Editorial

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

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At the last Congress of the American Heart Association, in November 2014, the results of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) were presented. This study was designed to examine whether a reduction in LDL-cholesterol levels to <70 mg/dL with the addition of ezetimibe to a statin would achieve a further reduction in cardiovascular events.[1,2] A total of 18,144 patients with a recent (<10 days) acute coronary syndrome (ACS) and LDL-cholesterol levels ≤125 mg/dL (≤100 mg/dL if they had taken previous hypolipidaemic medication) were enrolled and were randomised to either 40 mg simvastatin alone or 40 mg simvastatin plus 10 mg ezetimibe daily. In those who did not achieve a reduction in LDL cholesterol to <80 mg/dL, the simvastatin dose was increased to 80 mg. This was necessary in 27% of the patients in the simvastatin group and 6% in the simvastatin/ezetimibe group. The patients were followed up for at least 2.5 years and until 5250 cardiovascular events had occurred. The composite primary endpoint included cardiovascular death, non-fatal myocardial infarction, re-hospitalisation for unstable angina, coronary reperfusion (≥30 days after randomisation), and non-fatal cerebrovascular stroke. The mean level of LDL-cholesterol achieved in the simvastatin group was 69.5 mg/dL, compared with 53.7 mg/dL in the combined treatment group. The median follow-up time was ~6 years. In the simvastatin/ezetimibe group there were 170 fewer cardiovascular events than in the simvastatin monotherapy group (32.7% versus 34.7%, p=0.016), representing a relative risk reduction of 6.4%. Table 1 shows the cardiovascular events in the two groups in more detail. There was no difference between the two groups as regards the occurrence of adverse effects. The number needed to treat in order to prevent one cardiovascular event was 50. It should be noted that 42% of participants in both groups withdrew prematurely from the study.

The results of this study were received with satisfaction by the cardiological community, as for the first time ezetimibe added to a statin in a "difficult" group of patients was associated with a further modest clinical benefit: patients who received ezetimibe in addition to a statin reduced their LDL cholesterol level by a further ~16 mg/dL compared to the group receiving simvastatin monotherapy. It is notable that this comparison was made with patients who had succeeded, albeit marginally, in achieving a target LDL-cholesterol level of <70 mg/dL by taking a statin.

Although nobody questions the fact

Table 1. Primary endpoints in the two arms of the IMPROVE-IT trial.

Endpoints	Simvastatin (n=9077)	Simvastatin/ ezetimibe (n=9067)	p
Primary endpoints	34.7	32.7	0.016
Total mortality	15.3	15.4	0.782
Myocardial infarction	14.8	13.1	0.002
Stroke	4.8	4.2	0.052
Ischaemic stroke	4.1	3.4	0.008
Unstable angina	1.9	2.1	0.618
Coronary reperfusion	23.4	21.8	0.107

that the IMPROVE-IT trial was a positive development in the field of hypolipidaemic intervention, and one that reinforces the hypothesis of "the lower the better" as regards LDL-cholesterol levels, there is a series of observations that must also be taken into account in order to give a clear picture of this study:

1. The results of IMPROVE-IT have not yet been published in a peer-reviewed medical journal. Their publication will give a more complete picture of the study, while the criticism and discussion that will ensue will shed light on its strong points as well as its weaknesses. Consequently, it is risky to carry out any dogmatic, absolute, and selective evaluation of the results when their publication has not been studied carefully.
2. The positive findings of this study are referred to patients who had suffered an ACS; as a result, they cannot be generalised to other populations, e.g. for primary prevention of coronary artery disease.
3. This study was designed approximately 10 years ago and as a result it does not correspond to today's clinical practice. The recent American Guidelines[3] for the treatment of hypercholesterolaemia recommend high-intensity statin therapy with rosuvastatin (20-40 mg) or atorvastatin (40-80 mg) in patients with an ACS, and not the 40 mg of simvastatin that was given in the IMPROVE-IT trial. In consequence, a more modern study of the IMPROVE-IT type is needed to compare high-dose rosuvastatin or atorvastatin, with or without the addition of ezetimibe, to show whether the addition of ezetimibe to today's recommended treatment leads to a further clinical benefit.
4. The ~6% relative risk reduction in cardiovascular events was mainly driven by the reduction in myocardial infarctions and ischaemic strokes. The total mortality was not affected by the addition of ezetimibe.
5. The clinical benefits of IMPROVE-IT are considered to be modest. After 6-7 years' combined administration of simvastatin/ezetimibe there was a 2% reduction in the absolute risk of the composite primary endpoint. This means that 98% of the patients who received the combined hypolipidaemic therapy showed no additional benefit in relation to statin monotherapy. If we take into account the cost of the simvastatin/ezetimibe combination, which is greater than the cost of monotherapy with atorvastatin (this is also likely to apply to rosuvastatin, which loses its patent protection in ~2 years), it is clear that studies will need to be performed to assess the cost-effectiveness of the combined simvastatin/ezetimibe therapy. Hence, we do not yet know to what extent these studies will be able to support the use of this combination compared to monotherapy with the newer statins.
6. Before we embrace the "lower the better" hypothesis, there must also be evidence as to the safety of very low LDL-cholesterol levels. A recent *post hoc* analysis of the JUPITER trial (study of primary prevention of coronary artery disease via the administration of 20 mg rosuvastatin daily) found that individuals who had LDL-cholesterol levels <30 mg/dL, despite the clinical benefits, showed an increase in the physician-reported type 2 diabetes mellitus and a higher incidence of haematuria, insomnia and musculoskeletal and hepatobiliary disorders, in comparison to the placebo group.[4] This reinforces the concerns about the safety of very low LDL-cholesterol levels, to which the addition of ezetimibe to the most powerful statins might lead. Besides, the recent American Guidelines recommend that a reduction in statin dose may be considered in a patient who has LDL-cholesterol levels <40 mg/dL in two successive measurements.[3]

The above concerns should not be allowed to overshadow the positive aura of the IMPROVE-IT trial. This study is one of the most important of the last decade in the area of preventive cardiology. For the first time, additional benefits have been reported from the addition of a non-statin to a statin in patients who have experienced an ACS and who have achieved LDL-cholesterol levels significantly lower

than the 70 mg/dL target. This finding reinforces, *but is not sufficient to prove*, the "lower the better" hypothesis. Clinical outcome data from trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (Fourier and Odyssey long- term trials) will also be needed before this hypothesis can be definitely confirmed or rejected.

We are impatiently awaiting the publication of the IMPROVE-IT trial results. The productive dialogue that will ensue will allow the medical community to form an objective picture of the study's findings, and it will be apparent to what extent we may be able to alter our daily clinical practice for the treatment of hypercholesterolaemia.

Disclosure

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