Intensive treatment with statins and the progression of cardiovascular diseases: the beginning of a new era?

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Introduction

Statins represent one of the major therapeutic revolutions in the modern era of cardiovascular medicine. However, the advent of these drugs has not only afforded solutions, but has also raised new questions. Perhaps the most intriguing one is: how much low-density lipoprotein (LDL) reduction must we achieve to obtain the greatest benefits? From a theoretical point of view, Grundy [1] discussed three different possibilities. The first one was that below a threshold LDL level, no further benefit was obtained. The second was that decreasing LDL levels would continue to yield proportional cardiovascular risk reduction. The third hypothesis was that the benefit achieved progressively decreased as LDL levels did, without a clear cut-off point.


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Henceforth, classic reports suggested that people with spontaneously low cholesterol levels were at low risk for coronary events [2,3]. However, it was necessary to demonstrate subsequently that achieving such low cholesterol levels by using drugs was actually followed by clinical benefits that were not offset by their adverse effects.

**Early trials**

At first, answers to this question were looked for in the data of classic landmark statin trials. The CARE study results suggested that there was no further benefit below LDL levels of 130 mg/dl [4]. In contrast, the 4S data did not display a threshold value, but showed a progressive diminution in risk reduction with progressively decreasing LDL [5]. However, these studies had not been designed for that purpose. They had been set up mainly to demonstrate the ability of statins to reduce the incidence of cardiovascular events. As we are presently dealing with lower therapeutic cholesterol targets, a retrospective look into the data of these studies would remind us why they were not suitable to answer this question: in the 4S, for example, mean LDL levels declined from 188 mg/dl in placebo patients to 122 mg/dl in the simvastatin group [5].

In 1997, the post-Coronary Artery Bypass Graft trial began to shed light on this question. In patients with a previous coronary artery bypass graft, intensive treatment with lovastatin achieving mean LDL levels of 93 mg/dl decreased the percentage of saphenous grafts occluded, as compared with a moderate regimen achieving 136 mg/dl with the same drug [6]. Two years later, in low-risk patients with single-vessel disease, the administration of 80 mg/day of the more potent agent atorvastatin in the Atorvastatin versus Revascularization Treatment (AVERT) study reduced LDL levels to 77 mg/dl and led to clinical results comparable to angioplasty plus a standard treatment that reached only a mean value of 119 mg/dl [7]. Although both therapeutic modalities are complementary, with the angioplasty working selectively at one lesion and the statin targeting the entire vascular tree, this comparative design demonstrated the power of aggressive management with statins on atherosclerosis. Was the intensive decrease in LDL levels the basis of the risk reduction achieved? Later studies would support this hypothesis.

**Recent trials**

In 2001, the MIRACL trial suggested again that intensive statin treatment was most effective [8]. Atorvastatin at 80 mg/day decreased the mean LDL level to 72 mg/dl as compared with 135 mg/dl with placebo in patients with unstable angina or non-Q myocardial infarction. Within only 4 months, this aggressive management diminished the incidence of stroke and objective symptomatic ischaemia requiring hospitalization. The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCe) study, presented at the scientific sessions of the American College of Cardiology in March 2004, confirmed the hypothesis of further benefits with aggressive cholesterol-lowering [9]. In this trial, 2442 patients with coronary artery disease were randomized to achieve LDL levels <80 mg/dl, receiving atorvastatin titrated at doses ≤80 mg/day, or standard therapy with the statins and doses chosen by the treating physicians. Intensive lipid-lowering therapy demonstrated a significant reduction in the primary end-point of combined incidence of cardiac death, myocardial infarction, coronary revascularization and unstable angina requiring hospitalization.

Nevertheless, the study with the greatest impact has been the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial [10]. In this study, 4162 patients who had suffered an acute coronary syndrome in the preceding 10 days were randomized on a factorial design to receive pravastatin 40 mg/day vs atorvastatin 80 mg/day in addition to gatifloxacin vs placebo. While the results of the antibiotic trial have not yet been published, the data of the lipid-lowering therapy have been reported recently [10]. Mean LDL levels were 95 mg/dl in the pravastatin group, in compliance with present guidelines of clinical practice, and 62 mg/dl in the atorvastatin group. After a follow-up of 2 years, the intensive lipid-lowering group showed a significant reduction in the incidence of the combined end-point of death, myocardial infarction, unstable angina requiring hospitalization, revascularization and stroke, from 26.3 to 22.4%. There was even a trend towards a reduction in overall mortality, which could have well been significant if the follow-up had been more prolonged, as in classic landmark statin trials. Therefore, it appears that recommending a statin to our patients is not enough; there are differences in the final outcome depending on the intensity of the treatment used.

**Why is intensive lipid-lowering more effective?**

In 2001, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial study demonstrated that atorvastatin 80 mg/day partially reversed carotid intima–media thickness in patients with familial hypercholesterolaemia, as compared with simvastatin 40 mg/day [11]. Very recently, the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial study showed that high-dose atorvastatin delayed progression of coronary atherosclerosis, as assessed by intravascular ultrasound, while 40 mg/day pravastatin did not [12]. These trials demonstrated that aggressive statin therapy is more effective in terms of atherosclerosis progression.

However, acute ischaemic events are not due merely to progression of atherosclerosis, but also to
a thrombotic complication of the plaques. Statins have long been demonstrated to reduce endothelial dysfunction [13,14], inflammation [15,16] and blood thrombogenicity [17,18], which all seem to be responsible for plaque thrombosis. These actions could explain the reduced incidence of ischaemic events achieved by this therapy. In fact, in addition to reducing C-reactive protein (CRP) levels, high-dose atorvastatin also decreases CD40 ligand (CD40L) serum levels [19–21]. Moreover, the REVERSAL and PROVE-IT studies show that the decrease in CRP induced by atorvastatin 80 mg/day is greater than that achieved by pravastatin 40 mg/day [10,12]. At this point, the link between the inflammation markers and thrombosis must be emphasized. In keeping with this, CRP expression induces an increase in thrombosis in atherosclerotic mouse models [22]. Moreover, CD40L is necessary for the adequate stability of the thrombus, because it acts as a ligand for IIb–IIIa platelet receptors [23].

Recently, we have shown, in the AITOR study, that atorvastatin 80 mg/day diminishes not only macrophage infiltration [24], but also the activity of the pro-inflammatory nuclear transcription factor NF-κB (unpublished data) in human atherosclerotic carotid plaques within only 1 month, which is a time point at which the event curves began to separate in the PROVE-IT trial. However, in a study with a similar design, 3-months’ administration of pravastatin 40 mg/day reduced macrophage infiltration, but did not affect NF-κB activity [25]. All these data suggest that the clinical benefits achieved by intensive statin treatment as compared with standard regimens may be explained, at least in part, by a higher anti-inflammatory activity.

Clinical implications and the future

It seems clear at present that LDL should be lowered to a much greater degree than recommended by current practice guidelines. Of course, given the physiological role of cholesterol, there must be a level beyond which no further benefits are found and even deleterious consequences may occur. How far we are at present from that level will be determined as new, more potent lipid-lowering agents enable us to explore that possibility.

Another question is whether the benefits of LDL-lowering apply to drugs other than statins, such as the inhibitors of intestinal cholesterol absorption. For example, combining submaximal doses of atorvastatin with the cholesterol absorption inhibitor ezetimibe may reduce LDL levels even more than maximal doses of atorvastatin [26,27]. Nevertheless, these new drugs lack the extensive background of statins in demonstrating lipid-independent effects. In this sense, we and others have shown anti-inflammatory effects of statins in cell culture and animal models of atherosclerosis that were not related to cholesterol reduction [15,28–30]. Thus, using other drugs to intensively reduce cholesterol levels and expecting to have the same benefits achieved as with statins implies the assumption that either the cholesterol-independent effects of statins are clinically irrelevant or these actions are shared by non-statin lipid-lowering agents. We must await further studies to know whether LDL cholesterol should be targeted only with statins or if other agents lead to similar benefits. The end of this story will probably come in the next few years, as many other fascinating challenges arise.

References


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