Invited commentary

IMPROVE-IT clinical implications. Should the “high-intensity cholesterol-lowering therapy” strategy replace the “high-intensity statin therapy”?

Luis Masana a, Juan Pedro-Botet b, Fernando Civeira c, *

a Vascular Medicine and Metabolism Unit, Research Unit on Lipids and Atherosclerosis, “Sant Joan” University Hospital, Universitat Rovira i Virgili, IISPV, Spanish Biomedical Research Centre in Diabetes and Associated Metabolic Disorders (CIBERDEM), Reus, Spain
b Lipid and Vascular Risk Unit, Hospital del Mar, Universitat Autonoma de Barcelona, Barcelona, Spain
c Head Lipid Unit, Hospital Universitario Miguel Servet, IIS Aragon, Red Cardiovascular Research Network (RIC), Zaragoza, Spain

ARTICLE INFO

Article history:
Received 2 March 2015
Received in revised form 2 March 2015
Accepted 3 March 2015
Available online 10 March 2015

Keywords:
High-intensity cholesterol-lowering therapy
Ezetimibe
IMPROVE-IT

The recently presented results of the IMProved Reduction of Outcomes: Vytorin Ef good news for patients, physicians and researchers [1]. Patients can search for clinical support to lower lowering in the management of high risk patients; and re-
successions can be drawn from the IMPROVE-IT results [1]. First, the additional LDL cholesterol reduction achieved with ezetimibe is of the same quality, in terms of CVD risk reduction, as that obtained with statins in monotherapy. Each mmol/L (38.7 mg/dL) of LDL cholesterol reduction obtained with statins in monotherapy or with the combination statin plus ezetimibe is associated with an approximate decrease in CVD relative risk of 20% in concordance with the “Cholesterol Treatment Trialist” equation [5]. This result questions the clinical relevance of the pleiotropic effects of statins, and highlights the effects of LDL cholesterol reduction [6]. Second, the CVD benefit associated with LDL cholesterol lowering is maintained up to at least 53 mg/dl, and this benefit is independent of the LDL cholesterol at baseline, if over 50 mg/dL. Third, LDL cholesterol concentrations far below 70 mg/dL during a mean follow-up of six years are not associated with any increase in side effects or comorbidities. This are very good news for potent statins, lipid lowering combinations, and some drugs under clinical development, as PCSK9 inhibitors, which are capable in some patients to lower LDL cholesterol to these concentrations [7]. Forth, subjects over 65 years of age (almost half of the IMPROVE-IT popu-
ation), benefit, at least, as much as younger patients. “Never is too late for cardiovascular prevention”. Finally, the IMPROVE-IT was designed to test the benefit of two different LDL goals (70 mg/dL in the simvastatin arm, and 55 mg/dL in the simvastatin plus ezetimibe arm), rather than a two fixed treatment strategies. The positive results of the IMPROVE-IT trial support the ATP-III and the Cardi-
ology and Atherosclerosis European Society concept of treatment based on lipid goals [8,9].

Should IMPROVE-IT results modify our clinical practice? In this respect, some aspects on CVD prevention should be taken into account. CVD continues to be the leading cause of morbidity and mortality worldwide. Despite tremendous efforts to control cholesterol levels in patients at very high risk, only an unacceptably low percentage meets LDL cholesterol targets [10]. Moreover, even those reaching low LDL cholesterol concentrations with statin therapy still have a high residual CVD risk [11].

The 2013 ACC/AHA guidelines recommend using high-intensity statin therapy in patients with atherosclerotic cardiovascular disease [12]. Even with the highest doses of the most efficient statins, it is difficult to reduce LDL cholesterol beyond 50%. Therefore, no patient with baseline LDL cholesterol >140 mg/dl will achieve an
LDL cholesterol value <70 mg/dL and even less <50 mg/dL.

The actual clinical scenario is even worse [10]. A non-negligible group of patients does not tolerate full statin treatment owing to side effects such as myalgia, and some patients, particularly those with prediabetes or metabolic syndrome components, could favor the development of new-onset diabetes while on high-dose, high-potency statin treatment [13].

We consider that by applying the lessons of the IMPROVE-IT study, we could better manage hypercholesterolemia in high-risk patients. We would change the “concept” of high-intensity statin therapy for high-intensity cholesterol-lowering therapy (Table 1). Although subtle, this message would have many clinical implications, allowing for combination therapy (statin plus ezetimibe) to achieve lower LDL goals (only high-dose, high potency statin plus ezetimibe can lower LDL by more than 60%) or, alternatively, increasing statin tolerance using intermediate statin doses.

Furthermore, the IMPROVE-IT trial strongly supports “the lower (LDL), the better theory” in contrast to “the higher (the statin intensity treatment), the better”. Future guidelines should take this paradigm change into consideration. We propose that high risk patients should follow ACC/AHA recommendations but also EAS/ESC goals being put on high or very high intensity cholesterol lowering treatment. Lipid lowering treatment in high risk patients with baseline LDL cholesterol >70 mg/dL should reach at least 50% reduction in the LDL cholesterol, as proposed by the ACC/AHA, but also LDL cholesterol <70 mg/dL, as proposed by EAS/ESC. These goals should be preferably obtained with high dose of potent statins, and with statins plus ezetimibe when necessary.

Conflict of interest


References


Table 1

<table>
<thead>
<tr>
<th>Low-intensity cholesterol-lowering therapy (LICLT)</th>
<th>Mild-intensity cholesterol-lowering therapy (MILCIT)</th>
<th>High-intensity cholesterol-lowering therapy (HICLT)</th>
<th>Very-high-intensity cholesterol-lowering therapy (VHICLT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin 10 mg</td>
<td>Atorvastatin 10–20 mg</td>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 40–80 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td>Pravastatin 10–20 mg</td>
<td>Rosuvastatin 5–10 mg</td>
<td>Rosuvastatin 20–40 mg</td>
<td>Rosuvastatin 20–40 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td>Lovastatin 10–20 mg</td>
<td>Simvastatin 20–40 mg</td>
<td>Simvastatin 20–40 mg + Ezetimibe 10 mg</td>
<td>Simvastatin 20–40 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td>Fluvastatin 40 mg</td>
<td>Pravastatin 40 mg</td>
<td>Pravastatin 40 mg + Ezetimibe 10 mg</td>
<td>Pravastatin 40 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td>Pitavastatin 1 mg</td>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 40 mg + Ezetimibe 10 mg</td>
<td>Lovastatin 40 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td>Ezetimibe 10 mg</td>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 80 mg + Ezetimibe 10 mg</td>
<td>Fluvastatin 80 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td>Pitavastin 2–4 mg + Ezetimibe 10 mg</td>
<td>Pitavastatin 2–4 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 10 mg + Ezetimibe 10 mg</td>
<td>Simvastatin 10 mg + Ezetimibe 10 mg</td>
<td>Simvastatin 10 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 20 mg + Ezetimibe 10 mg</td>
<td>Pravastatin 10–20 mg + Ezetimibe 10 mg</td>
<td>Pravastatin 10–20 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 20 mg + Ezetimibe 10 mg</td>
<td>Lovastatin 20 mg + Ezetimibe 10 mg</td>
<td>Lovastatin 20 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg + Ezetimibe 10 mg</td>
<td>Fluvastatin 40 mg + Ezetimibe 10 mg</td>
<td>Fluvastatin 40 mg + Ezetimibe 10 mg</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 1 mg + Ezetimibe 10 mg</td>
<td>Pitavastatin 1 mg + Ezetimibe 10 mg</td>
<td>Pitavastatin 1 mg + Ezetimibe 10 mg</td>
</tr>
</tbody>
</table>

LDLc, low-density lipoprotein cholesterol.