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REVIEW

French expert group proposal for lipid-lowering therapy in the first 3 months after acute myocardial infarction

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ABSTRACT

In patients admitted for acute myocardial infarction (MI), it has been demonstrated that reducing LDL cholesterol (LDL-c) is associated with a reduction in major adverse cardiovascular events. We describe a consensual proposal made by a French group of experts for lipid-lowering therapy at the acute phase of acute myocardial infarction. A group of French experts comprising cardiologists, lipidologists and general practitioners prepared a proposal for a lipid-lowering strategy with a view to optimizing LDL-c levels in patients hospitalized for myocardial infarction. We describe a strategy for the use of statins, ezetimibe and and/or proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, with a view to reaching target LDL-c levels as early as possible. This approach, which is currently feasible in France, could considerably improve lipid management in patients after ACS, thanks to its simplicity, rapidity and the magnitude of the decrease in LDL-c that it achieves.

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KEY WORDS: Ezetimibe; Cholesterol, LDL; Myocardial infarction.

In patients admitted for acute myocardial infarction (MI), it has been demonstrated that reducing low density lipoprotein (LDL) cholesterol (LDL-c) to the target via the early introduction of high-intensity statins, associated with ezetimibe and/or proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, is associated with a reduction in major adverse cardiovascular events. Based on this evidence, the European Society of Cardiology (ESC) and the French Society of Cardiology issued high-grade recommendations in favor of the early introduction of high-intensity statins (as early as admission), regardless of baseline LDL. To reach a target LDL-c level <0.55 mg/dL (1.4 mmol/L) plus a reduction of 50% in baseline LDL-c levels, treatment optimization is recommended, notably intensification of the lipid-lowering therapy with the use of ezetimibe and/or PCSK9 inhibitors. Observational studies from France and elsewhere have shown that these guidelines are poorly implemented, and notably, high-intensity statins are prescribed initially in only half of patients. During follow-up, not only is there no intensification of treatment,

but in fact, there is even a reduction in treatment intensity over time, culminating in insufficient cardiovascular protection.[1, 2] This situation is all the more disappointing and perplexing since in France at least, high-intensity statins, ezetimibe and PCSK9 inhibitors are all available (albeit with some conditions for PCSK9 inhibitors), and their use in compliance with the regimens currently reimbursed by the social security system would provide extremely efficacious lipid management.

In this context, a group of French expert cardiologists and lipidologists came together to propose a therapeutic strategy that is in line with evidence from the scientific literature, international guidelines, and reimbursement conditions within the French healthcare system. This strategy is simple, applicable in routine practice, and achieves optimal lipid-lowering therapy in patients with recent MI. The proposed strategy is focused on the demonstrated importance of reducing LDL-c starting at the acute phase, the value of adapting treatment intensity according to baseline LDL, and on the importance of follow-up during the first few months after the index event. Indeed, the detection and management of possible muscular symptoms, and the potential initiation of PCSK9 inhibitor therapy on top of maximally tolerated oral statins early after the index hospitalization remain under the shared responsibility of the acute phase prescriber, the cardiac rehabilitation center cardiologist and if possible the patient's referring cardiologist.

Statins, but also LDL-c reduction in acute coronary syndrome are evidence-based

The need for systematic introduction of high-intensity statins starting at admission for acute coronary syndrome (ACS) is not always perceived by clinicians to be on a par with coronary reperfusion, anti-thrombotic therapy, or beta-blockers, for example. Yet, randomized studies have shown for over 20 years that there is a clinical benefit to be yielded from the systematic use of high-intensity statins, regardless of baseline LDL. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study, the use of 80 mg of atorvastatin was shown to reduce recurrent ischemic events occurring within the first 16 weeks.[3] This effect as compared to placebo was confirmed by the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) Trial,[4] which demonstrated the greater protection against death or major cardiovascular events with an intensive lipid-lowering strategy, *versus* the standard, moderate-intensity regimen. The recommendation to introduce high-intensity statins at admission, regardless of baseline LDL, is predominantly based on these two studies. In parallel, studies including patients undergoing coronary angioplasty for ACS or stable coronary disease also showed that the prescription of a statin prior to percutaneous coronary intervention (PCI) was associated with a reduction in the risk of subsequent cardiovascular events.[5] A meta-analysis of 26 randomized studies suggested that the earlier statins are prescribed, the greater the benefit.[6] Taken together, these findings from acute ACS and PCI provide a compelling rationale for urgent prescription of high-intensity statins. The addition of ezetimibe on top of high intensity statin therapy during the acute phase of ACS, provides additional cardiovascular prevention. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the use of 10mg ezetimibe on top of simvastatin 40 mg daily led to an additional 20% reduction in LDL-c (which dropped from 69 mg/dL [1.8 mmol/L] to 54 mg/dL [1.4 mmol/L]), and this reduction was associated with a significant reduction in cardiovascular events.[7]

The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) study investigated the value of adding the PCSK9 inhibitor alirocumab, on top of the maximum tolerated dose of statins in terms of cardiovascular outcomes after recent ACS.[8] Alirocumab was introduced in patients with an LDL-c >70 mg/dL (1.8 mmol/L) under maximal tolerated oral lipid-lowering therapy, and on average, 2.6 months after the index event. The study reported a relative reduction of 15% in major adverse cardiac events at 3 years,[8] with a numerically lower rate of all-cause mortality in the alirocumab group.

The clinical benefit of a rapid and marked drop in LDL-c with high-intensity statins, ezetimibe and PCSK9 inhibitors can be explained by the direct effects observed on the atheromatous plaque *in vivo* with endovascular imaging, such as intravascular ultrasound (IVUS), near-infrared spectroscopy (NIR) and optical coherence tomography (OCT). The degree of inhibition of the progression of atheroma, and the reduction in atheroma and markers of vulnerability such as lipid content or fibrous cap thickness, are all proportional to the decrease in LDL-c, both in stable disease and in the setting of ACS.[9-15]

Statin+ezetimibe: systematic, or based on LDL-cholesterol under treatment?

If we adhere strictly to the provisions of what has been demonstrated by randomized clinical trials at the acute

phase of ACS, then the lipid-lowering strategy shown to be most efficacious is a dual strategy: Firstly, high-intensity statins should be initiated at admission and prior to PCI. Secondly, the addition of ezetimibe will make it possible to achieve LDL-c targets, when these goals cannot be attained by high-intensity statins alone. The scientific rationale for the use of ezetimibe comes from the IMPROVE-IT Trial, and may be debated when using atorvastatin 80 mg, since this drug yields a reduction in LDL-c comparable to that achieved with simvastatin 40 mg plus ezetimibe.

Nevertheless, the safety of using the association, initiated early after ACS, is established, also by IMPROVE-IT. The association can therefore be given systematically and regardless of either baseline LDL-c or LDL-c under statin therapy. This approach is no less congruent with the scientific evidence than a strategy consisting of a stepwise increase in intensity, with prescription of high-intensity statins as early as possible, followed by addition of ezetimibe at a later stage as a function of the LDL-c level observed at 4 to 6 weeks.[16, 17] The main advantage of the first-line combination is the substantial and early decrease in LDL-c, which has been shown to be associated with better long-term outcomes in a nationwide observational study.[18]

Additionally, the use of this combination as first-line therapy has been suggested as a means of timely achieving therapeutic goals.[19] Indeed, the therapeutic goals for cholesterol defined in 2019 are such that they cannot be achieved with statins alone (even high-intensity) in the majority of patients. From a purely mathematical viewpoint, it is unlikely that a patient will achieve an LDL-c <55 mg/dL (1.4 mmol/L) with a statin if the baseline LDL-c is greater than 110 mg/dL (2.8 mmol/L), since the expected reduction with high intensity statin therapy is around 50%. This is the case in France, where the average baseline LDL-c level among patients admitted for ACS is 132±0.39 mg/dL (3.4±0.01 mmol/L).[20] It therefore appears logical to adapt the initial prescription to achieve the therapeutic goals. The magnitude of the reduction in LDL-c achieved with various lipid-lowering regimens (statins alone, statin+ezetimibe or PCSK9 inhibitors) is established, as is the relatively limited effect of dietary measures. Indeed, at best, dietary measures will achieve a 10% reduction in cholesterol.[17]

A treatment strategy based on both scientific evidence and the likelihood of achieving therapeutic goals (the "Treat to target" approach) would therefore logically consist of a high-intensity statin initiated at admission, with addition of ezetimibe prior to discharge, according to baseline LDL. The introduction of a PCSK9 inhibitor, in line with the design of the Odyssey-Outcomes trial, can be considered according to the observed LDL-c under maximal tolerated therapy.

The French strategy since 2018

After the publication of the results of IMPROVE-IT study in late 2014, it became apparent that combination therapy with statins plus ezetimibe was of interest as a means to achieve an LDL-c level <55 mg/dL (1.4 mmol/L), a level that would provide greater cardiovascular prevention than the 70 mg/dL (1.8 mmol/L) threshold recommended by the guidelines in force at the time. To achieve the 55 mg/dL (1.4 mmol/L) target, a group of French experts proposed a treatment algorithm comprising high-intensity statins alone in patients admitted with baseline LDL-c <100 mg/dL (2.6 mmol/L), or combotherapy directly in patients with LDL-c >100 mg/dL (2.6 mmol/L) at admission.[21] The same algorithm was adopted by the EAS in its taskforce published in 2020, notably for the association of high-intensity statin plus ezetimibe in patients with baseline LDL-c >100 mg/dL (2.6 mmol/L).[22] When applied in routine practice in an unselected cohort of patients admitted for ACS, this approach led to prescription of high-intensity statins in 95% of cases, associated with ezetimibe in 65% of cases.[21] The value of this prescription at discharge after the acute phase was reflected by the average LDL-c level achieved in the study (57±28 mg/dL [1.47±0.7 mmol/L]), which was lower than that reported in international registries. In addition, more than 75% of the patients reached an LDL-c<70 mg/dL (1.8 mmol/L)[21].

With the ESC 2019 LDL-c targets, the algorithm proposed by the French expert group and the European Atherosclerosis Society performs less well, with only 50% of patients who satisfy both criteria.[21] Faced with renewed difficulties reaching the target, and in an attempt to simplify the prescription, a new "Fire to target" strategy was retained by the French expert group, namely combination therapy (statin plus ezetimibe) for all, immediately, and without conditions. The "Fire to target" strategy makes it possible to bring more patients to the ESC 2019 target early on, while also being aligned with the scientific literature validating the utility of statins plus ezetimibe at the acute phase of ACS (Figure 1).

Optimization: first follow-up visit - tolerance and efficacy

Observational studies and surveys suggest that the first clinical and biological follow-up visit, recommended at

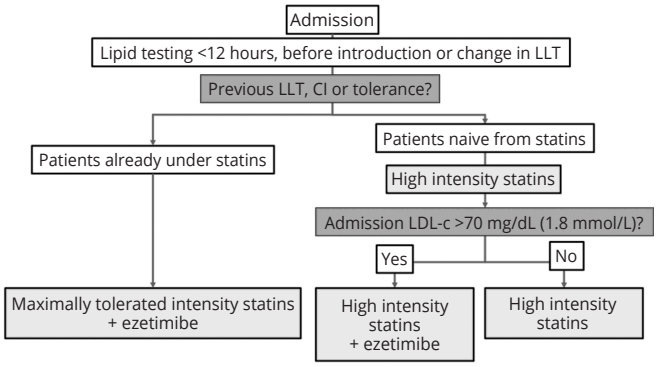

Figure 1.—Proposed algorithm for lipid-lowering prescription at admission.

4 to 6 weeks to verify tolerance and efficacy, is usually performed late, and treatment adjustment at this visit is usually ineffective. A survey of 555 physicians pertaining to prescriptions for 2775 post-ACS patients found that the time to first follow-up after discharge was on average 3 months, and at this visit, treatment had been intensified in only 39% of patients, while 68% still had an LDL-c level >70 mg/dL (1.8 mmol/L).[23] In France, a study that examined prescriptions over a 5-year period for 165,000 patients after an initial ACS showed that on average, treatment was not intensified; on the contrary, there was a decline in both intensity and compliance, resulting in a significant fall-off in prevention.[2] The advantage of prescribing an association of high-intensity statin plus ezetimibe from the outset is to avoid this stage of treatment intensification, making it possible to focus on tolerance of oral therapy, and the potential need for optimization with PCSK9 inhibitors. The initial strategy should therefore not neglect the follow-up, in a "Fire to Target and Follow" approach (Figure 2).

The IMPROVE IT study included more than 15,000 patients who had a long follow-up of almost 6 years, which confirms that the long-term tolerance of the combination

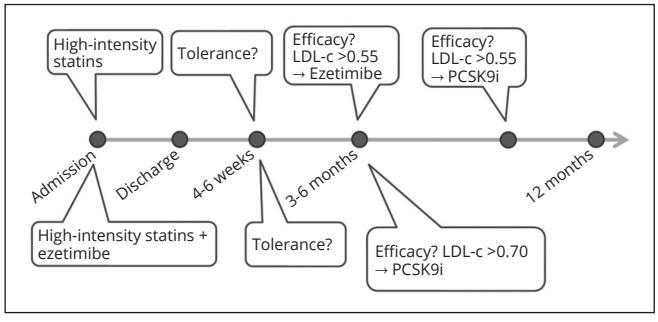

Figure 2.—Proposed algorithm for intensification of lipid-lowering treatment after the acute phase of acute coronary syndrome.

is generally good,[7] confirmed by a randomized trial with 3780 ASCVD patients, comparing clinical outcomes, tolerance and adherence of either combination first line moderate intensity statins+ ezetimibe vs high intensity statin monotherapy. At 3 years, the MACE rate was numerically albeit non-significantly lower, more patients were at the ESC 2016 LDL-c target (72% *vs.* 58%), there were lower LDL-c levels (58 mg/dL [1.5 mmol/L] *vs.* 66 mg/dL [1.7 mmol/L]), and fewer occurrences of intolerance-related or discontinuation/dose reduction (4.8% *vs.* 8.2%) in the combination arm.[24] Lastly, the use of a single pill combining high intensity statins+ezetimibe could improve adherence as compared to separate components. The utility of a polypill was recently shown by the SECURE study, which tested a single-pill combination of aspirin, ramipril and atorvastatin.[25]

Conversely, a non-negligible proportion of patients report statin-related symptoms, mostly muscle symptoms.[26] In these patients, specific management is warranted, including dechallenge and rechallenge, in order to identify the maximal tolerated statin dose.[27]

From 6 weeks, or as soon as the maximal tolerated oral lipid-lowering therapy has been determined, the efficacy of the treatment on LDL-c levels will guide the need for optimization with PCSK9 inhibitors. The ESC guidelines propose addition of a PCSK9 inhibitor for all patients whose LDL-c is not at target (*i.e.* anyone who remains >55 mg/dL (1.4 mmol/L) under statins and ezetimibe), but the reimbursement criteria in the different countries of Europe limit the wide application of this recommendation. In France, reimbursement of PCSK9 inhibitors via the national social security system is possible for patients with prior ACS whose LDL-c is >70 mg/dL (1.8 mmol/L) under maximal tolerated statin plus ezetimibe, and above this threshold value, introduction of a PCSK9 inhibitor can be considered. This threshold is derived from cardiovascular outcome trials with evolocumab and alirocumab. One of the specificities of the French context in this regard is that the PCSK9 inhibitor must be prescribed by the cardiologist, and is subject to prior written agreement from the health insurance system, after verification that the eligibility criteria have been met; one of the requirements being co-prescription of maximal tolerated statin and ezetimibe.

The proposed strategy comprises initial prescription of an association of high-intensity statin plus ezetimibe, preferably in the form of a single-pill combination, which may enhance compliance with treatment. Ideally, the monitoring of treatment efficacy and assessment of treatment tolerance should be anticipated through a collaboration

between the acute-phase prescriber and the cardiologists in charge during the cardiac rehabilitation program and/or the patients' follow-up for two key reasons: first, the management of patients with statin-associated muscle symptoms is complex, and second, because general practitioners are less familiar with the modalities for initiating PCSK9 inhibitors. Compliance with treatment should also be closely investigated through discussion with the patient, and regular monitoring of LDL-c levels (Figure 2).

Conclusions

This approach, which is currently feasible in France, could considerably improve lipid management in patients after ACS, thanks to its simplicity, rapidity and the magnitude of the decrease in LDL-c that it achieves.

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