 2) = \ln(x) + \ln(2)$ and that $\ln(2) = 0.69$, by multiplying the statin-specific log coefficient (6.3–7.3) for 0.69 we can predict that, by doubling the dose, the expected further decline in LDL-C approaches 5% (4.4–4.9%) regardless of the individual statin used. This is close to the 6% commonly reported in the scientific literature [9, 10] although the reasons supporting this figure [11] are not given. The apparently small effect of doubling the statin dose is a consequence of the log shape of the curve depicting the relationship between statin concentrations and degree of HMG-CoA reductase inhibition [12], which predicts a doubling of the effect for a tenfold increase in drug concentration. Moreover, as the potency largely depends on the difference in the constant coefficients of the equations, the log coefficients are very similar. Consequently, in relative terms, the difference among statins becomes progressively greater in the lower strength range. It is expected that rosuvastatin 2.5 mg/day will lower LDL-C by 34%, similar to atorvastatin 10 mg/day and simvastatin 40 mg/day, and possibly pravastatin 120 mg/day. A fourfold relationship is present among doses of equipotent statins in the lower portion of the dose–response curve, whereas a threefold factor is present for the higher dose ranges (rosuvastatin 10 mg/day is equipotent to atorvastatin 30 mg/day and simvastatin 90 mg/day) (Fig. 1). Of note, when the effect of the treatment is expressed as absolute concentration gradients (mg/dL or mmol/L), the three treatment strategies defined by the American Heart Association (AHA) on the basis of the expected LDL-C percent reduction (low − 20/− 30%, moderate − 30/− 50%, and high − 50/70%) will produce extremely different results in each individual subject, depending on baseline LDL-C values (Fig. 2).

Clinical tip: use Fig. 1 and/or 2 to select the most appropriate statin strategy. If the patient needs to reach a specific

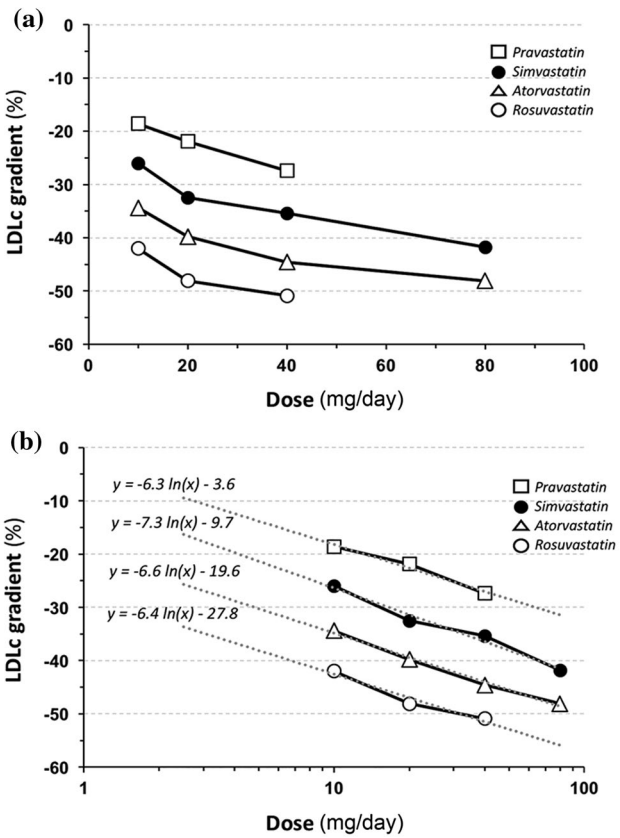

Fig. 1 Scatterplot of the percent change in plasma low-density lipoprotein cholesterol (LDL-C) vs. the dose of statin. Statin dose is presented on **a** a normal scale and **b** on a log scale, and data are fitted (dotted lines) through linear regression. Drawn from data reported in the STELLAR trial main publication [8]

target, or a 50% reduction, calculate the necessary LDL-C concentration gradient (in mg/dl or mmol/L) and use Fig. 2 to select the statin strength. Alternatively, translate the gradient in percent terms with respect to baseline values and use Fig. 1 to choose which statin at which dose is more useful to reach it. If the objective is missed by more than 5%, go for a fourfold increase in the dose of the same statin or shift to a more potent statin at the same dose; if neither option is feasible, add a second LDL-C-lowering drug.

3 Statin Resistance vs Statin Reluctance

It is worth noting that, although the standard errors (≤ 1%) reported in the STELLAR trial [8] indicate that interindividual variability in response to statins is extremely small, some large clinical trials have shown a wide variability in the response to statins. The JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial [13] found (as expected) a 50% average decline in LDL-C in response to rosuvastatin 20 mg but also reported that 20% of the patients had a poor response, ranging from + 30 to − 30%. This generated some doubt about the possibility that a reasonable proportion of individuals might be resistant to statins, which in turn fueled a series of genome-wide studies that essentially failed to identify loci that could fully justify a true statin resistance of this size. In fact, one of the most relevant loci (rs10455872) appeared to be associated with the modulation of plasma lipoprotein(a) [Lp(a)] levels, which is not affected by statin treatment and is frequently and inappropriately included in the LDL-C fraction, thus giving the appearance of statin inefficacy. Furthermore, the few other statistically significant loci justified only a small portion of the response variability, with estimated effects ranging between − 2 and − 6% [14]. A mild degree of real statin resistance can be found in a very select group of patients, such as those with familial hypercholesterolemia, some of whom might have increased cholesterol intestinal absorption [15], or, occasionally and transiently, in subjects exposed to factors such as acute inflammation or drastic variations in dietary habits, which are known to contribute to the natural variability of plasma LDL-C concentrations and to interfere directly with statin action [16]. Therefore, a true genetic and clinically relevant resistance to statins appears unlikely. On the other hand, a closer look at the clinical characteristics of PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial participants [17] who appeared to be poor statin responders, revealed a greater proportion of smokers and patients consuming high levels of alcohol and with lower cognitive function, conditions all known to be associated with poor drug compliance. Thus, even within the context of controlled clinical trials, poor compliance appears to be the major factor contributing to apparent statin resistance, a phenomenon that should instead be called statin "reluctance." In our clinical practice, patients often do not regularly consume the drug because they do not trust the idea that the beneficial effects depend on either the gradient or the level achieved (which can be perceived as being too low) or they fear the potential adverse effects. These factors might also contribute to poor compliance with statins.

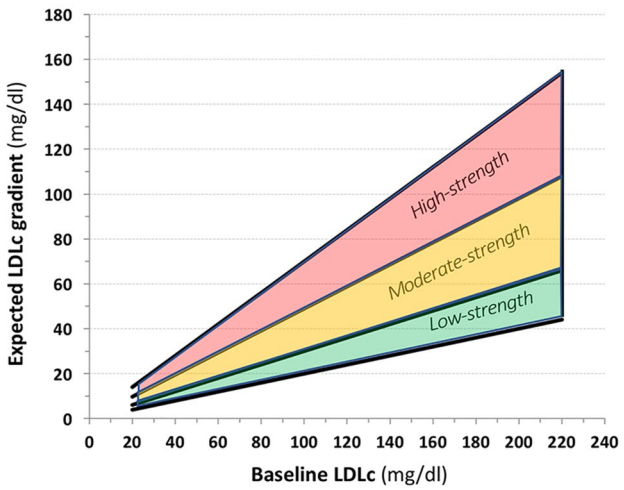

Fig. 2 Predicted absolute changes in low-density lipoprotein cholesterol (LDL-C) are plotted according to baseline plasma LDL-C values and the intensity of statin therapy as defined by the American Heart Association

Clinical tip: overcome statin reluctance. Where LDL-C control is lower than expected, measure Lp(a) or LDL-C with the direct method and accurately verify compliance. If adherence to statin therapy is low because of reluctance, it is wise to suggest a treatment that is equally effective but seemingly less invasive in the patient's view by proposing a very low dose of a more potent drug instead of "the full dose" of a less potent one. This approach could also reduce the risk of adverse events while maintaining equal effectiveness in the reduction of LDL [18]. In this setting, it is worth noting that, extrapolating from the dose–response curves shown in Fig. 1, an extremely low dose of rosuvastatin (1.25 mg/day) might also be a rational choice if an LDL-C reduction of approximately 25% is required. Moreover, thanks to its relatively long half-life (19 h), rosuvastatin could be administered on a regimen of alternate days with minimal loss of efficacy, reduced statin "intolerance", and a significantly lower cost burden [19]. Notably, simvastatin once daily has a half-life of approximately 3 h. Clearly, this strategy has not been proven to decrease ARCVE in clinical trials and should only be considered as a rational alternative to no treatment.

4 A Closer Look at the LDL-C–Atherosclerosis-Related Cardiovascular Events Risk Relationship

By pooling individual participant data from major clinical trials of statins, the Cholesterol Treatment Trialists (CTT) group, in their 2012 analysis [20], found that a 21% reduction in the risk of ARCVEs is expected for 1 mmol/L (38 mg/dL) reduction in LDL-C, which results from the combination of a 24% reduction in coronary events and a 15% reduction in cerebrovascular events. Notably, the relation was extremely consistent among subgroups and only marginally affected by sex, age, concomitant risk factors, baseline LDL-C, and primary versus secondary prevention. This also clearly emerged from the very small 95% confidence interval (CI) of the estimate (21% [95% CI 19–23]), which is particularly striking if we consider the abovementioned expected variability in compliance in large clinical trials. We can therefore calculate that, in most subjects, statins will provide a 0.55% reduction in ARCVE risk for each mg/dL reduction of plasma LDL-C (21% per 38 mmol/L). Interestingly, in the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study [21], an LDL-C reduction down to 55 mg/dL (1.42 mmol/L) with ezetimibe resulted in a 7% reduction in ARCVE risk, which is exactly what was expected from the small LDL-C gradient achieved in that study, i.e. − 15 mg/dL (from 70 to 55 mg/dL [from 1.81 to 1.42 mmol/L]). A recent meta-analysis [22] found that the effect of LDL-C lowering on ARCVE risk appeared to be quantitatively similar (− 0.60% per mg/dL) regardless of whether the intervention was based on statin, diet, bile acid sequestrant, ileal bypass, ezetimibe, or niacin, supporting the idea that what is relevant is the LDL-C gradient and not the other non-LDL-mediated effects.

This is somewhat in contrast with the results of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) study [23] with evolocumab (a proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor), which showed a smaller-than-expected efficacy. In fact, in response to a 60 mg/dL gradient (from 90 to 30 mg/dL [from 2.33 to 0.78 mmol/L]), the observed risk reduction was 20%, yielding a 0.33% risk reduction per each milligram of LDL-C instead of the expected 0.55–0.60%. As thoroughly discussed in the main paper, the short duration of the study (2 years) might have led to an underestimation of the true size of the effect. Nevertheless, recent data from the ODYSSEY OUTCOMES study [24] with alirocumab confirmed the lower-than-expected efficacy of extreme LDL-C lowering (from 90 to 50 mg/dl [from 2.33 to 1.29 mmol/L]) with an observed − 0.30% risk reduction per each milligram of LDL-C. However, in the subgroup with baseline LDL-C > 100 mg/dl (2.58 mmol/L), the observed risk reduction was greater (approximately 0.42% per mg/dL), supporting the possibility that, at least down to 60 mg/dL (1.55 mmol/L), the extent of ARCVE risk reduction remains essentially proportional to the absolute reduction of circulating plasma LDL-C, regardless of the drug(s) used. On the other hand, for patients with baseline LDL 80 to < 100 mg/dL and < 80 mg/dL, the risk reduction for the primary endpoint was small (− 4 and − 14%, respectively) and not statistically significant. Possibly, the curve depicting the change in ARCVE risk as a function of LDL-C gradients is not entirely linear, its slope becoming less steep in the very low LDL-C range (below 60 mg/dL). Considering all the abovementioned data, it is possible to draw the relative ARCVE risk reduction in any given individual as a function of statin strength and baseline LDL-C (Fig. 3a). A reduction of cardiovascular risk of approximately 20% will be achieved by a low-intensity regimen only when baseline LDL-C is in the range 120–170 mg/dL (3.10–4.39 mmol/L), whereas the corresponding threshold values for moderate- and high-intensity regimens will be 70–120 mg/dl (1.81–3.10 mmol/L) and 50–70 mg/dl (1.29–1.81 mmol/L), respectively (with some concern for the latter estimate, which could be shifted higher if the slope becomes less steep below 60 mg/dL).

This concept has been, to a certain extent, incorporated into the joint European Society of Cardiology guidelines for cardiovascular prevention [25], which suggest aiming for a 50% reduction in LDL-C in high- and very high-risk subjects if baseline LDL-C is low–normal (70–135 mg/dL [1.81–3.49 mmol/L]) or moderately elevated (100–200 mg/dL [2.58–5.17 mmol/L]). On the other hand, AHA guidelines for prescribing a 50% reduction in high-risk patients regardless of baseline LDL-C makes an important discrimination. A much greater benefit would be offered to subjects with higher LDL-C values than those with lower values. In fact, if baseline LDL-C is 180 mg/dL (4.65 mmol/L), a 90 mg/dL (2.33 mmol/L) gradient would grant a 50% risk reduction, whereas if baseline LDL-C is 100 mg/dL (2.58 mmol/L), a 50 mg/dL (1.29 mmol/L) gradient would produce a risk reduction of 28%.

Clinical tip: be cost effective rather than intuitive. Intuitively, one can think that a higher baseline LDL-C level or higher cardiovascular risk deserves a higher-potency statin and vice versa. On the contrary, by simply merging the information about the efficacy in terms of LDL-C gradient and on ARCVE reduction of the different statin treatment strengths (Figs. 2, 3a) in relation to baseline LDL-C values, we can appreciate the counterintuitive concept that, the lower the baseline LDL-C, the stronger the potency of statin required when aiming for a significant risk reduction. Taking into consideration this simple relationship, it is not surprising that, in the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm)

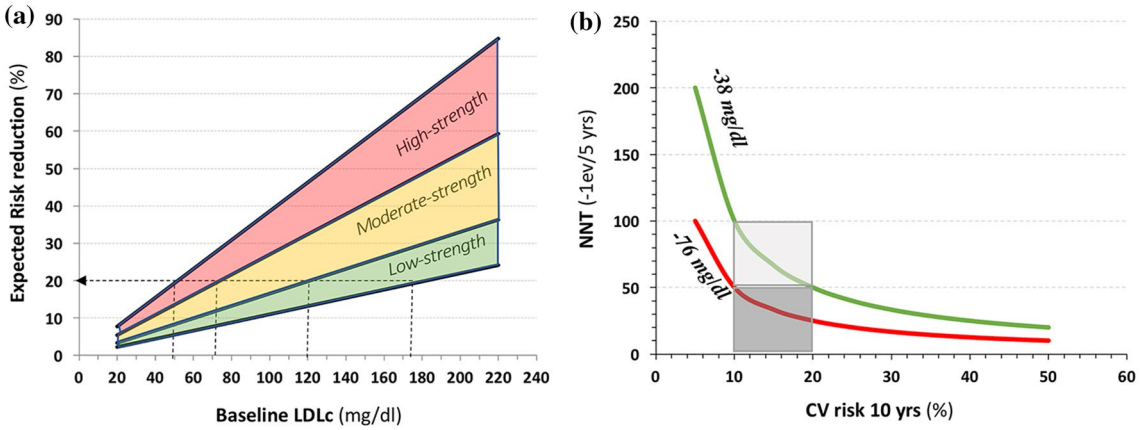

Fig. 3 **a** Predicted changes in atherosclerosis-related cardiovascular event (ARCVE) risk are plotted according to baseline plasma low-density lipoprotein cholesterol (LDL-C) values and the strength of statin therapy as defined by the American Heart Association. The dotted lines indicate the baseline LDL-C ranges for which a reduction of at least 20% can be achieved using the three different statin regimens. **b** The number of patients needed to be treated (NNT) for 5 years to prevent one event is plotted according to baseline ARCVE risk and to two different statin-induced LDL-C gradients (Green − 38 mg/dL, Red − 76 mg/dL). The shaded area indicates that, in patients at low-moderate risk, the NNT with a gradient of − 76 mg/dL is between 50 and 25 and with a gradient of − 38 mg/dL is 100–50

trial, a moderate-intensity statin therapy (atorvastatin 10 mg) was effective only in those with baseline LDL-C values ≥ 131 mg/dl (3.39 mmol/L) [26]. Moreover, provided that the absolute risk reduction will depend on the absolute LDL-C gradient and the baseline level of ARCVE risk, the lower the cardiovascular disease risk, the greater must be the LDL-C gradient. From a pharmacoeconomic perspective, as depicted in Fig. 3b, the number needed to treat at 5 years will fall below the value of 50 in the low-medium risk class (10–20%) only when a 76 mg/dL (1.96 mmol/L) LDL-C gradient is obtained. Thus, if we decide to treat a low-risk patient, we should always use a high-intensity statin treatment and, preferably, treat those in whom a 76 mg/dL gradient can be achieved. If we aim at using statins only, this implies a baseline LDL-C value ≥ 140 mg/dL (3.62 mmol/L), otherwise we should use a combination of lipid-lowering drugs.

5 How to Reconcile the Gradient-vs-Threshold Hypotheses

The concept that a target is important is fueled by the idea that, below a given LDL-C level, the atherosclerotic process can be inverted and plaque regression achieved, as also recently suggested in a consensus paper of the European Atherosclerosis Society [27]. Indeed, in recent years, a series of randomized intervention studies have employed intravascular ultrasound [28–31] to evaluate the degree of reduction in atherosclerosis burden in response to pharmacologic decrease in LDL-C. Overall, these studies suggested that plaque regression was more likely to occur concomitantly with LDL-C reduction below 80 mg/dL (2.07 mmol/L). In other words, progression (or regression) of atherosclerosis seems to depend on the absolute levels of LDL-C achieved rather than on LDL-C gradients (Fig. 4). This contrasts somewhat with data from hard outcome studies showing a reduction in ARCVE risk proportional to the gradient of LDL-C reduction over baseline. The reasons for this apparent discrepancy include first, the limited power and consistency of the available plaque regression studies and, second, the uncertainty of the relationship between changes in plaque volume and parallel change in ARCVE risk. From Fig. 4, it is evident that most of the studies showing regression observed very small changes in plaque volume and that the best data fit is not linear but polynomial, implying it is possible to halt progression rather than induce regression. Moreover, by pooling the studies and/or the arms observing a regression, one can estimate that the expected and most optimistic regression rate would be − 0.63 ± 0.13% per year for a mean LDL-C value of 60 ± 4 mg/dL and a mean gradient of − 53 ± 4 mg/dL. This, in turn, would translate into an absolute reduction of plaque volume of 3% in 5 years, which, for an average plaque volume value of 40%, would translate into a 7.5% reduction of the overall atherosclerotic burden. It is difficult to imagine that such a change would really justify the expected 25% reduction in ARCVE events. It is possible that the limited duration of the studies (average 19 months), coupled with the relatively small LDL-C gradients applied and the limited resolution of the imaging technique, compromised the ability of such studies to accurately measure how LDL-C influences the rate of atherosclerosis progression.

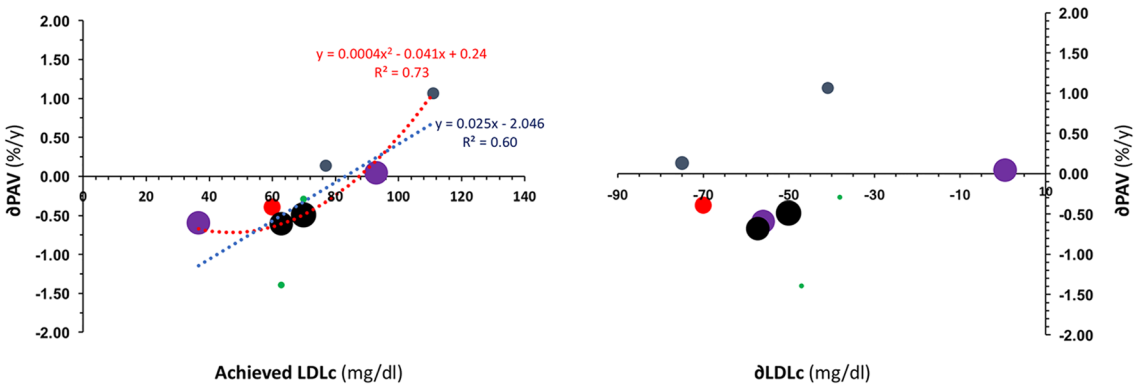

Fig. 4 Mean percent atheroma volume (PAV) changes per year plotted according to **a** the plasma low-density lipoprotein cholesterol (LDL-C) values achieved and **b** the induced LDL-C gradients. The code color identifies the specific clinical trial, and dimensions are proportional to sample size. *Violet* GLAGOV, black SATURN, *green* PRECISE, *blue* REVERSAL, *red* ASTEROID. In **a**, data have been fitted with either a linear (blue line) or a polynomial (red line) regression

As an accurate measure of risk factor exposure and sensitivity, the overall atherosclerotic burden predicts ARCVE risk among individuals [32]. On the other hand, whether in the same individual the risk changes in response to variations in the severity of atherosclerosis is unknown. Indeed, in the SATURN (Study of Coronary Atheroma by Travascular Ultrasound: Effect of Rosuvastatin Versus AtorvastatiN) trial, the LDL-C values (and the regression) achieved with the treatment were not predictors of major cardiovascular events. More than regression, plaque stabilization might be more significant and more influenced by LDL-C manipulations, as recently suggested by a meta-analysis of trials using intravascular ultrasound virtual histology [33]. Whether this is proportional to the LDL-C gradient or a consequence of the pleiotropic effects of statins remains under discussion.

6 LDL-C and Atherosclerosis: A Working Hypothesis Based on Clinical Data

Regarding the relationship between the pharmacologically induced chronic LDL-C gradients and atherosclerosis progression, it is uncertain whether what matters is the exposure (i.e., number of circulating LDL particles × time) or whether there is a safe threshold that should be crossed. The data from hard endpoint trials and to some extent plaque regression trials are congruent with the hypothesis that the number of LDL particles entering and damaging the vessel (remaining trapped in the subendothelial space) is a linear function of time and plasma LDL-C concentration. It is possible to envisage that any individual has a coefficient of LDL entrapment, which is independent of LDL-C concentration but affected by systemic (hypertension, cigarette smoking, diabetes, genetic) and local (shear stress) factors and acts by modifying either endothelial permeability and/or the rate of subendothelial LDL particle retention favored by their chemical modifications. LDL-C would then act mainly by increasing the flux of particles entering the intima-media compartment. The genetic factors likely to play a role in modulating the LDL–atherosclerosis relationship and the response to lipid-lowering therapy are possibly linked to *KIF6* gene polymorphisms. In fact, Arg carriers, who constitute approximately 60% of the population, appear to be at higher risk of ARCVE and also benefit to a greater extent from treatment with statins in terms of ARCVE reduction independently from potential confounders [34]. By reducing LDL-C exposure, it appears possible to halt the progression of the disease in volumetric terms and probably also as a biologic dynamic process. Possibly, once progression is halted, the removal of cholesterol from the subendothelial space might overcome the entry, resulting in some degree of regression. This is clearly an oversimplification that should only be considered a working hypothesis subject to experimental verification.

The observation that no consistent relationship has been found between the extent of atherosclerosis and plasma cholesterol in autopsy or angiography studies [35] is congruent with this hypothesis. Indeed, major guidelines [4, 6], while emphasizing the undisputable role of LDL-C on atherosclerosis, also agree upon not adopting pharmacologic interventions for mild-moderate elevated LDL-C in low-risk individuals. Clearly, an exception is familial hypercholesterolemia, a condition characterized by extensive atherosclerosis, even in those with a low burden of ARCVE risk factors. However, in this condition, the extremely long exposure (since birth) and the compensatory overactivation of the nonreceptor-mediated LDL-C removal explains the apparent incongruence.

Compliance with Ethical Standards

Conflict of interest Lorenzo Nesti, Alessandro Mengozzi, and Andrea Natali have no conflicts of interest that are directly relevant to the content of this article.

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