Editorial

Are Lower Levels of LDL-Cholesterol Really Better? Looking at the Results of IMPROVE-IT: Opinions of Three Experts – I

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Dyslipidaemia, and hypercholesterolaemia in particular, is recognised as one of the main causes of atherosclerosis and cardiovascular disease. Today, the causal relationship between hypercholesterolaemia and atherosclerosis has been fortified by an accumulation of experimental, genetic, epidemiological, biochemical, and invasive observations.

Almost all studies of statins, in both primary and secondary prevention, have shown a linear correlation between the reduction in LDL as a result of statin administration and a decrease in the incidence of cardiovascular events. A similar linear correlation has been confirmed when high doses of statins were compared with low doses.[1] This direct association between the reduction of LDL levels by statins and a fall in cardiovascular events led the AHA/ACC to draw up new guidelines for the treatment of hypercholesterolaemia.[2]

What characterises these guidelines is the complete change in their philosophy. First of all, the concept of a target LDL level has been completely abolished, as being not sufficiently supported by scientific data. Only randomised, controlled trials are taken into account, while epidemiological data and pathophysiology are demoted to lesser importance. Effectively, only statins are considered and are categorised according to their strength, so that according to the risk category, statins of high or moderate strength may be selected. The risk is calculated using a new score, which appears to overestimate the risk. If the 10-year risk of stroke or acute myocardial infarction based on this score is greater than 7.5%, this is classified as high risk, requiring the commencement of therapy; if it is between 5% and 7.5%, statin administration should be considered (for reference, the latter value corresponds to a European Risk Score of 2.5% and not the 5% that applies today as the threshold of high risk). Based on this scoring system, one in three adult Americans should be taking statins.

According to the members of the Task Force, studies have not provided sufficient indications for the use of an LDL target level. A statin of appropriate strength should be used to reduce cardiovascular risk in those individuals most likely to benefit. Hypolipidaemic therapies other than statins have not been shown to reduce cardiovascular risk, as long as we await the results of the IMPROVE-IT trial.

The big problem with these guidelines is that a patient with a recent infarction and an initial LDL of 180 mg/dL will usually have, after high-dose statin treatment, an LDL level between 80-100 mg/dL, assuming the expected response to statins.

In other words, the level will be outside the old target. While the guidelines recognise that a further drop would be beneficial, they disagree that the addition of any other hypolipidaemic drugs would help, considering that there are no clinical trials of ezetimibe or fibrates to show that they have a real beneficial effect on the cardiovascular system. While acknowledging that the SHARP trial was well executed and achieved the expected reduction in LDL and cardiovascular events, the guidelines relegate that trial to secondary status because the comparison was with placebo and not with simvastatin. At the same time, they stress that if the patient has a smaller reduction in LDL than expected, or shows intolerance to high-dose statins, then it is worth considering ezetimibe for LDL reduction.

So here we have a significant contradiction. Either we believe that ezetimibe really helps and we wait for IMPROVE-IT for further confirmation, while using it in addition to statins when their effect alone is insufficient, or we believe that it does not help, in which case it makes no sense to use it as an adjunctive therapy in patients who have a poor response to statins.

The view that because studies have been designed with fixed doses of statins and not with target LDL levels the latter should be abolished is extremely dangerous for the future of medicine. If we take into account that at least 90% of large trials were funded by the pharmaceutical industry, we will have a medical practice that is no longer based either on pathophysiology or on epidemiological indications, but only on what kind of clinical trials the industry chooses to fund. And anyone who does not fall into any of these categories that are funded by industry will find themselves left out of the indications. Let us not forget that there is no double-blinded clinical trial showing that smoking kills, whereas epidemiologically there can be no doubt about it.

Although large trials such as TNT were indeed designed with fixed doses of atorvastatin, 10 mg versus 80 mg, it was estimated that one group would achieve an LDL level of 70 mg/dL and the other 100 mg/dL. The GREACE[3] trial was designed so that one group would take atorvastatin in order to reach the target level, while the other group remained on standard treatment. To view these studies as only drug dosages and not as an attempt to use what was then the most powerful statin as a means to achieve a target represents a philosophical change in viewpoint that may prove extremely dangerous for patients by the time we realise our mistake. Most criticism of the guidelines within the United States has been based on the way the risk is calculated, but the ESC-EAS guidelines consider that, apart from the risk score, abandoning target levels may have a detrimental effect on patient management.[3]

Against this background, the results of the IMPROVE-IT trial are anxiously awaited. This is a study of patients with acute coronary syndromes, which was designed to test the hypothesis of "the lower the better", regardless of the use of statins. Following the failure of fibrates, niacin, and CETP inhibitors in combination with a statin to further reduce cardiovascular events compared to statin monotherapy, ezetimibe is now trying its luck in this area in a comparative trial.

Ezetimibe inhibits the NPC_1L_1 protein, which is mainly found in epithelial cells of the gastrointestinal tract, leading to a reduction in cholesterol absorption. At the AHA 2014 Scientific Sessions, simultaneously with its publication in the New England Journal of Medicine, a genetic analysis was reported showing that NPC_1L_1 protein polymorphisms that lead to lower LDL levels from birth are associated with a lower incidence of coronary artery disease, thus providing an epidemiological and genetic foundation linking the NPC_1L_1 protein, namely the point of action of ezetimibe, and atheromatosis.[5] In this study, 18,144 patients with an acute coronary syndrome (STEMI, NSTEMI, unstable angina) and an initial LDL level in the range 50-125 mg/dL were randomised within 10 days after the event either to simvastatin 40 mg (with the possibility of an increase to 80 mg for LDL levels >79 mg/dL) or to a combination of ezetimibe and simvastatin 10/40 mg for at least 2.5 years' follow up and until 5250 endpoints had occurred, including cardiovascular death, acute myocardial infarction, unstable angina, revascularisation (>30 days after randomisation), or stroke. Although 42% of the patients withdrew from the study (it was the period when the SEAS study was published and there was temporary concern about malignancies), the mean follow-up time of six years allowed the required events to be completed. The LDL level in the simvastatin group was 69.5 mg/dL, compared with 53.7 mg/dL in the ezetimibe+simvastatin group.

The results showed a statistically significant reduction in the incidence of the composite endpoint in the group receiving combined therapy ($p=0.016$), with 32.7% versus 34.7% of patients recording events, while the number needed to treat was 50. The dif-

ference in endpoints was due to infarctions and ischaemic strokes, which were reduced to a statistically significant degree in the group with lower LDL levels.

Given its timing, the outcome of this study is really of huge clinical significance. First, it mandates a change of course for hypolipidaemic treatment away from that indicated by the AHH/ACC guidelines, namely that cholesterol reduction using statins is the only approach that confers a clinical benefit. The addition of ezetimibe seems to offer a clinical benefit with a significance equal to that of statins. Second, it confirms the theory of "the lower the better", in that for every 50 patients who reduce their LDL levels from 69 mg/dL to 53 mg/dL we will have one less endpoint. Third, it confirms the safety of both ezetimibe and such low LDL levels (50 mg/dL) after an acute coronary syndrome. Fourth, it opens the way for PCSK9 inhibitors and their use in clinical practice. Fifth, it shows that there is no point in changing guidelines after a drug has been in use for a decade, six months before the most important study of its effectiveness is published. The American guidelines managed to get ahead of themselves, becoming outdated less than a year after their publication, before they even had time to become current.

Disclosure

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