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Perspective
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Statins Lower Cholesterol Percent Wise, But Prevent Cardiovascular Disease by the Absolute LDL Concentration Gradient

*Andrea Natali**

Department of Clinical and Experimental Medicine, University of Pisa, Italy

Introduction

Statins are effective LDL-cholesterol (LDLc) lowering drugs. By inhibiting HGMCoA reductase in liver cells they reduce intracellular cholesterol synthesis, which in turn produces an enrichment of cell membrane LDL-receptors and an enhanced removal of LDL particles from the circulation. Statins are also effective in both primary and secondary cardiovascular disease prevention [1], they in fact have been shown to reduce the risk for atherosclerosis-related events to an extent that appears to be proportional to the achieved (and maintained) plasma LDL-cholesterol concentration gradient. Therefore, legitimately, guidelines insist on the use of statin in subjects at risk for CVD, but do differ on whether physicians should aim at targets [2] or should only select a treatment of adequate potency [3]. The target/threshold strategy is supported to some extent by studies on plaque progression. In this perspective, by elaborating on information exclusively based on clinical evidence we aim at offering the physicians support for autonomous decision making. To this aim we first describe the major characteristics of the response of LDL cholesterol to statin treatment and then discuss the relationship between LDL-cholesterol lowering and both cardiovascular events.

The Statin-LDLc Dose-Response Curves

By using data from the STELLAR trial [4], it is possible to draw the different dose response curves for each of the four most widely used statins. This study recruited 2,268 adult subjects with polygenic hypercholesterolemia and familial combined hyperlipemia (LDLc: 160-250 mg/dl, triglycerides <400 mg/dl) and measured the effect of 6 weeks of treatment with the four statins, each at the most commonly used daily dose, in a total of 15 treatment groups, each of approximately 150 subjects. As shown in (Figure 1a), when the effect is expressed as percent reduction over baseline, the four statins, as expected, differ widely in potency and the small standard errors reported (≤ 1%) indicate that the inter individual variability is extremely small. Interestingly, the shape of the dose-response is essentially logarithmic, as evident from the fact that after log transformation (Figure 1b) the responses are well fitted by straight lines, which notably are also almost parallel. This simple observation allows some inferences. First, the effect of doubling the dose of any statin is extremely similar and also easily predictable. Provided that $\ln(x*2)=\ln(x)+\ln(2)$ and that $\ln(2)=0.69$, by multiplying the log coefficients (6.3-7.3) for 0.69 we can predict that doubling the dose the additional further decline in LDLc is close to 5% (4.4-4.9%), regardless of the individual statin potency. It is unclear why in most of the scientific literature this figure is 6%. Provided that the potency is expressed by the constant term of the equations, the difference among statins becomes progressively greater as we move in the low dose range. Accordingly, the lowest dose of rosuvastatin (2.5 mg/die) will lower LDLc by 34%, like 10 mg of atorvastatin and 40 mg of simvastatin and, possibly, 120 mg of pravastatin. A 4-fold relationship is present among statins in this portion of the curve; while a 3-fold factor is present for the higher dose range (10 mg of rosuvastatin are equal to 30 mg of atorvastatin and 90 mg of simvastatin). Another implication is that also extremely low doses of rosuvastatin (1.25 mg/die) might represent a rational choice when an LDL reduction of approximately 25% is aimed at; not only, but thanks to its relatively long half-life (19h) rosuvastatin could be given on an alternate day regimen with a minimal loss of efficacy, notably simvastatin is given UID and has a half-life of approx. 3 hours. Another important corollary is that when the effect is expressed in absolute terms (mg/dl), the three statin treatment strategies strength defined by the AHA (Low: -25%- Moderate: -40% and High: -60%) will produce different concentration gradients depending on baseline LDLc values (Figure 2).

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Correspondence:
Andrea Natali, Department of Clinical and Experimental Medicine, University of Pisa, Italy,
E-mail: andrea.natali@med.unipi.it

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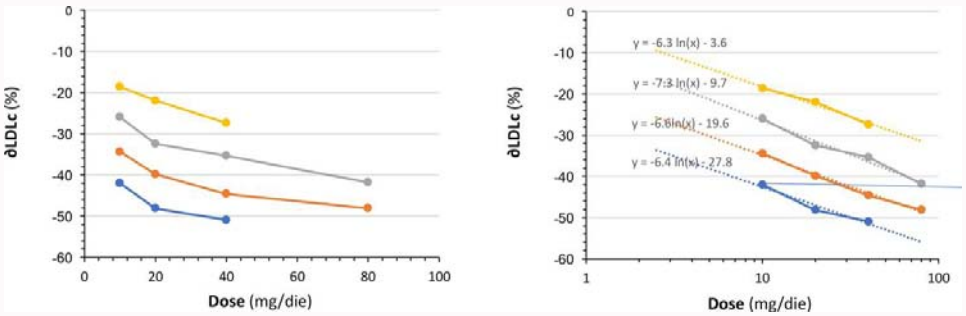

Figure 1: The percent change in plasma LDLc is plotted *vs* the dose of statin daily assumed. Yellow: pravastatin, gray: simvastatin, orange: atorvastatin, blue: rosuvastatin. In a) statin dose is represented in a normal scale, in b) is represented in a log scale and data of each statin have been fitted (dotted lines) through a linear regression. (Data are taken from the STELLAR trial main publication).

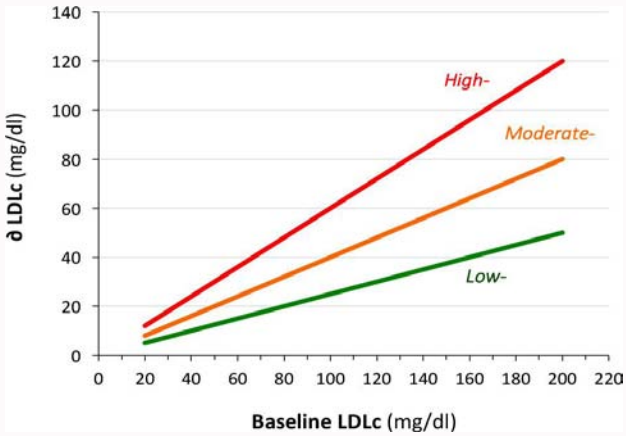

Figure 2: The predicted changes in LDLc (a) and in CVD risk (b) are plotted as functions of baseline LDLc values and the strength of statin therapy as defined by the AHA (High: red, Moderate: orange, Low: green).

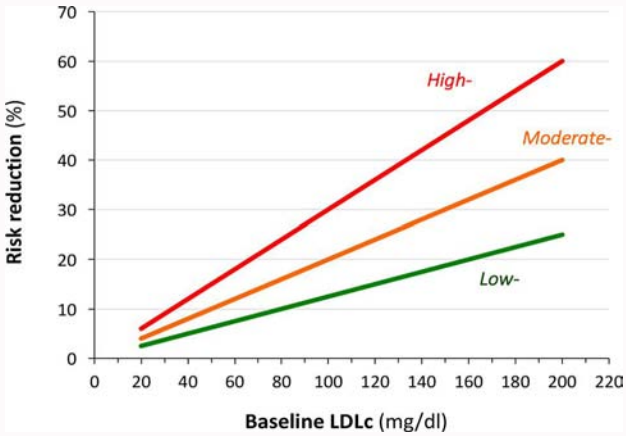

Figure 3: The number of patients to be treated for 5 years in order to prevent one event is plotted according to the baseline CVD risk and to two different statins induced LDLc gradients (Green: -38 mg/dl, Red: -76 mg/dl).

The "false" Problem of Statin Non-Responders

Large clinical outcome trials show a wide variability in the response to statins. In the Jupiter trial [5] the average decline in LDLc in response to 20 mg of rosuvastatin was, as expected, approximately 50%; however, 20% of the patients showed a poor response ranging from +30 to -30% suggesting the presence of a sensible portion of individuals who are non-responders to statins. This has prompted a series of genome-wide studies, which however, essentially have failed to identify loci that could explain this resistance being the few statistically significant loci [6] able to justify only a small portion of the response variability with effects ranging between -2 and -6%. Moreover, one of the most relevant loci (rs10455872) is known to modulate plasma Lp (a) levels, which in turn are not affected by statin treatment, but are frequently - and inappropriately - included in the LDLc fraction. Therefore, a true genetic resistance to statin appears unlikely. In addition, the poor statin responders of the PROSPER Trial [7] was found to be more frequently smokers, a high alcohol consumers, to have lower cognitive function and lower LDLc values suggesting the that even within the context of controlled clinical trials, poor compliance is the major factor contributing to statin resistance, which should rather be called call reluctance. Occasionally, much selected group of patients (familial hypercholesterolemia) might have an increased cholesterol intestinal absorption [8] or might be exposed to factors like acute inflammation or drastic changes in dietary habits, which are known to contribute to some extent to the natural variability of plasma LDLc concentrations.

The Relationship between the Change in LDL Cholesterol and in CVD Risk

The CTT 2012 analysis by pooling all major available clinical trials with statins has established that there is a 21% reduction in the risk of a CV event for 1 mM (38 mg/dl) reduction in LDL cholesterol, which results from the combination of a 24% reduction in coronary events and a 15% reduction in cerebrovascular events. These numbers are incredibly consistent among subgroups regardless of gender, age, concomitant risk factors, baseline LDLc, and whether the patients were in primary and secondary prevention. This is reflected in the very small observed 95% confidence interval of the estimate (21% [19-23%]), particularly if we take into account the above-mentioned expected substantial variability in compliance. We can therefore establish that statins for each mg/dl less of plasma LDLc will provide a 0.55% reduction in CVD risk in the large majority the subjects. The IMPROVE-IT study [9] has provided evidence that this relationship holds true also for a different cholesterol lowering drug (ezetimibe) and down to LDLc values of 50 mg/dl reporting a congruent 7% reduction in risk for a LDLc gradient of -15 mg/dl (from 70 to 55 mg/dl). Whether below the value of 55 mg/dl this relationship continues to hold true remains to be established since we only have the FOURIER study [10] (with evolocumab) showing that in response to a 60 mg/dl gradient (from 90 to 30 mg/dl) the observed risk reduction was 20% therefore yielding a smaller than expected efficacy coefficient (0.33% per each mg of LDLc). As thoroughly discussed in the paper, possibly

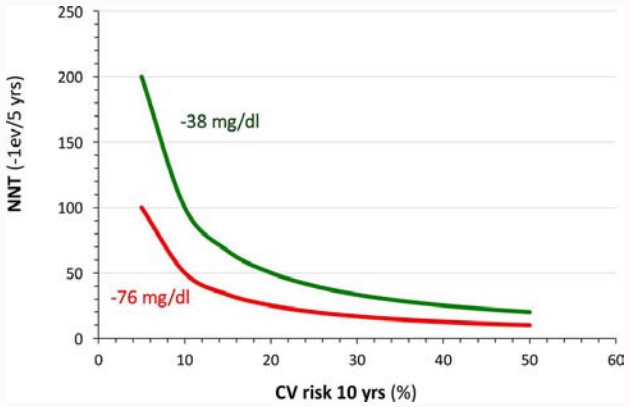

Figure 4: The NNT at 5 years will fall below the value of 50 in the low risk class (10-20%) only when a 2 mM (76 mg/dl) LDLc gradient is obtained.

the short duration of the study (2 years) might have led to a sensible underestimation of the true effect.

By simply merging the information with regard to the efficacy on LDLc of the different statin treatment strengths (Figure 2) and the expected effect of a given LDLc gradient according to baseline LDLc values, we can appreciate the contra-intuitive concept that the lower is baseline LDLc the stronger must be the potency of the statin if we aim at achieving a significant risk reduction (Figure 3). A ≥ 20% reduction in RR will be achieved with a low-intensity treatment only if baseline LDLc is greater than 160 mg/dl, while it will be achieved with moderate- and high-intensity statin treatment for baseline LDLc values ≥ 100 and ≥ 65 mg/dl, respectively. Taking into consideration this simple relationship, it is not surprising that in the ASCOT-LLA a moderate-intensity statin therapy (atorvastatin 10 mg) was effective only in those with baseline LDLc values ≥ 131 mg/dl [11].

The second somewhat contra-intuitive corollary is pharmaco-economic. Provided that the absolute risk reduction will depend on the absolute LDLc gradient and the level of CVD risk, in order to be cost-effective the lower is the CVD risk the greater must be the LDL gradient. As depicted in Figure 4 the NNT at 5 years will fall below the value of 50 in the low risk class (10-20%) only when a 2 mM (76 mg/dl) LDLc 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, which, at least with statins, means with a baseline LDLc value ≥ 140 mg/dl.

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